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2- AND 4-PYRIDYL GROUPS

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SIMPLE AMINES WHICH CONTAIN CYCLOHEPTYL,
4-METHYLCYCLOHEPTYL, CYCLOOCTYL,
2- AND 4-PYRIDYL GROUPS

by
Juan Azuara S.^{allos}

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of the requirements for the degree of
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1954

Committee in charge:

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Abstract

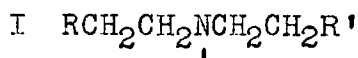
SIMPLE AMINES WHICH CONTAIN CYCLOHEPTYL, 4-METHYLCYCLOHEPTYL, CYCLOOCTYL, 2- AND 4-PYRIDYL GROUPS

by Juan Azuara S.

During this investigation, a number of analogs of the antispasmodic Cyverine, which is methyldi(β-cyclohexylethyl)-amine, were prepared in order that they might be tested for pharmacological activity.

These analogs represent amines in which one or both of the cyclohexyl groups in Cyverine were replaced by a seven- or eight-membered ring (cycloheptyl, 4-methylcycloheptyl or cyclooctyl) or by a heterocyclic radical (2- or 4-pyridyl). In some of the analogs, the NCH_3 group of Cyverine was represented by a five-, six-, seven-, eight- or nine-membered nitrogenous ring, that is by a pyrrolidino, piperidino, 1-heptamethylenimino or 1-octamethylenimino group. In other analogs the methyl group, attached to the nitrogen in Cyverine, was replaced by cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl radicals.

All of the tertiary amines prepared can be represented by the three general formulas, I, II, III, shown below.



$\text{R} = \text{cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- or 4-pyridyl; R}' = \text{phenyl, cyclohexyl, 4-methylcyclohexyl, cycloheptyl, 4-methylcycloheptyl, 2- or 4-pyridyl.}$

II $\text{RCH}_2\text{CH}_2\text{N}(\text{CH}_2)_n$ R = cycloheptyl, 4-methylcycloheptyl, cyclooctyl or 2-pyridyl; n = 4, 5, 6, 7, 8.

The synthesis of these compounds was accomplished by two different methods:

- A. Direct alkylation of a secondary amine with a β -cycloalkylethyl bromide.
- B. Interaction of a secondary amine with 2- or 4-vinylpyridine.

These methods were employed for the preparation of 17 tertiary amines of Type I and 16 of Type II.

III $\text{C}_6\text{H}_{11}\text{CH}_2\text{CH}_2\underset{\text{R}}{\text{N}}\text{CH}_2\text{CH}_2\text{C}_6\text{H}_{11}$ R = cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl.

These analogs were prepared by direct alkylation of the primary cycloalkylamines with β -cyclohexylethyl bromide. We prepared four tertiary amines of this type.

All the tertiary amines were submitted for pharmacological studies as their hydrochlorides and methobromides.

In addition to the tertiary amines mentioned above, a series of 13 secondary amines which contained cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- or 4-pyridyl radicals were synthesized and submitted as their hydrochlorides for pharmacological evaluation.

A total of 50 secondary and tertiary amines were synthesized; as far as we are aware, 47 of these compounds have not been reported in the literature.

For the preparation of these amines, a large number of intermediates were required; nine of which represent new compounds.

A mi esposa e hijos

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Juan Azuara S.^{alas}

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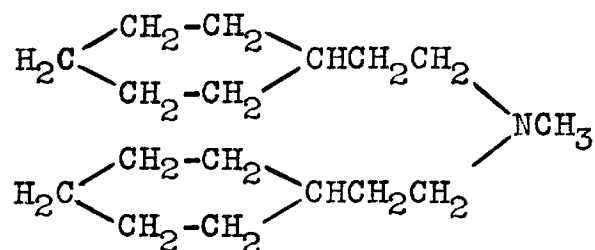
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GENERAL INTRODUCTION

The objective of this investigation was the preparation of a large number and variety of amines which possess structures analogous to that of methyl di-(3-cyclohexylethyl)amine. This substance, a musculotropic antispasmodic, is known as Cyverine.



Cyverine

Cyverine is characterized by the presence of cyclohexyl radicals in the molecule. The distinguishing structural features of the 50 amines described in this dissertation are the presence of a cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- or 4-pyridyl group. The more exact nature of these amines is indicated by the general formulas shown below:

- | | | |
|-----|--|---|
| I | $\text{RCH}_2\text{CH}_2\text{NHA}$ | $\text{R} = \text{Cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- and 4-pyridyl}$
$\text{A} = \text{Hydrogen, methyl, isopropyl, allyl, cyclopentyl}$ |
| II | $ \begin{array}{c} \text{RCH}_2\text{CH}_2 \diagup \\ \text{R}'\text{CH}_2\text{CH}_2 \diagdown \text{NCH}_3 \end{array} $ | $\text{R} = \text{Cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- and 4-pyridyl}$
$\text{R}' = \text{Phenyl, cyclohexyl, 4-methylcyclohexyl, cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- and 4-pyridyl}$ |
| III | $\text{RCH}_2\text{CH}_2\text{N} < (\text{CH}_2)_n$ | $\text{R} = \text{Cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- and 4-pyridyl}$
$n = 4, 5, 6, 7, 8$ |
| IV | $ \begin{array}{c} \text{Cyclohexyl-CH}_2\text{CH}_2 \diagup \\ \text{Cyclohexyl-CH}_2\text{CH}_2 \diagdown \text{NR} \end{array} $ | $\text{R} = \text{Cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl}$ |

Cyverine was synthesized (1) because it had been found that the di(β-phenylethyl)amine exhibits antispasmodic activity (2). The events which led to the discovery of the antispasmodic properties of the latter substance are related below.

Papaverine, 1-(3',4'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline, is the most important member of the benzylisoquinoline group of opium alkaloids. It is present in opium to the extent of about 0.8%, and it was isolated from this source by Merck (3) in 1848. The structure of papaverine was established by Goldschmiedt and associates during the years 1883-1889, and the alkaloid was synthesized by Pictet and Gams (4) in 1909. This synthesis, which is described in many textbooks, seems to be far from an ideal one, especially as far as the last step is concerned (see A. Dobrowsky, *Montash.*, 82, 122 (1951)).

Prior to 1914, papaverine, which was always obtained during the isolation of morphine from opium, was not generally recognized as a substance of medicinal value. In that year, Pal (5), in Vienna, was the first to use the alkaloid clinically for gastro-intestinal spasm and biliary colic. He also suggested its value in angina pectoris. The effect on smooth muscle was confirmed by Macht (6) in 1917-1918.

-
- (1) F. F. Blicke and E. Monroe, *J. Am. Chem. Soc.*, 61, 91 (1939).
(2) W. Buth, F. Külz and K. W. Rosenmund, *Ber.*, 72, 19 (1939).
F. Külz and K. W. Rosenmund, *ibid.*, 72, 2161 (1939).
(3) George Merck, *Ann.*, 66, 125 (1848).
(4) A. Pictet and A. Gams, *Ber.*, 42, 2943 (1909).
(5) J. Pal, *Deut. med. Wochschr.*, 39, 395 (1913); *ibid.*, 40, 164 (1914); *Wien. med. Wochschr.*, 63, 1050 (1913).
(6) D. I. Macht, *J. Pharmacol. Exp. Therap.*, 9, 473 (1917); *ibid.*, 11, 389, 419 (1918). *J. Am. Med. Assoc.*, 64, 1489 (1915).

Considerable interest in papaverine as an antispasmodic soon developed in Germany, and the demand for this substance increased greatly but the amount available was decreased through the international agreement to restrict the manufacture of morphine. In view of this situation, attempts were made to find a feasible, synthetic commercial process which could be used to augment the supply of papaverine (7). These efforts failed and attention was then directed to certain synthetic, papaverine-like compounds which could be manufactured by fairly satisfactory methods (8). Among these substances was 1-(3',4'-methylenedioxybenzyl)-3-methyl-6,7-methylenedioxyisoquinoline which was given the name Eupaverine (9).

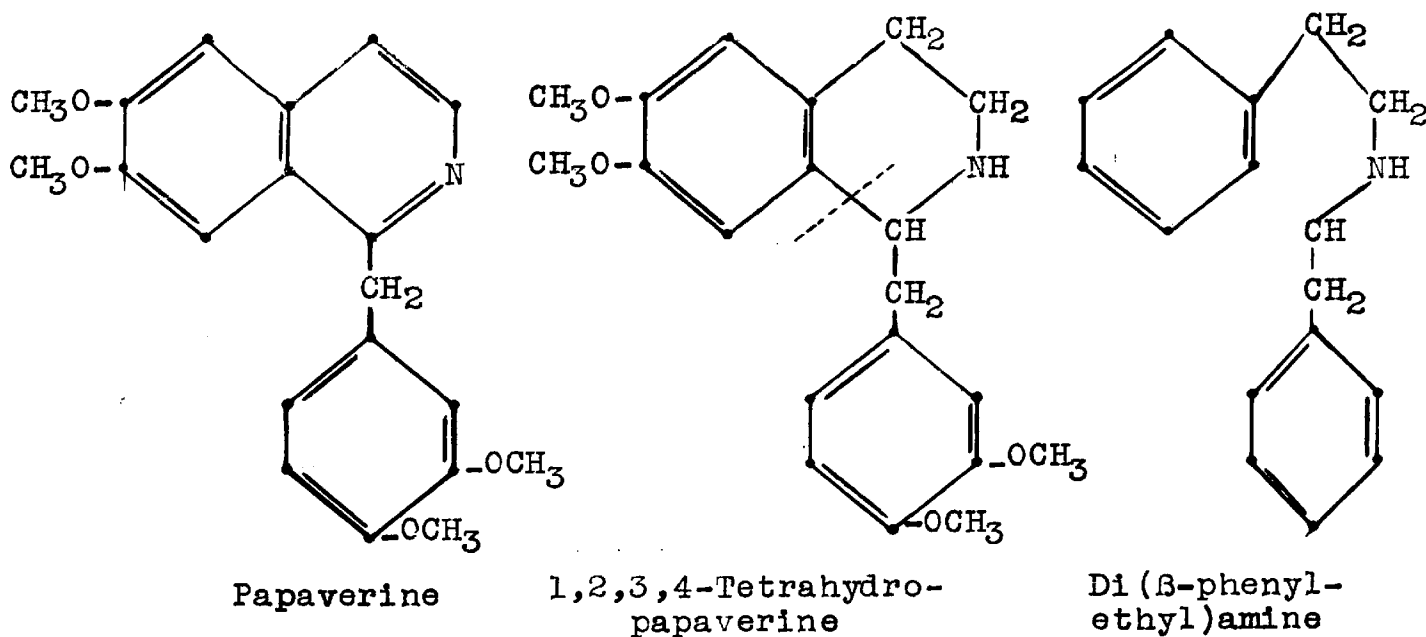
In 1951, Dobrowsky (10) described the synthesis and pharmacology of 46 isoquinoline derivatives which are closely related to papaverine in structure; a number of them were tested clinically. No parallelism was found between activity on the isolated rabbit intestine and clinical usefulness. Many compounds, when tested more thoroughly, were found to exhibit side effects which made them valueless for therapeutic application. Dobrowsky stated that even today papaverine occupies the first place among antispasmodics which are active on all smooth muscles.

-
- (7) For a review of papaverine syntheses, see D. Elad and D. Ginsburg, Bulletin on Narcotics, Vol. IV, No. 3 (1952) (United Nations).
 - (8) A good discussion of these compounds and their antispasmodic activity is to be found in "Merck's Jahresbericht", 1930, p. 12.
 - (9) British patent 348,956; Chem. Zentr., 1931, II, 1196. K. Samaan, Quart. J. Pharm. Pharmacol., 9, 23 (1936). J. Pal, Deut. med. Wochschr., 56, 1702 (1930). O. Wolfes and H. Kreitmair, *ibid.*, 56, 1703 (1930).
 - (10) A. Dobrowsky, Monatsh., 82, 122, 140 (1951).

About 1929 Buth, Külz and Rosenmund (2), in Germany, began their search for a synthetic antispasmodic but their first publication did not appear until 1939. These investigators felt that certain disadvantageous properties of papaverine (11) would be found in all isoquinoline derivatives, and their objective was the discovery of a new type of antispasmodic. They were impressed by the fact that if a ring-bond of a completely hydrogenated ring in a pharmacologically active compound is cleaved, the product obtained often is also highly active. As examples they mentioned nicotine and metan nicotine (1-(β -pyridyl)-4-methylamino-1-butene), and cocaine and its many synthetic substituents. They stated that the activity of 1,2,3,4-tetrahydropapaverine is qualitatively like, but quantitatively very much weaker than that of papaverine (12). A rupture of the ring-bond which attaches the nitrogen atom to the benzene ring in 1,2,3,4-tetrahydropapaverine, and the addition of two hydrogen atoms, would yield di(β -3,4-dimethoxyphenylethyl)amine. This compound was unknown, and it would have been troublesome to synthesize, so Buth et al. prepared di(β -phenylethyl)amine, a substance which could be obtained very easily. When this substance was tested

-
- (11) For example, the weakly basic properties of papaverine make it impossible to prepare water-soluble salts which are not hydrolyzed extensively by water; aqueous solutions of such salts are acidic, and their injection is painful.
- (12) According to A. Dobrowsky (Monatsh., 82, 122 (1951)), derivatives of 3,4-dihydro- and tetrahydroisoquinoline often produce an effect opposite to that of papaverine - they promote cramps and are strychnine-like in activity. However, if a tetrahydroisoquinoline is N-alkylated, a papaverine-like action, to some extent at least, can be obtained.

against barium chloride-induced spasm, it did show activity although it was less active than papaverine.



After a large number of homologs and analogs of di(β-phenylethyl)amine had been synthesized and tested, ethyldi-(γ-phenylpropyl)amine was placed on the market in Germany under the name of Sestron. About eight years ago this product, renamed Profenil (13) appeared on the American market.

Since di(β-phenylethyl)amine possessed antispasmodic activity, it was of interest to determine whether activity would also be found in di(β-cyclohexylethyl)amine. When it was discovered that this amine was active, the study of its homologs and analogs was begun in this laboratory and, prior to this investigation, 459 amines had been synthesized and tested for antispasmodic activity (1,14-19). One of these

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- (13) C. D. Smith Pharmacal Company.
 - (14) E. Monroe, Dissertation, University of Michigan, 1936.
 - (15) F. B. Zienty, Dissertation, University of Michigan, 1938.
 - (16) F. F. Blicke and F. B. Zienty, J. Am. Chem. Soc., 61, 93, 771, 774 (1939).
 - (17) J. B. Data, Dissertation, University of Michigan, 1941.
 - (18) F. Leonard, Dissertation, University of Michigan, 1946.
 - (19) F. F. Blicke and F. Leonard, J. Am. Chem. Soc., 74, 5105 (1952).

amines, methyldi(β-cyclohexylethyl)amine, came into use under the name of Cyverine (20) but not long after its introduction it was voluntarily withdrawn from the market after development of alopecia (21,22) in a patient which, allegedly, was due to its use.

It seems unfortunate, now, that Cyverine was withdrawn from use. Although it was never claimed to be a highly active antispasmodic (23), its therapeutic use may not have been without benefit (24).

The investigation described in this dissertation has been made possible by discoveries made during the past four years. Lactams can be obtained from cyclic ketones by the use of the Beckmann rearrangement or the Schmidt reaction, and it has been shown by Ruzicka et al. (25) that lactams (2-ketopolymethylenimines) can be reduced in excellent yields by lithium aluminum hydride to polymethylenimines. The commercial availability of epsilon-caprolactam and the discovery of practical procedures for the preparation of relatively large

(20) Frederick Stearns and Company.

(21) O. L. Levin and H. T. Behrman, J. Am. Med. Assoc., 118, 41 (1942).

(22) This effect, the loss of hair, was never observed during the tests on laboratory animals.

(23) Cyverine is classed as a musculotropic antispasmodic. Tested against barium chloride-induced spasm in the isolated rabbit intestinal strip, the maximum effective dilution for papaverine was found to be 1:200,000, and for Cyverine 1:400,000 (Ref. 17).

(24) In the case of some drugs, their true value can be determined only by long and extensive use by the practising physician. In testing such drugs such as antispasmodics and analgesics, it is difficult to eliminate psychic factors during their clinical evaluation.

(25) L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, Helv. Chim. Acta, 32, 544 (1949).

amounts of cycloheptanone (26) and cyclooctanone (27) has made it possible to use the seven- and eight-membered cyclic ketones as well as seven-, eight- and nine-membered basic ring compounds, hexa-, hepta- and octamethylenimines, for extensive research.

In view of these developments, it seemed desirable to prepare for pharmacological tests analogs of Cyverine which contained cycloheptyl and cyclooctyl groups in place of cyclohexyl, and also hexa-, hepta- and octamethylenimino radicals as the basic portions of the molecule.

Although antispasmodics relax the normal intestine, as shown by tests on isolated intestinal strips, it is more desirable in screening procedures to evaluate compounds for their antispasmodic effect with an intestinal strip in which a spastic state has been created by the use of acetylcholine or barium chloride. Acetylcholine is supposed to affect the muscle indirectly through the nerve endings, while barium chloride is supposed to produce its effect directly on the muscle; consequently, a compound which relieves a spasm created by acetylcholine is said to possess neurotropic activity, and one which relieves a barium chloride-induced spasm is said to have musculotropic activity. Atropine is predominantly neurotropic and papaverine musculotropic in activity. Furthermore, in general, the synthetic basic esters are especially effective against spasm produced by acetylcholine; the synthetic amines show activity particularly against spasm created

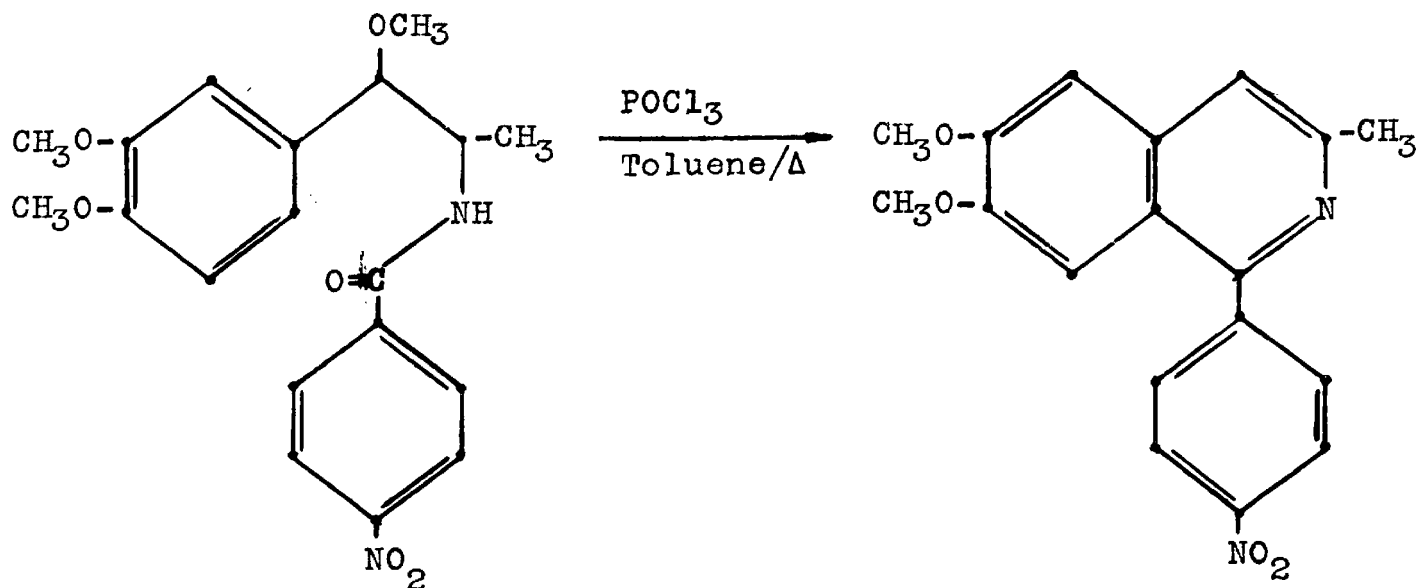
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- (26) F. F. Blicke, N. J. Doorenbos and R. H. Cox, J. Am. Chem. Soc., 74, 2924 (1952).
(27) F. F. Blicke, J. Azuara, N. J. Doorenbos and E. B. Hotelling, *ibid.*, 75, 5418 (1953).

by barium chloride.

In this dissertation, only antispasmodics which may be considered to belong to the amine type will be discussed.

A very large number of isoquinoline derivatives have been prepared during the last few years in attempts to find papaverine substitutes (10,28-40). It is of especial interest to note that Morimoto (28) in the synthesis of a 1-phenylisoquinoline reported a 90% yield in a one-step reaction which involves removal of a methoxy group, cyclization and dehydrogenation (see Ref. 4 and 7) as indicated below.

