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ANTISPASMODICS

BASIC ESTERS OF SUBSTITUTED α-PHENYL- AND α-CYCLOHEXYLPROPIONIC OR ACETIC ACIDS AND OF SUBSTITUTED MALONIC ACIDS

by
Juanito Beltran Abcede

A dissertation submitted in partial fulfillment
of the requirements for the degree of
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Abstract

ANTISPASMODICS

BASIC ESTERS OF SUBSTITUTED α-PHENYL- AND

α-CYCLOHEXYLPROPIONIC OR ACETIC ACIDS

AND OF SUBSTITUTED MALONIC ACIDS

by Juanito Beltran Abcede

During this investigation a number of substituted α-phenyl- and α-cyclohexyl-ß-hydroxypropionic acids, RR'C(OH)CHR''COOH, were prepared (R and R' = methyl, amyl, hexyl, tetramethylene, hexamethylene or 5-methylhexamethylene; R'' = phenyl or cyclohexyl). The substituted α-phenyl-ß-hydroxypropionic acids were obtained by the interaction of the chloromagnesium derivative of the chloromagnesium salt of phenylacetic acid, $C_6H_5CH(MgCl)COOMgCl$, with the required ketone (Ivanov reaction). α-Phenyl-α-(1-hydroxycyclopentyl)-acetic acid (α-phenyl-ß,ß-tetramethylene-ß-hydroxypropionic acid) and α-phenyl-α-(1-hydroxycycloheptyl)acetic acid were hydrogenated catalytically to the corresponding α-cyclohexyl acids.

With two exceptions, all of the ß-hydroxypropionic acids were converted into crystalline ß-diethylaminoethyl ester hydrochlorides by the use of the Horenstein-Pählicke procedure; the corresponding methobromides were also prepared. Crystalline salts could not be obtained from the

β-diethylaminoethyl esters of α-phenyl-β-methyl-β-n-amyl-β-hydroxypropionic and α-phenyl-α-(1-hydroxy-4-methylcyclohexyl)acetic acids. The hydrochlorides and methobromides of the β-(1-heptamethylenimino)ethyl esters of diphenylacetic, diphenylhydroxyacetic and α-phenyl-α-(1-hydroxycycloheptyl)-acetic acids, and of the β-(1-octamethylenimino)ethyl esters of diphenylacetic and diphenylhydroxyacetic acids were synthesized.

The bis(β-diethylaminoethyl) esters of substituted malonic acids, $RR'C(COOCH_2CH_2NEt_2)_2$ (R or R' = hydrogen, n-propyl, n-hexyl, cyclopentyl, cycloheptyl or phenyl), in the form of their hydrochlorides and methobromides, were prepared. The substituted malonic acids were obtained by the malonic ester synthesis. Some difficulty was experienced in the introduction of the second substituent into the diethyl monosubstituted malonate. Since the free disubstituted malonic acids readily underwent partial decarboxylation, the diethyl disubstituted malonates were hydrolyzed to the dipotassium salts of the corresponding acids; these salts reacted with β-diethylaminoethyl chloride to form the desired esters which were then converted into their hydrochlorides and methobromides.

The basic esters described in the dissertation are to be tested for antispasmodic activity in another laboratory.

ACKNOWLEDGEMENTS

The author wishes to express his deep appreciation to Professor F. F. Blicke who suggested this problem and directed the prosecution of this investigation.

Grateful acknowledgement is also made for the fellowships granted to the author by the University of the Philippines and the Sterling-Winthrop Research Institute and for the Fulbright travel grant from the United States Educational Foundation in the Philippines.

Juanito Beltran Abcede

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GENERAL INTRODUCTION AND DISCUSSION OF THIS INVESTIGATION

This dissertation represents a continuation of the subject of antispasmodics which has been in progress in this Laboratory for the last eighteen years. Since the general subject of antispasmodics has been discussed in detail so many times (1), only certain phases will be dealt with in this dissertation.

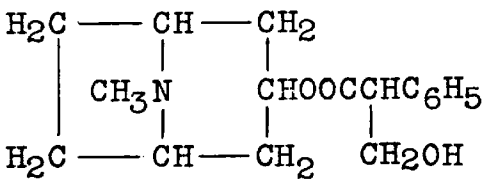
The structure of one of the oldest antispasmodics, the naturally occurring compound atropine, has served as a pattern for the preparation of hundreds of synthetic products. Many of these products, although simpler than atropine in structure, have been shown to exhibit antispasmodic activity but only a few of them have been found which equal it in potency. Unfortunately, many of the highly active synthetic antispasmodics exhibit the undesirable side-effects of atropine - tachycardia (excessive rapidity in heart action), xerostomia (dryness of the mouth) and mydriasis and cycloplegia (dilation of the pupil and loss of accommodation which produce visual disturbances). Consequently, the search for highly active, synthetic antispasmodics has been continued

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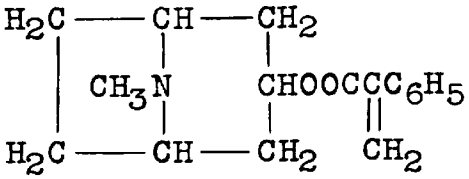
(1) See dissertations by the following individuals: (a) E. Monroe (1936); (b) F. B. Zienty (1938); (c) J. B. Data (1941); (d) N. Grier (1942); (e) R. F. Feldkamp (1943); (f) M. U. Tsao (1944); (g) F. Leonard (1946); (h) J. H. Biel (1947); (i) F. E. Anderson (1948); (j) J. A. Faust (1949); (k) E. L. Schumann (1949); (l) H. Raffelson (1951); (m) Chi-Jung Lu (1952); (n) J. Azuara (1954); (o) H. E. Millson (1954); (p) R. H. Cox (1954).

in the hope that products might be discovered which lack these side-effects.

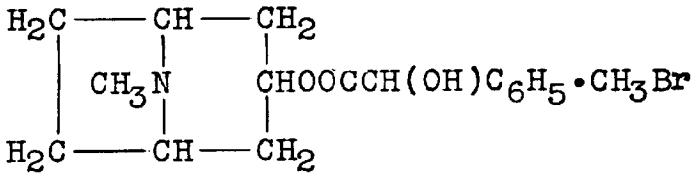
It can be seen from the structural formula that atropine is an ester which represents esterification of tropic acid (α-phenyl-β-hydroxypropionic acid) with the complex basic alcohol, tropine.



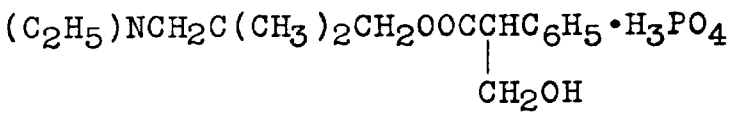
Atropine



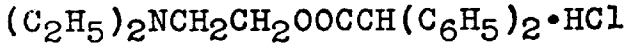
Apoatropine



Novatropine



Syntropan



Trasentin

Potent antispasmodics of the basic ester type have been known for a long time in which the acyl radical is not that of tropic acid, for example, apoatropine (2,3) and novatropine (homatropine methobromide) (4). The introduction of Syntropan as a commercial antispasmodic, many years ago,

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(2) See T. A. Henry, The Plant Alkaloids, pp. 71 and 107 (1949).
(3) See also J. C. Krantz, Jr. and C. J. Carr, The Pharmacologic Principles of Medical Practice, p. 653 (1949).
(4) See Ref. 3, p. 654.

illustrated that the radical of tropine is not essential for this type of activity. Furthermore, Trasentin, another commercial antispasmodic, is an ester which contains neither the radical of tropic acid nor that of tropine.

During a period of about twenty years, from about 1930 to 1950, great progress was made in the discovery of active basic esters. However, these achievements could not have been made if it had not been discovered that potent esters could be obtained by esterification of a simple acid, such as diphenylacetic acid, with a simple basic alcohol, such as ß-diethylaminoethanol. Neither tropic acid nor tropine were generally available for use in research, and it is only during the last few years that practical syntheses for the large scale production of both tropic acid and tropine have become known.

In the search for new antispasmodics of the basic ester type, an investigation is often limited to a study of esters which are obtained by esterification of the same basic alcohol, such as ß-diethylaminoethanol, with a number of new acids or to a study of the products obtained by esterification of a given acid with a variety of new basic alcohols. This investigation deals with the synthesis of basic esters obtained by esterification of a number of new acids with ß-diethylaminoethanol and also with the synthesis of esters prepared from well known acids and basic alcohols which contain an eight- or nine-membered nitrogenous ring.

Although it is not improbable that, in the future, entirely different types of acids will be found which will yield effective antispasmodics when they are esterified with basic alcohols, practically all of the acids which have been used so far for the synthesis of potent antispasmodics are di- or trisubstituted acetic acids. Tropic acid, although usually named α-phenyl-β-hydroxypropionic acid, is α-phenyl-α-(hydroxymethyl)acetic acid.

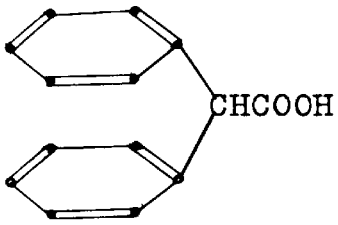
Basic-alkyl Esters of Substituted Acetic Acids

A list of di- and trisubstituted acetic acids which, in the form of basic esters and in one instance in the form of a lactone, are known to be potent antispasmodics is found below. The names of the commercial antispasmodics obtained from these acids are mentioned in parentheses.

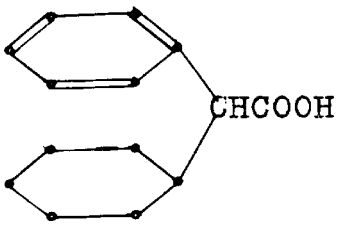
The use of an "α" to designate the position of a substituent in acetic acid in some instances is obviously superfluous; in other cases the use of the Greek letter avoids any ambiguity which might otherwise arise.

Disubstituted Acetic Acids:

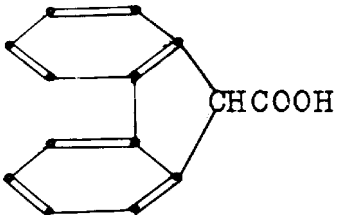
$C_6H_5CHCOOH$ $\quad\quad\vert$ $\quad CH_2OH$	Tropic acid α-Phenyl-α-(hydroxymethyl)acetic acid (Atropine, Syntropan)
$C_6H_5CHCOOH$ $\quad\quad\vert$ $\quad OH$	Mandelic acid α-Phenyl-α-hydroxyacetic acid (Homatropine)
$C_6H_5CHCOOH$ $\quad\quad\vert$ $\quad C_3H_7$	α-Phenylvaleric acid α-Phenyl-α-propylacetic acid (Propivan)



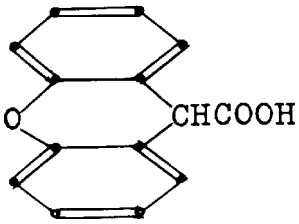
Diphenylacetic acid
(Trasentin)



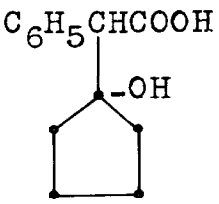
α-Phenyl-α-cyclohexylacetic acid
(Trasentin-6H)



Fluorene-9-carboxylic acid
(Pavatrine)

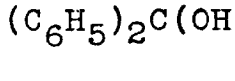


Xanthene-9-carboxylic acid
(Banthine)

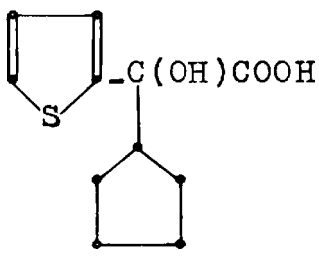


α-Phenyl-α-(1-hydroxycyclopentyl)acetic acid
(Cyclopentolate)

Trisubstituted Acetic Acids:



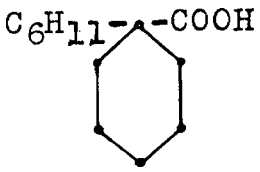
Benzilic acid
α,α-Diphenyl-α-hydroxyacetic acid
(Diphemin)



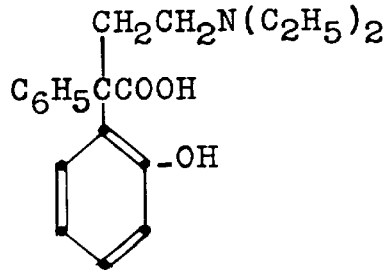
α-(2-Thienyl)-α-cyclopentyl-α-hydroxyacetic acid
(Monodral)



1-Phenylcyclopentanecarboxylic acid
α-Phenyl-α,α-tetramethyleneacetic acid
(Panparnit)

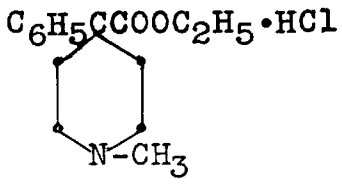


1-Cyclohexylcyclohexanecarboxylic acid
α-Cyclohexyl-α,α-pentamethyleneacetic acid
(Bentyl)



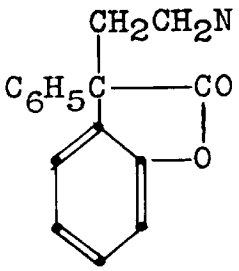
α-Phenyl-α-(2-hydroxyphenyl)-α-(β-diethylaminoethyl)acetic acid
(Amethone)

Two antispasmodics, Demerol* (5) and Amethone (6) possess structures which would make them seem to be totally unrelated to the basic esters which have been mentioned.



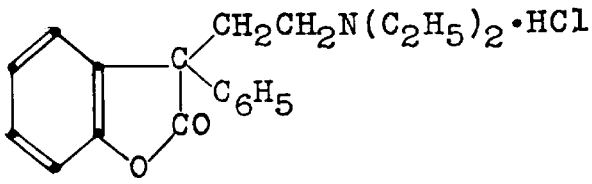
Demerol

Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride



Amethone

Lactone of α-phenyl-α-(2-hydroxyphenyl)-α-(β-diethylaminoethyl)acetic acid hydrochloride



3-Phenyl-3-(β-diethylaminoethyl)benzo-2-furanone hydrochloride

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* It should be emphasized that this compound is employed as an analgesic and not as an antispasmodic. However, it has very definite antispasmodic properties and it was first prepared in Germany during a search for antispasmodics. A fortuitous observation was responsible for the discovery of its analgesic activity.

(5) O. Eisleb and O. Schaumann, Deut. med. Wochschr., 65, 967 (1939).
(6) See Ref. 3, p. 657.

It is true that the basic nitrogen atoms in these two compounds are found in an acyl instead of an alcoholic radical. Nevertheless, both Demerol and Amethone may be regarded as derivatives of trisubstituted acetic acids. In Demerol one hydrogen atom of the methyl group in acetic acid has been replaced by a phenyl group and the other two hydrogen atoms by the divalent radical $-CH_2CH_2N(CH_3)CH_2CH_2-$. In Amethone again one hydrogen atom of the methyl group has been replaced by a phenyl group, a second hydrogen atom by a ß-diethylaminoethyl group and a third hydrogen by a 2-hydroxyphenyl radical; loss of water results in the formation of the lactone, Amethone. Clearer and more satisfactory chemical names for these two antispasmodics are found if Demerol is regarded as a derivative of piperidine, and Amethone as a derivative of benzo-2-furanone.

Some of the acids, required for the preparation of the ß-diethylaminoethyl esters described in this dissertation, are substituted ∝-phenyl- and ∝-cyclohexyl-ß-hydroxypropionic acids which conform to the following general formula:



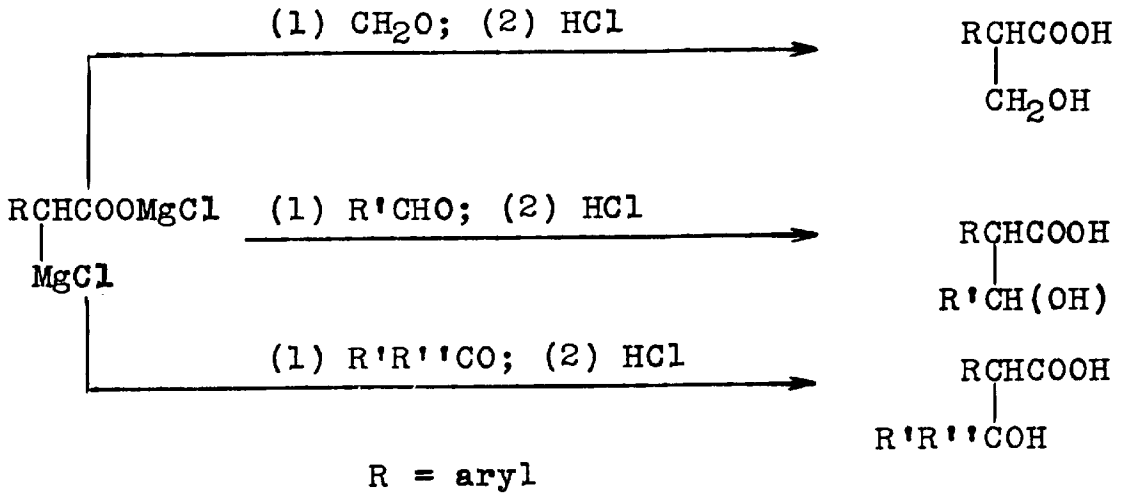
R = Phenyl or cyclohexyl

These acids are listed in Table I. The acids in which R represents cyclohexyl were obtained by catalytic hydrogenation of the corresponding compound in which R represents phenyl.

The preparation of acids of type A (R = phenyl) was

accomplished by the use of the Ivanov reaction*. In order to carry out this reaction, an arylacetic acid (usually phenylacetic acid) is treated with isopropylmagnesium chloride whereby propane is evolved and the acid is converted into the chloromagnesium derivative of the chloromagnesium salt, aryl-CH(MgCl)COOMgCl. This substance, a special form of a Grignard reagent, may be referred to as an Ivanov reagent.

As would be expected, an Ivanov reagent reacts with a wide variety of compounds which contain carbonyl groups with the formation of a substituted ß-hydroxypropionic acid in which the hydroxyl group may be primary, secondary or tertiary. A primary alcoholic group will be introduced if formaldehyde is employed; secondary and tertiary alcoholic compounds are obtained by the use of an aldehyde (other than formaldehyde) and a ketone, respectively.



*A thorough discussion of this reaction is to be found in the doctoral dissertation of Harold Raffelson (University of Michigan, 1951) (Ref. 1 (l)). See also R. H. Cox, Dissertation (University of Michigan, 1954) (Ref. 1 (p)).

During this investigation, the chloromagnesium derivative of the chloromagnesium salt of phenylacetic acid was allowed to react with the following ketones: methyl amyl ketone (2-heptanone), methyl hexyl ketone (2-octanone), cycloheptanone and 4-methylcycloheptanone. In this manner the substituted ß-hydroxypropionic acids mentioned below were obtained.

α-Phenyl-ß-methyl-ß-amyl-ß-hydroxypropionic acid
(α-Phenyl-ß-methyl-ß-hydroxyoctanoic acid)

α-Phenyl-ß-methyl-ß-hexyl-ß-hydroxypropionic acid
(α-Phenyl-ß-methyl-ß-hydroxynonanoic acid)

α-Phenyl-α-(1-hydroxycycloheptyl)acetic acid*

α-Phenyl-α-(1-hydroxy-4-methylcycloheptyl)acetic acid**

Two acids, α-phenyl-α-(1-hydroxycyclopentyl)acetic (7,8,9,10) and α-phenyl-α-(1-hydroxycycloheptyl)acetic acids, were hydrogenated with the aid of platinum oxide catalyst to produce α-cyclohexyl-α-(1-hydroxycyclopentyl)acetic and α-cyclohexyl-α-(1-hydroxycycloheptyl)acetic acid, respectively.

It has been found (8,9,10) that ß-diethylaminoethyl esters of substituted ß-hydroxypropionic acids, in the form of their hydrochloride or methobromide salts, exhibit unusually high potency as antispasmodics. It seemed desirable

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* In conformity with the usual nomenclature, this acid has been named as an acetic acid. However, it actually is a substituted ß-hydroxypropionic acid - α-phenyl-ß,ß-hexamethylene-ß-hydroxypropionic acid.

** α-Phenyl-ß,ß-(3-methylhexamethylene)-ß-hydroxypropionic acid.

(7) See Ref. 1 (1).

(8) A. W. Weston and R. W. DeNet, J. Am. Chem. Soc., 73, 4221 (1951).

(9) G. R. Treves (to Schieffelin & Co.), U. S. pat. 2,554,511; C. A., 46, 1035 (1952).

(10) F. F. Blicke and H. Raffelson, J. Am. Chem. Soc., 74, 1730 (1952).

to prepare additional representatives of this type of esters from the acids which had been obtained, and these esters are listed in Table II.

Unfortunately, α-phenyl-β-hydroxypropionic acids and their esters tend to undergo a characteristic degradation into the components from which they were prepared* (11-14). For example, α-phenyl-β-methyl-β-hydroxypropionic acid decomposes into phenylacetic acid and acetaldehyde. This decomposition takes place spontaneously but it is greatly

$$\begin{matrix} C_6H_5CHCOOH \\ | \\ CH_3CH(OH) \end{matrix} \longrightarrow C_6H_5CH_2COOH + CH_3CHO$$

accelerated by heat and the presence of alkali. It was found in this Laboratory (1 (p)) that the decomposition of a compound, such as α-phenyl-β-methyl-β-hydroxypropionic acid, is greatly retarded or prevented by conversion of the α-phenyl into α-cyclohexyl group. Consequently, some β-diethylaminoethyl esters were prepared from the acids which contained an α-cyclohexyl group (Table II).

