Phthaloyltaurylglycylglycine. Four grams (7.8 mmoles) of V was added to 100 ml. of 1.0*N* sodium hydroxide and the mixture was treated as described in the general method. The residue was treated with 20 ml. of 10% hydrochloric acid and the mixture cooled to 0°. The precipitate which resulted was collected by filtration. The yield was 2.5 g. (86%), m.p. 274–275°. No change in melting point was observed after recrystallization from an ethanol-water mixture.

Anal. Calcd. for $C_{14}H_{15}N_3O_7S$: N, 11.37. Found: N, 11.01.

Phthaloyltauryl-L-glutamic acid. Two grams (4.5 mmoles) of VI was added to 100 ml. of 1.0*N* sodium hydroxide and the mixture treated as described in the general method. The residue was treated with 20 ml. of 10% hydrochloric acid and cooled to 0°. An oil separated which solidified on shaking. Filtration gave 1.1 g. (64%) of product, gradual decomposition above 300°. The product was recrystallized from water.

Anal. Calcd. for $C_{15}H_{16}N_2O_8S$: N, 7.29. Found: N, 7.72.

Phthaloyltaurylglycyl-DL-methionine. Five grams (11 mmoles) of VII was added to 100 ml. of 1.0*N* sodium hydroxide and the mixture treated as described in the general method. The residue was treated with 20 ml. of 10% hydrochloric acid and cooled to 0°. The white precipitate which formed was collected by filtration, yield 3.2 g. (65%), gradual decomposition above 300°. The product was recrystallized from an ethanol-water mixture.

Anal. Calcd. for $C_{17}H_{21}N_3O_7S_2$: N, 9.47. Found: N, 9.01.

Acknowledgment. The authors are indebted to Dr. James F. Holland and Dr. Nancy Bruemmer of Roswell Park Memorial Institute for their suggestions and their active interest in the biological aspects of the work.

BUFFALO 14, N. Y.

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

Bicyclic Homologs of Piperazine. Synthesis of 8-Methyl-3,8-diazabicyclooctanes. I

GIORGIO CIGNARELLA AND GIANGIACOMO NATHANSOHN

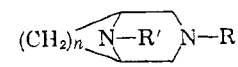
Received June 16, 1960

The synthesis of bicyclic homologs of piperazine belonging to the class of 8-methyl-3,8-diazabicyclo[3.2.1]octanes (VIII) is reported. The compounds are prepared by reduction with lithium aluminum hydride of the corresponding 3-substituted 8-carbobenzyloxy-3,8-diazabicyclo[3.2.1]octane-2,4-diones (VII) obtained from the still unknown pyrrolidine-2,5-dicarboxylic acid (III) through the *N*-carbobenzyloxy derivative IV. This was converted with acetic anhydride into the anhydride (V), which by reaction with ammonia or primary amines and subsequent cyclization with acetic anhydride gave the desired VIII.

In the last years several piperazine derivatives were found to possess interesting therapeutical properties. This is the case, for instance, of 1-diethylcarbamyl-4-methylpiperazine dihydrogen citrate (diethylcarbamazine) as antifungal agent,[1] *N*-methyl-*N'*-(4-chlorobenhydryl)piperazine dihydrochloride (chlorcyclizine) as antihistaminic agent,[2] piperazine citrate as an antihelmintic,[3] *N*-methyl-*N*-ethyl-*N'*-2-chlorobenzhydrylpiperazinium chloride as antiacetylcholinic agent,[4] and 1-(2'-cyclohexyl-2')hydroxy-2'-phenylethyl-4,4-dimethylpiperazinium methyl sulfate (hexocyclium methylsulfate) as gastric secretion inhibitor.[5]

In many instances an improvement in the activity of already known products was observed by introducing a piperazine ring in place of secondary aliphatic amino groups. *N*-(γ-[4-Hydroxyethyl-1-piperazinyl]-propyl)-3-chlorophenothiazine (chlorperphenazine) has recently been found to possess a more rapid effect than chlorpromazine.[6]

These results prompted us to consider a particular structure having the piperazine ring embodied in a condensed biheterocyclic system of general formula.



R, R' = H, alkyl etc.