-
- (28) Y. Morimoto, J. Pharm. Soc. Japan, 62, 446-52 (1942). C. A., 46, 115 (1952).
 - (29) T. Hosono, *ibid.*, 65, No. 7/8A, 11 (1945). C. A., 46, 115 (1952).
 - (30) M. Fujisawa, *ibid.*, 65, No. 9/10A, 1 (1945). C. A., 46, 116 (1952).
 - (31) T. Kametani, *ibid.*, 71, 322-4 (1951). C. A., 46, 511 (1952).
 - (32) T. Kametani and Y. Masuda, *ibid.*, 72, 85-87 (1952). C. A., 46, 11208 (1952).
 - (33) T. Kametani and S. Kano, *ibid.*, 72, 1081-84 (1952). C. A., 47, 10536 (1953).
 - (34) T. Kametani and J. Serizawa, *ibid.*, 1084-7. C. A., 47, 10536 (1953).
 - (35) T. Kametani, K. Ninomiya, H. Iida, and J. Serizawa, *ibid.*, 1087-90. C. A., 47, 10537 (1953).
 - (36) T. Kametani, *ibid.*, 1090-3. C. A., 47, 10538 (1953).
 - (37) T. Kametani, *ibid.*, 1357-9. C. A., 47, 10538 (1953).
 - (38) T. Kametani, *ibid.*, 1539-41. C. A., 47, 10538 (1953).
 - (39) G. Tsatsas and J. Fournel, Ann. pharm. franç., 9, 585-92 (1951).
 - (40) V. Iswariah and V. S. Venkata Sabbu, Current Sci. (India), 21, 131-3 (1952). C. A., 46, 10446 (1952).



The following abstracts show that a number of attempts have been made during the last few years to find antispasmodics of the amine type.

In a study of a series of 3-methylisoquinolines (41) it was found that the compounds investigated were less toxic than isoquinolines which were unsubstituted (42,43) in the 3 position. None of the products was appreciably better than 1-phenyl-3-methyl-6,7-diethoxyisoquinoline (41).

Several 1-(2',3'-dimethoxybenzyl)dialkoxisoquinolines were found to be inferior to Perparin (44) (1-(3',4'-diethoxybenzyl)-6,7-diethoxyisoquinoline).

2-Methyl-3-dialkylaminomethyl-4-hydroxyquinolines were shown to have antispasmodic activity (45).

-
- (41) G. Fodor, J. Kiss and M. Szekerke, J. Chem. Soc., 1681 (1949). See also V. Bruckner, G. Fodor, J. Kiss and J. Kovacs, *ibid.*, 885 (1948).
 (42) H. Kreitmair, Arch. expt. Path. Pharmacol., 164, 509 (1932).
 (43) S. Sugawara and N. Sugimoto, J. Pharm. Soc. Japan, 61, 62 (1941).
 (44) J. Fournel and G. Tsatsas, Ann. pharm. frag., 9, 439 (1951).
 (45) T. N. Ghosh, A. K. Kundu and A. R. Chaundhuri, J. Indian Chem. Soc., 29, 368 (1952).

Several bis(dialkoxyphenylethyl)amines and some of their N-methyl derivatives were investigated (46); although the N-methyl derivatives were more active, none of the compounds exceeded papaverine in potency.

Certain substituted β -phenylethylamines were prepared by Huebner and Troxell (47) but their pharmacological study did not reveal anything of unusual interest.

A series of amines and quaternary salts related to β -(o-methoxyphenyl)isopropylmethylamine (Orthoxine) was found to have a high order of bronchodilator and/or local anesthetic activity (48,49).

1,4-Disubstituted piperazines have been found to be neurotropic antispasmodics (50).

1-Alkyl-3-benzoyl-4-phenyl-1,2,5,6-tetrahydropyridines were described as useful antispasmodics (51).

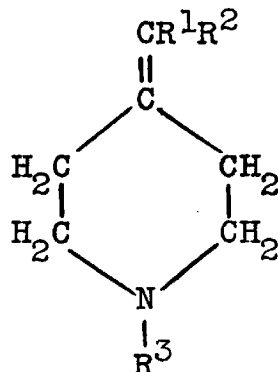
Certain substituted piperidines have been shown to be active as analeptics and spasmolytics (52). An example of the active compounds is 1-methyl-2,6-bis(β -p-methoxyphenyl)-piperidine.

N-substituted 4-aryl-4-aminomethylpiperidines are said to be of value as analgesics, antispasmodics and sedatives (53).

-
- (46) A. Doronow and G. Petsch, Arch. Pharm., 284, 153 (1951).
(47) C. F. Huebner and H. A. Troxell, J. Org. Chem., 18, 736 (1953).
(48) R. V. Heinzelman, J. Am. Chem. Soc., 75, 921 (1953).
(49) R. V. Heinzelman and B. D. Aspergren, Ibid., 75, 925 (1953).
(50) M. E. Hultquist and K. L. Howard (to American Cyanamid Co.), U. S. Patent 2,543,972 (1951); C. A., 45, 7157 (1951). See also U. S. Patent 2,562,036; C. A., 46, 3575 (1952).
(51) J. T. Plati and W. Wenner (to Hoffmann-LaRoche), U. S. Patent 2,537,854 (1951); C. A., 45, 5192 (1951).
(52) F. Hoffmann-LaRoche and Company, Swiss Patent 242,946 (1946); C. A., 44, 172 (1950).
(53) C. E. Kwartler and P. Lucas (to Sterling Drug Company), U. S. Patent 2,538,107 (1951).

Spasmolytic activity has been claimed for 1-alkyl-3-benzhydrylpiperidines (54).

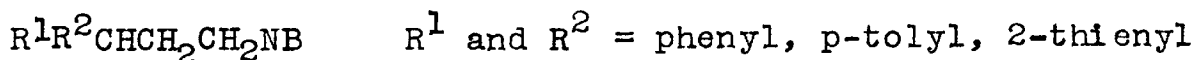
A new type of parasympathetic blocking agent is represented by the general formula shown below; N,N-dimethyl-4-piperidylidene-1,1-diphenylmethane methosulfate was selected



for detailed study (55).

Certain substituted allyl- and propylamines have been stated to be valuable antispasmodics and analgesics (56,57).

The propylamines possess the following general formula:



NB = dialkylamino, pyrrolidino, piperidino, morpholino

A series of 3-tertiary-amino-1,1-(2-thienyl)-1-butenes was found which contained potent analgesics (58); in the rat the compounds were as active as morphine. In addition, the products showed considerable antihistaminic, spasmolytic and local anesthetic activity.

-
- (54) L. Berger and J. Lee (to Hoffmann-LaRoche), German Patent 803,235 (1951); C. A., 45, 8561 (1951).
 (55) N. Sperber, F. J. Villani, M. Sherlock and D. Papa, J. Am. Chem. Soc., 73, 5010 (1951).
 (56) D. W. Adamson (to Wellcome Foundation), British Patent 624,117 (1949); C. A., 44, 3063 (1950). See also British Patent 657,301 (1951); C. A., 46, 9611 (1952).
 (57) D. W. Adamson, J. Chem. Soc., 5144 (1949).
 (58) D. W. Adamson and A. F. Green, Nature, 165, 122 (1950).

The most active musculotropic antispasmodic in a group of substituted 3-phenylpropylamines (59,60,61) was found to be 1-(3-isobutyl-3-phenylpropyl)piperidine (60).

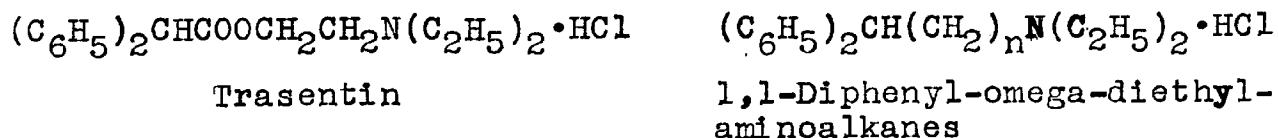
1,1-Diaryl-4-buteneylamines were stated to have spasmolytic, antihistaminic, analgesic and local anesthetic properties (62).

It has been reported (63) that 1,1-diphenyl-3-dimethylamino-1-butene strongly antagonizes the action of both acetylcholine and barium chloride on the isolated intestine; the compound also has some antihistaminic activity.

The spasmogenic action of acetylcholine, barium chloride and eserine on the intestine and uterus is antagonized by 6-methyl-heptyl-isoamylamine (64).

In an interesting study (65), the effect of the length of the carbon chain in 1,1-diphenyl-omega-diethylaminoalkanes on spasmolytic activity was determined. The activity of the compounds was compared with that of Trasentin.

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- (59) A. W. Ruddy and J. S. Buckley, J. Am. Chem. Soc., 72, 718 (1950).
(60) A. W. Ruddy, *ibid.*, 73, 4096 (1951).
(61) A. W. Ruddy (to Sterling Drug Company), U. S. Patent 2,592,191 (1952).
(62) J. R. Geigy, Swiss Patent 265,665 (1950); C. A., 44, 9481 (1950).
(63) P. P. Petersen, Acta Pharmacol. et Toxicol., 7, 51 (1951).
(64) E. Savini, Arch. intern. Pharmacodyn., 82, 127 (1950); C. A., 44, 7983 (1950).
(65) G. Benoit, J. Jacob and F. Eliopoulo, Compt. rend., 232, 1262 (1951).



	Acetylcholine	Barium Chloride	Histamine
Trasentin	0.6	1.5	3-6
n (in alkanes)			
1	1.5	3-6	2
2	0.75	1.5	0.1
3	0.15-0.3	1.5	0.4-1
4	0.1	0.15	0.3
5	1	1-1.5	1
6	0.10-0.2	0.6	1-2

The spasmolytic activity of a number of amines which contained a (2-thienyl)alkyl group has been studied (19).

Spasmolytic activity has been found in certain N-(bi-phenylalkyl)alkanediamines (66).

A series of 6-dialkylaminomethylphenanthridines has been studied (67) but all of these compounds proved to be poor antispasmodics.

Certain 2-aminoalkyl-9-fluorenones were stated to be useful as antispasmodics and analgesics (68).

Antispasmodic and antihistaminic activity have been claimed for certain 9-aminoalkyl-9,10-dihydroanthracenes (69)

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- (66) S. Goldschmidt (to N. V. Organon), Dutch Patent 65,819 (1950); C. A., 45, 2024 (1951).
 (67) J. Finlcestein and S. M. Linder, J. Am. Chem. Soc., 73, 302 (1951).
 (68) S. M. Olin and O. E. Fancher (to Miles Laboratories), U. S. Patent 2,556,102 (1951); C. A., 45, 10261 (1951).
 (69) J. R. Geigy, British Patent 618,034 (1949); C. A., 44, 3530 (1950).

and 1-dialkylaminoalkyl-1,2,3,4-tetrahydrofluoranthenes (70).

Compounds which possessed both musculotropic and neurotropic activity were found among the 3-aminoalkyl-3-aryl-2-benzofuranones (71); some of the compounds were also local anesthetics. The most promising compound, 3-(β -diethylaminoethyl)-3-phenyl-2-benzofuranone (Amethone), showed about one-tenth the activity of atropine against acetylcholine-spasm and twice the activity of papaverine against barium chloride-spasm.

Certain 2-alkyl-9-substituted tetrahydropyridinedenes (72) have been stated to be useful antispasmodics.

In addition to its effect on the smooth muscles of the gastrointestinal tract, papaverine relaxes the muscles of the coronary arteries. This latter type of activity is not found in all antispasmodics, and a product which relaxes the intestinal muscles may or may not produce the same effect on the coronary muscles.

Antispasmodics which relax the coronary muscles and bring about dilation of the coronary arteries are classified as coronary dilators. Since papaverine and a number of synthetic antispasmodics fall into this group and because of the therapeutic importance of these substances, it seemed pertinent to discuss this class of compounds in this dissertation.

(70) Ciba, British Patent, 630,704 (1949); C. A., 44, 4040 (1950).

(71) A. W. Weston and W. B. Brownell, J. Am. Chem. Soc., 74, 653 (1952).

(72) J. T. Plati and W. Wenner (to Hoffmann-LaRoche), U. S. Patent 2,546,652 (1951); C. A., 45, 7154 (1951).

Coronary Dilators

Nitrites and Nitrates: sodium nitrite, amyl nitrite, octyl nitrite, glyceryl trinitrate, erythrityl tetranitrate, mannitol hexanitrate, meso-inositol hexanitrate

Papaverine and its synthetic analogs

Khellin

Aminophylline

Miscellaneous substances

In the following discussion, no attempt has been made to cover all of the very extensive literature which deals with the drugs mentioned above. The references are limited, for the most part, to a few reports which have been made during the last few years.

For many years it had been assumed that the vasodilating action of organic nitrates was due to their hydrolysis in the body to inorganic nitrates; it was thought that the nitrate was then reduced to nitrite, and it was the nitrite ion which was supposed to be responsible for the depressor response. The nitrate ion does not produce any distinctive pharmacological effect (73). According to Krantz, Carr, Forman and Cone (73), the molecular structure of an organic nitrate itself is responsible for its depressor effect, and this effect is not produced through hydrolysis and the formation of a nitrite through reduction.

Monari and Baroni (74), in a plethysmographic study of

(73) "Pharmacologic Principles of Medical Practice", J. C. Krantz, Jr. and C. J. Carr, The Williams and Willkins Company, Baltimore, Md., 1949, pp. 741, 744.

(74) G. C. Monari and W. Baroni, Minerva med., 360, 1952, I; C. A., 46, 6735 (1952).

the vasodilating action of esters of nitric acid, reported that glyceryl trinitrate was the most toxic and had the least prolonged action, erytrityl tetranitrate was intermediate, and mannitol hexanitrate and meso-inositol hexanitrate were the least toxic and had the most prolonged action. Meso-inositol hexanitrate caused appreciable lowering of the blood pressure in 3-4 weeks (75) and gave more prolonged and more regular control than other commonly used polyalcohol nitrates.

Among the new organic nitrates which have been studied recently with respect to their action on blood pressure and smooth muscles, are bromopentaerythritol nitrates (76), ether nitrates of ethylene glycol such as $\text{ROCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{ONO}_2$ and $\text{O}_2\text{NOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{ONO}_2$ (R = lower alkyl) (77) and the bi-phosphate salt of triethanolamine trinitrate (78), recently introduced in the market under the name of Metamine (Leeming) (79).

Although Pal, in 1914, suggested that papaverine might be of value in angina pectoris, its subsequent use for this ailment was disappointing. During the last ten years interest

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- (75) W. Baroni and G. C. Monari, *Minerva med.*, 538, 1952, I; *C. A.*, 46, 6735 (1952).
(76) W. Kalow and J. Schunk, *Arch. exptl. Path. Pharmacol.*, 211, 388 (1950); *C. A.*, 47, 10714 (1953).
(77) E. Frommel, D. Vincent, P. Gold, C. Radouco, G. Burgermeister-Guex, D. Melkonian, F. Vallette, M. Ducommun and L. Strassberger, *Helv. Physiol. et Pharmacol. Acta*, 10, 438, 448 (1952); *C. A.*, 47, 5545 (1953).
(78) K. I. Melville and F. C. Lu, *Canadian Med. Assoc. J.*, 65, 11 (1951); *C. A.*, 46, 2687 (1952).
(79) *The Journal of the Modern Drug Encyclopedia*, May, 1953, p. 426.

in the use of papaverine in heart conditions has been revived.

The cause of angina pectoris is not entirely understood but it appears that the characteristic, terrorizing pain is the result of cardiac hypoxia, and if the coronary arteries are acutely dilated by a drug, relief is usually experienced (80).

It has been shown in laboratory animals that papaverine does dilate the coronary vessels, and it has been stated (81) that this drug heads the list in efficiency. Furthermore, it was found that papaverine will cause the cessation of fibrillation (extremely irregular heart- and pulse beats) of the heart similar to quinidine (82).

Papaverine is not free from side effects. Daily doses of 400-800 mg. have produced dizziness, constipation, general weakness, anorexia, headache and epigastric pain. Two fatalities have been reported after an intravenous injection of 30 mg. and 65 mg., respectively, of papaverine hydrochloride (83).

In 1940 it was shown (84) that papaverine, in laboratory

(80) Ref. 73, p. 727.

(81) Ref. 73, p. 733.

(82) "Quinidine in Disorders of the Heart", Harry Gold, Paul B. Hoeber, Medical Book Department of Harper and Brothers, 1950.

(83) "Side Effects of Drugs", L. Meyler, translated by Ph. Vuijsje and W. H. Corbet, Elsevier Publishing Co., New York, N. Y., 1952, p. 17.

(84) H. E. Essex, R. Wegria, J. F. Herrick and F. C. Mann, *Amm. Heart J.*, 19, 554 (1940).

C. G. McEachern, F. H. Smith and G. W. Manning, *ibid.*, 21, 25 (1941).

E. Lindner and L. N. Katz, *J. Pharmacol. Exp. Therap.*, 72, 306 (1941).

S. R. Elek and L. N. Katz, *J. Am. Med. Assoc.*, 120, 434 (1942).

animals, is a potent coronary dilator. Studies which began in 1932 showed (85) that Ethaverine (Perparin, 1-(3',4'-diethoxybenzyl)-6,7-diethoxyisoquinoline) is a general visceral and vascular spasmolytic agent. In recent experiments (86) Ethaverine has been shown to be equal to papaverine in peak potency with respect to coronary flow in the isolated rabbit heart; furthermore, the action of Ethaverine was more prolonged. Ethaverine has a special advantage in that it is not classified as a narcotic (87); it is only about one-third as toxic as papaverine and large doses can be given in man without untoward effects.

A very interesting study of Ethaverine in the treatment of angina pectoris was published in 1953 (88). The authors, Voyles et al., stated "In order to avoid the common errors of physician enthusiasm and 'new drug' psychological effect on the patient and because angina pectoris exhibits spontaneous variations, it was decided to perform a 'double-blind' experiment for more accurate evaluation of Ethaverine in this disorder."

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- (85) L. von Berkesy, *Therap. d. gegenw.*, 73, 55 (1932).
G. Pouchet, *Bull. Acad. de méd. Paris*, 110, 724 (1933).
W. Spychala, *Polska gaz. lek*, 13, 677 (1934).
K. Dobrazanski, *ibid.*, 14, 44 (1935).
E. Wolf, U. S. Patent 1,962,224 (1934).
(86) C. V. Winder, R. W. Thomas and O. Kamm, *J. Pharmacol. Exp. Therap.*, 100, 482 (1950).
(87) C. K. Himmelsbach, *Clinical Studies of Drug Addiction: I. The Absence of Addiction Liability in "Perparin"*, supp. 112, U. S. Treasury Department, Public Health Service, 1937.
(88) C. M. Voyles, H. A. Sieber and E. S. Orgain, *J. Am. Med. Assoc.*, 153, 12 (1953).

In other words, each patient received not only Ethaverine but also placebos (lactose) without the physician's knowledge of which was dispensed.

Previously, Greiner and coworkers (89) had used a similar technique in their evaluation of khellin in angina pectoris. In a group of 22 patients tested over a period of 12 weeks, Voyles et al. found that "The majority of the patients reported subjective improvement to an equal degree with both Ethaverine and placebo. Ethaverine was no more effective in reducing the severity or frequency of attacks of angina pectoris".

The vasodilator activity of papaverine had been observed by Macht in 1915 (90). However, the systematic study of a structural-activity relationship of papaverine analogs, to determine the influence of a variation in structure on the coronary dilator activity, was initiated in this country by Shepard and associates (91) in 1950. This work culminated in the introduction of the phosphate of 1-(3'-methoxy-4'-ethoxybenzyl)-3-methyl-6,7-dimethoxyisoquinoline under the name of Paveril Phosphate (Dioxaline Phosphate (92)). The

(89) T. Greiner et al., Am. J. Med., 9, 143 (1950).

(90) See C. M. Gruber and P. I. Robinson, J. Pharmacol. Exp. Therap., 37, 429 (1929).

(91) E. R. Shepard and J. F. Noth, J. Am. Chem. Soc., 72, 4364 (1950).

E. R. Shepard, H. D. Porter, J. F. Noth and C. K. Simmans, J. Org. Chem., 17, 568 (1952).

E. R. Shepard, J. F. Noth, H. D. Porter and C. K. Simmans, J. Am. Chem. Soc., 74, 4611 (1952).

(92) F. G. Henderson, R. E. Shipley and K. K. Chen, J. Am. Pharm. Assoc. Sci. Ed., 40, 207 (1951).

Eli Lilly and Company, British Patent 674,800 (1952); C. A., 47, 5455 (1953).

In the Journal of the American Medical Association (145, 645 (1951)), this product has been called, incorrectly, a 4-methyl derivative of isoquinoline. The same mistake is found in The Merck Index.

recent discovery of the usefulness of this compound seems especially remarkable since so many very similar compounds had been studied many years ago in Germany (93).