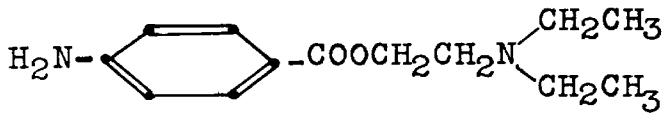
It is known that the potency of a pharmacologically active compound usually is retained if a dialkylamino group in a side chain is replaced by a cyclic basic radical such pyrrolidino or piperidino. For example, both β-diethylamino-

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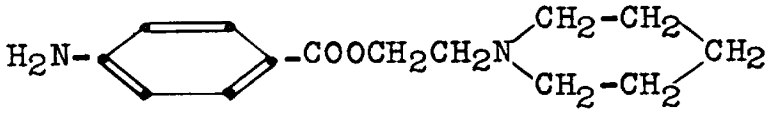
* A detailed discussion and a study of this degradation is to be found in the doctoral dissertation by R. H. Cox (University of Michigan, 1954) (Ref. 1 (p)).

(11) D. Ivanov and J. Popov, Bull. soc. chim., (4) 49, 1547 (1931).
(12) D. Ivanov, M. Mihova and T. Christova, ibid., (4) 51, 1321 (1932).
(13) D. Ivanov, ibid., (4) 53, 321 (1933).
(14) D. Ivanov, ibid., (5) 7, 569 (1940).

ethyl p-aminobenzoate and ß-piperidinoethyl p-aminobenzoate are potent local anesthetics. Very little is known about the

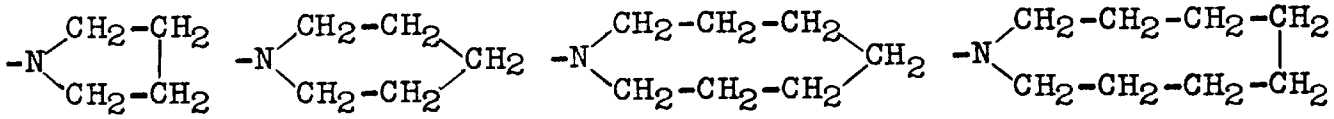


ß-Diethylaminoethyl p-aminobenzoate



ß-Piperidinoethyl p-aminobenzoate

pharmacological effect which might be produced by the use of a 1-heptamethylenimino or a 1-octamethylenimino radical, that is, an eight- or a nine-membered cyclic basic group, in place of a diethylamino group. In the past the intermediates which



Pyrrolidino Piperidino 1-Heptamethylen-imino 1-Octamethylen-imino

would be required for the introduction of the radicals of the seven-, eight- and also nine-membered rings - the cyclic imines themselves and the basic alkanols and alkyl chlorides which contained the radicals of the cyclic imines - were not available. The preparation in practical amounts of the required intermediates became possible only after the following developments had taken place: the commercial availability of epsilon-caprolactam*, the discovery that lithium hydride converts not only acyclic amides but also cyclic amides (lactams)

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*Manufactured by E. I. du Pont de Nemours and Company.

into amines in high yields (15) and the publication of practical procedures for the synthesis of cycloheptanone (16) and cyclooctanone (17). These developments made it possible to describe useful procedures for the preparation of a number of basic alcohols and basic alkyl chlorides which contain a 1-hexa-, 1-hepta- or 1-octamethylenimino radical (18).

During this investigation ß-(1-heptamethylenimino)ethyl chloride and ß-(1-octamethylenimino)ethyl chloride were used for the esterification of diphenylacetic, benzilic and ⍺-phenyl-⍺-(1-hydroxycycloheptyl)acetic acids (Table III). It had been found previously (19) that the ß-diethylaminoethyl esters of the first two mentioned acids were highly active antispasmodics.

Basic-alkyl Esters of Substituted Malonic Acids

The first basic-alkyl ester of a malonic acid described in the literature was bis(ß-diethylaminoethyl) diethylmalonate which was obtained by A. Einhorn and H. von Diesbach (20) in 1908. No report was made about any pharmacological properties.

In 1928, E. Gilman and T. B. Johnson (21) prepared bis-(ß-diethylaminoethyl) malonate and stated that it did not show marked local anesthetic properties.

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(15) L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, Helv. Chim. Acta, 32, 544 (1949).
(16) F. F. Blicke, N. J. Doorenbos and R. H. Cox, J. Am. Chem. Soc., 74, 2924 (1952).
(17) F. F. Blicke, J. Azuara, N. J. Doorenbos and E. B. Hotelling, ibid., 75, 5418 (1953).
(18) F. F. Blicke and N. J. Doorenbos, ibid., 76, 2317 (1954).
(19) B. N. Halpern, Arch. internal. pharmacodynamie, 59, 149 (1938).
(20) A. Einhorn and H. von Diesbach, Ann., 359, 185 (1908).
(21) E. Gilman and T. B. Johnson, J. Am. Chem. Soc., 50, 3341 (1928).

During the preparation of synthetic curare derivatives, R. Fusco and associates (22) obtained bis(ß-dimethylaminoethyl) malonate by transesterification. Almost at the same time, antispasmodic and analgesic properties were reported in the patent literature (23,24,25) for ethyl ß-diethylaminoethyl esters of some dialkylmalonic acids.

A. S. McBay et al. (26) found that not only ethyl ß-diethylaminoethyl dialkylmalonates but also bis(ß-diethylaminoethyl) disubstituted malonates showed some antispasmodic activity.

A compound, ß-(1-piperidyl)ethyl diphenylmalonate, was reported to have several times the activity of atropine or papaverine against spasm induced by barium chloride (27) but practically lacks acetylcholine activity.

Antispasmodic and analgesic activity was reported by J. Büchi and coworkers (28) for mono- and dibasic esters of disubstituted malonic acids and also for monobasic amide-esters and dibasic amides of dialkylmalonic acids. Some of the compounds were shown to be superior to Benadryl and Trasentin in antagonizing the effect of barium chloride on

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(22) R. Fusco, G. Palazzo, S. Chiavarelli and D. Bovet, Gazz. chim. ital., 79, 129 (1949).
(23) R. Hirt (to A. Wander A.-G.), U. S. pat., 2,494,875; C. A., 44, 4026 (1950).
(24) A. Wander A.-G., Swiss pat., 261,218; C. A., 44, 4027 (1950).
(25) A. Wander A.-G., British pat., 656,864; C. A., 46, 9587 (1952).
(26) A. S. McBay, G. L. Jenkins and J. B. Data, J. Am. Pharm. Assoc. Sci. Ed., 34, 138 (1950).
(27) M. Protiva and Z. J. Véjdelek, Collection Czech. Chem. Communs., 15, 541 (1950).
(28) J. Büchi, G. Enezian, H. Eichenberger and R. Liberherr, Helv. Chim. Acta, 35, 75 (1952).

smooth muscles but all were inferior to these commercial antispasmodics in nullifying the effects of acetylcholine. Noteworthy among these compounds were the bis(ß-diethylaminoethyl) amide and the bis(ß-diethylaminoethyl) ester of diethylmalonic acid for their analgesic properties and the ethyl ß-diethylaminoethyl ester of ethyl-n-butylmalonic acid for its antispasmodic action.

Basic-alkyl esters of substituted malonic acids were also described by C. P. Headlee and L. D. Edwards (29). One of the more active esters in their series was ethyl ß-diethylaminoethyl ethylisoamylmalonate.

Diethyl disubstituted malonates, in which one substituent was a ß-diethylaminoethyl group, the other a cyclic radical, were synthesized by R. B. Moffett and C. A. Hart (30). The pharmacological activity of these compounds was not reported. The malonates were hydrolyzed and decarboxylated to the corresponding disubstituted acetic acids. It was stated that the ß-diethylaminoethyl esters of the acetic acids did not possess antispasmodic activity in the useful range.

It is of interest to note that bis(ß-diethylaminoethyl) esters of phthalic and terephthalic acids have also been studied pharmacologically (31).

It seems that there may be three reasons why basic

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(29) C. P. Headlee and L. D. Edwards, J. Am. Pharm. Assoc., Sci. Ed., 42, 433 (1953).
(30) R. B. Moffett and C. A. Hart, ibid., 42, 717 (1953).
(31) F. Bovet-Nitti and D. Bovet, Arch. exptl. Pathol. Pharmakol., 220, 52 (1953); C. A., 48, 2253 (1954).

esters of substituted malonic acids have not been prepared and studied in greater number: the pharmacological activity of the esters which have already been described in the literature is of a low order; interest in the malonic esters has been chiefly in their use as intermediates for the preparation of substituted acetic acids which, in the form of their basic esters, are often potent antispasmodics; and the preparation of a disubstituted malonic ester, by the introduction of a second substituent into a monosubstituted malonic ester, has proven to be difficult in a number of cases.

Methods in the Malonic Ester Synthesis

Since difficulties were encountered during the introduction of a second substituent into certain monosubstituted malonic esters, it was of interest to report some of the methods used by other investigators to effect this type of substitution.

Alkyl and Δ^2-cyclopentenyl groups were introduced into Δ^2-cyclopentenemalonic acid with the use of sodium dispersed in toluene instead of sodium alkoxide (32).

In order to introduce an alkyl group, which contained five to nine carbon atoms, into Δ^2-cyclopentenylmalonate, sodium ethylate in ethanol was used as the condensation agent. However, most of the alcohol was removed from the reaction mixture before the addition of the alkyl bromide (33,34). In some instances, higher yields seemed to have

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(32) G. A. Perkins and A. D. Cruz, J. Am. Chem. Soc., 49, 518 (1927).
(33) J. A. Arvin with R. Adams, ibid., 49, 2941 (1927).
(34) See also (a) R. Adams, W. M. Stanley, S. G. Ford and

been obtained by the use of an inert solvent (35).

It was possible to introduce a sec.-alkyl group into an alkylmalonic ester but difficulties were experienced in the attempted introduction of an ethyl group into sec.-butyl-, sec.-amyl- or cyclopentylmalonic ester and of an allyl group into sec.-butylmalonic ester (36).

Although n-propyl iodide and a number of other iodides reacted with diethyl isopropylmalonate, it was found that a second isopropyl group could not be introduced into isopropylmalonic ester (37). However, it was found later that a second isopropyl group could be introduced into isopropylmalonic ester when the reaction was carried out in a sealed tube. It appeared that the reaction did not take place if ether- or alcohol-free sodio derivatives were used. Much better yields were obtained by the use of diethyl malonates instead of dimethyl malonates (38).

With an alcohol-free metallic alcoholate in a dialkyl carbonate medium, a number of disubstituted malonic esters was obtained in high yields; for example, ethylphenylmalonic ester (79%) and ethyl-sec.-butylmalonic ester (94.8%) (39). In a similar manner, diethyl ethyl(ß-cyclohexylideneethyl)-

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W. R. Peterson, J. Am. Chem. Soc., 49. 2937 (1927); (b) S. G. Ford and R. Adams, ibid., 52, 1259 (1930); (c) E. Browning, H. H. Woodrow and R. Adams, ibid., 52, 1281 (1930); (d) B. F. Armendt and R. Adams, ibid., 52, 1290 (1930).

(35) R. Adams, W. M. Stanley and H. A. Stearns, ibid., 50, 1475 (1928).

(36) H. A. Schonle, A. K. Keltch and E. E. Swanson, ibid., 52, 2440 (1930).

(37) F. C. B. Marshall, J. Chem. Soc., 2754 (1930).

(38) F. C. B. Marshall, ibid., 2336 (1931).

(39) V. H. Wallingford and A. H. Homeyer (to Mallinckrodt Chemical Works), U. S. pat. 2,478,853; C. A., 44, 1135 (1950).

malonate was prepared from ethylmalonic ester (40).

Diethyl methyl-ß-phenylethylmalonate was obtained from diethyl methylmalonate by the use of powdered potassium in xylene as a condensation agent (41).

By the use of the usual procedure in which an alcoholic solution of sodium ethoxide was employed, ⍺-naphthylmalonic, ⍺-naphthylmethylmalonic and benzylmalonic esters were alkylated in 43-73% yields (42).

It was of special interest to us to note that by cycloalkylation of cyclohexylmalonic ester, diethyl dicyclohexylmalonate had been obtained in 14.7% yield; by the same general procedure, diethyl bis(2-methylcyclohexyl)malonate was formed in 10% yield and diethyl 1-ethylcyclohexanemalonate in 1.4% yield (43).

The introduction of a second substituent into tert.-butylmalonic ester was accomplished recently for the first time. By the use of the procedure of Wallingford *et al.* (39), it was found possible to obtain allyl- (20%), ethyl- (20%) and methyl-tert.-butylmalonic ester (27%; 13% of pure product) (44).

Several unique disubstituted malonic esters which contain silicon have been obtained. These compounds are methyl-

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(40) A. Allais and J. Mathieu, Ann. pharm. franç., 9, 275 (1951); C. A., 45, 10499 (1951).
(41) H. Adkins and J. W. Davies, J. Am. Chem. Soc., 71, 2957 (1949).
(42) C. Ukita, O. Tamemasa and H. Motomatsu, J. Pharm. Soc., Japan, 71, 283 (1951).
(43) N. D. Zelinskii, L. S. Bondar, V. N. Kost and B. Y. Lifshits, Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk., 1951, No. 2, 96; C. A., 45, 10205 (1950).
(44) M. T. Bush and W. D. Beauchamp, J. Am. Chem. Soc., 75, 2949 (1953).

and allyltrimethylsilylmethylmalonic esters (45).

Some Phases of the Malonic Ester Synthesis

Although it is entirely beyond the scope of this dissertation to discuss the malonic ester synthesis in complete detail, some phases of this synthesis, such as the types of condensation agents which have been employed, the mechanism of the reaction and the side reactions, are discussed briefly in the following pages.

The commonly used condensation agents in the malonic ester synthesis are a metallic (sodium or potassium) alkoxide, in the presence of absolute ethanol or a dialkyl carbonate, and powdered sodium* or potassium suspended in benzene, toluene or xylene. About ten years ago, sodium triphenylmethyl**, which had been used previously (46) in the Claisen condensation, was employed in the malonic ester synthesis (47). By the use of this condensation agent, diethyl isopropylmalonate and ethyl iodide reacted to form diethyl ethylisopropylmalonate in 73% yield, and reaction with isopropyl iodide produced diethyl diisopropylmalonate in 23% yield.

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* Commercial sodium dispersions, sold by the U. S. Industrial Chemical Company, are now recommended for malonic ester syntheses. In general, it is claimed that the use of these dispersions lead to increased yields and reduced reaction time.

** The preparation of sodium or potassium triphenylmethyl has been described by R. Levine, E. Baumgarten and C. R. Hauser, J. Am. Chem. Soc., 66, 1230 (1944).

(45) L. H. Sommer, G. M. Goldberg, G. H. Barnes and L. S. Stone, Jr., J. Am. Chem. Soc., 76, 1609 (1954).

(46) B. Abramovitch and C. R. Hauser, ibid., 64, 2271 (1942).

(47) J. C. Shivers, B. E. Hudson, Jr. and C. R. Hauser, ibid., 66, 309 (1944).

In 1933 the use of magnesium in the malonic ester synthesis was reported. It had been found that magnesium will not react with malonic ester (48), and that magnesium which had been activated with iodine reacted with ethanol with the evolution of hydrogen and the formation of magnesium ethylate (49,50). It was then shown (51,52,53) that magnesium, which had been activated with iodine*, reacted vigorously with a mixture of absolute ethanol and diethyl malonate**. One atomic equivalent of magnesium and one molecular equivalent of diethyl malonate reacted to form a crystalline compound which, based on analytical data, seemed to be $MgC(COOC_2H_5)_2 \cdot 2\ C_2H_5OH$. At 80° the compound lost one molecular equivalent of alcohol and, presumably, diethyl ethoxymagnesiummalonate, $C_2H_5OMgCH(COOC_2H_5)_2$ was produced. Interaction of this reagent with an alkyl halide was represented (51) in the following manner.

$$RX + C_2H_5OMgCH(COOC_2H_5)_2 \longrightarrow RC(MgX)(COOC_2H_5)_2 + C_2H_5OH$$

$$RX + RC(MgX)(COOC_2H_5)_2 \longrightarrow R_2C(COOC_2H_5)_2 + MgX_2$$

It was claimed that by the use of these derivatives two

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* The activation may be carried out more conveniently by the addition of a small amount of carbon tetrachloride to the absolute alcohol which is employed in the synthesis (53).

** Unactivated magnesium will also react but only if absolutely dry alcohol and ester are employed.

(48) L. Meunier, Compt. rend., 137, 714 (1903).
(49) A. P. Terentiew, Zeitschr. anorg. allg. Chem., 162, 349 (1927).
(50) H. Lund and J. Bjerrum, Ber., 64, 210 (1931).
(51) H. Lund, A. U. Hansen and A. F. Voigt, Det Kgl. Danske Videnskabernes Selskab. Mathematisk-fysiske Meddelelser, XII, 9, 1 (1933).
(52) H. Lund, ibid., XIII, 13, 1 (1935).
(53) H. Lund, Ber., 67, 935 (1934).

groups can often be introduced simultaneously into malonic ester, and a second substituent can be introduced with ease into a monosubstituted malonic ester. However, it was stated that when the magnesium derivative was used, only one secondary or tertiary alkyl group can be put into diethyl malonate. But when diethyl isopropylmalonate was converted into the magnesium derivative and then alkylated with a primary alkyl halide there resulted the formation of the disubstituted ester in good yield.

Sodium hydride* has been used in Claisen reactions (54) and to effect condensation between alkyl halides and diethyl formamidomalonate or diethyl acetamidomalonate (55).

Although it is known that sodamide converts esters into amides (56), this condensation agent has been used successfully in the acylation of methyl ketones with aliphatic esters (57).

Regardless of the condensation agent employed, the alkylation of a malonic ester consists of two steps: (a) the formation of a metallo derivative of the ester; and (b) the interaction of the metallo derivative with an alkyl halide.

As early as 1891, Nef (58) believed that the formation

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* A number of possible applications of this substance have been suggested by N. Green and F. B. LaForge (J. Am. Chem. Soc., 70, 2287 (1948)).

(54) F. W. Swamer and C. R. Hauser, ibid., 72, 1352 (1950).

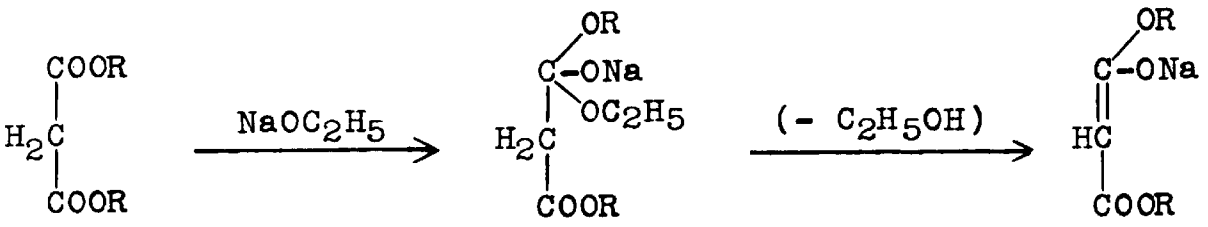
(55) J. Shapira, R. Shapira and K. Dittmer, ibid., 75, 3655 (1953).

(56) C. R. Hauser, R. Levine and R. F. Kibler, ibid., 68, 26 (1946).

(57) (a) J. T. Adams and C. R. Hauser, ibid., 66, 1220 (1944). (b) R. Levine, J. A. Conroy, J. T. Adams and C. R. Hauser, ibid., 67, 1510 (1945).

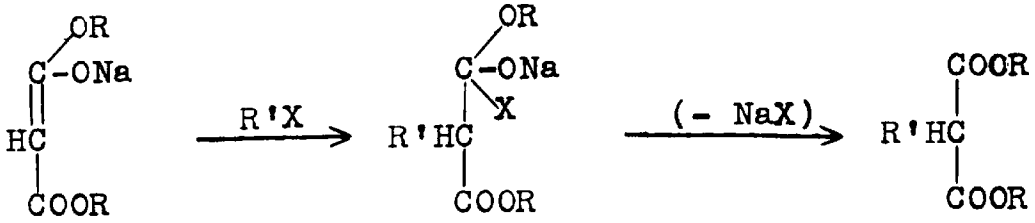
(58) J. V. Nef, Ann., 266, 52 (1891); 308, 283 (1899).

of a sodiomalonic ester depended on the addition of a molecule of sodium ethylate to one of the ester radicals followed by the elimination of ethanol:



It was proven later through molecular refraction studies by Haller and Muller (59) that the structure of sodiomalonic ester, as proposed by Nef and concurred in by Liebermann (60) and also by Michael (61), was correct.

In 1915, Jackson and Whitmore (62) furnished proof that the first step in the reaction of a sodiomalonic ester with an alkyl halide consists in the formation of an addition product; sodium halide is then eliminated with the formation of a monosubstituted malonic ester:



According to Dolique (63) the mechanism of dialkylation, starting from a monosubstituted malonic ester, follows the same course as that described above.

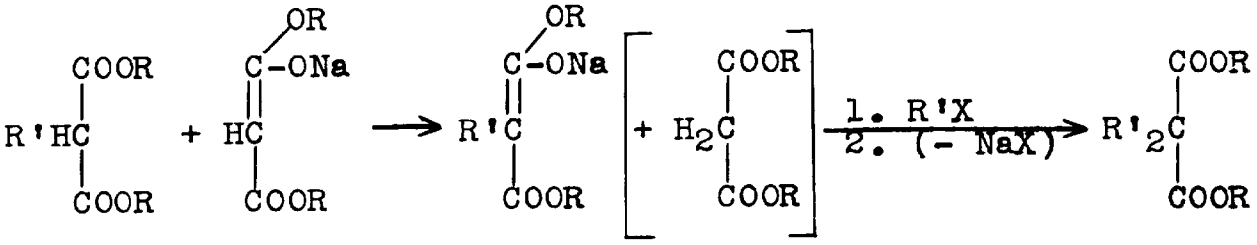
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(59) A. Haller and A. T. Muller, Ann. chim., (8) 15, 289 (1908).
(60) C. Liebermann, Ber., 27, 289 (1894).
(61) A. Michael, J. prakt. chem., 37, 473 (1888); 46, 194 (1892).
(62) C. L. Jackson and F. C. Whitmore, J. Am. Chem. Soc., 37, 1522 (1915).
(63) R. Dolique, Ann. chim., (10) 15, 429 (1931).

