The crude product, isolated by salting out with potassium carbonate into ether solution, was converted to the *dihydrochloride:* yield, 20.6 g. (84%) of colorless crystals. Recrystallization from ethanol gave a pure sample, m.p. 229–231°.

Anal. Calcd. for $C_{14}H_{24}O_2N_2Cl_2$: C, 52.01; H, 7.48; N, 8.67. Found: C, 51.87; H, 7.43. N, 8.75.

By the same procedure, two additional compounds were prepared from 3-aminopiperidine.[6]

3-(4'-Dimethylaminobenzylamino)piperidine was obtained by reduction of the *p*-dimethylaminobenzylidene derivative and isolated in 76% yield as the *trihydrochloride:* hygroscopic, light-sensitive crystals from ethanol, having no definite melting point (gradual decomposition when heated).

Anal. Calcd. for $C_{14}H_{26}N_3Cl_3$: C, 49.06; H, 7.65; N, 12.26. Found: C, 48.5; H, 7.50; N, 11.9.

3-(3-Pyridylmethylamino)piperidine was obtained by reduction of the 3-pyridylidene derivative, and isolated in 79% yield as the *trihydrochloride:* very hygroscopic crystals which, like the preceding compound, did not have a definite melting point.

Anal. Calcd. for $C_{11}H_{20}N_3Cl_3$: C, 43.94; H, 6.71; N, 13.98. Found: C, 44.02; H, 6.98; N, 13.96.

N,N-Dimethyl-N'-(3,4-dimethoxybenzyl)hydrazine. When 16.3 g. of veratraldehyde and 6.5 g. of *N,N*-dimethylhydrazine were mixed there was heat evolution. The oil was taken up in 200 ml. of benzene, and the solution was refluxed under a water separator for 4 hr., which resulted in slow, steady collection of water. After evaporation of the benzene, the oily hydrazone was dissolved in methanol and reduced with sodium borohydride by the usual procedure. The product, isolated by extraction with ether after dilution of the reaction mixture, was an oil. The *hydrochloride* separated in 13.9 g. (56%) yield, m.p. 172–174.5°, when this oil was treated with alcoholic hydrogen chloride. Recrystallization from ethanol-ether did not raise this melting point.

Anal. Calcd. for $C_{11}H_{19}O_2N_2Cl$: C, 53.54; H, 7.76; N, 11.36; Cl, 14.37. Found: C, 53.62; H, 7.2; N, 11.6; Cl, 14.46.

The other hydrazine derivatives listed in Table III were prepared by essentially the same procedure, except that toluene was used in place of benzene in condensation of *p*-dimethylaminobenzaldehyde with 1,1-dimethylhydrazine. Hydrazones which were obtained by condensation of various pyridine aldehydes with 1,1-dimethylhydrazine were not affected by treatment with sodium borohydride.

Acknowledgment. We take pleasure in acknowledging the services of Mr. George Robertson, Mrs. Patricia Giaimo, Mr. Rudolf Oeckinghaus, and Mrs. Louise Porter of the Micro-Analytical Laboratory, under the direction of Mr. Louis Dorfman. It is also a pleasure to thank Dr. E. Schlittler for his interest in and encouragement of the program which led to these results.

SUMMIT, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, LEPETIT S.P.A.]

Bicyclic Homologs of Piperazine. II. Synthesis of 3,8-Diazabicyclo[3.2.1]octane. New Synthesis of 8-Methyl-3,8-diazabicyclo[3.2.1]octane