It is claimed that Paveril is therapeutically similar to papaverine but that it has a wider margin of safety and greater freedom from side effects. It is used for relaxation of vascular spasm in coronary occlusion, angina pectoris and peripheral or pulmonary embolism. The product has very little effect on the isolated intact intestine.

Papaverine seems to be a better coronary dilator than theophylline (94).

It was found (95,96) that Trasentin and Benadryl, the former used chiefly as an antispasmodic, the latter as an antihistaminic, at certain sites are several times as potent as papaverine as smooth muscle relaxants; however, on coronary smooth muscles, in comparison with papaverine, they produced only a fleeting initial dilation which was followed by a sustained though moderate constriction.

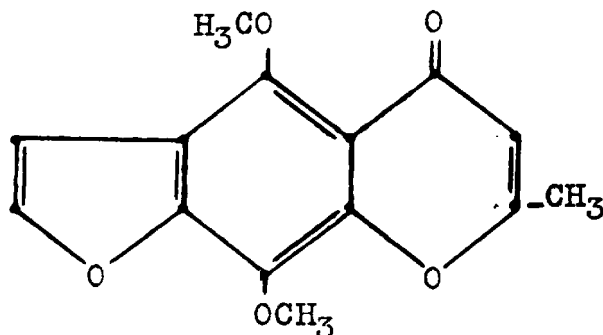
Hanna (97) studied the action of sixty-five papaverine analogs on the isolated rabbit heart for vasodilator action.

In view of statements which have already been made, it is

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- (93) See E. Merck's Jahresbericht, 1930, and Dobrowsky (Ref. 10)
(94) C. V. Winder and M. E. Kaiser, J. Pharmacol. Exp. Therap., 93, 86 (1948). See also J. F. Eckenhoff and J. H. Halkenschiel, *ibid.*, 91, 362 (1947).
(95) C. V. Winder and R. W. Thomas, *ibid.*, 91, 1. (1947).
(96) C. V. Winder, M. E. Kaiser, M. M. Anderson and E. M. Glassco, *ibid.*, 87, 121 (1946).
(97) C. Hanna, Dissertation, Department of Pharmacology, College of Medicine, State University of Iowa, 1953.

not surprising that divergent reports should have been published (98,99) concerning the potency of Paveril.

During recent years, Khellin (visammin) has attracted considerable attention (100). It is the active principle of a plant, *Ammi visnaga*, which grows in the Eastern Mediterranean countries. The natives have used decoctions of the seeds of this plant for centuries as an antispasmodic. It has been stated to be beneficial in angina pectoris and bronchial asthma. Prominent side effects are nausea, constipation, dizziness, sleep disturbances and dermatitis. Khellin, which was synthesized by Clarke and Robertson (101), is 5,8-dimethoxy-2-methylfuro(4',5',6,7)chromone.



Visnagin, a by-product in the manufacture of Khellin, has little pharmacological activity. It has been found (102) that this substance can be converted into Khellin.

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- (98) M. M. Best and W. S. Coe, *Am. J. Med. Sci.*, 222, 35 (1951); *C. A.*, 45, 9737 (1951).
(99) H. I. Russek, K. F. Urbach, A. A. Doerner and B. L. Zohman, *J. Am. Med. Assoc.*, 153, 207 (1953).
(100) For a review in the chemistry and physiological action of Khellin and related compounds, see C. P. Hutterer and E. Dale, *Chem. Revs.*, 48, 543 (1951).
(101) J. R. Clarke and A. Robertson, *J. Chem. Soc.*, 302 (1949).
(102) A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, 72, 3396 (1950).
A. Schönberg and A. Badran, *ibid.*, 73, 2960 (1951).

Active interest in Khellin as a drug began in 1946 when Anrep and associates explored its action in a series of pharmacological and clinical investigations. They found that this substance relaxes smooth muscles, and was reported (103) that the coronary dilator properties of Khellin are at least four times as strong as those of aminophyllin.

The action of Khellin as a coronary dilator has been confirmed by Hauler et al. (104) and by other investigators (105). However, the clinical evidence concerning the value of Khellin is confusing. Experiments by Greiner et al. (89) in which 39 patients were treated showed that Khellin had no greater effect than lactose in the control of pain in angina pectoris.

A careful analysis of the factors which may influence the results of the clinical evaluation of coronary dilators has been made by Silber and Katz (106).

The possibility that the side effects of Khellin may be due to the presence of impurities (107) has been studied (108).

Russek et al. (109) have evaluated coronary dilator drugs by electrocardiographic tests. They found that Khellin, administered orally or intramuscularly, failed to alter favorably

(103) G. V. Anrep, M. R. Kenaway and G. S. Barsoun, *Am. Heart J.*, 37, 531 (1949).

(104) H. F. Hausler, F. Lembeck and H. Sterz, *Arch. intern. pharmacodyn.*, 89, 245 (1952); *C. A.*, 46, 9192 (1952).

(105) See review, Ref. 100.

(106) E. N. Silber and L. N. Katz, *J. Am. Med. Assoc.*, 153, 1075 (1953).

(107) R. H. Roseman, A. P. Fishman, S. R. Kaplan, H. G. Levin and L. N. Katz, *ibid.*, 143, 160 (1950).

(108) M. B. Best, *Am. J. Med. Sci.*, 224, 308 (1952).

(109) H. I. Russek, K. F. Urbach, A. A. Doerner and B. L. Zohman, *J. Am. Med. Assoc.*, 153, 207 (1953).

the electrocardiographic response in all patients tested.

A considerable number of compounds, analogous to Khellin in structure, have been synthesized in the hope that a substance might be found which would not only be more active but which would lack the undesirable side effects (110-115). Unfortunately, none of these efforts was very successful.

It has been shown (116) that levulose relieves the spasm of the coronary musculature caused by barium chloride.

Strong coronary dilator action has been reported (117) for the hydrochlorides of diethylaminoethyl ethers of certain sex hormones; for example, the dihydrochloride of the dibasic ether of estradiol. Unlike the hydrochlorides, some of the methiodides exhibited strong curare-like action.

It has been claimed (118) that certain basic-alkyl esters of α,β,β -triarylpropionic acids are not only coronary dilators but are also antispasmodics, analgesics, antihistaminics and antiseptics.

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- (110) A. Schönberg and A. Sina, J. Am. Chem. Soc., 72, 1611 (1950).
(111) J. Schmutz, H. Lauener, R. Hirt and M. Sanz, Helv. Chim. Acta, 34, 767 (1951); *ibid.*, 35, 1168 (1952).
(112) J. Schmutz, R. Hirt, F. Kunzle, E. Eichenberger and H. Lauener, *ibid.*, 36, 620 (1953).
(113) S. Wawzonek and H. A. Ready, J. Org. Chem., 17, 1419 (1952).
(114) G. Jongebreur, Arch. intern. pharmacodyn., 90, 384 (1952).
(115) H. Abu-Shady and T. O. Soine, J. Am. Pharm. Assoc., Sci. Ed., 42, 351 (1953).
(116) G. Schimert, Arztl. Forsch., 4, 1, 178 (1950); Chem. Zentr., 1950, II, 2462; C. A., 47, 10726 (1953).
(117) G. Cavallini and E. Massaran, Farm. sci. e tec., 6, 291 (1951); C. A., 45, 8651 (1951).
(118) C. P. Krimmel to G. D. Searle and Company, U. S. Patent 2,576,230 (1951); C. A., 46, 6155 (1952).

A new group of coronary dilators is represented by derivatives of stilbene (119). An example of this group is 4,4'-bis(diethylaminoethoxy)- α,α' -diethylstilbene.

(119) E. Milla and E. Grumelli, Farm. sci. e tec., 6, 150 (1951); C. A., 45, 7249 (1951).

DISCUSSION OF THIS INVESTIGATION

The object of this investigation was the preparation for pharmacological studies of a number of analogs of Cyverine [methyldi(β-cyclohexylethyl)amine].

The compounds which were prepared represent amines which are quite simple in structure. However, the special features of these amines are the presence of seven- and eight-membered rings (cycloheptyl, 4-methylcycloheptyl, cyclooctyl) and of heterocyclic radicals (2- and 4-pyridyl) in place of the six-membered rings found in Cyverine, and the introduction of five-, six-, seven-, eight- and nine-membered nitrogenous rings (pyrrolidino, piperidino, 1-hexamethylenimino, 1-heptamethylenimino, 1-octamethylenimino) in place of the simple basic group, methylamino.

The amines prepared during this investigation can be classified in four general groups (I, II, III, IV) represented by the general formulas shown below:

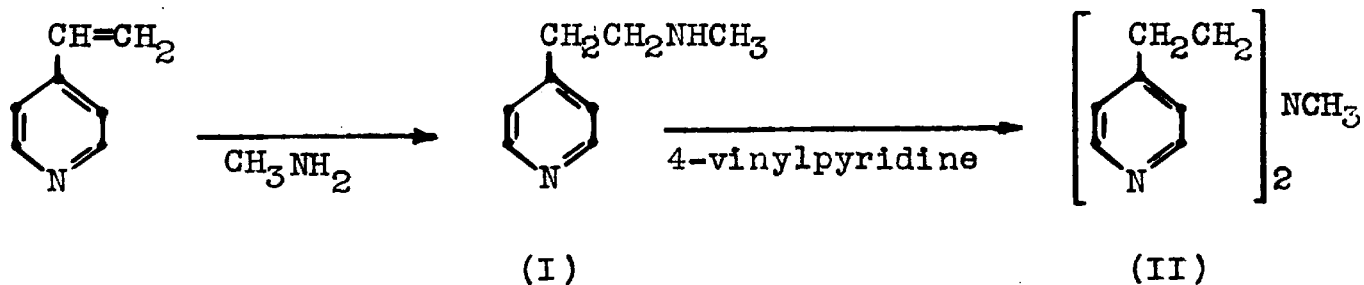
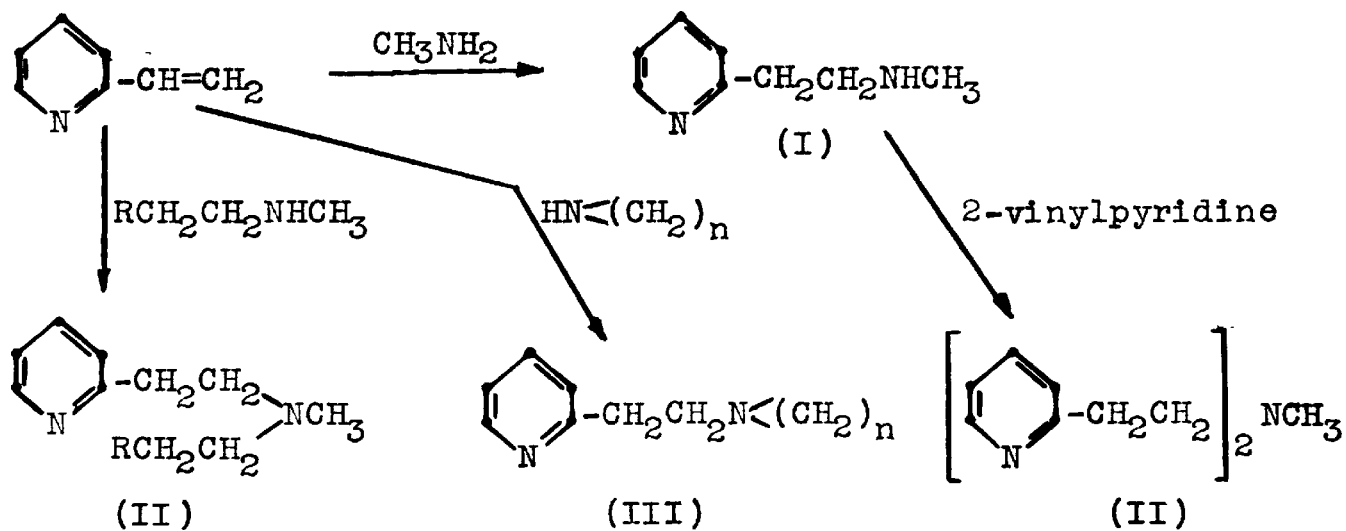
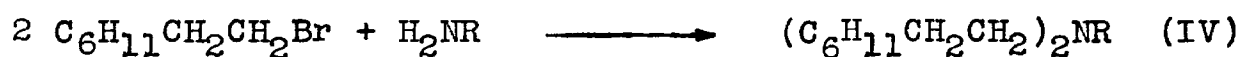
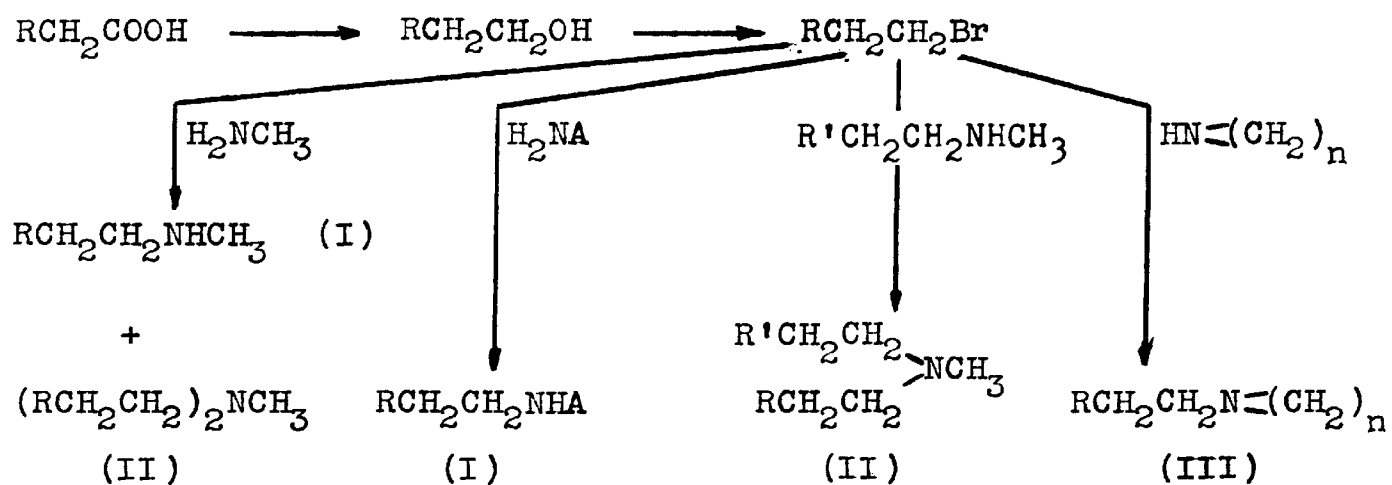
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|-----|--|--|
| I | RCH_2CH_2NHA | <p>R = Cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- and 4-pyridyl</p> <p>A = Hydrogen, methyl, isopropyl, allyl, cyclopentyl</p> |
| II | $RCH_2CH_2N \begin{array}{c} \\ CH_3 \end{array} CH_2CH_2R'$ | <p>R = Cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- and 4-pyridyl</p> <p>R' = Phenyl, cyclohexyl, 4-methylcyclohexyl, cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- and 4-pyridyl</p> |
| III | $RCH_2CH_2N<(CH_2)_n$ | <p>R = Cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- and 4-pyridyl</p> <p>n = 4, 5, 6, 7, 8</p> |

IV $(C_6H_{11}CH_2CH_2)_2NR$

R = Cyclopentyl, cyclohexyl,
cycloheptyl, cyclooctyl

The secondary amines were submitted for pharmacological tests as their hydrochloride salts, and the tertiary amines as their hydrochloride and methobromide salts. These salts are listed in Tables I, II, III, IV and V in the Experimental Part.

The following reaction scheme indicates the manner in which the secondary and tertiary amines were obtained:



Cycloalkylacetic Acids

The three cycloalkylacetic acids - cycloheptylacetic acid, 4-methylcycloheptylacetic acid, cyclooctylacetic acid - which were required are known compounds. However, cycloheptylacetic acid was synthesized by seven procedures; 4-methylcycloheptylacetic acid was obtained by one new procedure and cyclooctylacetic acid was prepared by a slight modification of a process described in the literature.

For the preparation of the cycloalkylacetic acids, the following intermediates were required:

Cycloheptanone
Ethylcycloheptylidenecyanoacetate
Cycloheptylidenecyanoacetic acid
1-Cycloheptenylacetonitrile (a)
1-Cycloheptenylacetic acid (b)
Cycloheptylideneacetic acid (b)
Cycloheptylacetonitrile (a)
Ethyl cycloheptylcyanoacetate
Cycloheptylmalonyl acid amide (a)
Cycloheptylmalonic acid
4-Methylcycloheptanone
Ethyl 4-methylcycloheptylidenecyanoacetate
Ethyl 4-methylcycloheptylcyanoacetate
Cyclooctyl bromide

Cycloheptylacetic Acid

Cycloheptylacetic acid has been obtained by Wallach (120) by the use of the Reformatzky reaction: cycloheptanone was condensed with methylbromoacetate and zinc to produce methyl

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- (a) To the best of our knowledge, these compounds have not been reported in the literature.
(b) The two acids were obtained in an equilibrium mixture, and they were hydrogenated without isolation.
(120) O. Wallach, Ann., 353, 301 (1907).

(1-hydroxycycloheptyl)acetate which was then converted into methyl (1-bromocycloheptyl)acetate; after elimination of hydrogen bromide and hydrogenation with the aid of zinc and acid, the acetic acid was obtained by hydrolysis of the ester.

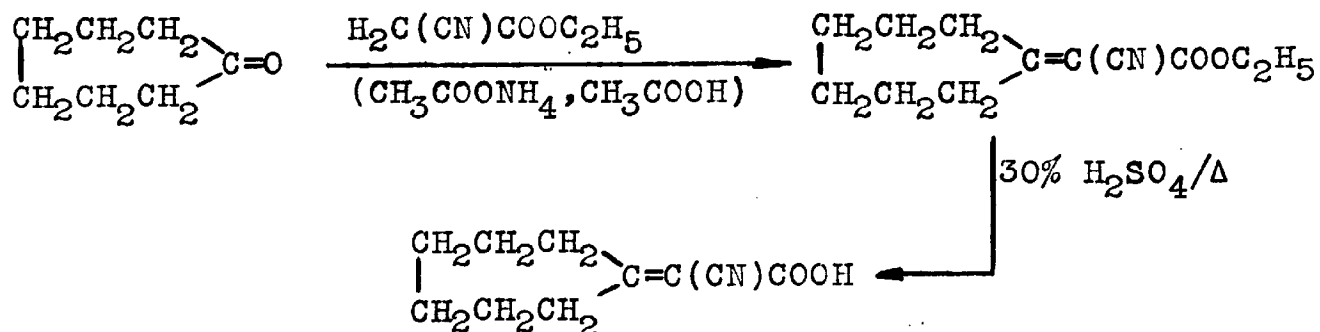
We prepared the acid by seven procedures (A-G) in order to determine which process was the most feasible for the synthesis of a cycloalkylacetic acid. It was found that if the required cycloalkanone is available, procedure F is the most convenient. In this process, the ketone is condensed with ethyl cyanoacetate, and the ethyl alkylidenecyanoacetate obtained is hydrogenated to the corresponding ethyl cycloalkylcyanoacetate. After hydrolysis and decarboxylation, the acetic acid is obtained.

If the required cycloalkyl bromide can be obtained readily, procedure G represents a good process. In this process, the malonic ester synthesis is employed but the intermediates are not isolated.

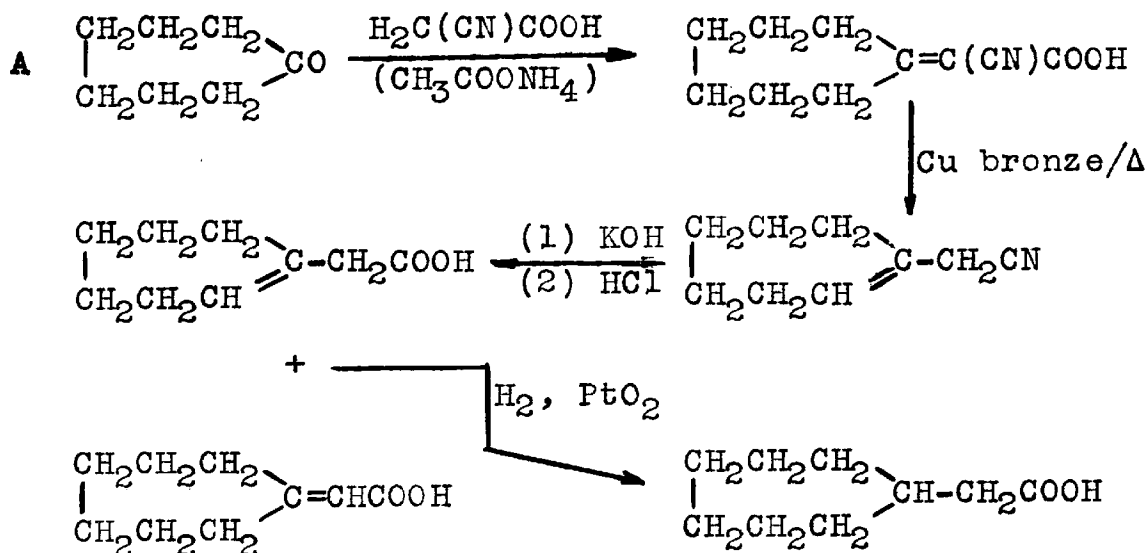
In the first attempt to obtain cycloheptylacetic acid, cycloheptanone (26) was condensed with ethyl cyanoacetate; ammonium acetate and acetic acid were used as condensing agents since they had been found by Cope (121) to be suitable in the condensation of cyclohexanone with ethyl cyanoacetate. Vogel (122) had prepared ethyl cycloheptylidenecyanoacetate in 31% yield by the condensation of cycloheptanone with ethyl cyanoacetate in the presence of piperidine.