In a paper published in 1932, Dunn *et al.* (64) stated,

> "The hypothesis that disubstituted products may be formed through the agency of a disodium malonic ester is still used by some authors despite the molecular weight experiments of Vorlander and von Schilling (65) and the spectroscopic investigations of Macbeth and Stewart (66) which point to the non-existence of the disodium compound."*

Support for the reactions postulated by Leuchs (67), which are shown below, was obtained by the experiments reported



by Dunn and his associates (64). They reported that,

> "Definite evidence was obtained for the formation of malonic ester from sodium malonic ester and benzylmalonic ester and of dibenzylmalonic ester from sodium benzylmalonic ester and benzyl chloride."

It has been found (68) that many substituted malonic esters undergo alcoholysis when heated in alcohol in the

$$C_6H_5CH(COOC_2H_5)_2 + C_2H_5OH \xrightarrow[\text{in } C_2H_5OH]{NaOC_2H_5} C_6H_5CH_2COOC_2H_5 + (C_2H_5O)_2CO$$

presence of sodium ethylate. After it had been shown that

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* In this connection it is of interest to note the postulation of the formation of $(C_6H_5)_2C(MgBr)_2$ in order to explain the production of diphenylmalonic acid from diphenylacetonitrile (F. F. Blicke and Eu-Phang Tsao, J. Am. Chem. Soc., 75, 5587 (1953). The reaction mechanism was suggested by Dr. P. A. S. Smith.)

(64) M. S. Dunn, C. E. Redemann and S. Lauritsen, J. Am. Chem. Soc., 54, 4335 (1932).
(65) D. Vorlander and R. von Schilling, Ber., 32, 1876 (1899).
(66) A. K. Macbeth and A. W. Stewart, J. Chem. Soc., Proc., 29, 11 (1913).
(67) H. Leuchs, Ber., 44, 1507 (1908).
(68) (a) A. C. Cope and S. M. McElvain, J. Am. Chem. Soc., 54, 4319 (1932).
(b) R. Connor, ibid., 55, 4597 (1933).

the cleavage (69) of diethyl phenylmalonate is reversible, a procedure was developed (69) by means of which a high yield of diethyl phenylmalonate could be obtained from ethyl phenylacetate and diethyl carbonate. The essential features of this procedure were the use of excess diethyl carbonate as a solvent and the removal of the alcohol from the reaction mixture by distillation.

$$R'CH_2COOR + (RO)_2CO + MOR \longrightarrow \left[R'C(COOR)_2\right]M + 2\ ROH$$

During the carbalkoxylation of some of the lower aliphatic esters it was found (69) that an appreciable amount of alkylation by the diethyl carbonate took place. For example, interaction of diethyl carbonate with ethyl n-butyrate yielded not only the expected product, diethyl ethylmalonate, but also a considerable quantity of diethyl diethylmalonate. The last mentioned product was produced by the alkylating action of diethyl carbonate on the sodio-derivative of diethyl ethylmalonate.

$$CH_3CH_2CH_2COOC_2H_5 + (C_2H_5O)_2CO \xrightarrow{NaOC_2H_5} CH_3CH_2CNa(COOC_2H_5)_2 + 2\ C_2H_5OH$$

$$CH_3CH_2CNa(COOC_2H_5)_2 + (C_2H_5O)_2CO \longrightarrow (CH_3CH_2)_2C(COOC_2H_5)_2 + (C_2H_5O)CO(ONa)$$

Subsequently, the alkylation of a number of monosubstituted malonic esters by dialkyl carbonates was reported (70). The required metallic derivatives were obtained by the action of metallic alcoholates on the diethyl monosubstituted

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(69) V. H. Wallingford, A. H. Homeyer and D. M. Jones, J. Am. Chem. Soc., 63, 2056 (1941).
(70) V. H. Wallingford and D. M. Jones, ibid., 64, 578 (1942).

malonate. The alcohol formed in this reaction was removed in order to force the formation of the metallic derivative to completion. If this were not done, the metallic alcoholate would have reacted with the dialkyl carbonate with the production of an ether and a metallic alkyl carbonate. Furthermore, to avoid the formation of mixed esters, the same alkoxy groups should be present in the dialkyl carbonate, the metallic alcoholate and the monosubstituted malonic ester.

It has been pointed out by a number of investigators* that the failure of certain diethyl monosubstituted malonates to undergo further alkylation to a satisfactory extent may be due to the incomplete formation of the sodio derivative. In this event the added alkyl halide can react with the sodium

$$R'HC(COOR)_2 + NaOR \rightleftharpoons R'(Na)C(COOR)_2 + ROH$$

alcoholate. Furthermore, the original malonic ester or the desired alkylated product may undergo alcoholysis with the formation of a dialkyl carbonate as has been pointed out. It has been stated (71) that by the use of a dialkyl carbonate instead of an alcohol, as a reaction medium, it is possible to complete the formation of the metallic derivative of the malonic ester by distillation of all of the alcohol from the reaction mixture, and alcoholysis also is avoided.

It has been shown (72) that ethyl dimethylacetate and carbon monoxide are produced by interaction of diethyl

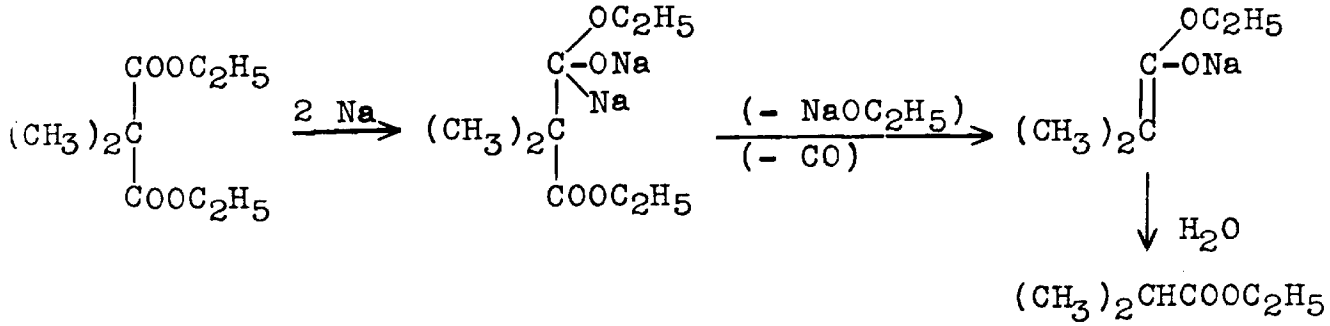
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* See V. H. Wallingford, M. A. Thorpe and A. H. Homeyer, J.Am. Chem. Soc., 64, 580 (1942) for references.

(71) V. H. Wallingford, M. A. Thorpe and A. H. Homeyer, ibid., 64, 580 (1942).

(72) F. Krollpfeiffer and A. Rosenberg, Ber., 69, 465 (1936).

dimethylmalonate with powdered sodium or potassium in ether. The following possible mechanism was suggested.



In order to prevent interaction between sodium ethylate and the original or the alkylated malonic ester, the alcoholic sodium ethylate solution has been added gradually to the mixture of the alkyl halide and the malonic ester which was to be alkylated (73). The addition was made at such a rate that only a slight pink color was produced on phenolphthalein paper by a drop of the reaction mixture.

The Preparation of Substituted Acetic Acids

As is often the case, the preparation of substituted malonic esters is but an intermediate step in the syntheses of a large variety of compounds, such as substituted acetic acids and esters, alcohols, halides, acetonitriles, amines, ethers, etc. Hydrolysis of the esters yields the substituted malonic acids which are easily decarboxylated to substituted acetic acids.

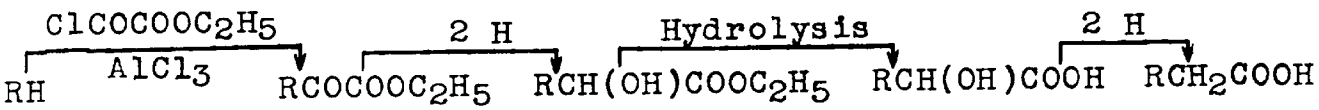
Instances in which substituted malonic acids have been employed for the synthesis of corresponding acetic acids are found in the following references (74-85).

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(73) M. A. Phillips, Ind. Chemist, 21, 678 (1945).
(74) F. F. Blicke and F. Leonard, J. Am. Chem. Soc., 68, 1934 (1946).

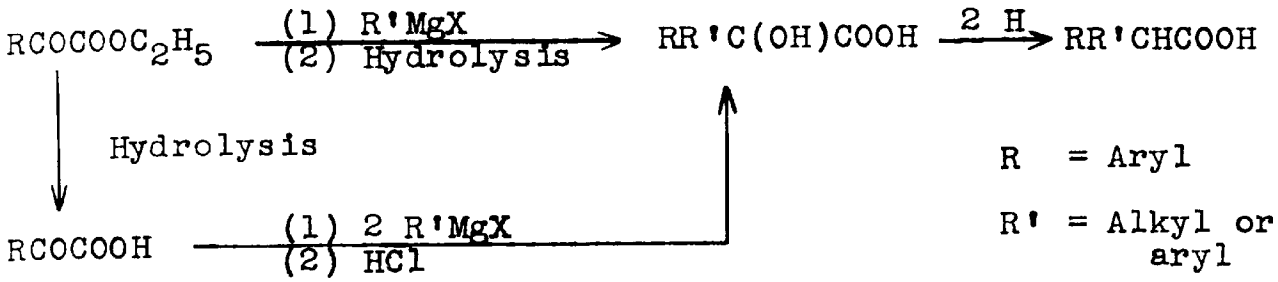
In those cases in which the malonic ester synthesis was not used, substituted acetic acids have been obtained by the processes outlined on the following pages.

Arylacetic, diarylacetic, arylalkylacetic and the corresponding α-hydroxyacetic acids can be obtained from ethyl oxalyl chloride by the procedures illustrated below (86-91).

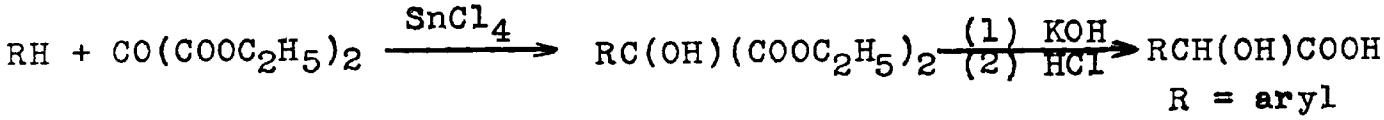


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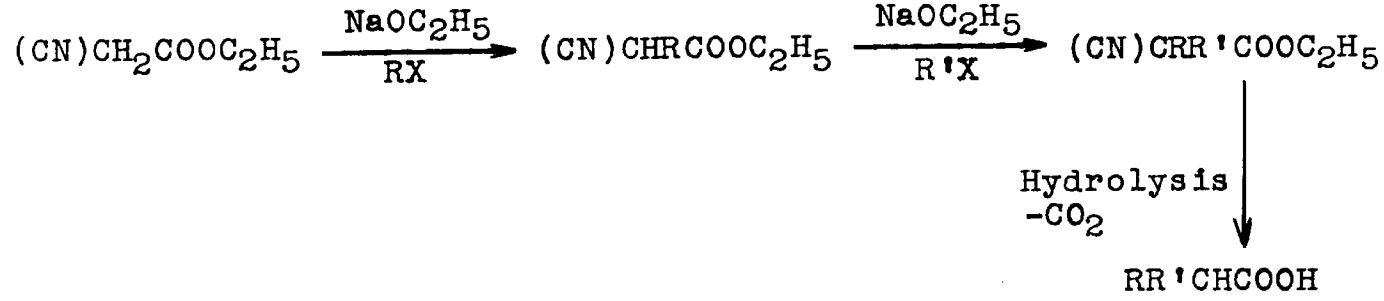
(75) R. B. Moffett, C. A. Hart and W. M. Hoehn, J. Am. Chem. Soc., 69, 1849 (1947).
(76) R. B. Moffett, C. A. Hart and W. M. Hoehn, ibid., 69, 1854 (1947).
(77) H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, ibid., 70, 3862 (1948).
(78) R. B. Moffett, C. A. Hart and J. Neil, J. Org. Chem., 15, 343 (1950).
(79) R. B. Moffett and J. Neil, ibid., 15, 354 (1950).
(80) R. B. Moffett (to George A. Breon and Co.), U. S. pat. 2,535,085; C. A., 45, 5181 (1951).
(81) R. B. Moffett (to George A. Breon and Co.), U. S. pat. 2,535,086; C. A., 45, 3872 (1951).
(82) R. B. Moffett and C. A. Hart (to George A. Breon and Co.), U. S. pat. 2,538,793; C. A., 45, 5181 (1951).
(83) R. B. Moffett and G. A. Hart (to George A. Breon and Co.), U. S. pat. 2,538,794; C. A., 45, 5182 (1951).
(84) R. B. Moffett and C. A. Hart (to George A. Breon and Co.), U. S. pat. 2,538,795; C. A., 45, 5182 (1951).
(85) F. F. Blicke (to Regents of the Univ. of Michigan), U. S. pat. 2,541,024; C. A., 46, 537 (1952).
(86) F. F. Blicke and N. Grier, J. Am. Chem. Soc., 65, 1725 (1943).
(87) F. F. Blicke and M. U. Tsao, ibid., 66, 1645 (1944).
(88) Sterling Drug, Inc., British pat. 625,811; C. A., 44, 2034 (1950).
(89) Ciba Ltd., Swiss pat. 261,124; C. A., 44, 5910 (1950).
(90) F. F. Blicke (to Regents of the Univ. of Michigan), U. S. pat. 2,541,634; C. A., 46, 538 (1952).
(91) K. Scholz, M. Spillmann, E. Tagmann and K. Hoffmann, Helv. Chim. Acta, 35, 2016 (1952).



Arylhydroxyacetic acids can also be prepared from ethyl oxomalonate (92-95).



The cyanoacetic ester synthesis is a useful one for the preparation of mono- and disubstituted acetic acids, and is especially advantageous for the synthesis of acids such as diisopropylacetic acid*.



By alkylation of a primary nitrile, and especially of an arylacetonitrile, di- (96) and trisubstituted acetic acids (97)

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* See R. B. Wagner and H. D. Zook, Synthetic Organic Chemistry, pp. 429, 599 (1953).

(92) T. Ando, J. Chem. Soc. Japan, 56, 745 (1935).
(93) J. L. Riebsomer, J. Irvine and R. Andrews, J. Am. Chem. Soc., 60, 1015 (1938).
(94) J. L. Riebsomer, R. Baldwin, J. Buchanan and H. Burkett, ibid., 60, 2974 (1938).
(95) J. L. Riebsomer, D. Stauffer, F. Glick and F. Lambert, ibid., 64, 2080 (1942).
(96) F. Leonard and L. Simet, ibid., 74, 3218 (1952).
(97) H. E. Zaugg and B. W. Horrom, ibid., 72, 3004 (1950). K. A. Jensen, O. R. Hansen and R. Hammer, Acta Chem. Scand., 6, 615 (1952); C. A., 47, 4859 (1953).

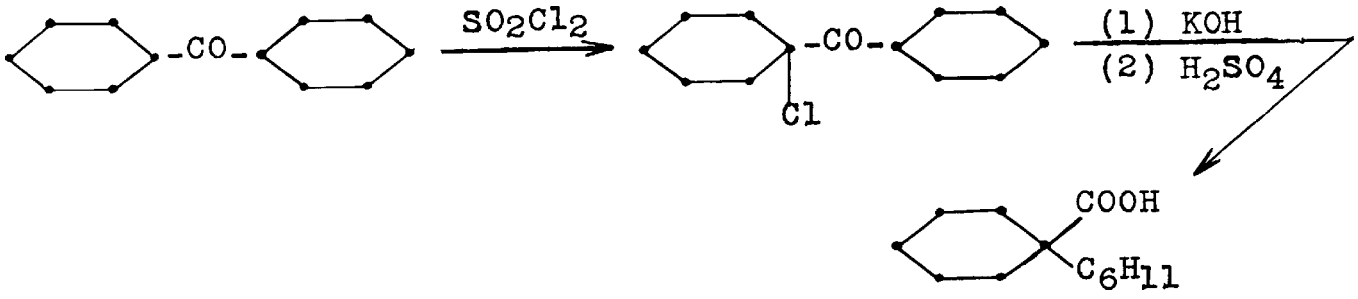
have been prepared.

$$RCH_2CN + R'X \xrightarrow{NaNH_2} RR'CHCN \xrightarrow{Hydrolysis} RR'CHCOOH$$

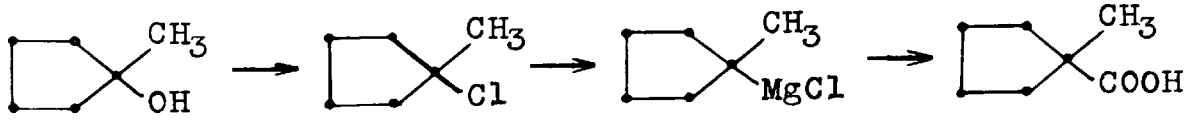
$$RR'CHCN + R''X \xrightarrow{NaNH_2} RR'R''CN \xrightarrow{Hydrolysis} RR'R''CCOOH$$

In a number of instances hydrolysis of a highly substituted nitrile by an acid or alkali has yielded the acid amide instead of the acid. It was found (98) that if the amides, which resist hydrolysis to the acid stage, are treated with butyl nitrite and hydrogen chloride, they are converted in excellent yields into the corresponding acids.

1-Substituted alicyclic carboxylic acids (polymethylene-substituted acetic acids) have been obtained by the following procedure (99). The same type of compound has been prepared



by carbonation of a Grignard reagent (100). The yields in the last steps were found to be low. Another procedure is



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(98) N. Sperber, D. Papa and E. Schwenk, J. Am. Chem. Soc., 70, 3091 (1948).
(99) M. Kopp and B. Tchoubar, Bull. soc. chim. France, 84 (1952).
(100) C. H. Tilford, L. A. Doerle, M. G. Van Campen, Jr. and R. S. Shelton, J. Am. Chem. Soc., 71, 1705 (1949).

the treatment of an arylacetonitrile with a polymethylene dibromide and sodamide (101).

$$RCH_2CN + Br(CH_2)_nBr \longrightarrow (CH_2)_n{>}C(R)CN \longrightarrow (CH_2)_n{>}C(R)COOH$$

The following reaction schemes illustrate the manner in which esters of substituted acetic acids which contain a basic or a basic-alkyl group have been prepared.

$$RCH(Br)COOCH_3 \xrightarrow{H_2NC_2H_5} RCH(NHC_2H_5)COOCH_3 \quad (102)$$

$$R_2CHCOOC_2H_5 \xrightarrow[NaNH_2]{Cl(CH_2)_nNR'_2} R_2C(CH_2)_nNR'_2COOC_2H_5 \quad (103)$$

$$RR'CHCN \xrightarrow[NaNH_2]{ClCH_2CH_2Cl} RR'C(CH_2CH_2Cl)CN \xrightarrow{R''_2NH} RR'C(CH_2CH_2NR''_2)CN \quad (104)$$

$$RR'C(CH_2CH_2NR''_2)CN \xrightarrow{H^+,\ C_2H_5OH} RR'C(CH_2CH_2NR''_2)COOC_2H_5$$

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(101) M. G. Van Campen, Jr. and C. Tilford (to the Wm. S. Merrell Company), U. S. pat. 2,474,796; C. A., 44, 3017 (1950).
(102) J. Klosa, Arch. Pharm., 285, 401 (1952).
(103) F. Leonard and I. Ehrental, J. Am. Chem. Soc., 73, 2216 (1951).
(104) F. B. Tutwiler, R. G. Child and S. N. Wrenn, J. Org. Chem., 19, 910 (1954).

Commercial Basic Esters Used Mainly as Antispasmodics

A relatively large number of basic esters of substituted acetic acids have appeared on the market for use in the treatment of spasms of the gastrointestinal and genitourinary tracts, in the reduction of hyperacidity and hypermotility in cases of peptic ulcer and in decreasing the rigidity and tremor in parkinsonism. The ophthalmologist uses some of these compounds to produce mydriasis and cycloplegia.

Although many of these esters probably do not equal atropine in anticholinergic activity, it is claimed that, in general, they have fewer undesirable side-effects.

It is of interest to be able to compare the structures of the various substituted acetic acids and basic esters which have been employed in the manufacture of clinically useful antispasmodics. In the following compilation, there have been included not only the commercial antispasmodics which have been assigned generic or brand names but also promising products which are still known only by their chemical names or code numbers. Unless otherwise indicated, a description of the compounds which bear brand or generic names will be found in the Modern Drug Encyclopedia and Therapeutic Index (5th Edition), Modern Drugs (The Journal of the Modern Drug Encyclopedia, a supplement to the Modern Drug Encyclopedia and Therapeutic Index) or Physicians Desk Reference to Pharmaceutical Specialties and Biologicals (1954). The compounds which are known by their code numbers are mentioned in Unlisted Drugs (1954).