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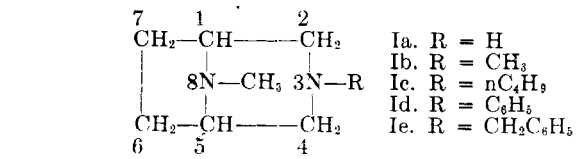
3,8-Diazabicyclooctane[3.2.1] (I) was obtained by a four step synthesis from 2,5-dicarbethoxypyrrolidine (II). This compound was converted into 2-benzylcarbamyl-5-carbethoxypyrrolidine (III) which, when heated, gave 3-benzyl-3,8-diazabicyclooctane[3.2.1]-2,4-dione (IV). The latter by reduction with lithium aluminum hydride to 3-benzyl-3,8-diazabicyclooctane[3.2.1] (V) and reductive debenzylation gave I. An alternate synthesis of I from the already known 8-carbobenzoxy-3,8-diazabicyclooctane[3.2.1]-2,4-dione (VIII) is also described. The known 8-methyl-3,8-diazabicyclooctane[3.2.1] has now been obtained by a new improved synthesis in five steps starting from II through V.

In the preceding paper of this series[1] we described the synthesis of several 3-substituted 8-methyl-3,8-diazabicyclooctanes[3.2.1] of general formula



Ia. R = H
Ib. R = CH_3
Ic. R = nC_4H_9
Id. R = C_6H_5
Ie. R = $CH_2C_6H_5$

obtained starting from 2,5-dicarbethoxypyrrolidine (II),[2] which was converted in three steps into *N*-carbobenz-oxy-2,5-pyrrolidine dicarboxylic acid anhydride. The latter reacted with appropriate amines to give 3-substituted 8-carbobenz-oxy-3,8-diazabicyclooctane[3.2.1]-2,4-diones from which the corresponding bicyclic bases were obtained by direct reduction with lithium aluminum hydride in ether.

We now describe the synthesis of the unsubstituted bicyclic ring, 3,8-diazabicyclooctane[3.2.1] (I). The key intermediate for the synthesis is 3-benzyl-3,8-diazabicyclooctane[3.2.1]2,4-dione (IV). This compound was initially prepared in a 52% yield by hydrogenolysis in methanol[3] of 3-benzyl-8-carbobenz-oxy-3,8-diazabicyclooctane[3.2.1]-2,4-dione[1] (VI). In the course of this reduction 2-benzylcarbamyl-5-carbomethoxypyrrolidine (VII) was also identified as by-product.

A more efficient method was subsequently found for obtaining the intermediate IV from 2,5-dicarbethoxypyrrolidine (II). 2-Benzylcarbamyl-5-carbethoxypyrrolidine (III) was obtained in 87%

(1) G. Cignarella and G. Nathansohn, *J. Org. Chem.*, in press.

(2) G. Cignarella and G. Nathansohn, *Gazz. Chim. Ital.*, **90**, 1695 (1960).

(3) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

yield (based on the diester used) by refluxing II with benzylamine in xylene. By heating III at 200° evolution of ethanol was observed with formation of a viscous oil, which, when distilled *in vacuo*, gave a fraction identical with IV obtained by hydrogenolysis of VI. In fact, the infrared spectrum of the distilled product lacked the ester band at 1730 cm.$^{-1}$ and the secondary amide band at 1530 cm.$^{-1}$ and showed two bands, characteristic of an imido group, at 1720–1680 cm.$^{-1}$

Reduction of IV with lithium aluminum hydride in ether solution[4] led in 65% yield to 3-benzyl-3,8-diazabicyclooctane[3.2.1] (V) which, when debenzylated with hydrogen and palladium, gave 3,8-diazabicyclooctane (I) in 80% yield. I is a colorless fluid boiling 178–180° with piperazine-like smell, which quickly adsorbs carbon dioxide when exposed to air.

The analytical data in accordance with the general formula $C_6H_{12}N_2$ and the presence of two secondary nitrogen atoms[5] confirmed the 3,8-diazabicyclooctane structure. I was also characterized through the dihydrochloride and the dipicrate.