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- (121) A. C. Cope, C. M. Hofmann, C. Wykoff, and E. Hardenberg, J. Am. Chem. Soc., 63, 3452 (1941).
(122) I. Vogel, J. Chem. Soc., 2024 (1928).

The ethyl cycloheptylideneacyanoacetate which was obtained in 75% yield, was refluxed with 30% sulfuric acid, in the hope that the cycloheptylidene malonic acid, which might be formed as the initial product, would decarboxylate with the formation of cycloheptylideneacetic acid; the last named compound could then be hydrogenated to the desired cycloheptylacetic acid. Unfortunately, cycloheptylideneacyanoacetic acid (123) was produced instead of cycloheptylideneacetic acid.



Method A was then employed to obtain cycloheptylacetic acid.



(123) F. Dickens, L. Horton, and J. F. Thorpe, J. Chem. Soc., 125, 1839 (1924), obtained the cycloheptylideneacyanoacetic acid as a by-product in the preparation of ethyl 1-cyanocycloheptane-1-cyanoacetate.

Cycloheptanone was condensed with cyanoacetic acid in the presence of ammonium acetate to produce cycloheptylidene-cyanoacetic acid in 70-75% yield. This method is similar to one which had been used by Cope et al. (124) in the condensation of cyclohexanone with cyanoacetic acid.

In some instances the crude cycloheptylidene-cyanoacetic acid was decarboxylated, with the aid of heat and copper-bronze, to form cycloheptenylacetonitrile (85-90% yield based on cycloheptanone). In other experiments the purified cycloheptylidene-cyanoacetic acid was decarboxylated with the formation of cycloheptenylacetonitrile in 87% yield.

The reason for the assumption that the double bond shifted during decarboxylation, and that cycloheptenylacetonitrile and not cycloheptylideneacetonitrile was obtained, is explained below. In view of the work of Hugh et al. (125) it seems very probable that after hydrolysis of cycloheptenylacetonitrile, an equilibrium mixture of cycloheptenylacetic and cycloheptylideneacetic acids was formed. It was stated by Hugh and co-workers (125) that "cycloheptylideneacetic acid on treatment with alkali passes into an equilibrium mixture from which about 25% of the unchanged acid could be recovered".

When the mixture of unsaturated acids was hydrogenated

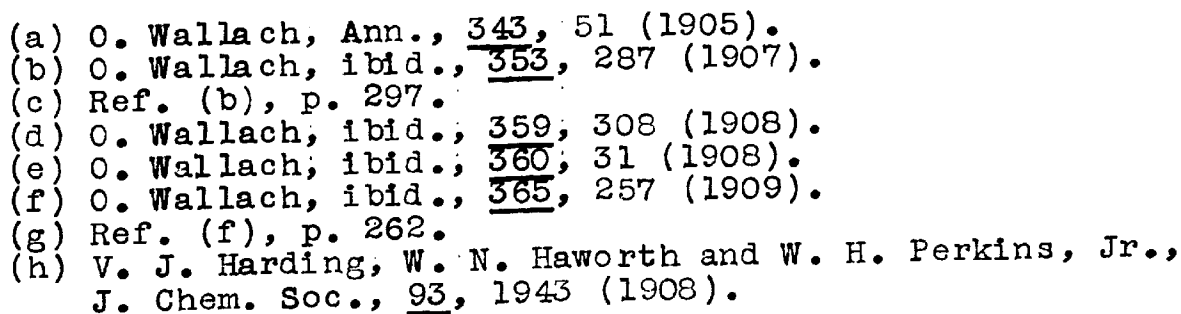
(124) A. C. Cope, A. A. D'Addieco, D. E. Whyte and S. A. Glickman, "Organic Syntheses", John Wiley and Sons, New York, N. Y., Vol. 31, p. 25.

(125) W. E. Hugh, G. A. R. Kon and T. Mitchel, J. Chem. Soc., 1436 (1929).

catalytically, cycloheptylacetic acid was obtained in 80% yield. The acid was identified by conversion into its amide which is a known derivative (120).

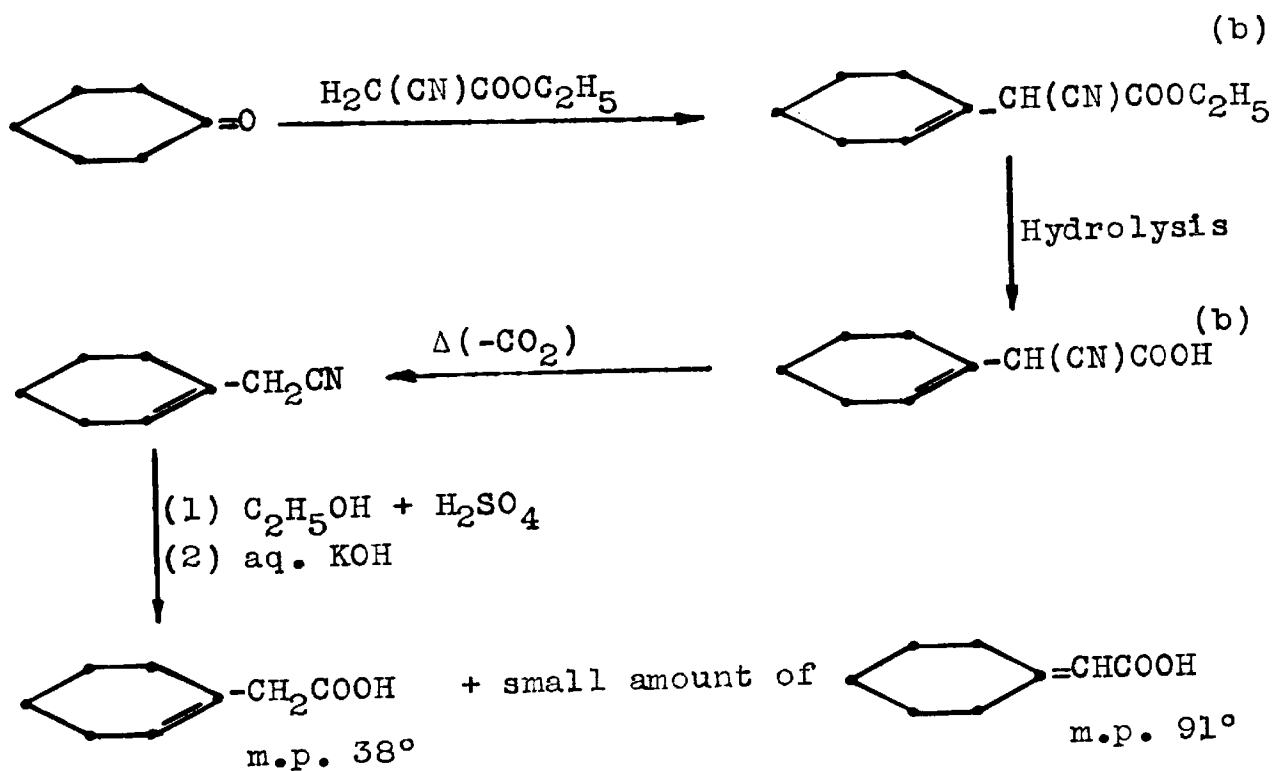
The assumption of a shift of the double bond during the decarboxylation of cycloheptylidenecyanoacetic acid is based on a number of observations made by various investigators during studies of cyclohexylidenecyanoacetic acid and related compounds.

Wallach found that dehydration of ethyl (1-hydroxycyclohexyl)acetate yielded a mixture of ethyl cyclohexenylacetate and ethyl cyclohexylideneacetate (see reaction scheme). After hydrolysis of the mixture and separation of the acids, one acid was found to melt at 38°, the other at 91°. Each acid was converted into its amide which was characterized by a fairly high melting point. The structure of cyclohexylideneacetic acid (m.p. 91°) was determined by its oxidation, with potassium permanganate, to cyclohexanone. The determination of the structure of cyclohexenylacetic acid (m.p. 38°) was more difficult. Wallach showed that oxidation of this acid yielded δ -acetylvaleric acid and a ketone which he did not identify correctly. It was shown by Harding et al. that the ketone which he and Wallach both had obtained was methyl 1-cyclopentenyl ketone. This ketone was shown by Harding, as well as by Wallach, to yield glutaric acid on oxidation.



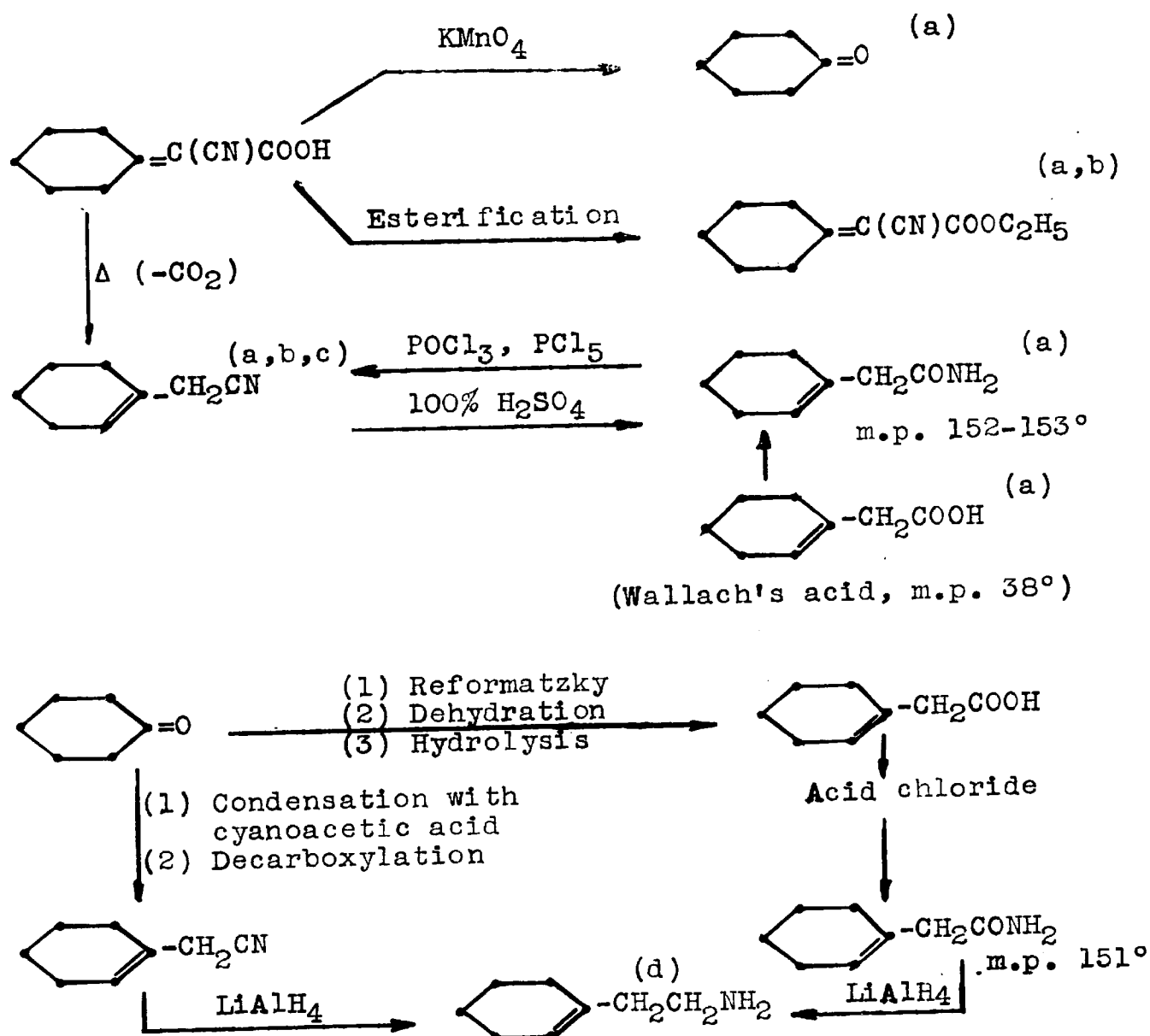
Other reactions in which the double bond shifted position and reactions which were used to establish the structure of a given compound are shown in the following reaction schemes.

Preparation of Cyclohexenylacetonitrile and Cyclohexenylacetic Acid from Cyclohexanone (a).



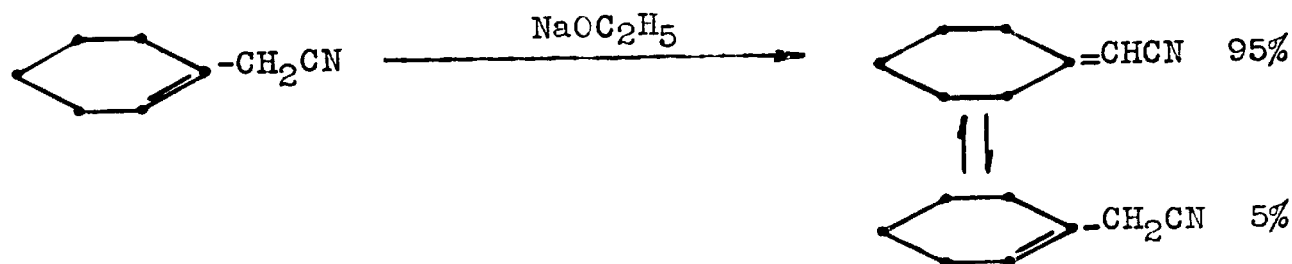
- (a) V. J. Harding, W. N. Haworth and W. H. Perkins, Jr., J. Chem. Soc., 93, 1943 (1908).
- (b) Although these products were assumed to be cyclohexenyl derivatives, it is known now by the work of A. Lapworth and J. A. McRae (J. Chem. Soc., 121, 2741 (1922); J. F. Birch, G. A. Kon and W. S. G. P. Norris (ibid., 123, 1361 (1923) and A. Kandiah and R. P. Linstead (ibid., 2124 (1929)), that these compounds are cyclohexylidene derivatives; a shift in the double bond takes place during the decarboxylation of the cyanoacetic acid.

Structure of 1-Cyclohexenylacetonitrile

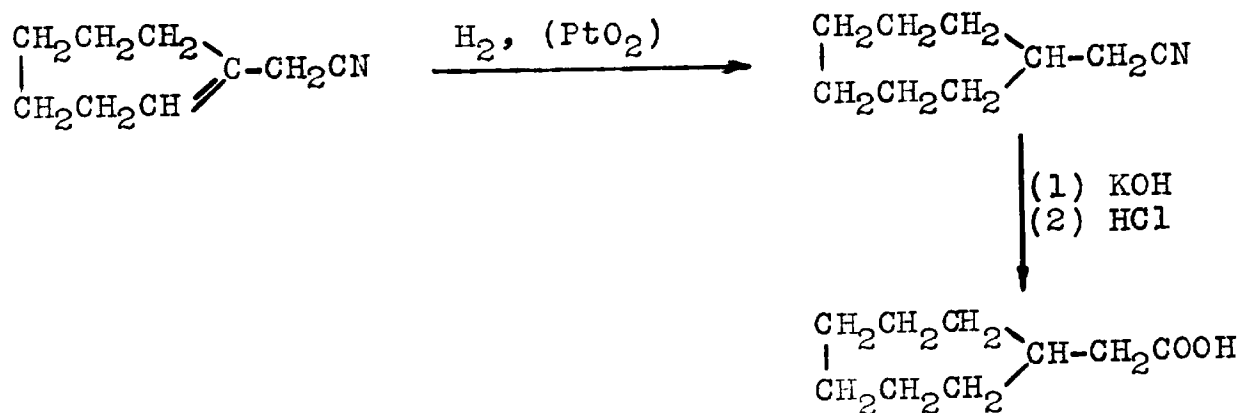


- (a) A. Kandiah and R. P. Linstead, J. Chem. Soc., 2142 (1929).
 (b) This ester had the same properties as the ester obtained by condensation of cyclohexanone with ethyl cyanoacetate by A. Lapworth and J. A. McRae (J. Chem. Soc., 121, 2741 (1922) and by J. F. Birch, G. A. Kon and W. S. G. P. Norris (ibid., 123, 1361 (1923)).
 (c) D. E. Whyte and A. C. Cope, J. Am. Chem. Soc., 65, 2002 (1943).
 (d) von O. Schnider and J. Hellerbach, Helv. Chim. Acta, 33, 1437 (1950).

The Mobility of the Double Bond
in Cyclohexenylacetonitrile (a)



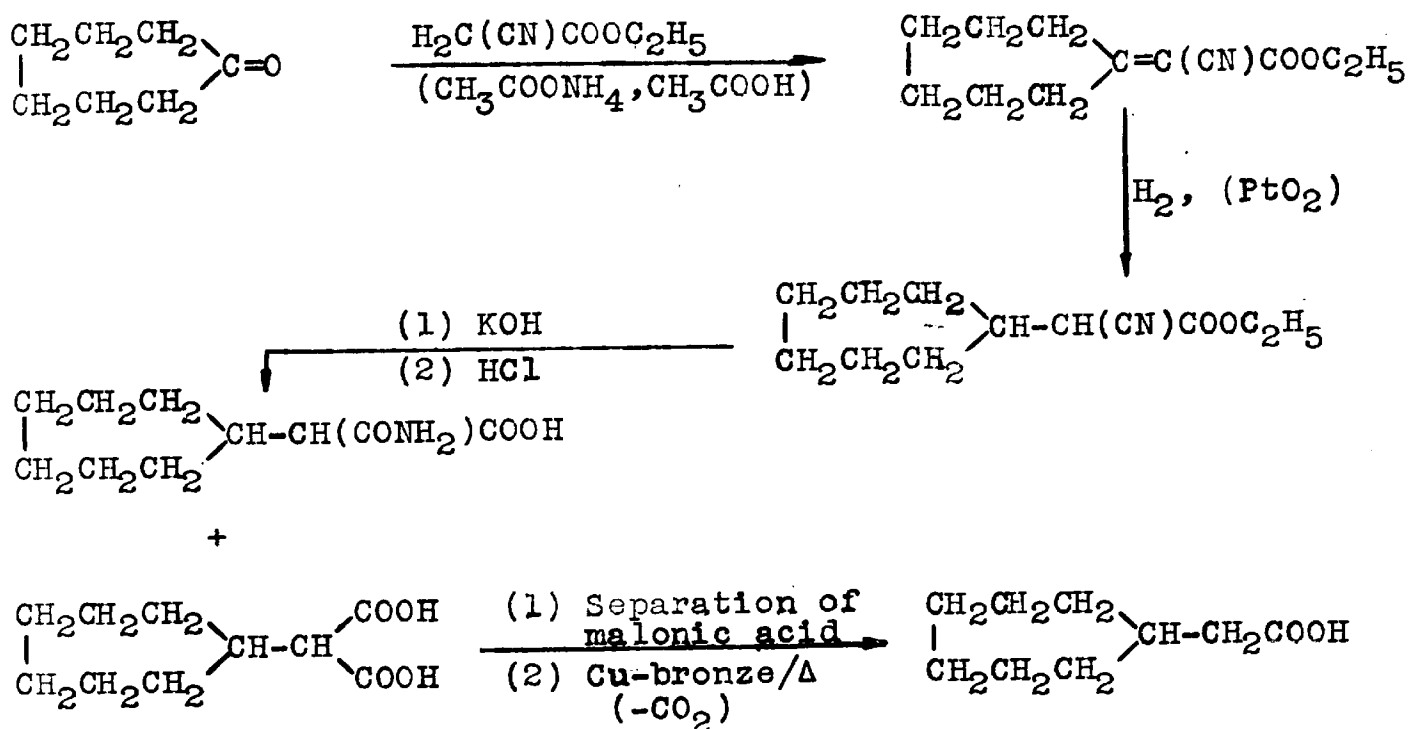
B. -



The cycloheptenylacetonitrile, obtained as described above, was hydrogenated catalytically, using platinum oxide as catalyst, and the resulting cycloheptylacetonitrile was hydrolyzed with alcoholic potassium hydroxide to the cycloheptylacetic acid in 51% yield.