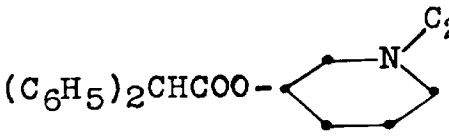
Basic Esters of Substituted Acetic Acids

(or Thioacetic Acids)

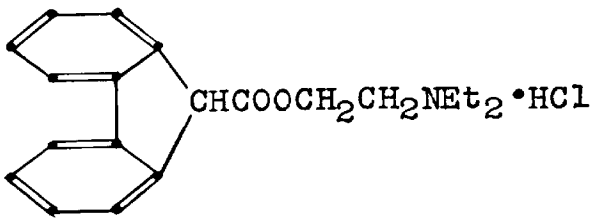
Trasentin Hydrochloride $(C_6H_5)_2CHCOOCH_2CH_2NEt_2 \cdot HCl$
(Adiphenine hydrochloride)
Ciba Pharmaceutical Products
ß-Diethylaminoethyl diphenylacetate hydrochloride
This ester possesses both neurotropic and musculotropic activity.

Trocinate $(C_6H_5)_2CHCOSCH_2CH_2NEt_2 \cdot HCl$
(Brand of Thiphenamil hydrochloride)
Wm. P. Poythress and Co.
ß-Diethylaminoethyl diphenylthioacetate hydrochloride.
This compound has strong atropine-like and papaverine-like actions on smooth muscle without narcotic or mydriatic effect.

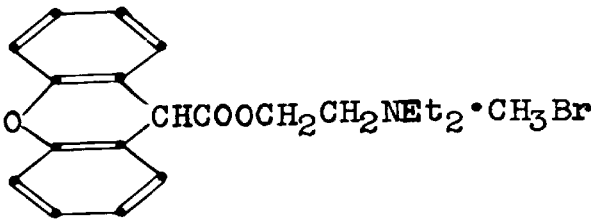
Dactil*
(JB 305)
Lakeside Laboratories
N-Ethyl-3-piperidyl diphenylacetate hydrochloride
This compound is used as a spasmolytic in the treatment of cardiospasm, upper gastrointestinal pain, biliary and pyloric spasm, etc.



Pavatrine
G. D. Searle & Co.
ß-Diethylaminoethyl fluorene-9-carboxylate hydrochloride
It is an effective non-narcotic antispasmodic which relaxes spastic smooth muscle by direct action and through the autonomic nervous system.



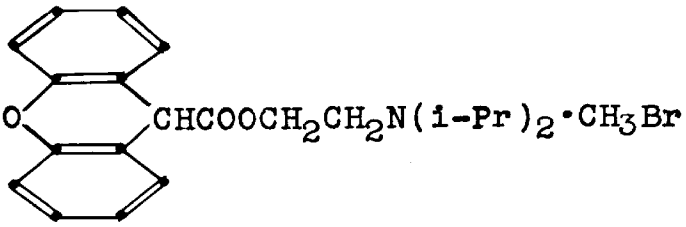
Banthine
(Banthine Bromide, Methantheline bromide)
G. D. Searle & Co.
ß-Diethylaminoethyl xanthene-9-carboxylate methobromide
This product is a true anticholinergic preparation for the treatment of peptic ulcer.



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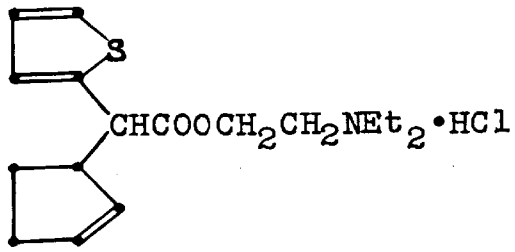
*(a) Unlisted Drugs, 6, 58 (1954).
(b) Modern Drugs, 10I7 (1954).

Pro-Banthine
(Brand of Propantheline Bromide)
G. D. Searle & Co.
ß-Diisopropylaminoethyl xanthene-9-carboxylate methobromide.



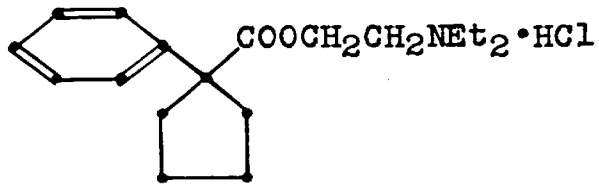
This compound has an activity of two to five times that of Banthine in the inhibition of neural impulses.

Neotropine
Warner
ß-Diethylaminoethyl ⍺-(2-Cyclopenten-1-yl)-⍺-(2-thienyl)acetate hydrochloride.



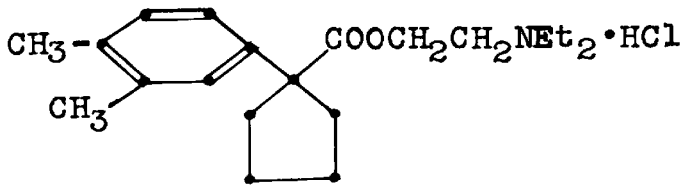
This ester is a specific antispasmodic for respiratory, gastrointestinal and genito-urinary systems.

Panparnit Hydrochloride
(Brand of Caramiphen hydrochloride; formerly known as Parpanit)
Geigy Pharmaceuticals
ß-Diethylaminoethyl 1-phenylcyclopentane-1-carboxylate hydrochloride.



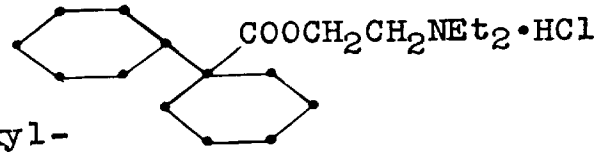
The compound is a potent spasmolytic for smooth muscle spasm and for the relief of rigidity and tremor in Parkinson's syndrome.

Metcaraphen Hydrochloride*
(Netrin hydrochloride)
Geigy Pharmaceuticals
ß-Diethylaminoethyl 1-(3',4'-dimethylphenyl)-cyclopentane-1-carboxylate hydrochloride.



This synthetic compound possesses similar spasmolytic activity as Panparnit.

Bentyl
(Brand of Dicyclomine hydrochloride)
Merrell
ß-Diethylaminoethyl 1-cyclohexyl-cyclohexane-1-carboxylate hydrochloride.

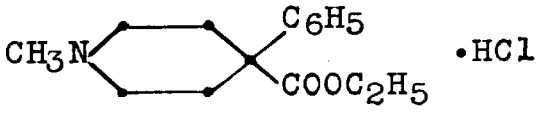


This ester has both musculotropic and neurotropic actions.

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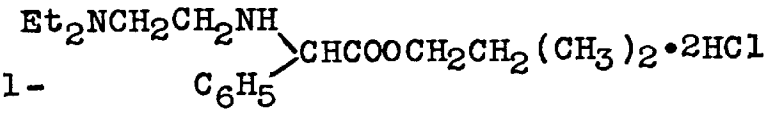
*Unlisted Drugs, 6, 71 (1954).

Demerol
(Meperidine, mephedine, pethidine, dolantin or isonipecaine hydrochloride)



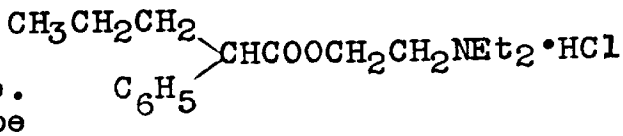
Winthrop-Stearns
Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.
This ester is an effective, morphine-like central analgesic and also an atropine-like smooth muscle neurospasmolytic.

Avacan*



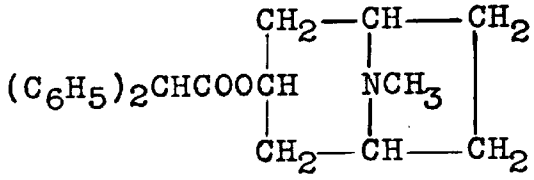
Isoamyl N-(ß-diethylaminoethyl)-α-aminophenylacetate dihydrochloride.
As a spasmolytic, this compound has proven to be faster acting and more potent than papaverine but slightly weaker than atropine although without undesirable side-effects.

Propivan**



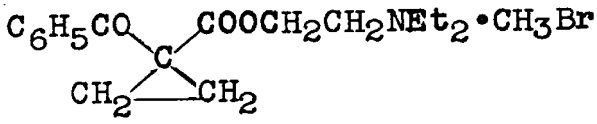
ß-Diethylaminoethyl α-phenylvalerate hydrochloride.
This basic ester is shown to be an acetylcholine antagonist.

Tropacin***



Tropyl diphenylacetate hydrochloride.
This synthetic compound is found to be beneficial in hyperkinesia cases such as Parkinson's disease or postencephalitic parkinsonism.

MC 2806



E. R. Squibb and Sons
ß-Diethylaminoethyl 1-benzoylcyclopropane 1-carboxylate methobromide.
This quaternary compound is being used as anticholinergic.

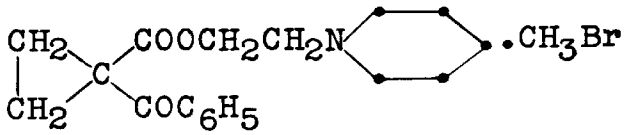
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* (a) N. Brock, D. Lorenz and H. Bartling, Naunyn-Schmiedeberg's Arch. exptl. Path. Pharmakol., 215, 512 (1952);
(b) J. Hiller and E. Strauss, Arzneimittel-Forsch., 3, 282 (1952);
(c) J. J. Sielaff, Z. ges. exptl. Med., 120, 599 (1953).

** (a) V. Ettel and J. Hebký, Collection Czechoslov. Chem. Communs., 15, 367 (1950).
(b) J. Büchi, H. Lauener, R. Meyer and R. Lieberherr, Helv. Chim. Acta, 34, 373 (1951).
(c) G. Dastugue and G. Costerizant, Therapie, 7, 536 (1952).

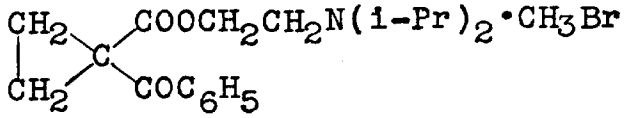
*** M. D. Mashkovskii, Farmakol. i Toksikol., 16, 3 (1953).

MC 2998
E. R. Squibb & Sons
ß-Piperidinoethyl
1-benzoylcyclopropane-
1-carboxylate methobromide.



This compound is being used as an antispasmodic.

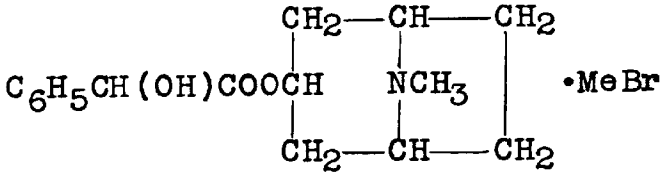
MC 3505
E. R. Squibb & Sons
ß-Diisopropylaminoethyl
1-benzoylcyclopropane-
1-carboxylate methobromide.



This basic ester quaternary salt is being tested for its anticholinergic property.

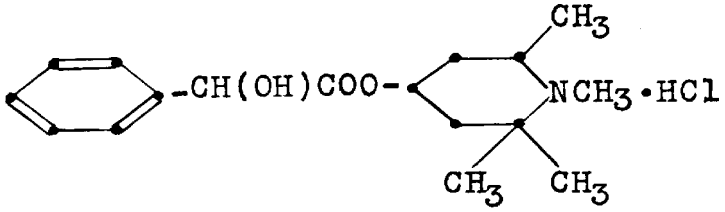
Basic Esters of Substituted Hydroxyacetic Acids

Homatropine Methobromide
(Brands of Mesopin, Novatropine and Camatropine)
Endo Products, Inc. and
Campbell Pharmaceutical Co.



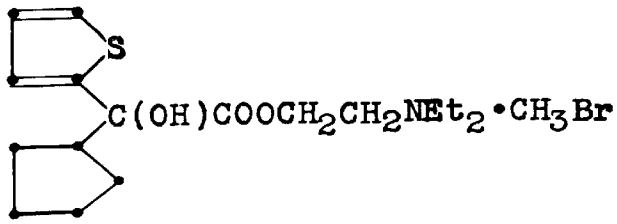
Tropyl mandelate methobromide.
This substance is used for the treatment of gastrointestinal spasm and hyperchlorhydria.

Euphthalmine
(Eucatropine hydrochloride)
Warner
4-Mandeloyloxy-1,2,2,6-tetramethylpiperidine hydrochloride.



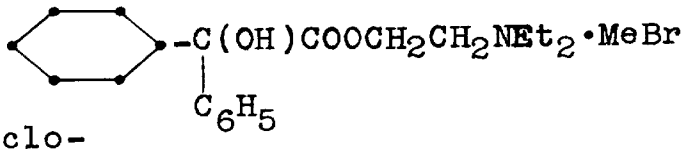
It produces immediate mydriasis without anesthetic action, pain, or corneal irritation.

Monodral
(Brand of Penthienate bromide)
Winthrop-Stearns
ß-Diethylaminoethyl
α-(2-thienyl)-α-cyclopentyl-α-hydroxyacetate methobromide.



Because of its antispasmodic and antisecretory properties, this ester is recommended in the treatment of peptic ulcer.

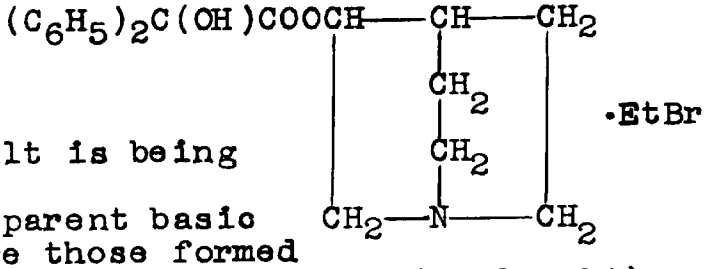
Antrenyl Bromide
(BA 5473, Oxyphenonium bromide)



Ciba Pharmaceutical Products
ß-Diethylaminoethyl ⍺-phenylcyclohexylglycolate methobromide.
This anticholinergic compound possesses marked inhibitory effect on gastric secretion and motility of the gastrointestinal tract.

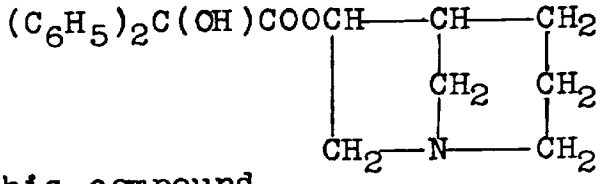
Diphemin* $(C_6H_5)_2C(OH)COOCH_2CH_2NEt_2 \cdot HCl$
ß-Diethylaminoethyl diphenylhydroxyacetate hydrochloride.
Although this ester is 10 times as toxic as trasentin, its activity on the smooth muscle is 100 times that of papaverine or atropine.

RO 2-4174



Hoffmann - LaRoche, Inc.
3-Quinuclidyl benzilate ethobromide.
This basic ester quaternary salt is being used as antispasmodic.
Other quaternary salts of the parent basic ester being similarly tried are those formed with butyl bromide (RO 2-4550), propenyl bromide (RO 2-5084), propyl bromide (RO 2-4665) and the d- and l-forms of the same basic ester quaternized by ⍺-camphorsulfonate (RO 2-5044 and RO 2-5109, respectively).

RO 2-4569



Hoffmann - LaRoche, Inc.
Benzilic acid ester of 1-azabicyclo-[3.2.1]-6-octanol.
Tested as the hydrochloride, this compound exhibited an acetylcholine activity in the same order as that of atropine.
The methobromide (RO 2-4570) of this basic ester is claimed to be as potent.

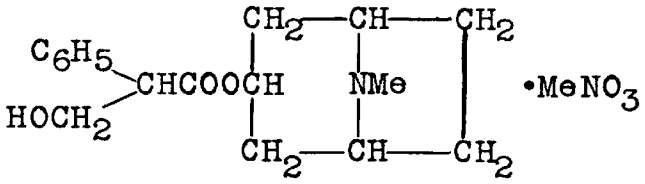
MC 2963 $(C_6H_5)_2C(OH)COOCH_2CH_2CH_2NMe_2 \cdot EtBr$
E. R. Squibb & Sons
γ-(Dimethylamino)-n-propyl benzilate ethobromide.
This quaternary compound is being used as anticholinergic agent.

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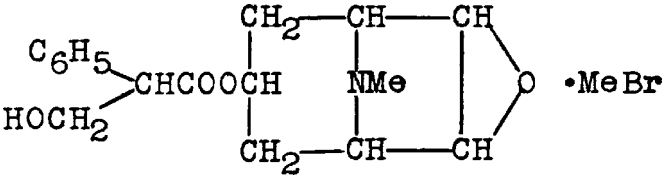
*J. Klosa, Deut. med. Wochschr., 75, 870 (1950).

Basic Esters of Substituted ß-Hydroxypropionic Acids

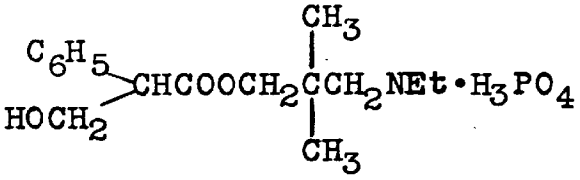
Atropine Methonitrate
(Brands of Eumydrin, Harvatrate, Metanite and Metropine)
Winthrop-Stearns, Inc., G. F. Harvey Co., Drug Products Co. and R. T. Strasenburgh Co.
Tropyl tropate methonitrate.
This compound is used as antispasmodic and mydriatic.



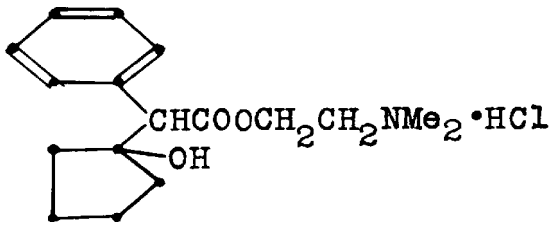
Pamine
(Brand of Epoxymethamine)
Upjohn Co.
Epoxytropyl tropate methobromide.
This quaternary salt is a parasympatholytic agent used in the treatment of gastric ulcer.



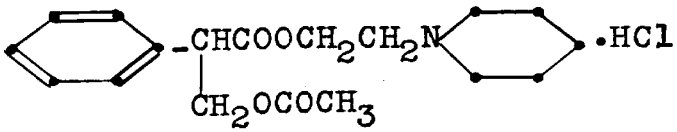
Syntropan
(Brand of amprotropine)
Hoffmann-LaRoche, Inc.
Phosphate of d,l-tropic acid ester of 3-diethylamino-2,2-dimethyl-1-propanol.
This substance is a neurotropic as well as musculotropic antispasmodic.



Cyclopentolate Hydrochloride
Cyclogyl hydrochloride
(Schieffelin)
ß-Dimethylaminoethyl ⍺-(hydroxycyclopentyl) phenylacetate hydrochloride.
It produces a rapid and intense cycloplegia and mydriasis when instilled in the eye.



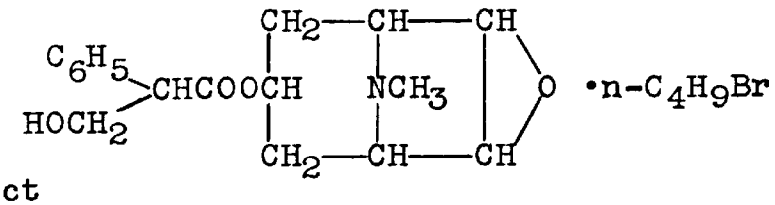
Navigan*
ß-Piperidinoethyl acetyltropate hydrochloride
Although this ester was chiefly used as a mydriatic agent, it could completely inhibit the action of acetylcholine.



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*C. A., 26, 2511 (1932).

Buscopan*
(SKF 1637)
levo-N-Butylscopolammonium Bromide.
This synthetic product exerts a profound effect on gastrointestinal motility and gastric secretion and can relieve the pain in duodenal ulcer.



Basic-Ester Antispasmodics Literature from January 1950 to October 1954

In conformity with the usual custom in dissertations from this Laboratory, a survey of the chemical and pharmacological literature has been compiled.

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*(a) H. Wick, Arch. exptl. Path. Pharmakol., 213, 485 (1951);
(b) E. C. Texter, Jr., G. J. Baylin, C. W. Legerton, Jr. and J. M. Ruffin, Am. J. Med. Sci., 224, 612 (1952);
(c) E. Philippot and M. J. Dallemagne, Arch. intern. pharmacodynamie, 93, 337 (1953).

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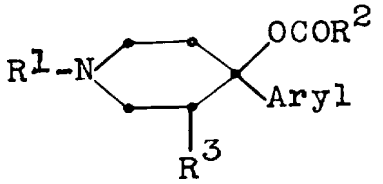
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Basic Esters of Substituted Acetic Acids

Monosubstituted Acetic Acids.--



R^1 and R^2 = alkyl, R^3 = H or alkyl, and Aryl = phenyl or cyclohexyl group.
J. Lee, A. Ziering and L. Berger (to Roche Products Ltd.), British pat. 629,196; C. A., 44, 5920 (1950).

$Ar(R^2CO_2)C<(CH_2CH_2)_2>NR^1 \cdot HX$: Ar = a monocyclic aryl radical, R^1 = alkyl radical, X = halogen and R^2 = a radical from group consisting of alkyl, phenyl and pyridyl radicals.
K. A. Jensen (to Aktieselskabet "Ferrosan"), U. S. pat. 2,589,943; C. A., 46, 11249 (1952).