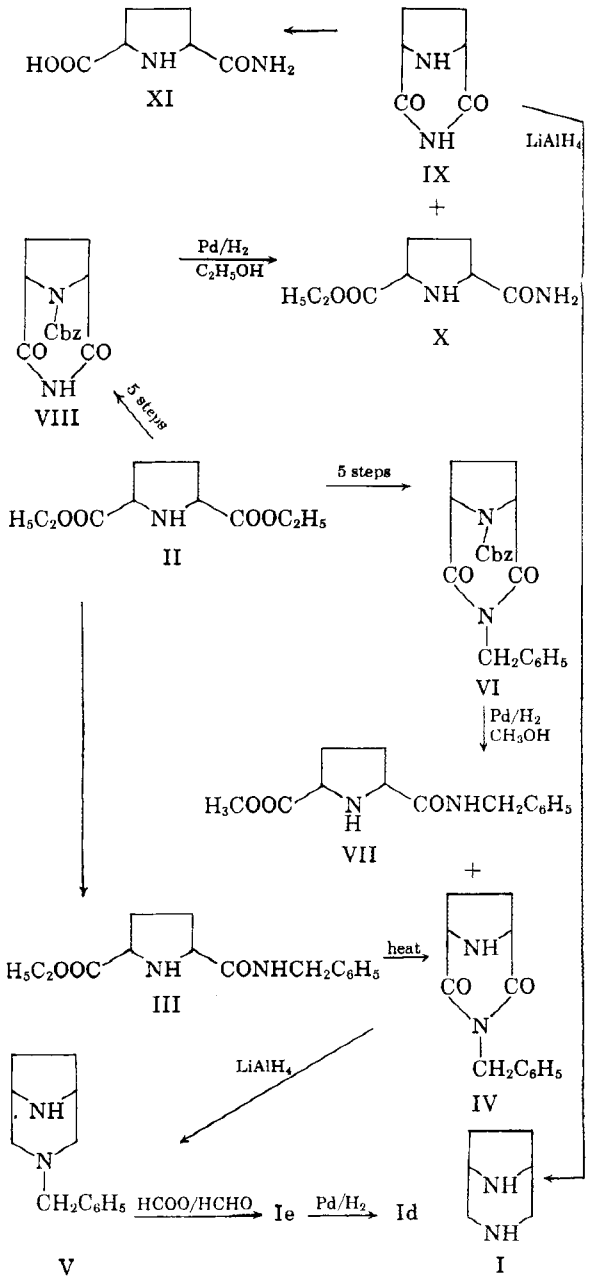
An alternative synthesis of I comprises reduction with lithium aluminum hydride of 3,8-diazabicyclooctane[3.2.1]-2,4-dione (IX) which can be obtained by hydrogenolysis from the corresponding 8-carbobenz-oxy derivative (VIII). Substance IX could be easily isolated from the reaction products and has a melting point of 225–226°. Its infrared spectrum showed a strong band at 1700 cm.$^{-1}$ characteristic of the imidic group. Moreover, by acid hydrolysis, the same substance gave a carboxylic acid (m.p. 255–256°) which has been identified as 2-carbamyl-pyrrolidine-5-carboxylic acid (XI). The 3,8-diazabicyclooctane[3.2.1]-2,4-dione (IX) structure can therefore be attributed to the product melting at 225–226°. The reduction of IX with lithium aluminum hydride in tetrahydrofuran led to the isolation of 3,8-diazabicyclooctane-[3.2.1] (I).

The splitting of the carbobenzoxy group from VIII, which led to IX, was also partially accompanied by the opening of the imidic ring with formation of 2-carbamyl-5-carbethoxypyrrolidine (X).

From the intermediate V it was also possible to carry out a new synthesis of the previously described 8-methyl-3,8-diazabicyclooctane[3.2.1] (Ia)[1] by methylation with formic acid and formaldehyde[6] to Ie (yield 90%) and final debenzylation with hydrogen and palladium (yield 89%).