(a) A. Kandiah and R. P. Linstead, J. Chem. Soc., 2139 (1929), studied the interconversion of the cyclohexylidene- and cyclohexenylacetonitriles. The two isomeric nitriles underwent extremely rapid interconversion in the presence of sodium ethoxide, the equilibrium being far on the side of the cyclohexylideneacetonitrile.

C. -



Suberone was condensed with ethyl cyanoacetate in the presence of ammonium acetate and acetic acid by a procedure similar to that described by Cope et al. The ethyl cycloheptylidencyanoacetate, obtained in 75% yield (126), was hydrogenated under pressure in alcoholic solution with platinum oxide as catalyst in 85-95% yield. Vogel (122) reduced the same compound by the use of aluminum amalgam and moist ether in 72% yield (127).

The hydrolysis of the ethylcycloheptylcynoacetate with alcoholic potassium hydroxide gave a mixture of cycloheptylmalonic acid (18% referred to the cyanoester) and monoamide.

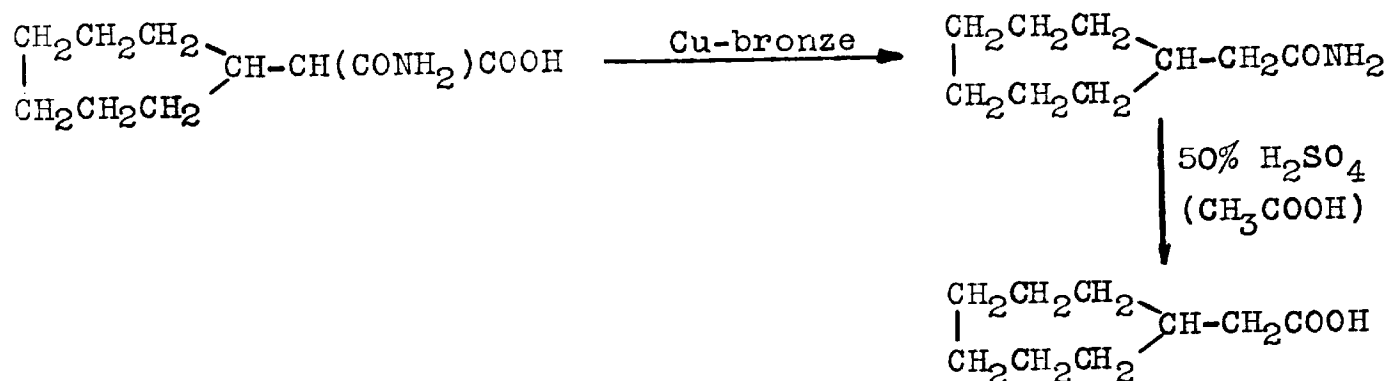
(126) Cope et al. (Ref. 124) prepared ethyl cyclohexylidencyanoacetate in 83% yield.

(127) Cope et al. (Ref. 124) reduced a number of ethyl alkylidenecyanoacetates in 90-96% yield by hydrogenation under pressure in alcoholic solution using palladinized charcoal as catalyst.

of cycloheptylmalonic acid (36.5% based on the cyanoester (128)).

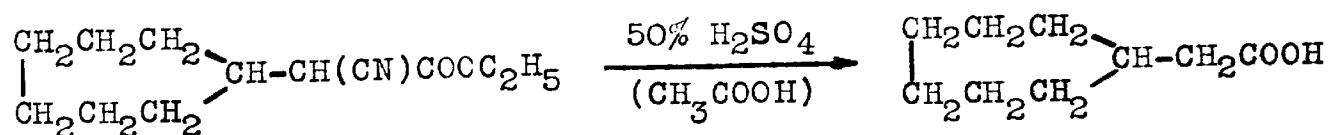
The cycloheptylmalonic acid was separated from the mixture and decarboxylated to the cycloheptylacetic acid by heating it with copper-bronze powder under reduced pressure; the yield was 88%.

D.-



The monoamide of cycloheptylmalonic acid, after separation from the cycloheptylmalonic acid, was decarboxylated and the resulting cycloheptylacetamide was hydrolyzed with a mixture of 50% sulfuric acid and acetic acid to the cycloheptylacetic acid in 87% yield.

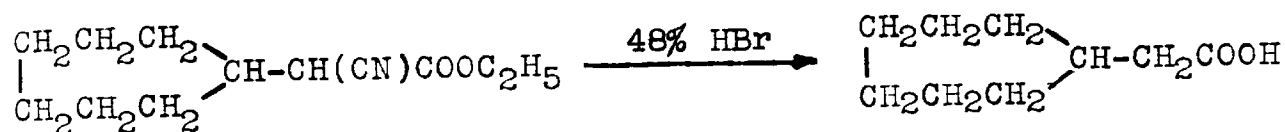
E. -



The ethyl cycloheptylcynoacetate was hydrolyzed and decarboxylated directly to the cycloheptylacetic acid by refluxing a mixture of the cyanoester with 50% sulfuric acid and acetic acid; the yield of cycloheptylacetic acid was 58%.

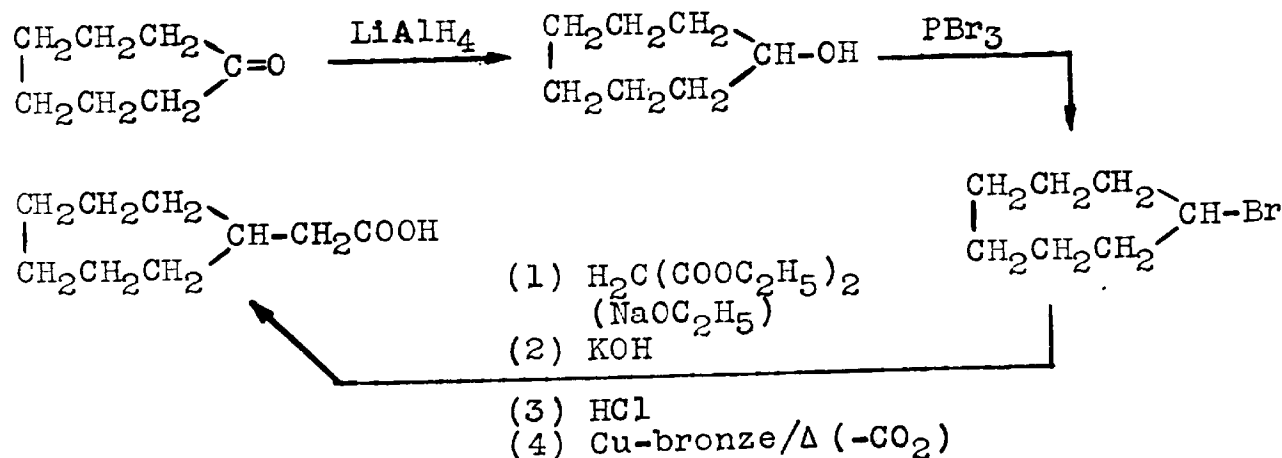
(128) Vogel, Ref. 122, prepared cycloheptylmalonic acid by the same method; the yield was not reported.

F. -



Ethyl cycloheptylcynoacetate was hydrolyzed and decarboxylated directly to cycloheptylacetic acid in 84% yield refluxing a mixture of the cyanoester and 48% hydrobromic acid. On account of the simplicity of this procedure and the high yield obtained, it was considered desirable to follow this method whenever the cycloalkanone was more directly available than the cycloalkyl bromide.

G. -



Cycloheptanone was reduced with lithium aluminum hydride to cycloheptanol, and the alcohol was then converted into cycloheptyl bromide by the use of phosphorus tribromide. The bromide was allowed to react with diethyl malonate and, without isolation of the diethyl cycloheptylmalonate, the product was hydrolyzed to the cycloheptylmalonic acid. Decarboxylation of the crude acid yielded cycloheptylacetic acid in 52% yield based on cycloheptylbromide.

4-Methylcycloheptylacetic acid had been prepared by Johnson (129) in 38% yield based on 4-methylcycloheptanone, according to procedure G. We prepared it through the ethyl cyanoacetate condensation from 4-methylcycloheptanone, according to procedure F. The overall yield was 55%.

Cyclooctylacetic acid was prepared by Ruzicka and Bockenoogen (130) through the Reformatzky reaction on cyclooctanone but the yield was not reported, and by Johnson (129) through the malonic ester synthesis. We prepared this acid also through the malonic ester synthesis with slight variations in the procedure and improved the yield by about 10%. In this case the malonic ester synthesis was employed because it was easier to obtain the cyclooctyl bromide in relatively large amounts, than the cyclooctanone.

B-Cycloalkylethanols

The following B-cycloalkylethanols were prepared:

B-(4-Methylcyclohexyl)ethanol*
B-Cycloheptylethanol
B-(4-Methylcycloheptyl)ethanol
B-Cyclooctylethanol*

B-(4-Methylcyclohexyl)ethanol (131) was prepared in 60% yield by the bromination of 4-methylcyclohexanol** with

* Known compounds.

** Purchased from the Eastman Kodak Co.

(129) W. K. Johnson, Dissertation, University of Michigan (1953).

(130) L. Ruzicka and H. A. Bockenoogen, *Helv. Chim. Acta*, 14, 1319 (1931).

(131) G. Darzens, *Compt. rend.*, 189, 852-854 (1929), prepared this compound by the reduction of ethyl 4-methylcyclohexylacetate with sodium and alcohol; the yield was not reported.

phosphorus tribromide, conversion of the bromide into the Grignard reagent, and treatment of this reagent with ethylene oxide as described by Blicke and Zienty (16).

B-Cycloheptylethanol, B-(4-methylcycloheptyl)ethanol and B-cyclooctylethanol (132) were prepared in 80-90% yields by the reduction of the corresponding cycloalkylacetic acids with lithium aluminum hydride.

B-Cycloalkylethyl Bromides

For the alkylation of the primary and secondary amines, the B-cycloalkylethyl bromides listed below were required.

B-(4-Methylcyclohexyl)ethyl bromide (a)
B-Cycloheptylethyl bromide (b)
B-(4-Methylcycloheptyl)ethyl bromide (b)
B-Cyclooctylethyl bromide (b)

We prepared all of the B-cycloalkylethyl bromides in 70-80% yields by treatment of the corresponding B-cycloalkylethanol with phosphorus tribromide.

-
- (a) F. F. Blicke and F. D. Zienty, Ref. 16, prepared this compound by treatment of the corresponding alcohol with PBr₃. R. P. Perkins, U. S. Patent 2,277,714 (C. A., 39, 4095 (1945)), prepared this compound in 59% yield by cleavage of di-B-4-methylcyclohexylethyl ether with gaseous hydrogen bromide.
- (b) As far as we are aware, these compounds have not been reported in the literature.
- (132) Ruzicka and Bokenoogen, Ref. 130, prepared the B-cyclooctylethanol by reduction of the ethyl cyclooctylacetate with sodium and alcohol.

Primary and Secondary Amines Used as Intermediates

In order to prepare the secondary and tertiary amines, listed in tables II-V in the Experimental Part, the following compounds were required; they are all known substances:

Methyl(β -phenylethyl)amine
Methyl(β -cyclohexylethyl)amine
Methyl(β -4-methylcyclohexylethyl)amine
Hexamethylenimine
Heptamethylenimine
Cyclooctanone
Octamethylenimine
Cyclopentanone oxime
Cyclopentylamine
Cycloheptanone oxime
Cycloheptylamine
Cyclooctanone oxime
Cyclooctylamine

Methyl(β -phenylethyl)amine, methyl(β -cyclohexylethyl)amine, and methyl(β -4-methylcyclohexylethyl)amine were prepared from the corresponding β -cycloalkylethyl bromides by treatment with a large excess of methylamine using ethanol or benzene as solvents following the procedure described in the Experimental Part for N-[β -(4-methylcycloheptyl)ethyl] - piperidine.

Hexamethylenimine was prepared by the reduction of 2-ketohexamethylenimine (epsilon-caprolactam) with lithium aluminum hydride as described previously by Doorenbos (133).

Cycloheptanone was reacted with sodium azide and hydrochloric acid as described by Doorenbos (133) and the crude 2-ketoheptamethylenimine was reduced with lithium aluminum hydride to the heptamethylenimine.

(133) N. J. Doorenbos, Dissertation, University of Michigan (1953).

Azelaic acid* was recrystallized twice from benzene, esterified with methanol and sulfuric acid to the dimethyl azelate which was cyclized in xylene, in high dilution, by the use of powdered sodium hydride to 2-carbomethoxy-cyclo-octanone. The keto ester was hydrolyzed with dilute sodium hydroxide and the keto acid was decarboxylated by the use of hydrochloric acid and mild heating to cyclooctanone (27).

Cyclooctanone was converted into 2-ketooctamethylenimine, and this ketimine was reduced to the octamethylenimine with lithium aluminum hydride.

Cyclopentylamine was prepared by reduction of the oxime of cyclopentanone with sodium and butanol in 50% yield.

We obtained the oxime in 75-85% yield by treatment of cyclopentanone** with hydroxylamine hydrochloride and sodium acetate according to the instructions of Hückel and Sachs (134).

Previously, Wislicenus and Hentzchel (135) had reduced cyclopentanone oxime with sodium and ethanol and then submitted the reaction mixture to steam distillation. After the addition of hydrochloric acid to the distillate, and evaporation to dryness, Wislicenus and Hentzchel obtained a "hygroscopic hydrochloride" in quantitative yield. We found that cyclopentanone oxime will distill with steam, and that it is basic enough to form a hydrochloride. Furthermore we found that the pure cyclopentylamine hydrochloride is not hygroscopic (136).

* A commercial grade of azelaic acid, purchased from The Matheson Co., Inc., was used.

** Purchased from the Bios Laboratories.

(134) W. Hückel and M. Sachs, Ann., 498, 166 (1932).

(135) J. Wislicenus and W. Hentzchel, Ibid., 275, 325 (1893).

(136) This observation had also been made by M. Mugdan (Ann., 298, 140 (1897)). This investigator did not report either the yield or the melting point of the hydrochloride.

Wislicenus and Hentzchel may have obtained a mixture of cyclopentylamine and cyclopentanone oxime in the distillate from the steam distillation, and then upon acidification a mixture of the hydrochlorides of these two compounds was formed.

When cyclopentanone oxime was reduced catalytically with a nickel catalyst (137), the reaction product was found to be a mixture of cyclopentyl-, dicyclopentyl- and tricyclopentylamine.

It was reported (138) that reduction of cyclopentanone oxime with lithium aluminum hydride in ether solution yielded cyclopentylamine in 33% yield.

By reduction of cycloheptanone oxime with sodium and butanol, we obtained cycloheptylamine in 50% yield.

By reduction of the oxime with sodium and ethanol, Smirnov (139) prepared the amine in 22% yield. Doorenbos (133) reduced the oxime with lithium aluminum hydride in ether-butyl ether, and obtained the amine in 51% yield.

We found that reduction of cyclooctanone oxime with sodium and butanol produced cyclooctylamine in 53% yield. Ruzicka et al. (140) obtained the amine in 67% yield by reduction of the oxime with sodium and ethanol, and Doorenbos (133), who used lithium aluminum hydride in ether-butyl ether as the reducing agent, isolated the amine in 74% yield.

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- (137) Sabatier and Mailhe, Compt. rend., 158, 989 (1914).
(138) D. R. Smith, M. Maienthal and J. Tipton, J. Org. Chem., 17, 294 (1952).
(139) A. S. Smirnov, J. Gen. Chem., 9, 1283 (1939); C. A., 34 730 (1940).
(140) L. Ruzicka, M. W. Goldberg and M. Hürbin, Helv. Chim. Acta, 16, 1340 (1933).

Secondary and Tertiary Amines

The secondary and tertiary amines (Tables II-V) were obtained, as indicated previously in the general reaction scheme at the beginning of this discussion, by general methods I and II:

I. By alkylation of a primary or secondary amine with the use of a β -cycloalkylethyl halide. The alkylation was carried out by one of the general procedures (H, I, J, K) described below.

H. The reaction was carried out in a pressure bottle, absolute alcohol or benzene was used as solvent, and the amine was employed in 50-100% excess.

This procedure was used for the alkylation of a low-boiling primary amine when we wished to obtain both the secondary amine (Type I) and the tertiary amine which contained a di(β -cycloalkylethyl) group (Type II).

I. The reaction was carried out in a pressure bottle, absolute alcohol or benzene was used as solvent, and about ten times the calculated amount of amine was employed. This process was utilized for the alkylation of a primary amine when only the secondary amine (Type I) was desired as a reaction product, or for the alkylation of a secondary amine which was available (for example, piperidine) to obtain a tertiary amine (Type III).

J. In this procedure the secondary amine, which was used in 20-50% excess, was dissolved in absolute ethanol, 100% excess potassium carbonate and the required bromide were

added, and the mixture was stirred and refluxed for 48-60 hours.

This method was used when the required secondary amine had to be synthesized by a time-consuming process.

Compounds of Type II were synthesized by this procedure.

K. The calculated amounts of the primary amine and the β -cyclohexylethyl bromide, absolute ethanol and 100% excess potassium carbonate were stirred and refluxed for 48-60 hours.

This process was used for the preparation of amines of Type IV.

II. This method was used for the preparation of amines that contain a 2- or 4-pyridyl group.

The addition of a primary amine (methylamine) to 2- or 4-vinyl pyridine (pyridylethylation) produced a secondary amine of Type I, when a secondary amine (for example, methyl- β -cyclohexylethylamine) was employed, the reaction product was a tertiary amine of Type II; addition of a polymethylenimine (piperidine) yielded an amine of Type III.

The general procedure used (L) consisted in refluxing a mixture of either 2- or 4-vinylpyridine with a 25-50% excess of the required amine, in the absence of a solvent, for five hours or heating the mixture for 60 hours on a steam-bath.

Methyl(β -2-pyridylethyl)amine had been obtained by Löffler (141) by interaction of β -(2-pyridylethyl) bromide

(141) K. Löffler, Ber., 37, 169 (1904).

into methylamine in alcoholic solution; the yield was not reported. We obtained the amine in 33% yield by reaction of 0.3 mole of 2-vinylpyridine with 0.45 mole methylamine in alcoholic solution. No methyldi(β -2-pyridylethyl)amine was formed under these conditions, however, this amine was obtained by interaction of methyl(β -2-pyridylethyl)amine and 2-vinylpyridine.

When 4-vinylpyridine was employed, the relative amount of methylamine was reduced in order to favor the formation of the tertiary amine, methyldi(β -4-pyridylethyl)amine. However, when 0.13 mole of methylamine was allowed to react with 0.2 mole of 4-vinylpyridine, the secondary amine methyl(β -4-pyridylethyl)amine was formed in 51% yield, methyldi(β -4-pyridylethyl)amine, was not found in the reaction mixture. The tertiary amine was produced in 28.5% yield by interaction of methyl(β -4-pyridylethyl)amine and 4-vinylpyridine.

We attempted to prepare β -2-pyridylethylamine by the substitution of ammonia for methylamine in the process used for the preparation of methyl- β -2-pyridylethylamine. However, this experiment was unsuccessful.

The addition of piperidine to 2-vinylpyridine to form N-(β -2-pyridylethyl)piperidine in 86% yield has been reported by Doering and Weil (142).

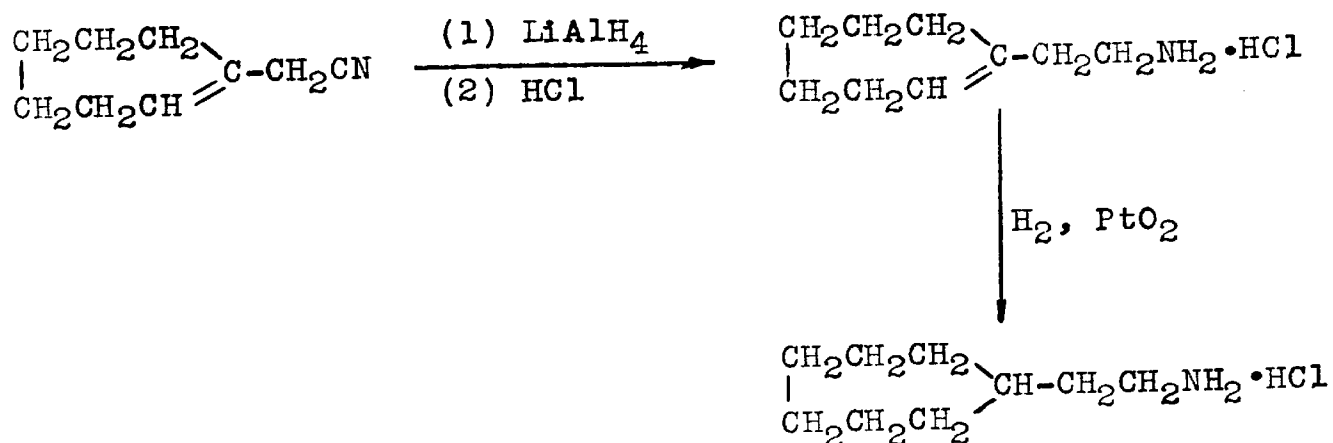
During the course of this investigation, Reich and Levine (143) described the pyridylethylation of a number of amines;

(142) W. E. Doering and R. A. N. Weil, J. Am. Chem. Soc., 69, 2461 (1947).