Disubstituted Acetic Acids.--

$p\text{-}PhC_6H_4CHRCO_2C_nH_{2n}N<(CH_2CH_2)_2>Y$: Y = $-CH_2-$, $-NH-$, $-S-$, or $-O-$, n = 2 to 4, and R = lower alkyl, aryl, cycloalkyl, aralkyl, and alkenyl.
F. F. Blicke (to Regents of the Univ. of Michigan), U. S. pat. 2,474,651; C. A., 44, 3528 (1950).

$RR'CHCOOCH_2CH_2N<(CH_2CH_2)_2>Y$: R = 1-naphthyl, R' = H, CH_3 or phenyl group, and Y = $-CH_2-$ or $-O-$.
F. F. Blicke (to Regents of the Univ. of Michigan), U. S. pat. 2,489,950; C. A., 44, 2031 (1950).

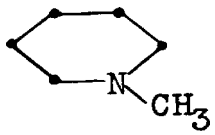
$C_6H_5CH(C_3H_7)COOCH_2CH_2N(C_2H_5)_2$: known in the market as propivan.
V. Ettel and J. Hebký, Collection Czechoslov. Chem. Communs., 15, 367 (1950).

$RR^1CHCOOCHR^2CR^2R^2N(CH_2)_4$: R and R^1 = phenyl, alkyl and cycloalkenyl or cycloalkyl groups, and R^2 = H or CH_3.
H. G. Kolloff, J. H. Hunter and R. B. Moffett, J. Am. Chem. Soc., 72, 1650 (1950).

$RR^1CHCOOCHR^2CR^2R^2CHR^2NR^3R^4$: R and R^1 = aryl, alkyl, cycloalkenyl, cycloalkyl, phenoxy; R^2 = H or CH_3; and R^3 and R^4 = alkyl or $-(CH_2)_n-$.
R. B. Moffett, J. H. Hunter and E. H. Woodruff, J. Org. Chem., 15, 1013 (1950).

$RR^1CHCOO(CH_2)_nA$: R and R^1 = aryl groups; n = 2 or 3; and A = 2- or 4-pyridyl.
R. R. Burtner and J. M. Brown (to G. D. Searle & Co.), U. S. pat. 2,529,865; C. A., 45, 2986 (1951).

$RR^1CHCOOCH_2(CH_2)_nCHR^1N(C_2H_5)_2$: R = 1-naphthyl and R^1 = H or alkyl, and n = 0 or 1.
Sterling Drug, Inc., British pat. 646,701; C. A., 45, 7599 (1951).

$C_6H_5CH(2\text{-}C_4H_3S)COOCH_2$-

: prepared by bubbling dry HCl into the benzene solution of the corresponding acid and alcohol.
R. F. Feldkamp (to Sterling Drug, Inc.), U. S. pat. 2,533,002; C. A., 45, 4271 (1951).

$(1\text{-}C_{10}H_7)CHRCOOCH_2CH_2Y$: R = H or alkyl and Y = 1-piperidyl or 4-morpholinyl group.
Sterling Drug, Inc., British pat. 647,846; C. A., 45, 7599 (1951).

$RCH(C_6H_5)COOCH_2CH_2N(C_2H_5)_2$ and $R^1COOCH_2CH_2N(C_2H_5)_2$: R or R^1 = 1-indanyl or 1,2,3,4-tetrahydronaphthalene-1-substituted.
M. Protiva, Z. J. Vejdělek and J. O. Jílek, Chem. Listy, 45, 478 (1951); C. A., 47, 8057 (1953).

$R_2NAOOCCHR^1R^2$: R = alkyl group with 4 or less carbon atoms, A = an alkylene group, R^1 = cyclohexenyl or cyclopentenyl group, and R^2 = 2-thienyl group which may be substituted with either a halogen or a short alkyl group.
F. Leonard (to Warner-Hudnut, Inc.), U. S. pat. 2,561,385; C. A., 47, 1191 (1953).

$C_6H_5CH(C_5H_9)COOCH_2CH_2N(CH_3)CH(CH_3)_2$: C_5H_9 = cyclopentyl.
R. B. Moffett (to Upjohn Co.), U. S. pat. 2,558,146; C. A., 46, 3073 (1952).

$R_2CHCHRCOOAB$: R = an aryl radical, A = an alkylene radical, and B = a nonaromatic amino radical.
C. P. Krimmel (to G. D. Searle and Co.), U. S. pat. 2,576,230; C. A., 46, 6155 (1952).

$R_2R^1CCOOCH_2CH_2B$: R = aryl group, R^1 = H or OH, and B = nonaromatic amino radical.
J. W. Cusic and R. A. Robinson, J. Org. Chem., 16, 1921 (1951).

$(C_6H_5)_2CHCOOCH_2CH_2N<(CH_2CH_2)_2>CH_2$: prepared from the acetyl chloride and the corresponding alcohol.
E. Muñoz Mena and E. F. Mavil Bueno, Ciencia, 12, 149 (1952); C. A., 47, 6092 (1953).

$C_6H_5CH(2\text{-}C_6H_9)COOCH_2CHRNRCH(CH_3)_2$: R = H or CH_3 and $2\text{-}C_6H_9$ = 2-cyclohexenyl group.
R. B. Moffett (to Upjohn Co.), U. S. pat. 2,586,849 and 2,586,850; C. A., 46, 9124 (1952).

$(C_6H_5)_2CHCOOCH_2CH_2NRR'$: R = CH_3 and R' = cycloheptyl group.
K. Hoffman and M. Spillmann (to Ciba Pharm. Prods., Inc.), U. S. pat. 2,599,996; C. A., 48, 6468 (1954).

$RCOOCHR^1(CH_2)_nR^2$: R = diphenylmethyl or 9-fluorenyl; R^1 = hydrogen or methyl, R^2 = 1-alkyl-4-piperidyl group and n = 1 or 2.
R. R. Burtner and J. M. Brown (to G. D. Searle and Co.), U. S. pat. 2,607,777; C. A., 47, 6988 (1953).

$RR^1CHCOOR^2$: R and R^1 = aryl, alkyl, cycloalkyl or cycloalkenyl groups and R^2 = 1-pyrrolidylalkyl group in which one or two methyl groups are substituted in all possible positions of the pyrrolidine ring.
R. B. Moffett and J. H. Hunter, J. Am. Chem. Soc., 74, 1710 (1952).

$(C_6H_5)_2CHCOOR$: R = basic bicyclicalkyl radicals.
L. H. Sternbach and S. Kaiser, J. Am. Chem. Soc., 74, 2219 (1952).

$RR^1CHCOOCH_2CH_2N(C_2H_5)_2$: R = 2-thienyl or 2-thienylmethyl, R^1 = alkyl, alkenyl, cycloalkyl and cycloalkenyl groups.
F. Leonard, J. Am. Chem. Soc., 74, 2915 (1952).

$(2\text{-}C_4H_3S)CHRCOOCH_2CH_2N(C_2H_5)_2$: R = 2-cycloalken-1-yl and $2\text{-}C_4H_3S$ = 2-thienyl group.
F. Leonard and L. Simet, J. Am. Chem. Soc., 74, 3218 (1952).

$ACOOCHR^1CHR^2(CH_2)_nNR^3R^4$: A = diphenylmethyl, diphenylhydroxymethyl or fluorenyl; R^1 = phenyl or substituted phenyl containing OH, lower alkoxy or lower acyloxy; R^2 = H or lower alkyl; R^3 = lower alkyl or dialkylaminoalkyl; R^4 = lower alkyl; and n = 0 or 1.
M. W. Goldberg and S. Teifel (to Hoffmann-LaRoche, Inc.), U. S. pat. 2,628,247; C. A., 48, 728 (1954).

$YCH{\cdot}CH_2{\cdot}CHCOO(CH_2)_nX$: Y = 2-thienyl or 2-pyridyl, n = 1,2, or 3, and X = piperidino, morpholino, or diethylamino group.
A. Burger (to Smith, Kline and French Labs.), U. S. pat. 2,638,471; C. A., 48, 7641 (1954).

$(C_6H_5)_2CHCOO(CH_2)_nN[CH(CH_3)_2]_2 \cdot MeX$: n = 2 to 8 and X = an anion.
R. A. Robinson (to G. D. Searle & Co.), U. S. pat. 2,648,699; C. A., 48, 7639 (1954).

RCOOAB: R = diphenylmethyl or p-aminophenyl, A = lower alkenyl radicals variously substituted with methoxy or methoxymethyl group, and B = dialkylamino group.
F. F. Blicke and J. H. Biel, J. Am. Chem. Soc., 76, 3163 (1954).

Trisubstituted Acetic Acids.--

$RR^1R^2CCOOAB$: R = 2-thienyl or 2-thenyl; R^1 and R^2 = aryl, aralkyl, cycloalkyl, cycloalkylalkyl or alkyl; A = lower alkyl group which may be substituted with an alkyl group; and B = 1-piperidyl or dialkylamino group.
Sterling Drug, Inc., British pat. 625,811; C. A., 44, 2034 (1950).

$(C_6H_5)_2CRCOOAB$: R = methyl, allyl or chloromethyl; A = substituted or unsubstituted lower alkyl group; and B = dialkylamino or 4-morpholinyl group.
H. E. Zaugg and B. W. Horrom, J. Am. Chem. Soc., 72, 3004 (1950).

$(C_6H_5)_2CRCOOCH_2CH_2X$: R = alkyl or alkenyl, and X = dialkylamino or 1-piperidyl group.
P. N. Craig, I. H. Witt, E. Macko, J. G. Dacanay, E. J. Fellows and G. E. Ullyot, J. Am. Chem. Soc., 73, 1339 (1951).

$C_6H_5CR^1R^2COOCH_2CH_2NR^3{}_2R^4X$: R = hydrogen, methyl or ethyl and X = Cl, Br, I or $MeC_6H_4SO_3$ group.
K. A. Jensen, O. R. Hansen and R. Hammer, Acta Chem. Scand., 6, 615 (1952); C. A., 47, 4859 (1953).

$R^1R^2R^3CCOOCH_2CH_2N(C_2H_5)_2$: R^1 = phenyl, cyclohexyl or cyclohexenyl; R^2 = cycloalkenyl or cycloalkylidene; and R^3 = hydrogen or hydroxyl.
K. Scholz, M. Spillmann, E. Tagmann and K. Hoffmann Helv. Chim. Acta, 35, 2016 (1952).

$(C_6H_5)_2C(NH_2)COXCH_2RNR^1R^2$: X = O or S, R = lower alkylene radical, and R^1 and R^2 = lower alkyl radicals, or in combination with a N-heterocyclic radical.
R. Duschinsky (to Hoffmann-LaRoche, Inc.), U. S. pat. 2,642,433; C. A., 48, 7638 (1954).

$(C_6H_5)_2CYOOCH_2CH_2N(C_2H_5)_2$: Y = Cl, Br, ethoxy, or dimethylamino.
F. F. Blicke, J. A. Faust and H. Raffelson, J. Am. Chem. Soc., 76, 3161 (1954).

Hydroxyacetic Acids.--

$C_6H_5(C_6H_{11})C(OH)COOCH_2CH_2N(C_2H_5)_2 \cdot CH_3Br$: prepared by bubbling gaseous methyl bromide into an ethyl acetate solution of the free base.
Ciba Ltd., Swiss pat. 259,958; C. A., 44, 5910 (1950).

$C_6H_5(C_5H_{11})C(OH)COOCH_2CH_2N(C_2H_5)_2$: prepared from the corresponding acid and basic chloride.
Ciba Ltd., Swiss pat. 261,124; C. A., 44, 5910 (1950).

$RCH_2CH_2OC(C_6H_5)_2COOR'$: R = dialkylamino or 4-morpholino, and R' = alkyl, alkenyl, dialkylaminoalkyl, allylmethyl- or diallylaminoethyl and 4-morpholinoethyl group.
A. L. Morrison, M. Konigstein and A. Cohen, J. Chem. Soc., 2887 (1950).

$RR^1C(OH)COOCH_2CH_2R^2$: R = 2-thienyl, R^1 = aryl, cycloalkyl, alkyl, and R^2 = dialkylamino, alkylarylamino, 1-piperidino or 4-morpholino group.
F. F. Blicke (to Regents of the Univ. of Michigan), U. S. pat. 2,541,634; C. A., 46, 538 (1952).

$(C_6H_5)RC(OR')COOAB$: R = phenyl, 2-thienyl or cycloalkyl and R' = alkyl, aryl, aralkyl group.
J. Büchi, H. Lauener, R. Meyer and R. Lieberherr, Helv. Chim. Acta, 34, 373 (1951).

$R_2C(OR')COOCH_2CH_2N(C_2H_5)_2$: R = aryl and R' = alkyl group.
R. Hirt (to A. Wander A.-G.), U. S. pat. 2,598,542; C. A., 47, 3882 (1953).

$(C_6H_5)_2C(OH)COOR$: R = 1-alkyl-3-piperidyl group. Also the desoxy-derivatives.
J. H. Biel, H. L. Friedman, H. A. Leiser and E. P. Sprengeler, J. Am. Chem. Soc., 74, 1485 (1952).

$(C_6H_5)_2C(OH)COOCH_2CH_2R$: R = trialkylammonium bromide or iodide, dialkyl-benzylammonium bromide and dialkylamino group.
P. Mantegazza and R. Tommasini, Il Farmaco Ed. Sci., 9, 73 (1954); C. A., 48, 8419 (1954).

$R_2CR'CH(OH)COOCH_2CH_2N(C_2H_5)_2$: R = aryl and R' = H or OH group.
F. F. Blicke and J. A. Faust, J. Am. Chem. Soc., 76, 3156 (1954).

$(C_6H_5)_2CHCR(OH)COOCH_2CH_2N(C_2H_5)_2$: R = alkyl or aryl.
F. F. Blicke and J. A. Faust, J. Am. Chem. Soc., 76, 3159 (1954).

$C_6H_5(p\text{-}ROC_6H_4)C(OH)COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$: R = 4-alkoxyphenyl, 4-phenoxyphenyl, 4-benzyloxyphenyl, dialkoxyphenyl, etc.
E. R. Bockstahler and D. L. Wright, J. Am. Chem. Soc., 71, 3760 (1949).

ß-Hydroxypropionic Acids.--

$(C_6H_5)_2C(CH_2OH)COOCH_2CH_2NR_2$: R = dialkyl.
H. E. Zaugg, J. Am. Chem. Soc., 72, 3001 (1950).

$(C_6H_5)_2C(OR)COOCH_2CH_2N(C_2H_5)_2$: R = alkyl group.
A. Wander A.-G., British pat. 641,571; C. A., 45, 2506 (1951).

$CH_3CH(OH)CHRCOOR'$: R = phenyl and R' = (1-methyl-3-piperidyl)methyl group.
R. F. Feldkamp (to Sterling Drug, Inc.), U. S. pat. 2,533,003; C. A., 45, 4271 (1951).

$RR'CHCOOCH_2CH_2N(CH_3)_2$: R = phenyl or p-methoxyphenyl and R' = 1-hydroxycyclopentyl group.
G. R. Treves (to Schieffelin & Co.), U. S. pat. 2,554,511; C. A., 46, 1035 (1952).

$(CH_2)_n{>}C(OH)CHRCOOCH_2CH_2NR'_2$: n = 5, R = aryl and R' = alkyl group.
G. R. Treves (to Schieffelin & Co.), U. S. pat. 2,558,020; C. A., 46, 1936 (1952).

$RR^1C(OH)CH(C_6H_5)COO(CH_2)_nNR^2_2 \cdot HCl$: R and R^1 = alkyl, $-(CH_2)_4-$, and $-(CH_2)_5-$; R^2 = lower alkyl; and n = 2 or 3.
A. Weston and R. DeNet, J. Am. Chem. Soc., 73, 4221 (1951).

$RR^1CHCOOCH_2CH_2R^2$: R = aryl, R^1 = 1-hydroxycycloalkyl, and R^2 = dialkylamino or piperidino group.
G. R. Treves and F. C. Testa, J. Am. Chem. Soc., 74, 46 (1952).

$C_6H_5CH(CH_2OH)COOCH_2CH_2R$: R = dialkylpiperidino group.
R. A. Robinson (to G. D. Searle & Co.), U. S. pat. 2,648,666; C. A., 48, 9406 (1954).

$RR^1C(OH)CHR^2COOCH_2CH_2N(C_2H_5)_2$: R and R^1 = H or alkyl, aryl, aralkyl, and R^2 = aryl groups.
F. F. Blicke and H. Raffelson, J. Am. Chem. Soc., 74, 1730 (1952).

$RR^1C(OH)CHR^2COOAB$: R and R^1 = H, alkyl or polymethylene group; R^2 = aryl or cycloalkyl; A = lower alkylene and B = dialkylamino group.
R. Cox, Doctoral Dissertation, University of Michigan (1954).

Thioacetic Acids.--

$RR^1CHCOS(CH_2)_nR^2 \cdot HCl$ (or acid citrate): R and R^1 = aryl, cyclopentyl, cyclopentenyl, alkyl or aryloxy; R^2 = pyrrolidyl, alkylpyrrolidyl or dialkylamino group; and n = 2 or 3.
H. G. Kolloff, J. H. Hunter, E. H. Woodruff and R. B. Moffett, J. Am. Chem. Soc., 71, 3988 (1949).

$C_6H_5CHRCOSCH_2CH_2N(C_2H_5)_2$: R = cyclopentyl or cyclopentenyl group.
E. H. Woodruff (to Upjohn Co.), U. S. pat. 2,488,253; C. A., 44, 1534 (1950).

$RCOSCHR'(CH_2)_nA$: R = diphenylmethyl, or 9-fluorenyl, R' = alkyl, A = dialkylamino or piperidino group, and n = 1, 2 or 3.
R. O. Clinton (to Sterling Drug, Inc.), U. S. pat. 2,510,773; C. A., 45, 1165 (1952).

$(CH_2)_n{>}C(C_6H_3RR')COSAlkB$: R and R' = H, methyl or methoxy group; Alk = alkylene radical containing 2 to 6 carbon atoms; B = a secondary aliphatic, cycloaliphatic or heterocyclic amine residue, and n = at least 4.
J. R. Geigy, A.-G. Swiss pat. 274,379; C. A., 47, 1185 (1953).

RR'CHCOSAlkB: R and R' = aryl, alkyl, cycloalkyl or cycloalkenyl; Alk = substituted or unsubstituted lower alkylene radical; and B = substituted or unsubstituted piperidino group.
J. H. Hunter (to Upjohn Co.), U. S. pat. 2,584,131; C. A., 47, 7548 (1953).

Cycloalkyl Carboxylic Acids.--

$(CH_2)_n{>}CRCOOCH_2CH_2N(C_2H_5)_2$: R = aryl, cycloalkyl, alkyl and cycloalkylalkyl groups, and n = 4 or 5.
C. H. Tilford, L. A. Doerle, M. G. van Campen and R. S. Shelton, J. Am. Chem. Soc., 71, 1705 (1949).

$RR'COOAB$: R = aryl, aralkyl or alicyclic; R' = alicyclic; A = substituted or unsubstituted lower alkylene group; and B = amino, dialkylamino or piperidino group.
M. G. van Campen, Jr. and C. Tilford (to Wm. S. Merrell Co.), U. S. pat. 2,474,796; C. A., 44, 3017 (1950).

$1\text{-}C_6H_{11}\cdot C_6H_{10}\cdot COOCH_2CH_2N(C_2H_5)_2\cdot HCl$: known in the market as Bentyl.
B. B. Brown, C. R. Thompson, G. R. Wahm and H. W. Werner, J. Am. Pharm. Assoc., Sci. Ed., 39, 305 (1950).

$RR'COOAB$: R = 2-phenyl; R' = 3,4,5,6-tetrahydrophenylene; A = straight or branched, saturated or unsaturated carbon chain, and B = dialkylamino group.
N. V. Organon (W. L. C. Veer and H. G. Wijmenga, inventors), Dutch pat. 65,824; C. A., 45, 2024 (1951).

$RCOOCH_2CH_2N(C_2H_5)_2$: R = cyclopentyl or cyclohexyl group.
F. Winternitz, M. Mousseron and M. Canett, Bull. soc. chim. France, 452 (1951).

$RR'COOCH_2CH_2N(C_2H_5)_2$: R = alkyl, R' = cycloalkylidene group.
C. H. Tilford and M. G. van Campen (to Wm. S. Merrell Co.), U. S. pat. 2,583,450; C. A., 46, 8674 (1952).

$RR'COXCH_2CH_2Y$: R = cyclohexyl, R' = cyclohexylidene, Y = diethylamino or piperidino, X = O, S, or NH.
M. Kopp and B. Tchoubar, Bull. soc. chim. France, 84 (1952).

$o\text{-}(o\text{-}ROCOC_6H_4)C_6H_4COOCH_2CH_2NR'_2$: R = alkyl, H; R' = alkyl.
F. Demers and G. L. Jenkins, J. Am. Pharm. Assoc., Sci. Ed., 41, 61 (1952).

$RCOOCH_2Y\cdot R'X$: R = aryl, aralkyl, biarylalkyl, diarylhydroxymethyl, alkylarylhydroxymethyl, etc.
R. F. Feldkamp, J. Am. Chem. Soc., 74, 3834 (1952).

$RR'COOCH_2CH_2N(C_2H_5)_2$: R = phenyl and R' = cyclopentylidene group.
T. Ito (to Sumitomo Chem. Industries Co.), Japan pat. 5278; C. A., 48, 8820 (1954).

p-$(CH_3)_2CC_6H_5COOAB$: A = substituted or unsubstituted lower alkylene and B = dialkylamino, piperidino and morpholino group.
J. T. Bryan, W. M. Lauter and P. A. Foote, J. Am. Pharm. Assoc., Sci. Ed., 42, 437 (1953).

$RCOO(CH_2)_nNR'_2 \cdot HCl$: R = 2-thienyl, R' = dialkyl and n = integers.
W. H. Houff and R. D. Schuetz, J. Org. Chem., 18, 916 (1953).