This five-step procedure for the preparation of Ia from II (over-all yield 25%) represents an important improvement on the already described synthesis which also started from II and gave Ia through 7 steps with an over-all yield of 16%.

All the prepared compounds have been tested for their pharmacological activities and Maffii and co-workers will later refer to the results obtained. Research on this class of heterocyclic compounds will be carried out.



EXPERIMENTAL

2-Benzylcarbamyl-5-carbethoxypyrrolidine (III). A mixture of 150 g. (0.698 mole) of diethyl-2,5-pyrrolidinedicarboxylate[1]), 75 g. of benzylamine (0.7 mole), and 450 ml. of xylene was refluxed for 18 hr. On cooling the solution a white solid (24 g.) separated which melted at 172–173° and was identified by the analysis as 2.5-dibenzylcarbamylpyrrolidine.

Anal. Calcd. for $C_{20}H_{23}N_3O_2$: C, 71.21; H, 6.82; N, 12.46 Found: C, 71.42; H, 6.83; N, 12.20.

(4) L. M. Rice, E. E. Reid, and C. H. Grogan, *J. Org. Chem.*, 19, 884 (1954).

(5) C. D. Wagner, R. H. Brown, and E. D. Peters, *J. Am. Chem. Soc.*, 69, 2611 (1947).

(6) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, 55, 4571 (1933).

The solvent was evaporated from the clear solution under reduced pressure and the oily residue was distilled *in vacuo*. The distillate (40 g., b.p. 90–92°/0.2 mm.) was formed by the unchanged ester. Distillation was stopped and the residual 2-benzylcarbamyl-5-carbethoxypyrrolidine (123 g., over-all yield 64%, 87% based on the ester used) was used for the subsequent step. A sample was distilled and analysed; b.p. 170–175°/0.2 mm.

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.21; H, 7.24; N, 10.14. Found: C, 64.98; H, 7.48; N, 10.13.

3-Benzyl-3,8-diazabicyclooctane[3.2.1]-2,4-dione (IV). (a) *From 2-benzylcarbamyl-5-carbethoxypyrrolidine* (III). One hundred and twenty grams of 2-benzylcarbamyl-5-carbethoxypyrrolidine was heated under stirring at 200–210° for 3 hr. under atmospheric pressure and the ethyl alcohol formed was collected. The residual viscous oil was distilled and the fraction (70 g.) boiling at 155–170°/0.2 mm. collected and rectified. Yield 55 g. (55%), b.p. 150–155°/0.2 mm.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.82; H, 6.08; N, 12.17. Found: C, 68.10; H, 6.30; N, 12.32.

The product obtained, dissolved in a small amount of ether and allowed to stand some days, crystallized as needles melting at 78°.

(b) *From 3-benzyl-8-carbobenzoxy-3,8-diazabicyclooctane-[3.2.1]-2,4-dione* (VI). A solution of 12 g. of 3-benzyl-8-carbobenzoxy-3,8-diazabicyclooctane[3.2.1]2.4-dione[1] in 600 ml. of 80% methanol containing 3 ml. of glacial acetic acid was hydrogenated in the presence of 2 g. of 10% palladium on charcoal. After about 3 hr. the carbon dioxide evolution subsided. The catalyst was filtered off, the mixture was made neutral by the addition of a sodium bicarbonate solution, and methanol was removed under reduced pressure. An oil separated which was extracted with ether and dried over sodium sulfate. After evaporation of the solvent the residue was distilled *in vacuo*. A fraction boiling at 150–152°/0.2 mm. was collected. Yield 4 g. of IV (52.6%). On standing the product crystallized in needles; m.p. 78°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.82; H, 6.08; N, 12.17. Found: C, 67.98; H, 6.3; N, 12.35. The hydrochloride was obtained in ethanol by the addition of hydrogen chloride; m.p. 210–213°.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_2$: N, 10.5; Cl, 13.7. Found: N, 10.35; Cl, 13.54.