(143) H. E. Reich and R. Levine, Division of Organic Chemistry of the American Chemical Society. Abstracts of papers presented at Chicago, Ill., Sept. 6 to Sept. 11, 1953. Section A, paper 88.

one of these amines was pyrrolidine, and by the use of this amine these investigators obtained N-(β-2-pyridylethyl)-pyrrolidine in 80% yield. We obtained the last named compound in only 50% yield when a mixture of 2-vinylpyridine and pyrrolidine was heated for 12 hours on a steam-bath.

β-Cycloheptylethylamine was obtained in 60% yield by reduction of cycloheptylacetonitrile (144) with lithium aluminum hydride. The amine was also obtained from 1-cycloheptenylacetonitrile (144):



(144) These compounds were intermediates in one of the processes used for the preparation of cycloheptyl-acetic acid.

EXPERIMENTAL PART

The following schemes indicate the general manner in which the amines listed in Tables II to V were obtained:

Cycloalkylacetic acid $\longrightarrow$ β -Cycloalkylethanol $\longrightarrow$

β -Cycloalkylethyl bromide.

Intermediate amine + β -Cycloalkylethyl bromide $\longrightarrow$

Secondary or tertiary amine.

Intermediate amine + 2- or 4-vinylpyridine $\longrightarrow$

Secondary or tertiary amine which contains a 2- or 4-pyridyl group.

The information in the Experimental Part is discussed under the following headings:

Cycloalkylacetic Acids:

Cycloheptyl-, 4-Methylcycloheptyl- and Cyclooctylacetic Acid.

β -Cycloalkylethanol and β -Cycloalkylethyl Bromides:

β -Cycloheptyl-, β -4-Methylcycloheptyl- and β -Cyclooctylethanol and Ethyl Bromides.

Intermediate Amines.

Amines which Represent the Final Products.

The preparation of the required intermediates is described before the preparation of the compounds mentioned in the headings.

Cycloalkylacetic Acids

Cycloheptylacetic Acid

Ethyl Cycloheptylidenecyanoacetate. - A mixture of 112.2 g. (1 mole) of cycloheptanone (26), 124.0 g. (1.1 mole) ethyl cyanoacetate, 7.8 g. (0.1 mole) ammonium acetate, 17 ml. (0.3 mole) acetic acid and 100 ml. of dry benzene was refluxed vigorously in a flask attached to a constant water-separator* which, in turn, was attached to an efficient reflux condenser. After four hours just about the calculated amount of water had separated from the reaction mixture. The mixture was refluxed two hours longer, cooled, and diluted with an equal volume of ether. The mixture was washed twice with water and then dried over anhydrous magnesium sulfate. The solvent was removed and the product was fractionated under reduced pressure; b.p. 122-124° (2 mm.) (145); yield 151.0 g. (73%).

Analysis Calcd. for $C_{12}H_{17}O_2N$: N, 6.76. Found: N, 6.93.

Reaction of Ethyl Cycloheptylidenecyanoacetate with 30% Sulfuric Acid. - It was hoped that ethyl cycloheptylidenecyanoacetate, when refluxed with sulfuric acid, would undergo hydrolysis and decarboxylation with the formation of cycloheptylideneacetic acid or cycloheptenylacetic acid or a mixture of the two acids. The reaction product could then be hydrogenated to the

* "Barrett Distilling Receiver, Laboratory Glassware Catalog, No. LP-31, Corning Glass Works, Corning, N. Y. (145) Ref. 122, b.p. 160° C (12 mm.).

desired cycloheptylacetic acid. However, under the conditions used in the experiment, the product obtained by reaction with sulfuric acid proved to be cycloheptylidenecyanoacetic acid.

A mixture of 31.2 g. (0.15 mole) of ethyl cycloheptylidenecyanoacetate and 250 g. of 30% sulfuric acid was stirred and refluxed for 15 hours. The mixture was extracted with ether, and the extract washed with concentrated sodium carbonate solution. From the ether layer there was obtained 22.0 g. of material which boiled at 111-113° (2 mm.). A nitrogen analysis indicated that this substance was unchanged ethyl cycloheptylidenecyanoacetate.

Analysis Calcd. for $C_{12}H_{17}O_2N$: N, 6.76. Found: N, 6.90. However, the boiling point that we found for this ester was 122-124° (2 mm.). We cannot explain this discrepancy.

Upon acidification of the sodium carbonate solution, an oily precipitate was obtained. After extraction with ether, the extract was dried with magnesium sulfate and the solvent was removed; the solid residue (5.0 g., 18.5%) melted at 89-90° after recrystallization from benzene. This product was cycloheptylidenecyanoacetic acid; mixed m.p. with an authentic sample, 89-90° (146).

Analysis Calcd. for $C_{10}H_{13}O_2N$: Neut. equiv., 179.2. Found: neut. equiv., 180.

Cycloheptylidenecyanoacetic Acid. - A mixture of 56.0 g. of cycloheptanone (0.5 mole), 46.8 g. (0.55 mole) of cyanoacetic acid, 3.9 g. (0.05 mole) of ammonium acetate and 35 ml.

(146) Ref. 123, m.p. 91°.

of dry benzene was refluxed for 6 hours. The reaction flask was attached to a constant water-separator which, in turn, was attached to a reflux condenser. After the mixture had been refluxed for 3 hours, practically all of the water formed in the reaction had collected in the water-separator. About 50 ml. of benzene was added to the reaction mixture in order to prevent crystallization of the product, and the mixture was then washed thoroughly with water. After it had been dried over magnesium sulfate, and filtered, about one-half of the benzene was removed. Most of the product precipitated when the solution was cooled, a further amount was obtained from the mother liquor. After recrystallization of the product from benzene, it was placed in an evacuated desiccator for 12 hours in order to remove solvent from the crystals; yield 64.0 g. (71%); m.p. 89-90°. A sample recrystallized from ethyl acetate melted at 89-90° (147).

Analysis Calcd. for $C_{10}H_{13}O_2N$: N, 7.81. Found: N, 7.91.

1-Cycloheptenylacetonitrile. - This compound was prepared in 87% yield by decarboxylation of pure cycloheptylidene-cyanoacetic acid, and in 89% yield (based on cycloheptanone) by decarboxylation of the crude material obtained by condensation of cycloheptanone with cyanoacetic acid.

Cycloheptylidene-cyanoacetic acid (26.8 g., 0.15 mole) and 1-2 g. of copper-bronze were placed in a flask to which a 15 cm. Vigreux column was attached. The mixture was heated

(147) Ref. 123, m.p. 91°.

in an oil-bath under 25 mm. pressure. The initial evolution of gas was very vigorous; the rate of decarboxylation was controlled by keeping the bath temperature at 130-140° and by removing the bath when the manometer read more than 50 mm. Decarboxylation was completed after about 15 minutes. The product was then distilled; b.p. 122-124° (25 mm.); yield 16.5 g. (89%).

Analysis Calcd. for $C_9H_{13}N$: N, 10.35. Found: N, 10.25.

Cycloheptylacetic Acid. - This acid was prepared by seven procedures (A-G).

- A. Hydrolysis of 1-Cycloheptenylacetonitrile to a Mixture of 1-Cycloheptenylacetic and Cycloheptylideneacetic Acids and Subsequent Hydrogenation of the Mixture.
- B. Hydrolysis of Cycloheptylacetonitrile.
- C. Decarboxylation of Cycloheptylmalonic Acid.
- D. Hydrolysis of Cycloheptylacetamide.
- E. Hydrolysis of Ethyl Cycloheptylcyanacetate with Sulfuric Acid.
- F. Hydrolysis of Ethyl Cycloheptylcyanacetate with Hydrobromic Acid.
- G. Use of the Malonic Ester Synthesis.

A. A mixture of 27.0 g. (0.2 mole) of 1-cycloheptenylacetonitrile, 50 g. of potassium hydroxide, 150 ml. of ethanol and 25 ml. of water was refluxed for 20 hours. The mixture was concentrated to about one-half of its volume under reduced pressure, 100 ml. of water was added and the mixture was

extracted with ether. The ether was discarded and the aqueous layer was acidified with concentrated hydrochloric acid. The cooled mixture was extracted with ether, the extract was dried with magnesium sulfate, the solvent was removed and the residue distilled; b.p. 108-110° (1.5 mm.); yield 15.0 g. (50%). The product probably is a mixture of 1-cycloheptenylacetic and cycloheptylideneacetic acids (125).

Nine and five tenths grams (0.0615 mole) of the product were dissolved in 15 cc. of absolute ethanol, 0.1 g. of platinum oxide catalyst was added and the mixture was hydrogenated under an initial pressure of 50 lbs. at 40-50°. After filtration of the mixture and removal of the solvent, the product was distilled; b.p. 111-112° (2 mm.) (148); yield 7.5 g. (80%).

In order to identify the acid, the acid amide was prepared; m.p. 147-148° (149) after recrystallization from dilute ethanol.

B. A mixture of 1-cycloheptenylacetonitrile (13.5 g., 0.1 mole), 20 ml. of absolute ethanol and 0.1 g. of platinum oxide was hydrogenated at 40-50° under an initial pressure of 50 lbs. After 6 hours, about 97% of the calculated amount of hydrogen had been absorbed. The solvent was removed from the filtered mixture, and the residue, the crude cycloheptylacetonitrile, was hydrolyzed in the manner described below.

A mixture of the crude nitrile, 60 g. of potassium hydroxide, 150 ml. of ethanol and 20 ml. of water was refluxed

(148) Ref. 120, b.p. 165° (19 mm.).

(149) Ref. 120, m.p. 146-148°.

36 hours. The solvent was removed under reduced pressure, the semisolid residue was dissolved in water, the solution was extracted with ether, and the aqueous solution was then acidified and extracted thoroughly with ether. The ether solution was dried over magnesium sulfate, the solvent was removed and the residue distilled; the cycloheptylacetic acid boiled at 111-113° (2 mm.); yield 8.0 g. (51%). The acid amide, prepared for identification, melted at 147-148°, after recrystallization from dilute alcohol; mixed m.p. 147-148°.

C. Ethyl Cycloheptylcyanoacetate. - Ethyl cycloheptylidene-cyanoacetate (103.6 g., 0.5 mole) was dissolved in 100 ml. of absolute ethanol and hydrogenated, in the presence of 0.2 g. of platinum oxide catalyst, under an initial pressure of 50 lbs. About 95% of the calculated amount of hydrogen was absorbed after 6 hours. After removal of the catalyst and the solvent, the residue was dissolved in ether, the ethereal solution was washed with dilute hydrochloric acid, in order to remove any basic products which might have been formed, and then dried over magnesium sulfate. After removal of the solvent, the residue was distilled; b.p. 108-110° (6 mm.) (150); yield 88.0 g. (85%).

Alkaline Hydrolysis of Ethyl Cycloheptylcyanoacetate. - A mixture of 241 g. (1.15 moles) of ethyl cycloheptylcyanoacetate, 168.0 g. (3.0 moles) of potassium hydroxide, 170 ml. of water and 620 ml. of alcohol was refluxed for 72 hours. The alcohol was removed by distillation under reduced pressure, (150) Ref. 122, b.p. 152-154° (12 mm.).

the residue was diluted with water and then extracted with ether. The aqueous solution was cooled and concentrated hydrochloric acid was added until the mixture was strongly acidic. An oily precipitate was obtained, which consisted of a mixture of cycloheptylmalonic acid and the half-amide of this acid. Ether was added whereupon some of the precipitate dissolved in the ether layer, and the remainder of the precipitate turned into a white solid. The solid (93.5 g.), the half-amide, was removed by filtration, and washed with ether. The filtrate was extracted with ether, the extract was dried over magnesium sulfate, and the solvent was removed. The residue (43.0 g.), cycloheptylmalonic acid, was recrystallized from acetone-benzene; m.p. 155-156° (dec.) (151).

Analysis Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.08; neut. equiv. 100.13. Found: C, 60.10; H, 8.13; neut. equiv., 105.9.

Cycloheptylacetic Acid by Decarboxylation of Cycloheptylmalonic Acid. - The malonic acid (40.0 g.), mixed with 2 g. of copper bronze, was heated in a bath under 16 mm. pressure. When the bath temperature reached 160°, decarboxylation began. The rate of decarboxylation was controlled by removal of the bath at intervals. After decarboxylation was completed, the product was distilled; b.p. 108-110° (1 mm.); yield 28.8 g. (88% or 15.8% based on ethyl cycloheptylcyanoacetate).

(151) I. Vogel, Ref. 122, who also prepared this malonic acid by alkaline hydrolysis of ethyl cycloheptylcyanoacetate, did not report the yield, and he did not isolate the half-acid amide. He stated that the melting point was 165.6° (dec.).

A portion of the acetic acid was converted into the amide; m.p. 147-148°; mixed m.p. 147-148°.

D. Decarboxylation of the Half-amide of Cycloheptylmalonic Acid. - The half-amide, obtained in the manner described above, was found to be only slightly soluble in ether but very soluble in ethanol. It melted at 159-160° (dec.) after recrystallization from acetone or 2-butanone.

Analysis Calcd. for $C_{10}H_{17}O_3N$: C, 60.27; H, 8.62; N, 7.03; neut. equiv., 199.28. Found: C, 60.37; H, 8.63; N, 6.89; neut. equiv., 203.6.

A sample of the half-acid amide was decarboxylated by heating it at 160° for 10 minutes. The product, after recrystallization from acetone, melted at 147-148°; mixed with an authentic sample of cycloheptylacetamide, 147-148°.

Cycloheptylacetic Acid by Hydrolysis of Cycloheptylacetamide. - A mixture of 65.5 g. (0.42 mole) of cycloheptylacetamide, 150 g. of 50% sulfuric acid and 25 ml. of acetic acid was refluxed for 24 hours. The acetic acid was removed by distillation under reduced pressure, the cold residue was poured into ice-water, and the mixture was extracted with ether. The ethereal solution was extracted with 10% sodium hydroxide solution, and the alkaline solution was then acidified. After extraction with ether, 56.5 g. (87% or 32% based on ethyl cycloheptylcynoacetate) of the acetic acid was obtained; b.p. 107-109° (0.7 mm.)

E. Cycloheptylacetic Acid by Hydrolysis of Ethyl Cycloheptylcynoacetate with Sulfuric Acid. - A mixture of 41.8 g.

(0.2 mole) of ethyl cycloheptylcynoacetate, 100 g. of 50% sulfuric acid and 175 ml. of acetic acid was refluxed for 60 hours. The acetic acid was removed by distillation under reduced pressure, the cold residue was poured into ice-water and the mixture was extracted with ether. The ethereal solution was extracted with 10% sodium hydroxide solution, the alkaline extract was acidified and then extracted with ether. The solvent was removed from the dried ethereal solution, and the residue was distilled. The characteristic odor of cycloheptylacetonitrile was noticed in the distillate. In order to remove the nitrile, the distillate was dissolved in ether, the solution was extracted with 10% sodium hydroxide solution, the extract was acidified and extracted with ether. The solvent removed from the dried ether extract and the residue was distilled; b.p. 116-119° (2 mm.); yield 18.0 g. (58%).

The acid amide, prepared from a sample of the acid, melted at 147-148°.

F. Cycloheptylacetic Acid by Hydrolysis of Ethyl Cycloheptylcynoacetate with Hydrobromic Acid. - A mixture of 209.2 g. (1.0 mole) of ethyl cycloheptylcynoacetate and 1400 g. of 48% hydrobromic acid was refluxed for 60 hours. The cold mixture was poured into ice-water and then extracted with ether. The ethereal solution was shaken with 10% sodium hydroxide solution. The alkaline extract was acidified and then extracted with ether. There was obtained 131.5 g. (84%) of the acetic acid; b.p. 104-106° (0.7 mm.). The amide melted at 147-148°; mixed m.p. 147-148°.

G. Cycloheptylacetic Acid by the Malonic Ester Synthesis. -

Diethylmalonate (32.8 g., 0.25 mole) was added to sodium ethylate which had been prepared from 4.6 g. (0.2 gram atom) of sodium and 100 g. of absolute ethanol. The mixture was stirred for 30 minutes, and was then heated on a steam-bath and stirred while 35.0 g. (0.2 mole) of cycloheptylbromide was added, dropwise. The mixture was stirred and refluxed for 3 hours. A solution of 28.0 g. (0.5 mole of potassium hydroxide in 30 ml. of water was added slowly and the material was stirred and refluxed for 12 hours. The alcohol was removed by distillation from the stirred mixture, and water was then added to dissolve most of the solid material. While the mixture was stirred, 62 ml. (0.7 mole of hydrogen chloride) of concentrated hydrochloric acid was added, and the material was then refluxed for 1 hour. The mixture was extracted with ether, and the ethereal solution was extracted with 10% sodium hydroxide solution. After the alkaline solution had been acidified with concentrated hydrochloric acid, it was extracted with ether. The solvent was removed from the dried extract, and the residue was mixed with 1 g. of copper-bronze. The mixture was heated in an oil-bath at 160° under 16 mm. pressure. The rate of evolution of carbon dioxide was regulated by removal of the bath at intervals. The decarboxylation required about 30 minutes. After distillation, 16.2 g. (52%) of the acetic acid was obtained; b.p. 106-108° (1 mm.). The amide melted at 147-148°; mixed m.p. 147-148°.

4-Methylcycloheptylacetic Acid

4-Methylcycloheptanone. - Crude 4-methyl-1-cyanocyclohexanol was reduced with lithium aluminum hydride by the method described by Johnson (129), and the crude 4-methyl-1-aminomethylcyclohexanol, in the form of the hydrochloride (129), was treated with sodium nitrite according to the directions of Tchoubar (152). The average yield of 4-methylcycloheptanone was 22% based on 4-methylcyclohexanone; b.p. 79-81° (16 mm.).

Ethyl 4-Methylcycloheptylidenecyanoacetate. - A mixture of 25.2 g. (0.2 mole) of 4-methylcycloheptanone, 28.0 g. (0.25 mole) of ethyl cyanoacetate, 1.6 g. (0.02 mole) of ammonium acetate, 3.3 g. (0.06 mole) of acetic acid and 35 ml. of dry benzene was refluxed for 3-1/2 hours; a continuous "water-separator" was used as described in the preparation of ethyl cycloheptylidenecyanoacetate; b.p. 128-129° (1.5 mm.); yield 34.0 g. (77%).

Analysis Calcd. for $C_{13}H_{19}O_2N$: N, 6.33. Found: N, 6.35.

Ethyl 4-Methylcycloheptylcyanoacetate. - A mixture of 33.0 g. (0.15 mole) of ethyl 4-methylcycloheptylidenecyanoacetate, 35 ml. of absolute ethanol and 0.1 g. of platinum oxide catalyst was hydrogenated under an initial pressure of 50 lbs. The distilled product weighed 28.9 g. (88%); b.p. 119-121° (1.3 mm.).

Analysis Calcd. for $C_{13}H_{21}O_2N$: N, 6.27. Found: N, 6.36.

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

4-Methylcycloheptylacetic Acid. - A mixture of 22.3 g. (0.1 mole) of ethyl 4-methylcycloheptylcyanoacetate and 130 g. (about 0.7 mole of hydrogen bromide) of 48% hydrobromic acid was refluxed for 60 hours. The material was then treated in the manner described under cycloheptylacetic acid; b.p. 105-107° (0.7 mm.) (153); yield 13.8 g. (81%).

The amide, prepared from a sample of the acid, melted at 136-137°, after recrystallization from dilute ethanol; mixed melting point with an authentic sample of the amide, 134-136°.

Cyclooctylacetic Acid

Cyclooctatetraene* was reduced to cyclooctene (154), and the crude material was treated with hydrobromic acid, in acetic acid solution by the method described by Willstätter and Waser (155). By these processes, 120.0 g. of cyclooctatetraene yielded 112.0 g. (51%) of cyclooctyl bromide; b.p. 94-97° (12 mm.) (156).

Cyclooctylacetic Acid. - Diethyl malonate (485.0 g., 3.0 moles) was added to a solution of sodium ethylate, prepared from 57.5 g. (2.5 gram atoms) of sodium and 1900 ml. of absolute ethanol, and the mixture was stirred for 2 hours. The mixture was heated to the boiling point and 191.2 g.

* Purchased from General Aniline and Film Corporation.
(153) This acid had been prepared by Johnson (Ref. 129) by the use of the malonic ester synthesis. He found the boiling point of the acid to be 124-130° (1 mm.), and the melting point of the amide to be 128-130°.
(154) W. Reppe, O. Schlichting, K. Klager and T. Toepel, Ann., 560, 1 (1948).
(155) R. Willstätter and E. Waser, Ber., 43, 1176 (1910).
(156) Ref. 155, b.p. 90.5-91.5° (10 mm.).