Amino Acids.--

$RCOOCH_2CH_2N(C_2H_5)_2$: R = 3-papaverine or 3-norpapaverine group.
J. Redel and A. Bouteville, Bull. soc. chim. France, 443 (1949).

$C_6H_5CH(OR)COOR$: R = dialkylaminoalkyl, piperidinoethyl and morpholinoethyl.
P. Truitt, E. E. Richardson, L. M. Long and W. J. Middleton, J. Am. Chem. Soc., 71, 3479 (1949).

$Et_2NCH_2CH_2COOCHPh_2$: an isomeride of Trasentin.
Z. J. Vejdělek and M. Protiva, Collection Czech. Chem. Communs., 15, 671 (1950); C. A., 45, 9515 (1951).

$ArCH_2CHROCOAlkB$: Ar = aryl or substituted aryl; R = aralkyl; Alk = lower alkylene chain and B = mono- or dialkylamino, piperidino, pyrrolidino or morpholino group.
J. W. Cusic (to G. D. Searle & Co.), U. S. pat. 2,543,764; C. A., 46, 531 (1952).

$RR^1R^2CCOOEt$: R = 2-thienyl, R^1 = aryl and R^2 = dialkylaminoalkyl group.
F. Leonard and I. Ehrenthal, J. Am. Chem. Soc., 73, 2216 (1951).

$CH_3CHRCOOR'$: R = dialkylamino and R' = phenyl or p-aminophenyl group.
T. O. Soine and F. E. Digangi, J. Am. Pharm. Assoc., Sci. Ed., 41, 236 (1952).

o-$[(XX'C_6H_3)(YY'C_6H_3)N]C_6H_3COORB$: X, X', Y, Y' = H, lower alkyl or lower alkoxy groups, R = lower alkylene, and B = disubstituted amino group.
C. P. Krimmel (to G. D. Searle & Co.), U. S. pat. 2,596,156; C. A., 47, 2210 (1953).

$C_6H_5CH(NHR)COOR' \cdot HCl$: R and R' = alkyl groups.
J. Klosa, Arch. Pharm., 285, 401 (1952).

$C_6H_5CH(NHR)COOR'$: R = diethylaminoethyl and R' = isoamyl.
G. Ghielmetti, Farm. sci. e tec., 7, 625 (1952); C. A., 47, 11161 (1953).

$p\text{-}RR'NC_6H_4COOCH_2CH_2NEt_2$: R = H or benzyl and R' = 2-dialkylaminoethyl, dibenzylaminoethyl, piperidinoethyl or morpholinoethyl group.
A. Schlesinger, N. Weiner and S. M. Gordon (to Endo Products, Inc.), U. S. pat. 2,623,045; C. A., 47, 10555 (1953).

$RCH_2CH_2C(Ph)(Et)COOEt$: R = dialkylamino or piperidyl group.
F. B. Tutwiler, R. G. Child and S. N. Wrenn, J. Org. Chem., 19, 910 (1954).

Carbamic Acids.--

$R_3CNHCOOCH_2CH_2NR'_2$: R and R' = alkyl group.
D. Papa, N. Sperber and E. Schwenk (to Schering Corp.), U. S. pat. 2,536,079; C. A., 45, 5179 (1951).

$RCOOCH_2CH_2NR'_2$: R = 1-piperazine and R' = alkyl.
R. J. Turner (to Am. Cyanamid Co.), U. S. pat. 2,617,803; C. A., 48, 2124 (1954).

$R_2NCOX(CHR^1)NR^2_2$: R_2N = group derived from phenothiazine, carbazole, acridan, 5,10-dihydro-5-methylphenazine; R^1 = H or methyl; X = O, S, NH, NCH_3 and NR^2_2 = dialkylamino, pyrrolidino or morpholino group.
A. W. Weston, R. W. DeNet and R. S. Michaels, Jr., J. Am. Chem. Soc., 75, 4006 (1953).

EXPERIMENTAL PART

Discussion of the Experiments

The substituted propionic acids listed in Table I are all new acids. Four of them were prepared by the Ivanoff reaction (105) in which the chloromagnesium derivative of the chloromagnesium salt of phenylacetic acid was prepared from isopropylmagnesium chloride and phenylacetic acid; the Ivanoff reagent was then allowed to react with an aliphatic or a cyclic ketone. One of the acids thus prepared, α-phenyl-α-(1-hydroxycycloheptyl)acetic acid and an already known acid, α-phenyl-α-(1-hydroxycyclopentyl)acetic acid (7-10), were hydrogenated to the corresponding α-cyclohexyl acids.

Four of the acids (compounds 2, 3, 4 and 5, Table I) were esterified by the Horenstein-Pählicke procedure (106). The hydrochlorides and the methobromides of the β-diethylaminoethyl esters of these acids are tabulated in Table II. Acids 1 and 6 (Table I) were also subjected to the Horenstein-Pählicke process but in spite of many attempts neither the hydrochlorides nor the methobromides could be isolated in crystalline form. The products were obtained either in the form of gels or viscous liquids.

In the first attempt to prepare the hydrochloride of the β-diethylaminoethyl ester of α-phenyl-α-(1-hydroxycycloheptyl)acetic acid by the Horenstein-Pählicke process, a mixture of α-phenyl-α-(1-hydroxycycloheptyl)acetic acid,

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(105) D. Ivanoff and A. Spassoff, Bull. soc. chim., (4) 49, 377 (1931).
(106) H. Horenstein and H. Pählicke, Ber., 71, 1644 (1938).

ß-diethylaminoethyl chloride and isopropyl alcohol were refluxed for 18 hours. After removal of the solvent, a gummy residue was obtained. A crystalline, extremely hygroscopic compound was formed after the residue had been triturated with ether. When ether was added to an alcoholic solution of the compound, in an attempt to purify it, a liquid precipitated which became crystalline upon trituration with ether. This material was so hygroscopic that a sharp melting point could not be obtained. Nitrogen and chlorine analyses indicated that the compound was not the desired hydrochloride but that it probably was the hydrochloride of the ß-diethylaminoethyl ester of phenylacetic acid*.

The formation of the hydrochloride of the ß-diethylaminoethyl ester of phenylacetic acid during the Horenstein-Pählicke procedure would not be surprising. It could have been formed by the degradation** of ⍺-phenyl-⍺-(1-hydroxycycloheptyl)acetic acid into phenylacetic acid and cycloheptanone; the phenylacetic acid could have then been esterified by the ß-diethylaminoethyl chloride. The hydrochloride of ß-diethylaminoethyl phenylacetate might also have been

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* The ester base has been obtained from ethyl phenylacetate and ß-diethylaminoethanol by transesterification (V. Ettel and J. Hebký, Collection Czechoslov. Chem. Communs., 15, 367 (1950); C. A., 45, 3823 (1951)).

Although we have been unable to find any mention of the melting point of the ester hydrochloride in the chemical literature, the pharmacology of this salt has been described: A. M. Lands, V. L. Nash and K. Z. Hooper, J. Pharmacol. Exptl. Therap., 86, 129 (1946); A. M. Lands, J. O. Hoppe, J. R. Lewis and E. Ananenko, ibid., 100, 19, 26 (1950).

The ester methobromide has been reported in the literature (Ref. 10).

** This type of degradation has been discussed on page 10.

formed by the degradation of the desired product, ß-diethylaminoethyl α-phenyl-α-(1-hydroxycycloheptyl)acetate hydrochloride, into ß-diethylaminoethyl phenylacetate hydrochloride and cycloheptanone.

Instances in which such degradations have been observed in the Horenstein-Pählicke procedure are reported in references 1 (p), 8 and 10.

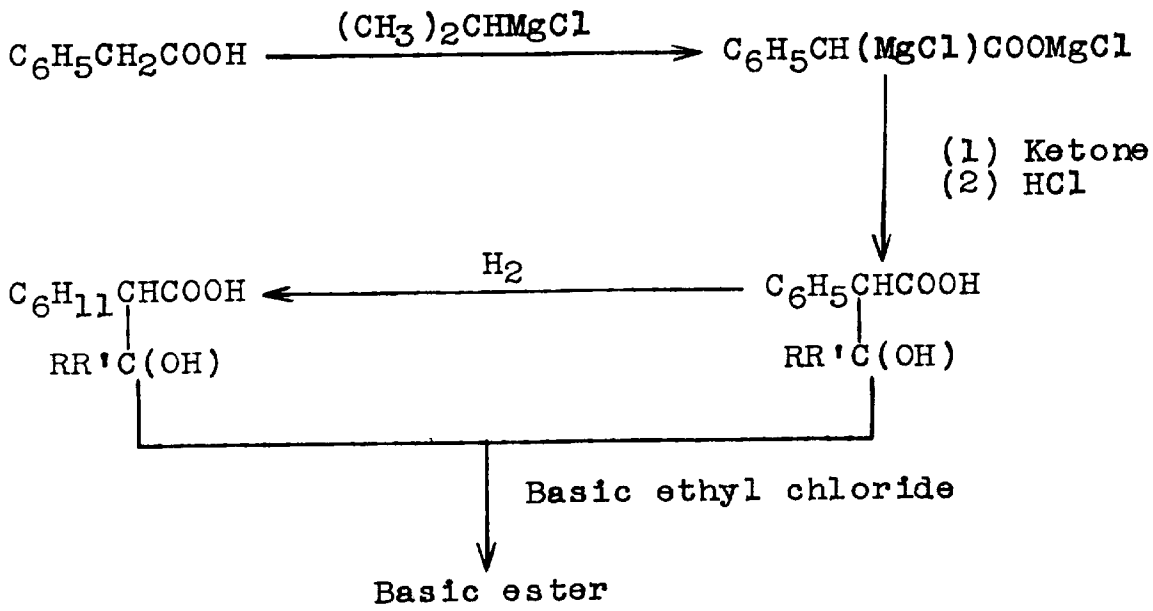
It seemed to us that the type of decomposition mentioned above might be initiated by the basic nature of the ß-diethylaminoethyl chloride, and that the decomposition might be avoided by a slow, dropwise addition of the basic chloride to the refluxing solution of the substituted acetic acid in isopropyl alcohol. Excess basic chloride then would not be present in the reaction mixture since the chloride, as fast as it was added, would be converted into the hydrochloride of the ß-diethylaminoethyl ester of the desired substituted acetic acid.

It was found that, by the adoption of the procedure just mentioned, the desired ester hydrochloride could be obtained without any apparent formation of the hydrochloride of the basic ester of phenylacetic acid.

Since basic alcohols which contain five- and six-membered nitrogenous rings, such as ß-pyrrolidino- and ß-piperidinoethanol, are often used for the preparation of pharmacologically-active basic esters, it was of interest to synthesize esters from basic alcohols which contained eight- and nine-membered nitrogenous rings. Consequently, diphenylacetic

and diphenylhydroxyacetic (benzilic) acids, two acids which are well known because of the very high antispasmodic activity of their ß-diethylaminoethyl esters, were esterified with ß-(1-heptamethylenimino)ethanol and with ß-(1-octamethylenimino)-ethanol. The esters were isolated as hydrochlorides and methobromides. In addition, the hydrochloride and methobromide of the ß-(1-heptamethylenimino)ethyl ester of α-phenyl-α-(1-hydroxycycloheptyl)acetic acid were prepared. These compounds are listed in Table III.

The following reaction scheme indicates the manner in which the compounds in Tables I-III were obtained.



Ketones employed:

1. Cycloheptanone
2. 4-Methylcycloheptanone
3. 2-Heptanone
4. 2-Octanone

Basic ethyl chlorides employed:

1. ß-Diethylaminoethyl Chloride
2. ß-Heptamethyleniminoethyl Chloride
3. ß-Octamethyleniminoethyl Chloride

Seven new diethyl disubstituted malonates (Table IV) were prepared by the malonic ester synthesis. One of the

substituents in these esters was either a cyclopentyl or a cycloheptyl group; the other substituent was an alkyl, phenyl or cycloalkyl radical.

Two already known monosubstituted malonic acids, cyclopentylmalonic and cycloheptylmalonic acids, were esterified with ß-diethylaminoethyl chloride to obtain the dibasic esters which were isolated as dihydrochlorides and dimethobromides. In addition, the dihydrochloride and the dimethobromide of the bis(diethylaminoethyl) ester of n-hexylcycloheptylmalonic acid were synthesized. These esters are listed in Table V.

The Preparation of Substituted ß-Hydroxypropionic Acids

α-Phenyl-ß-methyl-ß-n-amyl-ß-hydroxypropionic Acid (α-Phenyl-ß-methyl-ß-hydroxyoctanoic Acid).--In a liter, three-necked flask fitted with a condenser, stirrer and a dropping funnel, there were placed 12.2 g. (0.5 mole) of magnesium, 350 ml. of ether and 1 ml. of isopropyl bromide. The 43.2 g. (0.55 mole) of isopropyl chloride was added at such a rate that the mixture refluxed. After the addition had been completed, the mixture was refluxed for 1 hour, cooled to room temperature, stirred and 34.0 g. (0.25 mole) of phenylacetic acid, dissolved in 200 ml. of dry benzene, was added dropwise. The mixture was refluxed for 1 hour and then cooled to room temperature. After the slow addition of 28.5 g. (0.25 mole) of methyl amyl ketone (2-heptanone)*,

*Purchased from Distillation Products Industries, Division of Eastman Kodak Company.

the material was refluxed for 18 hours, cooled in an ice-bath and acidified with dilute hydrochloric acid. The aqueous layer was separated and extracted with ether. The extract was combined with the organic layer, dried with fused sodium sulfate, the solvent was removed and the residue was recrystallized four times from toluene-petroleum ether (60-75°); yield 36.0 g. (57%); m.p. 123-124°.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; neut. equiv., 250.3. Found: C, 71.90; H, 8.94; neut. equiv., 248.4.

α-Phenyl-β-methyl-β-n-hexyl-β-hydroxypropionic Acid (α-Phenyl-β-methyl-β-hydroxynonanoic Acid).--Isopropylmagnesium chloride was prepared from 24.3 g. (1.0 mole) of magnesium, 500 ml. of dry ether, 2 ml. of isopropyl bromide and 86.4 g. (1.1 moles) of isopropyl chloride and then a solution of 68 g. (0.5 mole) of phenylacetic acid in 400 ml. of dry benzene was added slowly. After the reaction was completed, 70.5 g. (0.55 mole) of methyl hexyl ketone (2-octanone)* was introduced, gradually, into the reaction mixture. After completion of the reaction, the mixture was worked up in the usual manner and the crude product thus obtained was recrystallized four times from toluene-petroleum ether (60-75°); yield 58 g. (44%); m.p. 124-128° (softening at 120°).

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.70; H, 9.15; neut. equiv., 264.35. Found: C, 72.81; H, 9.22; neut. equiv., 266.8.

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*Purchased from Distillation Products Industries, Division of Eastman Kodak Company.

α-Phenyl-α-(1-hydroxycycloheptyl)acetic Acid.--A solution of 27.2 g. (0.2 mole) of phenylacetic acid in 300 ml. of dry benzene was slowly added to the Grignard reagent prepared from 12.2 g. (0.5 mole) of magnesium, 800 ml. of dry ether, 46 g. (0.6 mole) of isopropyl chloride and 5 ml. of methyl iodide. At the end of the reaction, 44.8 g. (0.4 mole) of cycloheptanone (107) was gradually added and the mixture was refluxed for 12 hours, extracted with ether and the ethereal extract evaporated. The solid residue was recrystallized four times from benzene-petroleum ether (30-40°); yield 28.3 g. (58%); m.p. 150-151°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; neut. equiv., 248.31 Found: C, 72.71, H, 8.35; neut. equiv., 248.90.

α-Cyclohexyl-α-(1-hydroxycyclopentyl)acetic Acid.--A mixture of 11.0 g. of α-phenyl-α-)1-hydroxycyclopentyl)acetic acid (7-10), 50 ml. of glacial acetic acid and 0.1 g. of platinum oxide was shaken with hydrogen under an initial pressure of 50 pounds for 24 hours. At the end of this time about 0.15 mole of hydrogen had been absorbed. The mixture was filtered and the filtrate was evaporated. The solid residue was recrystallized three times from toluene; yield 9.0 g. (81%); m.p. 109-110°.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80; neut. equiv., 226.31. Found: C, 68.91; H, 10.01; neut. equiv., 226.75.

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(107) F. F. Blicke, N. J. Doorenbos and R. H. Cox, J. Am. Chem. Soc., 74, 2924 (1952).

α-Cyclohexyl-α-(1-hydroxycycloheptyl)acetic Acid.--After it had been dissolved in 50 ml. glacial acetic acid, 12.4 g. (0.05 mole) of α-phenyl-α-(1-hydroxycycloheptyl)acetic acid was hydrogenated in the presence of 0.1 g. of platinum oxide under an initial pressure of 50 pounds. The reaction was completed after 24 hours. The filtered solution was evaporated to dryness and the residue was recrystallized four times from toluene; yield 9.5 g. (76%); m.p. 122-124°.

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.82; H, 10.32; neut. equiv., 254.36. Found: C, 70.82; H, 10.38; neut. equiv., 252.6.

α-Phenyl-α-(1-hydroxy-4-methylcycloheptyl)acetic Acid.--The solution of 13.6 g. (0.1 mole) of phenylacetic acid in 100 ml. of dry benzene was added to the Grignard solution prepared from 4.9 g. (0.2 mole) of magnesium, 15.7 g. (0.2 mole) of isopropyl chloride, 1 ml. of methyl iodide and 200 ml. of dry ether. To the reaction mixture there was added 13.7 g. (0.11 mole) of 4-methylcycloheptanone (108). The mixture was then worked up in the usual manner; yield 14.5 g. (55%); m.p. 149-150° after four recrystallizations from benzene-petroleum ether (30-40°).

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; neut. equiv., 262.34. Found: C, 73.38; H, 8.62; neut. equiv., 263.3.

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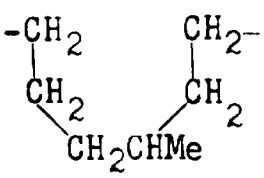
(108) B. Tchoubar, Bull. soc. chim. France, 160 (1949).

TABLE I

Substituted α-Phenyl- and α-Cyclohexyl-β-hydroxypropionic Acids

RCHCOOH *

R'R''COH

	R	R'	R''	M.p., °C.	Formula	Analyses % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Neut. Equiv. Calcd.	Neut. Equiv. Found
1.	C_6H_5	CH_3	C_5H_{11}	123-124	$C_{15}H_{22}O_3$	71.97	71.90	8.86	8.94	250.3	248.4
2.	C_6H_5	CH_3	C_6H_{13}	124-128	$C_{16}H_{24}O_3$	72.70	72.81	9.15	9.22	264.4	266.8
3.	C_6H_{11}	$-(CH_2)_4-$		109-110	$C_{13}H_{22}O_3$	68.99	68.91	9.80	10.01	226.3	226.8
4.	C_6H_5	$-(CH_2)_6-$		150-151	$C_{15}H_{20}O_3$	72.55	72.71	8.12	8.35	248.3	248.9
5.	C_6H_{11}	$-(CH_2)_6-$		122-124	$C_{15}H_{26}O_3$	70.82	70.82	10.32	10.38	254.4	252.6
6.	C_6H_5			149-150	$C_{16}H_{22}O_3$	73.25	73.38	8.45	8.62	262.3	263.3

* R = phenyl or cyclohexyl; R' and R'' = alkyl or polymethylene group. Compounds 1 and 2 were recrystallized from toluene-petroleum ether (60-75°); 4 and 6 from benzene-petroleum ether (30-40°); and 3 and 5 from toluene.

The Preparation of ß-Diethylaminoethyl Esters of Substituted ß-Hydroxypropionic or Acetic Acids

ß-Diethylaminoethyl α-Cyclohexyl-α-(1-hydroxycyclopentyl)-acetate Hydrochloride (JBA-109).--ß-Diethylaminoethyl choride (3.4 g., 0.025 mole) was added slowly to a stirred, refluxing solution of 5.7 g. (0.025 mole) of α-cyclohexyl-α-(1-hydroxycyclopentyl)acetic (α-cyclohexyl-ß,ß-tetramethylene-ß-hydroxypropionic) acid in 30 ml. of isopropyl alcohol. The mixture was stirred and refluxed for 20 hours and then filtered while still hot. The filtrate, cooled to room temperature, was treated with anhydrous ether until it became turbid and it was then cooled in an ice bath. The precipitate was recrystallized four times from n-butanol-ether; yield 3.7 g. (41%); m.p. 125-128°.

Anal. Calcd. for $C_{19}H_{36}O_3NCl$: C, 63.04; H, 10.03; N, 3.87; Cl, 9.80. Found: C, 63.15; H, 10.07; N, 4.09; Cl, 10.01.

ß-Diethylaminoethyl α-Cyclohexyl-α-(1-hydroxycyclopentyl)-acetate Methobromide (JBA-110).--An ice-cold, aqueous solution of 1.8 g. (0.005 mole) of the ester hydrochloride described above was treated with sodium hydroxide solution, the liberated ester base was extracted with ether and the extract was dried with anhydrous sodium sulfate. After the addition of 3 g. (0.03 mole) of methyl bromide, the mixture was allowed to remain at room temperature for 7 days. The crystalline precipitate was recrystallized three times from ethyl acetate-ether; m.p. 112-114°.

Anal. Calcd. for $C_{20}H_{38}O_3NBr$: C, 57.15; H, 9.10; N, 3.33; Br, 19.02. Found: C, 56.89; H, 9.23; N, 3.27; Br, 19.20.