By further concentration and salting out with sodium bicarbonate, the mother liquors of the ether extraction gave an oil which was extracted with ether, dried over sodium sulfate, and distilled. Yield 1.5 g. of 2-benzylcarbamyl-5-carbomethoxypyrrolidine (VII) b.p. 175–177°/0.2 mm.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.12; H, 6.87; N, 10.69. Found: C, 64.40; H, 7.01; N, 10.80.

3-Benzyl-3,8-diazabicyclooctane[3.2.1] (V). A solution of 60 g. of 3-benzyl-3,8-diazabicyclooctane[3.2.1]-2,4-dione (IV) in 600 ml. of anhydrous ethyl ether was dropped with stirring into a suspension of 30 g. of lithium aluminum hydride in 500 ml. of ether, keeping the temperature at 0°. At the end of the addition the solution was gently refluxed for 30 hr., then it was cooled to −5° under stirring and the reaction mass was decomposed with 90 ml. of water.

The mixture was stirred 1 hr. at room temperature; the organic hydroxides were filtered and thoroughly washed with ether. The ether extracts were collected, dried over sodium sulfate, and evaporated. The residual oil was distilled at 0.2 mm. pressure and the fraction boiling at 95–98° was collected; yield 34 g. of V (65%).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.22; H, 8.91; N, 13.86. Found: C, 77.10; H, 8.72; N, 13.81. The dihydrochloride, crystallized from ether-alcohol, melted at 150–152° and was slightly hygroscopic.

Anal. Calcd. for $C_{13}H_{20}Cl_2N_2$: N, 10.18; Cl, 25.82. Found: N, 9.93; Cl, 25.73. The dipicrate crystallized from ethanol with m.p. 232–235°.

Anal. Calcd. for $C_{25}H_{24}N_8O_{14}$: C, 45.45; H, 3.63; N, 16.97. Found: C, 46.00; H, 3.90; N, 16.78.

3,8-Diazabicyclooctane[3.2.1] (I). (a) *From 3-benzyl-3,8-diazabicyclooctane[3.2.1]* (V). A solution of 20 g. of 3-benzyl-3,8-diazabicyclooctane[3.2.1] in 400 ml. of absolute ethanol was hydrogenated in the presence of 10 g. of 10% palladium on charcoal in an autoclave at 60° and 40 atm. pressure. After 3 hr., heating was stopped and the solution allowed to cool to room temperature. Then the catalyst was filtered off, the alcohol removed at atmospheric pressure, and the concentrated solution was distilled; yield 8.8 g. of I (80%); b.p. 176–178°. The product easily adsorbed carbon dioxide when exposed to air. A sample was distilled again and the fraction boiling at 78–80°/40 mm. was collected and immediately analyzed.

Anal. Calcd. for $C_6H_{12}N_2$: C, 64.28; H, 10.71; N, 25.0. Found: C, 64.24; H, 10.90; N, 24.6 (tit), secondary N^s 24.6. The slightly hygroscopic dihydrochloride crystallized from ethanol; m.p. 314–315° dec.

Anal. Calcd. for $C_6H_{14}Cl_2N_2$: N, 15.13; Cl, 38.38. Found: N, 15.06; Cl, 38.21. The dipicrate crystallized from 80% ethanol; m.p. 248–250° dec.

Anal. Calcd. for $C_{18}H_{18}N_8O_{14}$: C, 37.89; H, 3.16; N, 19.65. Found: C, 39.0; H, 3.29; N, 19.21.