(1 mole) of cyclooctyl bromide was added, dropwise, to the stirred refluxing mixture during a 24-hour period. The material was then stirred and refluxed for 36 hours. A solution of 394.0 g. (7 moles) of potassium hydroxide in 394 ml. of water and the mixture was stirred and refluxed for 20 hours. After removal of most of the alcohol by distillation, and the addition of 300 ml. of water, the mixture was stirred, and 840 ml. of concentrated hydrochloric acid was added. The material was then refluxed for 1 hour. The mixture was extracted with ether, and the ethereal solution was extracted with 2640 g. of 10% sodium hydroxide solution. The alkaline solution was then acidified with concentrated hydrochloric acid, the product was extracted with ether, and the extract was dried over magnesium sulfate. The residue, obtained after removal of the ether, was mixed with 2.0 g. of copper-bronze and heated under reduced pressure (16 mm.) in an oil-bath at 180° (bath temperature). The evolution of carbon dioxide was controlled by removal of the oil-bath at intervals. Decarboxylation was completed after about 45 minutes, and the material was then distilled; b.p. 131-133° (1.8 mm.) (157); yield 90 g.

A small portion of the acid was converted to the amide; m.p. 133-134.5° (158) after recrystallization from dilute ethanol.

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- (157) Ruzicka and Bockenoogen (Ref. 130) obtained this acid by the use of cyclooctanone and the Reformatzky reaction; b.p., 130° (1 mm.).
(158) Ref. 129, m.p. 130-132°.

β -Cycloalkylethanols and β -Cycloalkylethyl Bromides

The ethanols and ethyl bromides were prepared by the general methods which are illustrated below for the β -cycloheptylethanol and β -cycloheptylethyl bromide.

β -Cycloheptylethanol. - A solution of 78.1 g. (0.5 mole) cycloheptylacetic acid in 80 ml. anhydrous ether was added, dropwise, to a stirred mixture of 19.0 g. (0.5 mole) lithium aluminum hydride and 400 ml. anhydrous ether. After the addition was completed, the mixture was stirred and refluxed for 12 hours. Water (38 ml.) was added, dropwise, while the mixture was stirred rapidly. The material was filtered through a sintered glass funnel, and the insoluble portion was washed several times with ether. The solvent was removed and the residue distilled.

β -Cycloheptylethyl Bromide. - β -Cycloheptylethanol (71.1 g., 0.5 mole) was stirred and maintained at about 40° while 91.0 g. (0.33 mole) of phosphorus tribromide was added, dropwise. The mixture was stirred for 12 hours at room temperature and then heated in a boiling water-bath for 1 hour. The cold mixture was poured into ice-water and stirred for 30 minutes, the oily precipitate was extracted with ether, and the extract was shaken with concentrated sodium bicarbonate solution. The ether solution was dried over magnesium sulfate, the solvent was removed and the residue was fractionated.

β -4-Methylcyclohexylethanol and the corresponding ethyl bromide were also synthesized. Both the alcohol (16,131) and

the bromide (16,159) have been reported in the literature.

TABLE I

β -Cycloalkylethanols and β -Cycloalkylethyl Bromides

	<u>Ethanol</u>			<u>Ethyl Bromide</u>		
	Yield, %	B.p., °C.	Mm.	Yield, %	B.p., °C.	Mm.
Cycloheptyl	85	119-121	16	78(b)	115-118	16
4-Methylcycloheptyl	84	77-78	0.5	70(c)	118-121	15
Cyclooctyl	90	97-99(a)	1.5	79(d)	82-85	1.3

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- (a) Ref. 130, b.p. 125-127° (12 mm.).
 (b) Anal. Calcd. for $C_9H_{17}Br$: Br, 38.95. Found: Br, 39.14.
 (c) Anal. Calcd. for $C_{10}H_{19}Br$: Br, 36.46. Found: Br, 36.70.
 (d) Anal. Calcd. for $C_{10}H_{19}Br$: Br, 36.46. Found: Br, 36.58.
 (159) R. P. Perkins, U. S. Patent 2,277,714 (C. A., 39, 4095 (1945)), prepared this compound in 59% yield by cleavage of di- β -4-methylcyclohexylethyl ether with gaseous hydrogen bromide.

Primary and Secondary Amines Used as Intermediates

The following three amines are known compounds. They were obtained by the general method described under N-[β -(4-methylcycloheptyl)]ethyl piperidine.

Methyl- β -phenylethylamine. - The yield from 18.6 g. (0.6 mole) of methylamine, 100 ml. of absolute ethanol and 27.8 g. (0.15 mole) of β -phenylethyl bromide* was 12.8 g. (67%); b.p. 80-82° (10 mm.) (160). The hydrochloride melted at 158-159° (161) after recrystallization from ethyl acetate-ethanol.

Methyl- β -cyclohexylethylamine. - Thirteen and three tenths grams of this amine were obtained from 18.6 g. (0.6 mole) of methylamine, 100 ml. of absolute ethanol and 28.7 g. (0.15 mole) of β -cyclohexylethyl bromide**; b.p. 70-72° (162); yield 65%. The hydrochloride melted at 169-170° (162) after recrystallization from ethyl acetate-ethanol.

Methyl- β -(4-methylcyclohexyl)ethylamine. - From 30.0 g. (0.15 mole) of β -(4-methylcyclohexyl)ethyl bromide (16), 18.6 g. (0.6 mole) of methylamine and 100 ml. of absolute ethanol, 14.5 g. (60%) of the amine was obtained; b.p. 87-88° (12 mm.) (163). The amine hydrochloride melted at 169-171° (164) after recrystallization from ethyl acetate-ethanol.

* Purchased from the Eastman Kodak Company, Rochester, N. Y.

** Purchased from The Dow Chemical Company, Midland, Mich.

(160) G. Barger and A. J. Ewins, J. Chem. Soc., 97, 2255, (1910), b.p. 205° (760 mm.).

(161) H. Decker and P. Becker, Ann., 395, 368 (1913), m.p. 156-157°.

(162) F. F. Blicke and E. Monroe, Ref. 1, found that the amine boiled at 89-90° (14 mm.) and that the hydrochloride melted at 169-170°.

(163) Ref. 17, b.p. 81-82° (9 mm.).

(164) Ref. 17, m.p. 162-163°.

Cyclopentylamine. - This amine, as well as cycloheptyl- and cyclooctylamine, are known compounds. In spite of the fact that Wislicenus (135) had obtained cyclopentylamine by the reduction of cyclopentanone oxime with sodium and alcohol, this process is described in detail below since it was employed also for the preparation of cycloheptyl- and cyclooctylamine.

Sodium (69.0 g., 3.0 gram atoms) and 275 ml. of reagent toluene were placed in a 3-liter, 3-necked flask fitted with an efficient stirrer, dropping funnel, a nitrogen-inlet tube and a large-bore condenser. The mixture was heated until the toluene refluxed, stirred and a solution of 29.7 g. (0.3 mole) of cyclopentanone oxime (165) in a mixture of 315 ml. of butanol (3.45 mole) and 315 ml. of dry toluene was added, gradually, at such a rate that the mixture refluxed vigorously without the application of external heat. The addition of oxime required about 25 minutes. Heat was then applied to the reaction flask, 15 cc. of butanol was added and the material was refluxed for 20 minutes. The mixture was cooled in an ice-bath, and 280 ml. (3.3 moles) of concentrated hydrochloric acid was added, slowly. The pH of the mixture at this stage should be below 4; when necessary, more hydrochloric acid was added. The mixture was evaporated almost to dryness, cooled, filtered and the solid product (sodium chloride) was washed with boiling ethanol. The filtrate and the alcoholic wash solution were combined and evaporated to dryness. The

(165) W. Hentzchel, J. Wislicenus, Ann., 275, 314 (1893).

solid residue (the amine hydrochloride) was dissolved in the minimum amount of water, and the solution was extracted with ether; the ethereal extract was discarded. The aqueous solution was made strongly alkaline with 50% sodium hydroxide solution. Ether was added, the mixture was stirred and the ether layer was decanted. After the addition of solid sodium hydroxide, the mixture was treated with ether repeatedly, the mixture was stirred and the ether layer was decanted. The combined ether solutions were dried with solid sodium hydroxide, the solvent was removed and the residue was fractionated; the large forerun was saved, and the amine present in it was recovered in the form of the hydrochloride.

The fraction (7.0 g., 27.5%) which boiled at 106-109° (745 mm.) (166) was the desired amine.

When the forerun, dissolved in ether, was treated with hydrogen chloride, 8.0 g. of the amine hydrochloride precipitated. This hydrochloride, contrary to the statement in the literature (135), was not hygroscopic. The hydrochloride without purification, melted at 201-202°; m.p. 201-202° after recrystallization from ethyl acetate-ethanol.

Analysis Calcd. for $C_5H_{12}NCl$: N, 11.52; Cl, 29.17. Found: N, 11.53; Cl, 28.97.

Cycloheptylamine. - By the described procedure, 21.5 g. (63.5%) of the amine was obtained from 38.2 g. (0.30 mole) of cycloheptanone oxime (167); b.p. 164-165° (745 mm.) (168).

(166) Ref. 135, b.p. 106-108°.

(167) L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

(168) Ref. 133, b.p. 165-169° (750 mm.).

The amine hydrochloride melted at 246-247° (169) after recrystallization from ethyl acetate-ethanol.

Cyclooctylamine. - From 40.0 g. (0.28 mole) of cyclooctanone oxime (170), 16.6 g. (47%) of the amine was obtained; b.p. 96-98° (33 mm.) (171). The amine in the forerun was converted into the hydrochloride; yield 3.0 g. The salt melted at 246-248° (172) after recrystallization from ethyl acetate-ethanol.

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- (169) V. Prelog, M. Fausy, E. Neweihy and O. Häfliger, Helv. Chim. Acta, 33, 365 (1950), found 242-246°.
Ref. 133, m.p. 246-247°.
(170) Ref. 167, m.p. 36-37°.
(171) Ref. 133, b.p. 65-68° (10 mm.).
(172) Ref. 140, m.p. 244-245°.

Secondary and Tertiary Amines

Examples of methods H-L are illustrated below.

H. Methyl- β -cyclooctylethylamine and Methyl Di-(β -cyclooctylethyl)amine. - β -Cyclooctylethyl bromide (43.8 g., 0.2 mole) was added to a cold solution of 21.7 g. (0.7 mole) of methylamine in 150 ml. of benzene. The mixture was heated in a pressure bottle on a steam-bath for 6 days. The mixture was then treated with concentrated sodium hydroxide solution, the benzene layer was separated and the aqueous layer was extracted with ether. The combined ether and benzene layers were dried over potassium carbonate, and the solvent and excess methylamine were removed by distillation. Upon fractionation, 20.0 g. (59%) of methyl- β -cyclooctylethylamine, b.p. 71-73° (0.7 mm.), and 8.0 g. (26%) of methyl-di(β -cyclooctylethyl)amine, b.p. 172-174° (0.5 mm.), were obtained.

Compounds 2, 6, 8 and 12 in Table II, and compounds 7, 8, 13, 14, 23, and 24 in Table III were prepared by this general method.

I. N-[β -(4-Methylcycloheptyl)ethyl]piperidine. - A mixture of 11.0 g. (0.05 mole) of β -(4-methylcycloheptyl)ethyl bromide and 21.0 g. (0.25 mole) of piperidine in 50 ml. of absolute ethanol, was heated in a pressure bottle for 6 days on a steam-bath. The mixture was acidified with concentrated hydrochloric acid, the alcohol was removed and the residue was extracted with ether. The extract was discarded. The aqueous solution was made alkaline with concentrated sodium

hydroxide solution and then extracted with ether. The extract was dried over potassium carbonate, the solvent was removed and the residue was fractionated; b.p. 159-161° (14 mm.); yield 8.5 g. (76%).

Compounds 3, 4, 5, 7, 9, 10 and 14 in Table II and compounds 1-6 and 11-18 in Table IV were prepared by this general process.

J. N-(β-Cycloheptylethyl)octamethylenimine. - A mixture of 10.2 g. (0.05 mole) of β-cycloheptylethyl bromide, 7.6 g. (0.6 mole) of octamethylenimine, 10.6 g. (0.1 mole) of anhydrous potassium carbonate and 25 ml. of ethanol was stirred and refluxed for 48 hours. The mixture was cooled in an ice-bath, acidified with concentrated hydrochloric acid and evaporated almost to dryness, the residue was triturated with ether and the mixture filtered. The solid material was the amine hydrochloride. The filtrate was evaporated to dryness and the residue was washed with ether. This residue often represented an appreciable amount of the amine hydrochloride.

Sodium hydroxide solution (20%) was added to the amine hydrochloride, and the amine base was extracted with ether. The ethereal solution was dried over anhydrous potassium carbonate, the solvent was removed and the residue fractionated; b.p. 113-116° (0.2 mm.); yield 9.0 g. (72%).

Compounds 5 and 11 in Table II, compounds 1-6, 9-12 and 15-22 in Table III and compounds 7-10 and 19-22 in Table IV were obtained by this process.

K. Cycloheptyldi(β-cyclohexylethyl)amine. - A mixture

of 5.6 g. (0.05 mole) of cycloheptylamine, 20.1 g. (0.10 mole) of β -cyclohexylethyl bromide, 21.2 g. (0.2 mole) of potassium carbonate, and 25 ml. of ethanol was stirred and refluxed for 60 hours. The mixture was acidified with concentrated hydrochloric acid and then treated in the manner described in process J. The yield of amine was 11.5 g. (75.5%); b.p. 187-189° (0.7 mm.).

All the compounds in Table V were obtained by this procedure.

L. Methyldi-(β -2-pyridylethyl)amine. - Methyl(β -2-pyridylethyl)amine (141) (9.5 g., 0.07 mole) and 10.5 g. (0.10 mole) of 2-vinylpyridine* was refluxed for 5 hours. The excess 2-vinylpyridine was removed by distillation, and the residue was fractionated; b.p. 141-142° (0.3 mm.); yield 7.7 g. (46%).

An attempt was made to obtain the trimethobromide. The reaction product was a hygroscopic solid which could not be purified by recrystallization.

Compound 13 in Table II, compounds 25-29 in Table III and compounds 23-27 in Table IV were synthesized by this process.

β -Cycloheptylethylamine. - Cycloheptylacetonitrile (51.2 g., 0.3 mole), dissolved in 100 ml. of absolute ether, was reduced with 11.4 g. (0.3 mole) of lithium aluminum hydride dissolved in 300 ml. of ether. The reaction mixture was refluxed and stirred for 40 hours, and 23 ml. of water

*Purchased from Matheson, Coleman and Bell, Inc., Norwood, Ohio.

was then added, carefully. The filtrate from the filtered mixture was extracted with dilute hydrochloric acid. The acidic solution was treated with concentrated sodium hydroxide solution, and then extracted with ether. The ethereal solution was dried over potassium carbonate, the solvent was removed and the residue was distilled; b.p. 93-96° (12 mm.); yield 25.2 g. (60%).

β -Cycloheptylethylamine. - Thirteen and five tenths grams (0.1 mole of cycloheptenylacetonitrile, dissolved in 100 ml. anhydrous ether, was reduced with 3.8 g. (0.1 mole) of lithium aluminum hydride dissolved in 100 ml. of anhydrous ether. When the addition was completed, the mixture was stirred and refluxed for 12 hours. After the careful addition of 7.5 ml. of water with rapid stirring the mixture was filtered and the solid material was washed thoroughly with ether. The ethereal solution was dried, the solvent was removed by distillation, and the residue was fractionated; yield 7.5 g. (53%); b.p. 124-126° (25 mm.).

The amine was dissolved in ether, and precipitated as its hydrochloride by the addition of hydrogen chloride. This hydrochloride, which was not isolated for identification, was filtered and dissolved in 20 ml. of absolute ethanol, 0.1 g. platinum oxide catalyst was added and the mixture was hydrogenated under an initial pressure of 50 lbs. at 40-50°. After 2 hours, about 97% of the calculated amount of hydrogen had been absorbed. The mixture was filtered, ether was added to the hot alcoholic filtrate until the product began to

precipitate. The mixture was then cooled. The product weighed 8.5 g. (90% yield); m.p. 255-257°; mixed melting point with an authentic sample, 255-257°.

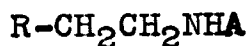
β-Cyclooctylethylamine. - β-Cyclooctylethyl bromide (8.8 g., 0.04 mole) was mixed with 8.5 g. (0.5 mole) of ammonia, dissolved in 80 ml. ethanol and the mixture was heated in a pressure bottle on a steam-bath for 6 days. The excess ammonia was removed by distillation, and, after cooling, the mixture was acidified with concentrated hydrochloric acid and then proceeded as described in process I described for N-β-(4-methylcycloheptyl)ethyl piperidine.

The product, after redistillation, weighed 3.5 g. (65%); b.p. 113-115° (15 mm.).

Methyl[β-(4-pyridyl)ethyl]amine. - A mixture of 21.0 g. (0.2 mole) 4-vinylpyridine and 4.1 g. (0.133 mole) methylamine, dissolved in 80 ml. of absolute ethanol, was heated in a pressure bottle on a steam-bath for 6 days. The excess of methylamine and the solvent were removed by distillation and the residue fractionated; yield 14.0 g. (51%); b.p. 118-120 (15 mm.).

No methyldi[β-(4-pyridyl)ethyl]amine was obtained as reaction product under these conditions, although it had been hoped that both the secondary and tertiary amines could be obtained by this process.

TABLE II



JAS-	No.	R	A	B.p. °C	Mm.	Yield %	Salt	M.p. °C
130	1	Cycloheptyl	Hydrogen	93-96	12	60	HCl	256-257*
135	2	Cycloheptyl	Methyl	103-106	18	62	HCl	183-184
103	3	Cycloheptyl	Isopropyl	127-129	18	88	HCl	194-195
106	4	Cycloheptyl	Allyl	120-123	10	63	HCl	239-240*
107	5	Cycloheptyl	Cyclopentyl	94-95	0.3	72	HCl	227-229*
138	6	4-Methyl- cycloheptyl	Methyl	116-118	17	33	HCl	168-170
149	7	Cyclooctyl	Hydrogen	113-115	15	56	HCl	258-260*
131	8	Cyclooctyl	Methyl	105-107	9	59	HCl	183-185
116	9	Cyclooctyl	Isopropyl	122-124	9	91	HCl	184-185
117	10	Cyclooctyl	Allyl	131-133	9	94	HCl	242-243*
150	11	Cyclooctyl	Cyclopentyl	167-170	12	45	HCl	230-232*
133	12	2-Pyridyl	Methyl	104-105 (a)	15	33	di-HCl	153-154 (b)
141	13	4-Pyridyl	Methyl	118-120	15	51	di-HCl	183-185 (c)

Analyses, %

	Formula	Carbon		Hydrogen		Nitrogen		Halogen	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	C ₉ H ₂₀ NC1	60.83		11.34		7.88	7.95	19.95	19.91
2	C ₁₀ H ₂₂ NC1	62.60		11.57		7.33	7.35	18.48	18.52
3	C ₁₂ H ₂₆ NC1	65.57		11.93		6.37	6.36	16.15	16.18
4	C ₁₂ H ₂₄ NC1	66.16		11.10		6.43	6.36	16.28	16.50

TABLE II (concluded)

Analyses, %

Formula	Carbon		Hydrogen		Nitrogen		Halogen	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
5 $C_{14}H_{28}NCl$	68.40	68.41	11.48	11.52	5.70	5.60	14.42	14.52
6 $C_{11}H_{24}NCl$	64.20		11.76		6.81	6.85	17.23	17.15
7 $C_{10}H_{22}NCl$	62.63		11.57		7.31	7.27	18.49	18.50
8 $C_{11}H_{24}NCl$	64.18		11.76		6.81	6.84	17.23	17.32
9 $C_{13}H_{28}NCl$	66.77		12.06		5.99	6.17	15.19	15.23
10 $C_{13}H_{26}NCl$	67.35		11.30		6.04	6.19	15.31	15.24
11 $C_{15}H_{30}NCl$	69.33		11.63		5.39	5.35	13.65	13.75
12 $C_8H_{14}N_2Cl_2$	45.93		6.75		13.40	13.35	33.91	34.08
13 $C_8H_{14}N_2Cl_2$	45.93		6.75		13.40	13.24	33.91	34.00

Compounds 1, 2, 3, 4, 5, 6, 7, 8, 10 and 11 were recrystallized from ethyl acetate-ethanol; compound 12 from ethanol-ether; compound 13 from ethanol; and compound 9 from 2-butanone.

* Melts with decomposition.

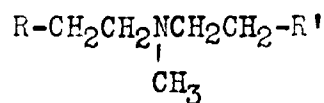
(a) Ref. 141 B.p. 113-114° (30 mm.).

(b) Ref. 141 M.p. 148-149°.

(c) This compound melted at 183-185°, solidified immediately and then melted again, with decomposition, at 216-220° C.