ß-Diethylaminoethyl α-Phenyl-α-(1-hydroxycycloheptyl)-acetate Hydrochloride (JBA-101).--The product obtained from 12.4 g. (0.05 mole) of α-phenyl-α-(1-hydroxycycloheptyl)acetic acid, 6.8 g. (0.05 mole) of ß-diethylaminoethyl chloride and 50 ml. of isopropyl alcohol, in the manner described above, was recrystallized four times from ethyl acetate-ethanol; yield 9.1 g. (47%); m.p. 142-143°.

Anal. Calcd. for $C_{21}H_{34}O_3NCl$: C, 65.69; H, 8.93; N, 3.65; Cl, 9.24. Found: C, 65.79; H, 9.05; N, 3.54; Cl, 9.32.

ß-Diethylaminoethyl α-Phenyl-α-(1-hydroxycycloheptyl)-acetate Methobromide (JBA-102).--A mixture of an ethereal solution of the required ester base, obtained from 5.0 g. of the ester hydrochloride, and 5 g. of methyl bromide was allowed to remain at room temperature for 7 days. The precipitated, crystalline product was recrystallized three times from ethanol-methyl ethyl ketone; m.p. 174-175°.

Anal. Calcd. for $C_{22}H_{36}O_3NBr$: C, 59.74; H, 8.20; N, 3.17; Br, 18.06. Found: C, 59.70; H, 8.32; N, 3.20; Br, 17.97.

ß-Diethylaminoethyl α-Cyclohexyl-α-(1-hydroxycycloheptyl)-acetate Hydrochloride (JBA-111).--This product was obtained from the interaction of 12.7 g. (0.05 mole) of α-cyclohexyl-α-(1-hydroxycycloheptyl)acetic acid and 6.8 g. (0.05 mole) of ß-diethylaminoethyl chloride in 50 ml. of isopropyl alcohol. The material was recrystallized four times from butanol-ether; yield 7.8 g. (40%); m.p. 195-197°.

Anal. Calcd. for $C_{21}H_{40}O_3NCl$: C, 64.67; H, 10.34; N, 3.59; Cl, 9.09. Found: C, 64.71; H, 10.36; N, 3.64; Cl, 9.02.

ß-Diethylaminoethyl α-Cyclohexyl-α-(1-hydroxycycloheptyl)-acetate Methobromide (JBA-112).--The ester base, obtained from 4.0 g. (0.01 mole) of ß-diethylaminoethyl α-cyclohexyl-α-(1-hydroxycycloheptyl)acetate hydrochloride, was allowed to react with 5 g. (0.05 mole) of methyl bromide in the described manner. After seven days, the precipitate was recrystallized three times from ethanol; m.p. 139-141°.

Anal. Calcd. for $C_{22}H_{42}O_3NBr$: C, 58.91; H, 9.44; N, 3.12; Br, 17.82. Found: C, 58.76; H, 9.46; N, 2.98; Br, 17.95.

ß-Diethylaminoethyl α-Phenyl-ß-methyl-ß-n-hexyl-ß-hydroxypropionate Hydrochloride (JBA-126).--In the manner which has been described, an ethereal solution of ß-diethylaminoethyl chloride (obtained from 8.6 g., 0.05 mole, of the chloride hydrochloride) was allowed to react with 13.2 g. (0.05 mole) of α-phenyl-ß-methyl-ß-n-hexyl-ß-hydroxypropionic acid in 50 ml. of isopropyl alcohol. The product was recrystallized three times from ethyl acetate; yield 11.6 g. (58%); m.p. 95-98°.

Anal. Calcd. for $C_{22}H_{38}O_3NCl$: C, 66.05; H, 9.58; Cl, 8.87. Found: C, 65.80; H, 9.60; Cl, 9.10.

ß-Diethylaminoethyl α-Phenyl-ß-methyl-ß-n-hexyl-ß-hydroxypropionate Methobromide (JBA-127).--In this instance, when an ethereal solution of the required ester base was allowed to react with methyl bromide for 7 days, a viscous oil separated from the mixture. The oil was triturated with dry ether

until it solidified and the solid was recrystallized three times from methyl ethyl ketone-ether; m.p. 124-128° (softened at 117°). The analytical data indicated that the product was not entirely pure; it could not be obtained in a purer state by additional recrystallizations.

Anal. Calcd. for $C_{23}H_{40}O_3NBr$: C, 60.25; H, 8.79; Br, 17.43. Found: C, 58.34; H, 8.77; Br, 18.09.

TABLE II

Salts of ß-Diethylaminoethyl Esters of Substituted ⍺-Phenyl- and ⍺-Cyclohexyl-ß-hydroxypropionic Acids

$$\begin{matrix} R & & \\ | & & \\ R'R''COH & & \end{matrix} CHCOOCH_2CH_2N(C_2H_5)_2 \cdot HCl \text{ or } CH_3Br^*$$

	R	R'	R''	Salt	M.p., °C.	Code No. JBA-
1.	C_6H_{11}	$-CH_2(CH_2)_2CH_2-$		HCl	125-128	109
2.	C_6H_{11}	$-CH_2(CH_2)_2CH_2-$		CH_3Br	112-114	110
3.	C_6H_5	$-CH_2(CH_2)_4CH_2-$		HCl	142-143	101
4.	C_6H_5	$-CH_2(CH_2)_4CH_2-$		CH_3Br	174-175	102
5.	C_6H_{11}	$-CH_2(CH_2)_4CH_2-$		HCl	195-197	111
6.	C_6H_{11}	$-CH_2(CH_2)_4CH_2-$		CH_3Br	139-141	112
7.	C_6H_5	CH_3	C_6H_{13}	HCl	95-98	126
8.	C_6H_5	CH_3	C_6H_{13}	CH_3Br	124-128	127

*R = phenyl or cyclohexyl; R' and R'' = alkyl or polymethylene.

TABLE II (concluded)

	Formula	Analyses % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
1.	$C_{19}H_{36}O_3NCl$	63.04	63.15	10.03	10.07	3.87	4.09	9.80	10.06
2.	$C_{20}H_{38}O_3NBr$	57.15	56.89	9.10	9.23	3.33	3.27	19.02	19.20
3.	$C_{21}H_{34}O_3NCl$	65.69	65.79	8.93	9.05	3.65	3.54	9.24	9.32
4.	$C_{22}H_{36}O_3NBr$	59.74	59.70	8.20	8.32	3.17	3.20	18.06	17.97
5.	$C_{21}H_{40}O_3NCl$	64.67	64.71	10.34	10.36	3.59	3.64	9.09	9.02
6.	$C_{22}H_{42}O_3NBr$	58.91	58.76	9.44	9.46	3.12	2.98	17.82	17.95
7.	$C_{22}H_{38}O_3NCl$	66.05	65.80	9.58	9.60	-	-	8.87	9.10
8.	$C_{23}H_{40}O_3NBr$	60.25	58.34	8.79	8.77	-	-	17.43	18.09

Compounds 1 and 5 were recrystallized four times from n-butanol-ether mixture; 2 from ethyl acetate-ether; 3 from ethyl acetate-ethanol; 4 from ethanol-butanone and also from isopropyl alcohol; 6 from ethanol; 7 from ethyl acetate; and 8 from butanone.

The Preparation of ß-Polymethyleniminoethyl Esters of Substituted Acetic Acids

ß-(1-Heptamethylenimino)ethyl Diphenylacetate.--Into a solution of 12.8 g. (0.055 mole) of diphenylacetyl chloride (109) in 10 ml. of dry benzene there was added, dropwise and with stirring, 7.9 g. (0.05 mole) of ß-(1-heptamethylenimino)-ethanol (110) dissolved in 10 ml. of dry benzene. The mixture was stirred and refluxed for 12 hours. After removal of the solvent, the residue was dissolved in a small amount of water, the solution was cooled, made alkaline with sodium hydroxide, and extracted with ether. The solvent was removed from the dried extract and the residue was distilled; b.p. 213-215° (1.2 mm.); yield 7.4 g. (42%).

ß-(1-Heptamethylenimino)ethyl Diphenylacetate Hydrochloride (JBA-114).--An ethanol-ether solution of 2.5 g. of the required ester was treated with a slight excess of an ethereal hydrogen chloride solution. The oily precipitate became solid after it had been triturated with ether. After three recrystallizations from ethanol-ethyl acetate. 2 g. of product was obtained; m.p. 134.5-137°.

Anal. Calcd. for $C_{23}H_{30}O_2NCl$: C, 71.21; H, 7.80; N, 3.61; Cl, 9.14. Found: C, 71.54; H, 7.84; N, 3.62; Cl, 9.15.

ß-(1-Heptamethylenimino)ethyl Diphenylacetate Methobromide (JBA-115).--From 2.5 g. of the ester base, dissolved in methyl ethyl ketone-ether, and about 2 ml. of methyl

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(109) D. Libermann and L. Hengl, Bull. soc. chim. France, 974 (1951).

(110) F. F. Blicke and N. J. Doorenbos, J. Am. Chem. Soc., 76, 2317 (1954).

bromide there was obtained 2.2 g. of product after three recrystallizations from methyl ethyl ketone-ether; m.p. 155-159°.

Anal. Calcd. for $C_{24}H_{32}O_2NBr$: C, 64.56; H, 7.23; N, 3.14; Br, 17.90. Found: C, 64.23; H, 7.62; N, 3.18; Br, 18.03.

ß-(1-Heptamethylenimino)ethyl Diphenylhydroxyacetate Hydrochloride (JBA-116).--A solution of 10.6 g. (0.05 mole) of ß-(1-heptamethylenimino)ethyl chloride hydrochloride (110) in 50 ml. of isopropyl chloride was added, slowly, to a stirred suspension of 26.6 g. (0.10 mole) of potassium diphenylhydroxyacetate in 100 ml. of isopropyl alcohol. The mixture was stirred and refluxed for 2 days, cooled and filtered from solid material. The solid was washed with ether and the ether was then added to the initial filtrate. After removal of the solvents from the filtrate, the residue was dissolved in ether and the solution was treated with ethereal hydrogen chloride. The precipitated hydrochloride was recrystallized four times from ethanol-ethyl acetate; yield 8.1 g. (40%); m.p. 172-175° (decomp.).

Anal. Calcd. for $C_{23}H_{30}O_3NCl$: C, 68.39; H, 7.49; N, 3.47; Cl, 8.78. Found: C, 68.50; H, 7.55; N, 3.56; Cl, 8.73.

ß-(1-Heptamethylenimino)ethyl Diphenylhydroxyacetate Methobromide (JBA-117).--The ester hydrochloride (4.0 g.) was dissolved in water, the solution was cooled, made alkaline and extracted with ether. Methyl bromide (4 g.) was added to the dried extract, and after 10 days the crystalline precipitate was recrystallized four times from ethanol-methyl

ethyl ketone; yield 2.5 g.; m.p. 179-180° (dec.).

Anal. Calcd. for $C_{24}H_{32}O_3NBr$: C, 62.34; H, 6.98; N, 3.03; Br, 17.29. Found: C, 62.11; H, 7.08; N, 3.16; Br, 17.42.

ß-(1-Octamethylenimino)ethyl Diphenylacetate.--A solution of 12.6 g. (0.055 mole) of diphenylacetyl chloride in 30 ml. of dry benzene was added to a stirred solution of 10.4 g. (0.06 mole) of ß-(1-octamethylenimino)ethanol (110) in 20 ml. of dry benzene. After the mixture had been stirred for 12 hours, it was refluxed for 30 minutes. The solvent was removed and the residue was dissolved in water. The solution was extracted thoroughly with ether and the ether was discarded. The aqueous solution was cooled in an ice-bath, made alkaline with sodium hydroxide and extracted with ether. After the extract had been dried, the solvent was removed and the residue was distilled; b.p. 195-198° (0.004 mm.); yield 15.3 g. (76%).

ß-(1-Octamethylenimino)ethyl Diphenylacetate Hydrochloride (JBA-120).--The hydrochloride precipitated when the ester base, dissolved in a mixture of ethanol and ether, was treated with hydrogen chloride. After three recrystallizations from ethanol-ethyl acetate, it melted at 117-119°.

Anal. Calcd. for $C_{24}H_{32}O_2NCl$: C, 71.70; H, 8.03; N, 3.49; Cl, 8.82. Found: C, 71.50; H, 8.01; N, 3.53; Cl, 9.08.

ß-(1-Octamethylenimino)ethyl Diphenylacetate Methobromide (JBA-121).--Methyl bromide (5 g.) was added to 5 g. of the ester base dissolved in a mixture of methyl ethyl ketone and ether. After ten days the crystalline precipitate

was recrystallized from methyl ethyl ketone; m.p. 133.5-134.5°. However, after the product had been recrystallized from isopropyl alcohol-ether, it melted at 152°.

The analytical data found for carbon and hydrogen, in the case of both the lower and the higher melting product, checked with the calculated data.

Anal. Calcd. for $C_{25}H_{34}O_2NBr$: C, 65.21; H, 7.44; N, 3.05; Br, 17.36. Found (compound, m.p. 133.5-134.5°): C, 64.94; H, 7.54; N, 3.25; Br, 17.44. Found (compound, m.p. 152°): C, 65.59; H, 7.65.

β-(1-Octamethylenimino)ethyl Diphenylhydroxyacetate Hydrochloride (JBA-122).--β-(1-Octamethylenimino)ethyl chloride hydrochloride (110) (11.3 g., 0.05 mole) was dissolved in water, the cooled solution was treated with sodium hydroxide and the chloride base was extracted with ether. After the extract had been dried with anhydrous sodium sulfate, it was added, dropwise and slowly, to a stirred refluxing solution of 12.5 g. (0.055 mole) of diphenylhydroxyacetic acid in 50 ml. of isopropyl alcohol. The ether was allowed to escape from the boiling solution through the top of the condenser. After the mixture had been stirred and refluxed for 15 hours, the hot solution was filtered, cooled and ether was added until the solution became slightly cloudy. When the mixture was cooled and stirred, 17.2 g. (82%) of product precipitated; m.p. 166-169.5° after three recrystallizations from ethanol-ether.

Anal. Calcd. for $C_{24}H_{32}O_3NCl$: C, 68.96; H, 7.72; N, 3.35;

Cl, 8.48. Found: C, 68.97; H, 7.74; N, 3.35; Cl, 8.32.

ß-(1-Octamethylenimino)ethyl Diphenylhydroxyacetate Methobromide (JBA-123).--An ethereal solution (the volume was about 45 ml.) of the ester base, which had been obtained from 5.0 g. of the ester hydrochloride, was mixed with 5 ml. of butanone, 2 ml. of methyl bromide was added and the mixture was allowed to remain at room temperature for 10 days. The precipitate was recrystallized three times from butanol; m.p. 182° (dec.).

Anal. Calcd. for $C_{25}H_{34}O_3NBr$: C, 63.02; H, 7.19; N, 2.94; Br, 16.77. Found: C, 62.91; H, 7.40; N, 3.01; Br, 17.18.

ß-(1-Heptamethylenimino)ethyl α-Phenyl-α-(1-hydroxycycloheptyl)acetate Hydrochloride (JBA-124).--This compound was prepared, in the manner which has been described, by the Horenstein-Pählicke process. From the chloride base, which had been obtained from 10.6 g. (0.05 mole) of ß-(1-heptamethylenimino)ethyl chloride hydrochloride (110), 12.4 g. (0.05 mole) of α-phenyl-α-(1-hydroxycycloheptyl)acetic acid and 50 ml. of isopropyl alcohol, 11.5 g. (54%) of product was obtained after three recrystallizations from ethanol-ethyl acetate; m.p. 172-173.5°.

Anal. Calcd. for $C_{24}H_{38}O_3NCl$: C, 67.98; H, 9.03; Cl, 8.36. Found: C, 68.00; H, 9.23; Cl, 8.47.

ß-(1-Heptamethylenimino)ethyl α-Phenyl-α-(1-hydroxycycloheptyl)acetate Methobromide (JBA-125).--The ester base, which had been obtained from 5.0 g. of the ester hydrochloride, was dissolved in a mixture of 45 ml. of ether and 5 ml. of

methyl ethyl ketone, and 2 ml. of methyl bromide was added. After 7 days the precipitate was recrystallized three times from methyl ethyl ketone-ether; m.p. 195-196° (dec.).

Anal. Calcd. for $C_{25}H_{40}O_3NBr$: C, 62.23; H, 8.36; Br, 16.56. Found: C, 62.47; H, 8.31; Br, 16.71.

TABLE III

Salts of β-(1-Polymethylenimino)ethyl Esters of α-Substituted Phenylacetic Acids

$(C_6H_5)CRR'COOCH_2CH_2N<(CH_2)_n \cdot HCl$ or CH_3Br*

	R	R'	n	Salt	M.p., °C.	Code No. JBA
1.	C_6H_5	H	7	HCl	134.5-137	114
2.	C_6H_5	H	7	CH_3Br	155-159	115
3.	C_6H_5	OH	7	HCl	172-175 (dec.)	116
4.	C_6H_5	OH	7	CH_3Br	179-180 (dec.)	117
5.	$(CH_2)_6>C(OH)$	H	7	HCl	172-173.5	124
6.	$(CH_2)_6>C(OH)$	H	7	CH_3Br	195-196 (dec.)	125
7.	C_6H_5	H	8	HCl	117-119	120
8.	C_6H_5	H	8	CH_3Br	133.5-134.5 (a) 152 (b)	121
9.	C_6H_5	OH	8	HCl	166-169	122
10.	C_6H_5	OH	8	CH_3Br	182 (dec.)	123

*R = phenyl or 1-hydroxycycloheptyl; R' = hydrogen or hydroxyl; n = 7 or 8.

TABLE III (concluded)

	Formula	Analyses % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
1.	$C_{23}H_{30}O_2NCl$	71.21	71.54	7.80	7.84	3.61	3.62	9.14	9.15
2.	$C_{24}H_{32}O_2NBr$	64.56	64.23	7.23	7.62	3.14	3.18	17.90	18.03
3.	$C_{23}H_{30}O_3NCl$	68.39	68.50	7.49	7.55	3.47	3.56	8.78	8.73
4.	$C_{24}H_{32}O_3NBr$	62.34	62.11	6.98	7.08	3.03	3.16	17.29	17.42
5.	$C_{24}H_{38}O_3NCl$	67.98	68.00	9.03	9.23	-	-	8.36	8.47
6.	$C_{25}H_{40}O_3NBr$	62.23	62.47	8.36	8.31	-	-	16.56	16.71
7.	$C_{24}H_{32}O_2NCl$	71.70	71.50	8.03	8.01	3.49	3.53	8.82	9.08
8.	$C_{25}H_{34}O_2NBr$	65.21	64.94(a) 65.59(b)	7.44	7.54(a) 7.65(b)	3.05	3.25	17.36	17.44
9.	$C_{24}H_{32}O_3NCl$	68.96	68.97	7.72	7.74	3.35	3.35	8.48	8.32
10.	$C_{25}H_{34}O_3NBr$	63.02	62.91	7.19	7.40	2.94	3.01	16.77	17.18

Compounds 1, 3, 5 and 7 were recrystallized from ethanol-ethyl acetate; 3 from water also; 2, 4 and 6 from butanone-ether; 8 from isopropyl alcohol-ether (if from butanone-ether the m.p. dropped to 133.5-134.5°); 9 from ethanol-ether; and 10 from n-butanol.
(a) Found for the lower melting compound; (b) found for the higher melting compound.

The Preparation of Diethyl Disubstituted Malonates

Diethyl Substituted Cyclopentylmalonates

Diethyl Cyclopentylmalonate.--To 1,000 ml. of absolute alcohol in a 3-liter, 3-necked flask, provided with a stirrer, condenser and dropping funnel, there was added, through the condenser, 46 g. (2 moles) of sodium in small pieces. After all of the sodium had reacted, 352.4 g. (2.2 moles) of diethyl malonate was introduced. The mixture was stirred and refluxed for an hour and then 298.1 g. (2 moles) of cyclopentyl bromide was added slowly. After the mixture had been refluxed for 20 hours it was made slightly acidic with acetic acid. Most of the alcohol was removed by distillation and water was added to dissolve the gummy residue. The aqueous layer was separated, extracted with ether and the extract was added to the organic layer. After the ether solution had been dried with anhydrous sodium sulfate, the solvent was removed and the residue was disilled; b.p. 95-103° (1.7 mm.)*; yield 342 g. (73%).

Diethyl n-Propylcyclopentylmalonate.--A suspension of 4.6 g. (0.2 mole) of sodium in 60 ml. of dry toluene was

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*T. Wagner-Jauregg and H. Arnold (Ann., 529, 274 (1937)), who used the same general procedure but heated the reaction mixture in an autoclave, obtained the product in 70% yield; b.p. 135-140° (12 mm.).

V. N. Ipatieff, J. E. Germain and H. Pines (Bull. soc. chim. France, 259 (1951)) prepared the ester in 64% yield from cyclopentyl bromide and the sodium derivative of diethyl malonate in alcoholic solution; however, neither the experimental details nor the boiling point were reported.

A. Verwey (Ber., 29, 1996 (1896)) obtained the ester in 50% yield from cyclopentyl iodide, diethyl malonate and sodium in toluene; he stated that the boiling point was 137-138° (13 mm.).

refluxed and stirred vigorously until the sodium had melted and formed very small globules. Diethyl cyclopentylmalonate (50.4 g., 0.22 mole) was added in a slow stream and the refluxing and stirring were continued until all of the sodium had reacted. After the addition of 30.8 g. (0.25 mole) of n-propyl bromide, the mixture was stirred and refluxed for 48 hours. Water was added to the cold mixture to dissolve the precipitate, the aqueous layer was separated and extracted with ether. The extract was combined with the organic layer, the ether solution was dried with anhydrous magnesium sulfate, the solvent was removed and the residue was distilled; b.p., after two distillations, 110-113° (1.8 mm.); yield 29.8 g. (55%).

Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.64; H, 9.70. Found: C, 66.67; H, 9.59.

Diethyl n-Hexylcyclopentylmalonate.--This compound was prepared in the same general manner as the one described above. From 7.3 g. (0.317 mole) of sodium, 60 ml. of toluene, 68.5 g. (0.30 mole) of diethyl cyclopentylmalonate and 70 g. (0.40 mole) of n-hexyl bromide there was obtained 41 g. (44%) of product; b.p. 127-128° (0.8 mm.).

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.18; H, 10.33. Found: C, 69.37; H, 10.50.

Diethyl Phenylcyclopentylmalonate.--A solution of sodium ethoxide was prepared from 12.5 g. (0.54 mole) of metallic

sodium and 225 ml. of specially prepared absolute alcohol*. After the addition of 129.9 g. (0.55 mole) of diethyl phenylmalonate**, the mixture was heated and stirred for 2 hours. Cyclopentyl bromide (89.4 g., 0.60 mole) was then added slowly and the mixture was heated and stirred for 18 hours. After treatment in the usual manner, 22.0 g. (13%) of product was obtained; b.p. 137-140° (0.6 mm.).

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.80; H, 8.05.

Diethyl Substituted Cycloheptylmalonates

Although cycloheptyl bromide, required for the experiment described below, is a known compound, its preparation from cycloheptanol and phosphorus tribromide has not been reported in the literature.

Cycloheptanol had been obtained previously by reduction of cycloheptanone (suberone) with sodium and alcohol (111), by reduction with aluminum isopropoxide (112), from hexahydrobenzylamine, sodium nitrite and acetic acid (113) and

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* The alcohol was obtained by the azeotropic distillation of absolute alcohol with 10% dry benzene (See E. S. Gyngell, M. A. Phillips and E. L. Smith, The Industrial Chemist, 21, 526 (1945).

** Purchased from Matheson Coleman and Bell, Inc., Division of The Matheson Company.

(111) (a) W. Markownikow, J. prakt. Chem., (2) 49, 409 (1894) (50% yield); (b) R. Willstätter, Ann., 317, 218 (1901) (87% yield).

(112) M. Mousseron, R. Granger and A. Merle, Bull. soc. chim. France, 459 (1947)(82% yield).

(113) (a) L. Ruzicka and W. Brugger, Helv. Chim. Acta, 9, 399 (1926); (b) N. J. Doorenbos, Dissertation, University of Michigan, 1953, p. 26.

from cycloheptyl bromide (114) by an indirect process.

We prepared cycloheptanol in 87% yield by reduction of cycloheptanone (107) with lithium aluminum hydride. This method had been used previously in this Laboratory (115) but the procedure had not been described.

Cycloheptyl bromide has been obtained from cycloheptanol and hydrobromic acid (116); the yields obtained were not reported. By the use of phosphorus tribromide, we found that cycloheptyl bromide could be obtained from cycloheptanol in 87.5% yield.

Cycloheptanol.--Lithium aluminum hydride (45.6 g., 1.2 mole) and 1,500 ml. of absolute ether were placed in a 5-liter, 3-necked flask fitted with a dropping funnel, condenser and stirrer. The mixture was stirred and 448.7 g. (4.0 moles) of cycloheptanone, dissolved in 500 ml. of absolute ether, was added, dropwise, at such a rate that the ether refluxed. The mixture was then stirred and refluxed for 18 hours, cooled to room temperature and 91 ml. of water was added, very slowly, to the stirred material. After it had been stirred for 15 hours, the mixture was filtered through a sintered glass filter and the solid material was washed thoroughly with dry ether. The filtrate and ethereal wash solution were combined and the solution was dried with anhydrous sodium sulfate. The solvent was removed and the

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(114) S. L. Friess and R. Pinson, Jr., J. Am. Chem. Soc., 73, 3512 (1951).
(115) J. Azuara, Ref. 1 (n), p. 39.
(116) (a) N. Zelinsky, Ber., 35, 2687 (1902); (b) W. Markownikow, Ann., 327, 59 (1903).

residue was distilled; b.p. 83-87° (15 mm.); yield 394.7 g. (87%).

Cycloheptyl Bromide.--Phosphorus tribromide (541.6 g., 2 moles) was placed in a 1-liter, 3-necked flask fitted with a dropping funnel, condenser and stirrer. It was cooled in an ice-bath, stirred and 342.6 g. (3 moles) of cycloheptanol was added, dropwise. After the mixture had been stirred for 48 hours it was poured onto 1,000 g. of ice. The oily precipitate was dissolved in ether, the aqueous layer was separated and extracted with the same solvent. The combined ether solution and ether extract was washed successively with water, sodium bicarbonate solution and water. After the solution had been dried with anhydrous magnesium sulfate, the solvent was removed and the residue was distilled; b.p. 81-87° (21 mm.); yield 465.5 g. (87.5%).

Diethyl Cycloheptylmalonate.--A solution of sodium ethoxide was prepared from 46.2 g. (2 moles) of sodium and 1,500 ml. of absolute ethanol. After reaction with 352.4 g. (2.2 moles) of diethyl malonate, 355.2 g. (2 moles) of cycloheptyl bromide was added. The yield of product was 353.6 g. (69%); b.p. 105-110° (0.6-0.8 mm.)*.

Diethyl Cyclopentylcycloheptylmalonate.--To a boiling, vigorously stirred suspension of 6.9 g. (0.3 mole) of sodium in 75 ml. of dry toluene there was added 76.9 g. (0.3 mole) of diethyl cycloheptylmalonate and, finally, 60.0 g. (0.4

*This compound has been described by J. Azuara (Doctoral Dissertation, University of Michigan, 1954).

mole) of cyclopentyl bromide; yield 22.0 g. (23%); b.p. 145-150° (1 mm.).

Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.52; H, 9.78.

Diethyl n-Propylcycloheptylmalonate.--From the interaction of 4.6 g. (0.2 mole) of sodium in 60 ml. of toluene, 51.3 g. (0.2 mole) of diethyl cycloheptylmalonate and 30.7 g. (0.25 mole) of n-propyl bromide there was obtained, in the manner which has been described, 42 g. (70%) of product; b.p. 130-134° (1.7 mm.).

Anal. Calcd. for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.50; H, 10.37.

Diethyl n-Hexylcycloheptylmalonate.--From 6.9 g. (0.3 mole) of sodium in 75 ml. of dry toluene, 76.9 g. (0.3 mole) of diethyl cycloheptylmalonate and 66 g. (0.4 mole) of n-hexyl bromide there was obtained 56.5 g. (55%) of product; b.p. 147-148° (0.8 mm.).

Anal. Calcd. for $C_{20}H_{36}O_4$: C, 70.55; H, 10.67. Found: C, 70.74; H, 10.95.

Diethyl Phenylcycloheptylmalonate.--Interaction of 11.6 g. (0.5 mole) of sodium in 100 ml. of dry toluene, 117.6 g. (0.5 mole) of diethyl phenylmalonate and 92 g. (0.52 mole) of cycloheptyl bromide, dissolved in 150 ml. of dry toluene, there was obtained 18.8 g. (11%) of product; b.p. 155-158° (0.6 mm.).

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.62; H, 8.31.

TABLE IV

Diethyl Disubstituted Malonates

$RR'C(COOC_2H_5)_2$*

	R	R'	B.p., °C.	mm.	Formula	Analyses % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1.	C_5H_9(a)	n-C_3H_7	110-113	1.8-1.9	$C_{15}H_{26}O_4$	66.64	66.67	9.70	9.59
2.	C_5H_9	n-C_6H_{13}	127-128	0.8	$C_{18}H_{32}O_4$	69.18	69.37	10.33	10.50
3.	C_5H_9	C_6H_5	137-140	0.6	$C_{18}H_{24}O_4$	71.03	70.80	7.95	8.05
4.	C_5H_9	C_7H_{13}(b)	145-150	1.0	$C_{19}H_{32}O_4$	70.33	70.52	9.94	9.78
5.	C_7H_{13}	n-C_3H_7	130-134	1.7	$C_{17}H_{30}O_4$	68.42	68.50	10.13	10.37
6.	C_7H_{13}	n-C_6H_{13}	147-148	0.8	$C_{20}H_{36}O_4$	70.55	70.74	10.67	10.95
7.	C_7H_{13}	C_6H_5	155-158	0.6-0.7	$C_{20}H_{28}O_4$	72.26	72.62	8.49	8.31

*R = Cycloalkyl; R' = phenyl, cycloalkyl or alkyl.

(a) C_5H_9 = Cyclopentyl.

(b) C_7H_{13} = Cycloheptyl.

The Preparation of Bis(ß-Diethylaminoethyl) Esters of Substituted Malonic Acids

Bis(ß-diethylaminoethyl) Cyclopentylmalonate Dihydrochloride (JBA-107).--A solution of 8.6 g. (0.05 mole) of cyclopentylmalonic acid* in 50 ml. of isopropyl alcohol was treated with the chloride, obtained from 13.6 g. (0.10 mole) of ß-diethylaminoethyl hydrochloride, in the manner which has been described. The product was dissolved in absolute ethanol, precipitated with dry ether, and then recrystallized three times from isopropyl alcohol-ether; m.p. 138-141° (dec.); yield 12.3 g. (56%).

Anal. Calcd. for $C_{20}H_{40}O_4N_2Cl_2$: N, 6.32; Cl, 15.99. Found: N, 6.53; Cl, 16.24.

Bis(ß-diethylaminoethyl) Cyclopentylmalonate Dimethobromide (JBA-108).--The ester base, obtained from the dihydrochloride described above, was dissolved in ether and about 5 molecular equivalents of methyl bromide were added. After 7 days, the precipitated dimethobromide was recrystallized three times from isopropyl alcohol-ether; m.p. 154° (dec.).

Anal. Calcd. for $C_{22}H_{44}O_4N_2Br_2$: N, 5.00; Br, 28.52. Found: N, 4.88; Br, 28.47.

Bis(ß-diethylaminoethyl) Cycloheptylmalonate Dihydrochloride (JBA-105).--This product was prepared from a

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*Diethyl cyclopentylmalonate was hydrolyzed to cyclopentylmalonic acid with alcoholic potassium hydroxide according to a described process (A. Verwey, Ber., 29, 1996 (1896).

solution of 10.0 g. (0.05 mole) of cycloheptylmalonic acid* (m.p. 165°, dec.) in 50 cc. of isopropyl alcohol and the chloride obtained from 13.6 g. (0.10 mole) of ß-diethylaminoethyl chloride hydrochloride. The product was recrystallized three times from acetone; yield 14.5 g. (62%); m.p. 135-137°.

Anal. Calcd. for $C_{22}H_{44}O_4N_2Cl_2$: C, 56.64; H, 9.41; N, 5.94; Cl, 15.04. Found: C, 56.21; H, 9.60; N, 5.81; Cl, 15.07.

Bis(ß-diethylaminoethyl) Cycloheptylmalonate Dimethobromide (JBA-106).--This compound was obtained in the manner described above. The product was recrystallized three times from butanol-ether; m.p. 150-156° (dec.).

Anal. Calcd. for $C_{24}H_{48}O_4N_2Br_2$: C, 48.98; H, 8.22; N, 4.77; Br, 27.16. Found: C, 48.70; H, 8.27; N, 4.92; Br, 27.31.

Bis(ß-diethylaminoethyl) n-Hexylcycloheptylmalonate Dihydrochloride (JBA-118).--In this instance, the ester dihydrochloride was prepared from the dipotassium salt of n-hexylcycloheptylmalonic acid and ß-diethylaminoethyl chloride (Horenstein-Pählicke method). In order to obtain the dipotassium salt, diethyl n-hexylcycloheptylmalonate (33.1 g.) was dissolved in 10 ml. of absolute ethanol, and 4 molar equivalents (22.4 g.) of potassium hydroxide, dissolved in

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*The acid was obtained by hydrolysis of the diethyl ester with alcoholic potassium hydroxide; the process was the same as that employed for the hydrolysis of diethyl cyclopentylmalonate.

I. Vogel (J. Chem. Soc., 2010 (1928)), who prepared the acid by hydrolysis of ethyl cycloheptylcyanoacetate, reported the melting point to be 164.5° (dec.).

30 ml. of 95% ethanol, was added. The mixture was refluxed for 48 hours, cooled to room temperature, the precipitated dipotassium salt was filtered, washed thoroughly with absolute ethanol and air dried.

Two molecular equivalents of flake sodium hydroxide were added to 1 mole of ß-diethylaminoethyl chloride hydrochloride in a distillation flask. While the mixture was being stirred rapidly, the basic chloride was distilled under reduced pressure*. The ß-diethylaminoethyl chloride (8.1 g., 0.06 mole) was added, dropwise and very slowly, to a refluxing suspension of 9.8 g. (0.033 mole) of the dipotassium salt in 120 ml. of isopropyl alcohol. The mixture was refluxed for 48 hours and then filtered while still hot. The solvent was partially removed from the filtrate by distillation and the residual solution was divided into two equal portions. One portion was treated with ethereal hydrogen chloride. The precipitated salt was recrystallized three times from ethyl acetate-ether; yield 3.0 g. (36%); m.p. 150-155°.

Anal. Calcd. for $C_{28}H_{56}O_4N_2Cl_2$: N, 5.06; Cl, 12.76. Found: N, 5.29; Cl, 13.10.

Bis(ß-diethylaminoethyl) n-Hexylcycloheptylmalonate Dimethobromide (JBA-119).--The ethereal solution of the ester base, obtained in the manner described above, was treated with 2 ml. of methyl bromide. After 7 days, the precipitate was recrystallized four times from ethanol-methyl

*This process has been described by R. R. Burtner (J. Am. Chem. Soc., 71, 2578 (1949).

ethyl ketone; yield 3.3 g. (33%); m.p. 154-160° (dec.).

Anal. Calcd. for $C_{30}H_{60}O_4N_2Br_2$: C, 53.56; H, 8.99; N, 4.17; Br, 23.77. Found: C, 53.27; H, 9.00; N, 4.29; Br, 24.19.

TABLE V

Salts of Bis(ß-diethylaminoethyl) Substituted Malonates

$RR'C(COOCH_2CH_2NEt_2 \cdot 2\ HCl$ or $2\ CH_3Br$*

	R	R'	Salt	M.p., °C.	Code No. JBA
1.	C_5H_9 (a)	H	di-HCl	138-141 (dec.)	107
2.	C_5H_9	H	di-CH_3Br	154 (dec.)	108
3.	C_7H_{13} (b)	H	di-HCl	135-137	105
4.	C_7H_{13}	H	di-CH_3Br	150-156 (dec.)	106
5.	C_7H_{13}	n-C_6H_{13}	di-HCl	150-155	118
6.	C_7H_{13}	n-C_6H_{13}	di-CH_3Br	154-160 (dec.)	119

*R = Cycloalkyl; R' = hydrogen or alkyl.
(a) Cyclopentyl. (b) Cycloheptyl.

TABLE V (concluded)

	Formula	Analyses % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
1.	$C_{20}H_{40}O_4N_2Cl_2$	-	-	-	-	6.32	6.53	15.99	16.24
2.	$C_{22}H_{44}O_4N_2Br_2$	-	-	-	-	5.00	4.88	28.52	28.47
3.	$C_{22}H_{44}O_4N_2Cl_2$	56.04	56.21	9.41	9.60	5.94	5.81	15.04	15.07
4.	$C_{24}H_{48}O_4N_2Br_2$	48.98	48.70	8.22	8.27	4.77	4.92	27.16	27.31
5.	$C_{28}H_{56}O_4N_2Cl_2$	-	-	-	-	5.06	5.29	12.76	13.10
6.	$C_{30}H_{60}O_4N_2Br_2$	53.56	53.27	8.99	9.00	4.17	4.29	23.77	24.19

Compounds 1 and 2 were recrystallized from isopropyl alcohol-ether; 3 from acetone; 4 from n-butanol-ether; 5 from ethyl acetate-ethanol; and 6 from butanone-ethanol.

SUMMARY

During this investigation a number of substituted α-phenyl- and α-cyclohexyl-β-hydroxypropionic acids, RR'C(OH)CHR''COOH, were prepared (R and R' = methyl, amyl, hexyl, tetramethylene, hexamethylene or 3-methylhexamethylene; R'' = phenyl or cyclohexyl). The substituted α-phenyl-β-hydroxypropionic acids were obtained by the interaction of the chloromagnesium derivative of the chloromagnesium salt of phenylacetic acid, $C_6H_5CH(MgCl)COOMgCl$, with the required ketone (Ivanov reaction). α-Phenyl-α-(1-hydroxycyclopentyl)-acetic acid (α-phenyl-β,β-tetramethylene-β-hydroxypropionic acid) and α-phenyl-α-(1-hydroxycycloheptyl)acetic acid were hydrogenated catalytically to the corresponding α-cyclohexyl acids.

With two exceptions, all of the β-hydroxypropionic acids were converted into crystalline β-diethylaminoethyl ester hydrochlorides by the use of the Horenstein-Pählicke procedure; the corresponding methobromides were also prepared. Crystalline salts could not be obtained from the β-diethylaminoethyl esters of α-phenyl-β-methyl-β-n-amyl-β-hydroxypropionic and α-phenyl-α-(1-hydroxy-4-methylcyclohexyl)acetic acids. The hydrochlorides and methobromides of the β-(1-heptamethylenimino)ethyl esters of diphenylacetic, diphenylhydroxyacetic and α-phenyl-α-(1-hydroxycycloheptyl)-acetic acids, and of the β-(1-octamethylenimino)ethyl esters

of diphenylacetic and diphenylhydroxyacetic acids were synthesized.

The (ß-diethylaminoethyl) esters of substituted malonic acids, $RR'C(COOCH_2CH_2NEt_2)_2$ (R or R' = hydrogen, n-propyl, n-hexyl, cyclopentyl, cycloheptyl or phenyl), in the form of their hydrochlorides and methobromides, were prepared. The substituted malonic acids were obtained by the malonic ester synthesis. Some difficulty was experienced in the introduction of the second substituent into the diethyl monosubstituted malonate. Since the free disubstituted malonic acids readily underwent partial decarboxylation, the diethyl disubstituted malonates were hydrolyzed to the dipotassium salts of the corresponding acids; these salts reacted with ß-diethylaminoethyl chloride to form the desired esters which were then converted into their hydrochlorides and methobromides.

The incidental preparation of 5-cycloheptylbarbituric acid and the unsuccessful attempts which were made to synthesize a number of compounds, or to obtain them in crystalline form, are mentioned in the appendix.

The basic esters described in the dissertation are to be tested for antispasmodic activity in another laboratory.

APPENDIX

It was found that diethyl cycloheptylmalonate condensed with urea in the presence of sodium ethylate to yield 5-cycloheptylbarbituric acid. However, only uncrystallizable oils were obtained when attempts were made to prepare barbituric acids from diethyl n-hexylcyclopentylmalonate and from diethyl n-hexylcycloheptylmalonate.

The catalytic hydrogenation of two ß-hydroxypropionic acids, namely α-phenyl-ß-methyl-ß-n-amyl-ß-hydroxypropionic acid (α-phenyl-ß-methyl-ß-hydroxyoctanoic acid) and α-phenyl-ß-methyl-ß-n-hexyl-ß-hydroxypropionic acid (α-phenyl-ß-methyl-ß-hydroxynonanoic acid), resulted in the formation of oils which resisted attempts to crystallize them.

The Horenstein-Pählicke esterification procedure, which has already been described and employed successfully in the preparation of the basic esters discussed in this dissertation, was also used in the attempted syntheses of the following basic esters:

ß-Diethylaminoethyl α-phenyl-ß-methyl-ß-n-amyl-ß-hydroxypropionate hydrochloride

ß-Diethylaminoethyl α-phenyl-α-(1-hydroxy-4-methylcycloheptyl)acetate hydrochloride

ß-Diethylaminoethyl n-hexylcyclopentylacetate hydrochloride

ß-(4-Morpholino)ethyl α-phenyl-α-(1-hydroxycyclopentyl)-acetate hydrochloride and methobromide

ß-(4-Morpholino)ethyl α-phenyl-α-(1-hydroxycycloheptyl)-acetate hydrochloride

Ethyl ß-diethylaminoethyl cyclopentylmalonate hydrochloride

Ethyl ß-diethylaminoethyl cyclopentylcycloheptylmalonate hydrochloride

The products obtained were either uncrystallizable oils or gels.

Only the original starting materials were obtained when attempts were made to synthesize diethyl cyclohexylphenylmalonate from diethyl phenylmalonate, and diethyl cyclohexylcycloheptylmalonate from diethyl cycloheptylmalonate.

The attempt to hydrolyze diethyl cyclopentylphenylmalonate with the use of alcoholic potassium hydroxide resulted in the recovery of the original ester.

5-Cycloheptylbarbituric Acid.--Diethyl cycloheptylmalonate (25.6 g., 0.1 mole) was added to a solution of sodium ethoxide prepared from 2.3 g. (0.1 mole) of sodium and 50 ml. of absolute ethanol. After the addition of 6.0 g. (0.1 mole) of urea, dissolved in 50 ml. of hot absolute ethanol, the mixture was stirred and refluxed for 15 hours. A heavy precipitate had formed after the mixture had been heated for 1.5 hours. Water (100 ml.) was added, the mixture was warmed to about 50° in order to dissolve the precipitate, and 9 ml. of hydrochloric acid was then added. The mixture was cooled, the precipitate was filtered, washed with cold water and dried at 110°; yield 10.0 g. (45%); m.p. 263-265°. After three recrystallizations from absolute ethanol, the yield was 8.0 g.; m.p. 267-269°.

Anal. Calcd. for $C_{11}H_{16}O_3N_2$: C, 58.91; H, 7.19; N, 12.49. Found: C, 59.21; H, 7.15; N, 12.50.