(b) *From 3,8-diazabicyclooctane[3.2.1]-2,4-dione* (IX). A solution of 2 g. of 3,8-diazabicyclooctane[3.2.1]-2,4-dione in 20 ml. of tetrahydrofuran was added with stirring to a 2 g. suspension of lithium aluminum hydride in 20 ml. of tetrahydrofuran at such a rate that the temperature should not exceed 35–40°. At the end of the addition the solution was refluxed 4 hr., cooled to −5° and decomposed with 5 ml. of water. Then the mixture was allowed to return to room temperature, stirred 1 hr., filtered and the inorganic hydroxides were thoroughly washed with ether. The extracts were combined, dried over sodium sulfate, and distilled at ordinary pressure in a rectifying column keeping the external temperature at 80°. After removal of most of the solvent, the fraction boiling at 75–80°/40 mm. was collected; yield 0.85 g. (53%). A comparison between the obtained product and a sample of I, through the infrared spectra and the mixed melting points of the dihydrochlorides and dipicrates, showed a perfect identity.

3,8-Diazabicyclooctane[3.2.1]-2,4-dione (IX). A solution of 34 g. of 8-carbobenzoxy-3,8-diazabicyclooctane[3.2.1]-2,4-dione (VIII)[1] in 1000 ml. of 80% methanol was hydrogenated with stirring in the presence of 12 g. of 10% palladium on charcoal in a flask fitted with a gas outlet tube. After 3 hr. the carbon dioxide evolution subsided. The catalyst was filtered off and the solution was concentrated *in vacuo* to a small volume with mild heating. After addition of an equal amount of ethyl alcohol and cooling, 2.6 g. of (IX) melting at 225–226° was separated. A sample was recrystallized from 30% alcohol; m.p. 225–226°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.71; N, 20.00. Found: C, 51.26; H, 5.90; N, 19.87.

The mother liquors were evaporated to dryness with mild heating and the residual oil (15 g.) was taken up with ethyl ether. A solid (12.3 g.) separated and was recrystallized from benzene; m.p. 61–63°. The infrared spectrum showed bands at 1730 cm.$^{-1}$, characteristic of the ester group, and 1665 cm.$^{-1}$ characteristic of a primary amide. The 2-carbamyl-5-carbomethoxypyrrolidine (X) structure was confirmed by the analysis.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 6.97; N, 16.28. Found: C, 49.00; H, 7.10; N, 16.37.

2-Carbamyl-5-pyrrolidinecarboxylic acid (XI). A solution of 1 g. of 3,8-diazabicyclooctane[3.2.1]-2,4-dione (IX) in 50 ml. of water containing a few drops of concentrated hydrochloric acid was refluxed for 5 hr. Then it was made neutral by the addition of the theoretical amount of sodium hydroxide, and concentrated to a small volume. By the addition of an equal amount of ethyl alcohol, and by cooling, 0.8 g. crystals separated; they were collected and crystallized from dilute methanol; m.p. 255–257°.

Anal. Calcd. for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.33; N, 17.72. Found: C, 45.94; H, 6.60; N, 18.01.

3-Benzyl-8-methyl-3,8-diazabicyclooctane[3.2.1] (Ie). To 55 g. of 98% formic acid (0.2 mole) in a 500-ml. flask, 60.6 g. (0.3 mole) of 3-benzyl-3,8-diazabicyclooctane[3.2.1] (V) was added with cooling, followed by 25 g. of formaldehyde 38% (0.3 mole). The mixture was refluxed 15 hr., cooled, 60 ml. of concd. hydrochloric acid HCl was added, and the mixture was concentrated *in vacuo*. The mixture was made alkaline by the addition of 30% sodium hydroxide and extracted with three 250-ml. portions of ether. After drying over solid potassium hydroxide the combined extracts were evaporated and the residue was distilled *in vacuo;* yield 58.6. g. (90.4%): b.p. 113–115°/0.6 mm.

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.77; H, 9.26; N, 12.96. Found: C, 77.70; H, 9.40; N, 12.76. The infrared spectrum of the product was identical with that of an authentic sample.[1]

8-Methyl-3,8-diazabicyclooctane[3.2.1] (Ia) was obtained in 89.5% yield according to the procedure described in the preceding paper of this series[1]; b.p. 193–198°/760 mm. and 115–116°/40 mm. The infrared spectrum was identical with that of the authentic sample. The dihydrochloride and the dipicrate did not depress the melting points of authentic samples.