TABLE III

Cyverine Analogs



JAS- No.	R	R'	B.p. °C	Mm.	Yield %	Salt	M.p. °C
102 1	Cycloheptyl	Phenyl	144-146	1	59	HCl	210-211*
102A 2	Cycloheptyl	Phenyl				CH ₃ Br	158-159
104 3	Cycloheptyl	Cyclohexyl	198-201	16	68	HCl	257-258*
104A 4	Cycloheptyl	Cyclohexyl				CH ₃ Br	82 (a)
124 5	Cycloheptyl	4-Methylcyclohexyl	130-132	0.7	50	HCl	248-249*
124A 6	Cycloheptyl	4-Methylcyclohexyl				CH ₃ Br	94-96 (a)
101 7	Cycloheptyl	Cycloheptyl	215-217	18	24	HCl	249-250*
101A 8	Cycloheptyl	Cycloheptyl				CH ₃ Br	110 (a)
140 9	4-Methylcycloheptyl	Phenyl	134-136	0.3	74	HCl	191-192
140A 10	4-Methylcycloheptyl	Phenyl				CH ₃ Br	124-125.5
143 11	4-Methylcycloheptyl	Cyclohexyl	135-136	0.5	57	HCl	228-230*
143A 12	4-Methylcycloheptyl	Cyclohexyl				CH ₃ Br	109-110.5
139 13	4-Methylcycloheptyl	4-Methylcycloheptyl	143-144	0.2	39	HCl	222-224*
139A 14	4-Methylcycloheptyl	4-Methylcycloheptyl				CH ₃ Br	138-140
110 15	Cyclooctyl	Phenyl	145-146	0.4	55	HCl	199-200
110A 16	Cyclooctyl	Phenyl				CH ₃ Br	173-174
113 17	Cyclooctyl	Cyclohexyl	144-146	0.7	75	HCl	232-233*
113A 18	Cyclooctyl	Cyclohexyl				CH ₃ Br	112 (a)
120 19	Cyclooctyl	4-Methylcyclohexyl	146-148	0.2	69	HCl	236-238*
120A 20	Cyclooctyl	4-Methylcyclohexyl				CH ₃ Br	120 (a)
112 21	Cyclooctyl	Cycloheptyl	172-174	0.5	55	HCl	231-232*
112A 22	Cyclooctyl	Cycloheptyl				CH ₃ Br	100 (a)

TABLE III (continued)

JAS- No.	R	R'	B.p. °C	Mm.	Yield %	Salt	M.p. °C
114 23	Cyclooctyl	Cyclooctyl	172-174	0.5	26	HCl	221-222*
114A 24	Cyclooctyl	Cyclooctyl				CH ₃ Br	119 (a)
128 25	2-Pyridyl	Phenyl	197-200	15	47	di-HCl	157-158
129 26	2-Pyridyl	Cyclohexyl	188-190	15	73	di-HCl	172-173
127 27	2-Pyridyl	4-Methylcyclohexyl	195-196	15	73	di-HCl	169-170
134 28	2-Pyridyl	2-Pyridyl	141-142	0.3	46	tri-HCl	166-167
142 29	4-Pyridyl	4-Pyridyl	163-165	0.7	28	tri-HCl	224-225*

Analyses, %

No.	Formula	Carbon		Hydrogen		Nitrogen		Halogen	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	C ₁₈ H ₃₀ NC1	73.06	73.27	10.23	10.17	4.73	4.50	12.00	12.07
2	C ₁₉ H ₃₂ NBr	64.38	64.68	9.08	9.27	3.95	3.88	22.55	22.75
3	C ₁₈ H ₃₆ NC1	71.56	71.51	12.04	12.31	4.63	4.71	11.73	11.56
4	C ₁₉ H ₃₈ NBr	63.31	62.51	10.63	10.65	3.88	3.86	22.12	22.40
5	C ₁₉ H ₃₈ NC1	72.22	72.20	12.12	12.07	4.43	4.37	11.22	11.25
6	C ₂₀ H ₄₀ NBr	64.15		10.77		3.74	3.79	21.34	21.25
7	C ₁₉ H ₃₈ NC1	72.15	72.26	12.12	12.22	4.43	4.47	11.23	11.31
8	C ₂₀ H ₄₀ NBr	64.15	64.06	10.76	10.90	3.74	3.81	21.35	21.75
9	C ₁₉ H ₃₂ NC1	73.63	73.85	10.41	10.65	4.52	4.54	11.44	11.48
10	C ₂₀ H ₃₄ NBr	65.20	65.32	9.30	9.47	3.80	3.83	21.69	21.55
11	C ₁₉ H ₃₈ NC1	72.22	72.32	12.12	12.40	4.43	4.40	11.22	11.23
12	C ₂₀ H ₄₀ NBr	64.14	64.03	10.78	10.31	3.74	3.76	21.34	21.24
13	C ₂₁ H ₄₂ NC1	73.31	73.15	12.31	12.27	4.07	4.18	10.31	10.35
14	C ₂₂ H ₄₄ NBr	65.64	65.64	11.02	11.07	3.48	3.65	19.86	19.93
15	C ₁₉ H ₃₂ NC1	73.60	73.86	10.42	10.34	4.52	4.58	11.45	11.52

TABLE III (concluded)

No.	Formula	Analyses, %							
		Carbon		Hydrogen		Nitrogen		Halogen	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
16	$C_{20}H_{34}NBr$	65.21	65.26	9.31	9.36	3.80	3.87	21.68	21.75
17	$C_{19}H_{38}NCl$	72.22	72.40	12.12	12.15	4.43	4.33	11.23	11.19
18	$C_{20}H_{40}NBr$	64.15	64.00	10.75	10.67	3.64	3.82	21.34	21.40
19	$C_{20}H_{40}NCl$	72.80	72.42	12.22	12.21	4.23	4.39	10.73	10.93
20	$C_{21}H_{42}NBr$	64.91	64.60	10.89	10.87	3.60	3.70	20.57	20.50
21	$C_{20}H_{40}NCl$	72.80	72.87	12.21	12.38	4.24	4.40	10.76	10.81
22	$C_{21}H_{42}NBr$	64.91	64.93	10.92	10.67	3.60	3.57	20.56	20.64
23	$C_{21}H_{42}NCl$	73.29	73.26	12.32	12.42	4.07	4.09	10.32	10.28
24	$C_{22}H_{44}NBr$	65.64		11.03		3.48	3.57	19.85	19.78
25	$C_{16}H_{22}N_2Cl_2$	61.35		7.08		8.94	8.88	22.63	22.60
26	$C_{16}H_{28}N_2Cl_2$	60.25		8.84		8.77	8.82	22.20	22.33
27	$C_{17}H_{30}N_2Cl_2$	61.25		9.07		8.41	8.47	21.27	21.30
28	$C_{15}H_{22}N_3Cl_3$	51.38		6.33		11.98	11.95	30.34	30.25
29	$C_{15}H_{22}N_3Cl_3$	51.38		6.33		11.98	11.85	30.34	30.37

Compounds 3, 5, 9, 11, 13, 16, 17, 19, 21 and 23 were recrystallized from ethyl acetate-ethanol; compounds 4, 6, 8, 18, 20, 22 and 24 from benzene-ether; compounds 25, 26, 27 and 29 from ethanol-ether; compounds 1, 2 and 10 from 2-butanone; compounds 12 and 14 from 2-butanone-ether; compound 15 from ethyl acetate; compound 7 from ethanol-water; and compound 28 from ethanol-methanol.

* Melts with decomposition.

(a) These compounds were very hygroscopic and at the temperature indicated, they lost their crystalline structure forming a semisolid mass that became fluid gradually.

TABLE IV
Cyverine Analogs
 $R-CH_2CH_2N<(CH_2)_n$

JAS-	No.	R	n	B.p. °C	Mmc.	Yield %	Salt	M.p. °C
136	1	Cycloheptyl	4	139-141	15	71	HCl	219-220*
136A	2	Cycloheptyl	4				CH ₃ Br	163-164
109	3	Cycloheptyl	5	79-82	0.3	85	HCl	246-247*
109A	4	Cycloheptyl	5				CH ₃ Br	201-202
105	5	Cycloheptyl	6	162-164	11	63	HCl	231-232*
105A	6	Cycloheptyl	6				CH ₃ Br	203-204
108	7	Cycloheptyl	7	106-108	0.2	75	HCl	206-207
108A	8	Cycloheptyl	7				CH ₃ Br	190-191
132	9	Cycloheptyl	8	113-116	0.2	72	HCl	189-190
132A	10	Cycloheptyl	8				CH ₃ Br	184-185
137	11	4-Methyl- cycloheptyl	5	159-161	14	76	HCl	232-234*
137A	12	4-Methyl- cycloheptyl	5				CH ₃ Br	183-184
144	13	Cyclooctyl	4	155-157	15	57	HCl	224-226*
144A	14	Cyclooctyl	4				CH ₃ Br	186-187
111	15	Cyclooctyl	5	150-152	9	96	HCl	239-240*
111A	16	Cyclooctyl	5				CH ₃ Br	213-214*
118	17	Cyclooctyl	6	182-183	15	56	HCl	243-245*
118A	18	Cyclooctyl	6				CH ₃ Br	211-212*
115	19	Cyclooctyl	7	127-129	0.3	82	HCl	209-210
115A	20	Cyclooctyl	7				CH ₃ Br	188-189
119	21	Cyclooctyl	8	132-135	0.1	83	HCl	198-200*

TABLE IV (continued)

JAS- No.	R	n	B.p. °C	Mm.	Yield %	Salt	M.p. °C
119A 22	Cyclooctyl	8				CH ₃ Br	161-162
121 23	2-Pyridyl	4	139-141	20(a)	50	di-HCl	169-170
122 24	2-Pyridyl	5	147-148	18	77	di-HCl	184-185 (b)
123 25	2-Pyridyl	6	163-164	18	50	di-HCl	173-174
125 26	2-Pyridyl	7	172-174	17	55	di-HCl	172-173
126 27	2-Pyridyl	8	182-183	15	38	di-HCl	171-172

Analyses, %

Formula	Carbon		Hydrogen		Nitrogen		Halogen	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1 C ₁₃ H ₂₆ NCl	67.36		11.31		6.04	6.16	15.30	15.32
2 C ₁₄ H ₂₈ NBr	57.92	57.86	9.72	9.87	4.83	4.85	27.57	27.42
3 C ₁₄ H ₂₈ NCl	68.40	68.68	11.48	11.62	5.70	5.54	14.42	14.60
4 C ₁₅ H ₃₀ NBr	59.23	59.20	9.94	10.00	4.60	4.81	26.24	26.30
5 C ₁₅ H ₃₀ NCl	69.30	69.30	11.65	11.34	5.38	5.35	13.64	13.90
6 C ₁₆ H ₃₂ NBr	60.36	60.47	10.14	10.20	4.40	4.41	25.10	24.90
7 C ₁₆ H ₃₂ NCl	70.17	70.00	11.81	11.83	5.12	5.06	12.95	12.83
8 C ₁₇ H ₃₄ NBr	61.35	61.65	10.31	10.42	4.21	4.45	24.05	24.18
9 C ₁₇ H ₃₄ NCl	70.90	70.89	11.90	11.92	4.76	4.90	12.31	12.41
10 C ₁₈ H ₃₆ NBr	62.41	62.00	10.49	10.59	4.04	4.06	23.07	23.07
11 C ₁₅ H ₃₀ NCl	69.34		11.64		5.39	5.31	13.65	13.82
12 C ₁₆ H ₃₂ NBr	60.36	60.38	10.13	10.25	4.40	4.53	25.10	25.30
13 C ₁₄ H ₂₈ NCl	68.40		11.48		5.69	5.70	14.42	14.53
14 C ₁₅ H ₃₀ NBr	59.20	59.28	9.94	10.09	4.60	4.50	26.26	26.25
15 C ₁₅ H ₃₀ NCl	69.35	69.50	11.62	11.74	5.39	5.58	13.68	13.65

TABLE IV (concluded)

Analyses, %

Formula	Carbon		Hydrogen		Nitrogen		Halogen	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
16 C ₁₆ H ₃₂ NBr	60.35	60.71	10.15	10.23	4.40	4.35	25.10	24.98
17 C ₁₆ H ₃₂ NCl	70.15		11.78		5.12	5.13	12.95	13.13
18 C ₁₇ H ₃₄ NBr	61.43	61.28	10.31	10.32	4.21	4.25	24.05	24.10
19 C ₁₇ H ₃₄ NCl	70.83	70.65	11.91	11.48	4.86	5.00	12.33	12.38
20 C ₁₈ H ₃₆ NBr	62.42	62.03	10.48	10.11	4.04	4.09	23.07	23.09
21 C ₁₈ H ₃₆ NCl	71.60	71.42	12.02	11.85	4.64	4.69	11.74	11.83
22 C ₁₉ H ₃₈ NBr	63.30		10.62		3.89	4.06	22.17	22.26
23 C ₁₁ H ₁₈ N ₂ Cl ₂	53.00		7.39		11.24	11.17	28.45	28.47
24 C ₁₂ H ₂₀ N ₂ Cl ₂	54.75		7.66		10.66	10.70	26.94	27.00
25 C ₁₃ H ₂₂ N ₂ Cl ₂	56.30		8.00		10.11	10.01	25.58	25.64
26 C ₁₄ H ₂₄ N ₂ Cl ₂	57.70		8.30		9.62	9.54	24.35	24.45
27 C ₁₅ H ₂₆ N ₂ Cl ₂	59.03		8.62		9.18	9.15	23.22	23.50

Compounds 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21 were recrystallized from ethyl acetate-ethanol; compounds 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22 from 2-butanone; and compounds 23, 24, 25, 26 and 27 from ethanol-ether.

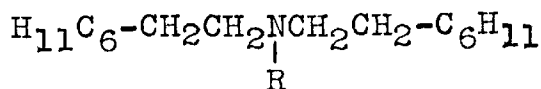
* Melts with decomposition

(a) H. E. Reich and R. Levine, Ref. 143, reported the preparation of this compound during the course of this investigation.

(b) Ref. 142, B.p. 121-127° C (4 mm.), or 108° C (1 mm.). Monohydrochloride salt, M.p. 173° C.

TABLE V

Cyverine Analogs



JAS- No.	R	B.p. °C	Mm.	Yield %	Salt	M.p. °C
145 1	Cyclopentyl	167-170	0.5	49	HCl	103-105(a)
145A 2	Cyclopentyl				CH ₃ Br	140-141
146 3	Cyclohexyl	171-173	0.5	63	HCl	168-169
146A 4	Cyclohexyl				CH ₃ Br	135-136
147 5	Cycloheptyl	187-189	0.7	75	HCl	161-162
147A 6	Cycloheptyl				CH ₃ Br	121-122
148 7	Cyclooctyl	191-194	0.4	38	HCl	209-211

Analyses, %

Formula		Carbon Calcd.Found		Hydrogen Calcd.Found		Nitrogen Calcd.Found		Halogen Calcd.Found	
1	C ₂₁ H ₄₀ NCl	73.74		11.79		4.10	4.22	10.37	10.60
2	C ₂₂ H ₄₂ NBr	65.95		10.60		3.50	3.56	19.95	20.02
3	C ₂₂ H ₄₂ NCl	74.21		11.85		3.95	3.90	9.97	9.87
4	C ₂₃ H ₄₄ NBr	66.63	66.72	10.70	10.98	3.38	3.35	19.28	19.25
5	C ₂₃ H ₄₄ NCl	74.64	74.90	11.98	12.08	3.79	3.98	9.58	9.76
6	C ₂₄ H ₄₆ NBr	67.26	67.52	10.82	10.70	3.27	3.27	18.65	18.65
7	C ₂₄ H ₄₆ NCl	75.04		12.07		3.65	3.76	9.23	9.24

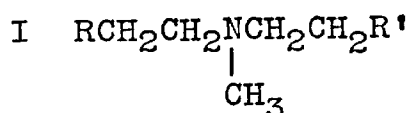
(a) The hydrochloride separated as a liquid which would not solidify after repeated washings with anhydrous ether. The liquid hydrochloride was dissolved in a small amount of boiling ethanol, and boiling water was added until the solution became slightly turbid. The sides of the flask containing the cooled solution were scratched until crystallization started. The dried crystalline product was recrystallized from ethyl acetate-ether (the solution exhibited a marked tendency to supersaturate). After preliminary drying at room temperature at 1 mm. pressure, it was dried for 12 hours at 55° C at 1 mm. pressure.

SUMMARY

During this investigation, a number of analogs of the antispasmodic Cyverine, which is methyldi(β-cyclohexylethyl)-amine, were prepared in order that they might be tested for pharmacological activity.

These analogs represent amines in which one or both of the cyclohexyl groups in Cyverine were replaced by a seven- or eight-membered ring (cycloheptyl, 4-methylcycloheptyl or cyclooctyl) or by a heterocyclic radical (2- or 4-pyridyl). In some of the analogs, the NCH₃ group of Cyverine was represented by a five-, six-, seven-, eight-, or nine membered nitrogenous ring, that is by a pyrrolidino, piperidino, 1-heptamethylenimino or 1-octamethylenimino group. In other analogs the methyl group, attached to the nitrogen in Cyverine, was replaced by cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl radicals.

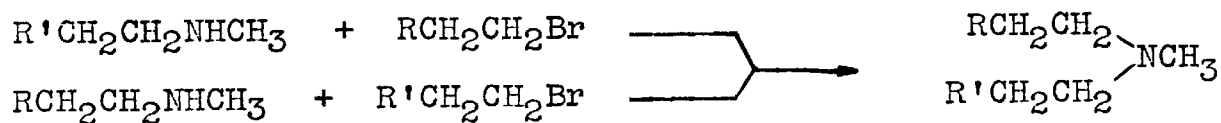
All of the tertiary amines prepared can be represented by the three general formulas, I, II, III, shown below.



R = cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- or 4-pyridyl; R' = phenyl, cyclohexyl, 4-methylcyclohexyl, cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- or 4-pyridyl.

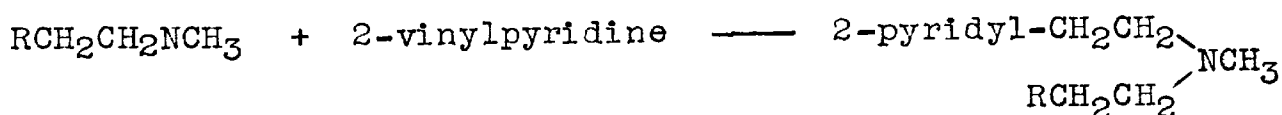
The synthesis of these compounds was accomplished by two different methods:

A. Direct alkylation of a secondary amine with a β-cycloalkylethyl bromide



By the use of this method 12 tertiary amines, listed in Table III were prepared.

B. Interaction of a secondary amine with 2- or 4-vinylpyridine



This method was employed for the preparation of five amines listed in Table III.

II $\text{RCH}_2\text{CH}_2\text{N}(\text{CH}_2)_n$ R = cycloheptyl, 4-methylcycloheptyl, cyclooctyl or 2-pyridyl; n = 4, 5, 6, 7, 8.

The same two general methods A and B, outlined above, were used for the preparation of these tertiary amines, but the secondary amines utilized in these instances were polymethylenimines. We prepared 16 tertiary amines of this type, 5 of which contain the 2-pyridyl radical.

III $\text{C}_6\text{H}_{11}\text{CH}_2\text{CH}_2\underset{\text{R}}{\text{N}}\text{CH}_2\text{CH}_2\text{C}_6\text{H}_{11}$ R = cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl.

These analogs were prepared by direct alkylation of the primary cycloalkylamines with β -cyclohexylethyl bromide. We prepared 4 tertiary amines of this type which are to be found listed in Table V.

All the tertiary amines were submitted for pharmacological studies as their hydrochlorides and methobromides.

In addition to the tertiary amines mentioned above, a series of 13 secondary amines which contained cycloheptyl, 4-methylcycloheptyl, cyclooctyl, 2- or 4-pyridyl radicals were synthesized and submitted as their hydrochlorides for pharmacological evaluation.

A total of 50 secondary and tertiary amines were synthesized; as far as we are aware, 47 of these compounds have not been reported in the literature.

For the preparation of these amines, a large number of intermediates were required. The preparation of these intermediates was far more time consuming than the preparation of the amines submitted for pharmacological studies; for example, to obtain the β -4-methylcycloheptylethyl bromide, it was necessary to transform, successively, 4-methylcyclohexanone to 1-cyano-4-methylcyclohexanol, 1-aminomethyl-4-methylcyclohexanol, 4-methylcycloheptanone, ethyl 4-methylcycloheptylidene-cyanoacetate, ethyl 4-methylcycloheptylcyanoacetate, cycloheptylacetic acid, β -4-methylcycloheptanol.

Since many of the final products were made by processes which consisted of a number of steps, it was necessary to synthesize the intermediates in large amounts even when good yields in the individual steps were obtained; each intermediate was prepared from two to seven times. Nine of the intermediates represent new compounds.