Acknowledgment. The authors gratefully acknowledge the useful discussion with Prof. Fusco during the experimental work, and wish to thank Dr. G. G. Gallo and co-workers for the infrared spectra interpretation, Mr. A. Restelli and Dr. G. Pelizza for the analytical data.

MILAN, ITALY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Synthesis of 3,8-Diazabicyclo[3.2.1]octane and Some of Its *N*-Substituted Derivatives

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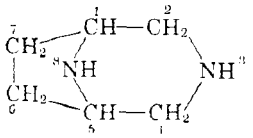
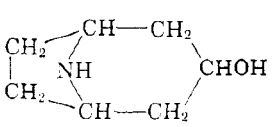
Received January 3, 1961

The preparation of 3,8-diazabicyclo[3.2.1]octane and some of its simple *N*-substituted derivatives is described.

As the ring-system of 3,8-diazabicyclo[3.2.1]-octane (A) is at once related to piperazine and to nortropine, both progenitors of many compounds of physiological importance, synthesis of A seemed likely to be rewarding.



A



Nortropine

The route followed in the preparation of A and of various simple derivatives is shown in Chart 1. The reactions used in passing from one derivative to another were chosen so as to minimize any ambiguity as to the nature of the products.

R = (a) C_6H_5; (b) $CH_2C_6H_5$; (c) C_2H_5
R′ = (a) C_6H_5; (b) H; (c) C_2H_5
R″ = (b) C_6H_5; (c) CH_3

The only operations involving serious experimental difficulties were the cyclizations leading to II and III. Both of these cyclizations are two-step reactions, the first step presumably following second order kinetics and the second step being intramolecular. In principle, therefore, it would be desirable to separate the steps, accomplishing the first in concentrated and the second in highly dilute solution. This may be feasible in passing from II to III but probably is not in the formation of II since here the steps are so similar in chemical nature that no great difference in rate is to be expected.

The esters of N—R pyrrolidine 2,5-dicarboxylic acids (II). The bromination of adipyl chloride followed by reaction with ethanol has been to shown give a mixture of isomers.[2] The higher-melting isomer (m.p., 66°) has been shown to be the *meso* form through its relatively facile conversion to the anhydride of *cis*-tetrahydrofuran 2,5-dicarboxylic acid.[2a] The "liquid" isomer, m.p., 9°,[2c] gives on comparable treatment mainly polymer, presumably of *trans*-tetrahydrofuran 2,5-dicarboxylic acid. Simple displacements by Walden Inversion should produce *cis* cyclic compounds from the *meso*, and *trans* from the *d-l* forms. As aside from the possibility of epimerization, only *cis* forms would be applicable to our purpose, the isolation of both solid forms of at least one variant of II was esse ntial. The only solid substance of this nature so far reported was dimethyl *N*-phenylpyrrolidine-2,5-dicarboxylate,[3] m.p. 88°. This had been obtained by the reaction of *meso*-dimethyl α,α'-dibromoadipate with aniline. Formation of another isomer was not mentioned, nor was the yield of that obtained. The steric identity of this compound was therefore uncertain.

The dimethyl esters of α,α'-dibromoadipic acid have somewhat more favorable properties than the diethyl esters. A modification of Ingold's proce-

(1) From a thesis submitted by S. W. Blackman to the School of Graduate Study of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1960.

(2)(a) R. Willstätter and R. Lessing, *Ber.*, **35**, 2066 (1902). (b) H. R. Le Seuer, *J. Chem. Soc.*, **95**, 275 (1909). (c) C. K. Ingold, *J. Chem. Soc.*, **119**, 967 (1921).

(3) A. J. Hill and J. T. Maynard, U. S. Patent **2,596,099.**