Only two derivatives of this type are known in the literature, *i.e.* 9-methyl-3,9-diazabicyclo[3.3.1]nonane (n = 3, R = H, R' = CH_3) and 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane (n = 3, R = $CH_2C_6H_5$, R' = CH_3).[7] A closely related bicyclic system was described by Grogan and Rice[8] who prepared 3-azabicyclo[3.2.1]octanes in the course of an extensive work on 3-azabicycloalkanes[9]: However, the 3,8-diazabicyclo[3.2.1]octane (n = 2) ring is still undescribed. This structure seemed to us of particular interest when R' = CH_3, because of the structural analogy with the tropane

(1) C. F. Otto and T. H. Maren, *Am. J. Hyg.*, **51**, 353 (1951).

(2) J. C. Castillo, E. J. Beer, and S. H. Jaros, *J. Pharmacol. Exptl. Therap.*, **96**, 388 (1949).

(3) R. H. R. White and O. D. Standen, *Brit. Med. J.*, 755 (1953).

(4) A. E. Light and R. V. Fanelli, *J. Am. Pharm. Assoc.*, **46**, 279 (1957).

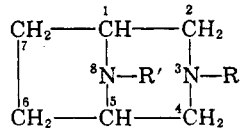
(5) H. E. Zaugg and co-workers, *J. Am. Chem. Soc.*, **80**, 2763, 2769 (1958).

(6) E. Frühmann and H. Gross, *Wiener Klin. Wschr.*, **71**, 808 (1959).

(7) R. A. Barnes and H. M. Fales, *J. Am. Chem. Soc.*, **75**, 975 (1953).

(8) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, **22**, 1223 (1957).

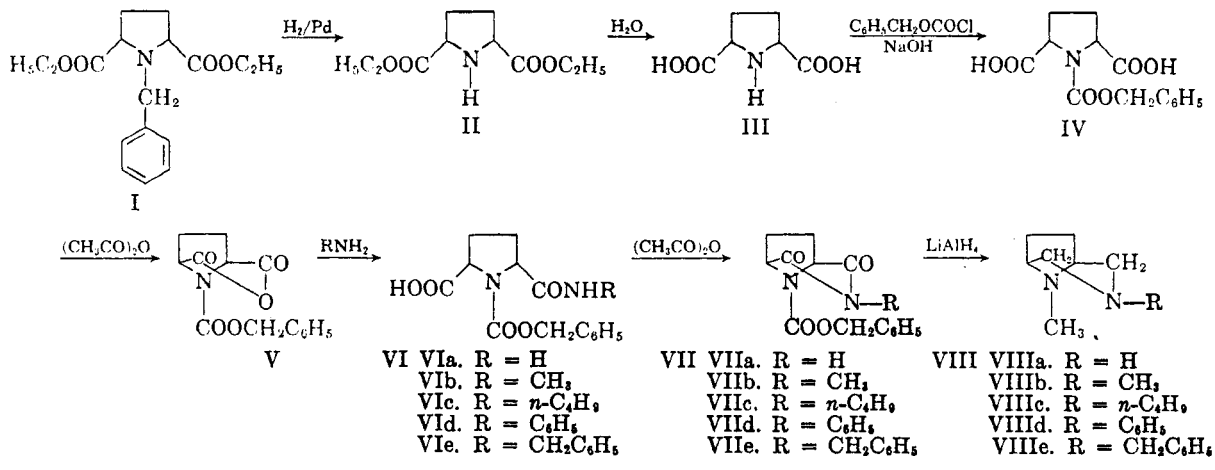
(9) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **24**, 7, (1959); see also previous works of the same series.



molecule from which it differs by having at position 3 a nitrogen instead of a carbon atom. In this first paper the synthesis and properties of 8-methyl-3,8-diazabicyclo[3.2.1]octanes in which R = H, CH_3, n-C_4H_9, C_6H_5, $-CH_2C_6H_5$ are described.

An attempt to prepare one of these terms, *i.e.* 3-benzyl-8-methyl-3,8-diazabicyclooctane (VIIIe), by the method of Barnes and Fales[7] starting from N-methyl-2,5-dicarbomethoxypyrrolidine[10] and benzylamine was unsuccessful as the reaction led exclusively to the corresponding mono- and dibenzylamide. Also no ring closure occurred when N-methyl-2-hydroxymethyl-5-benzamidomethylpyrrolidine[11] was treated with methyl trichloroacetate[12] and N-methyl-2-chloromethyl-5-benzamidomethylpyrrolidine[11] in alkali.[13] The reaction of N'-methyl-2,5-dichloromethylpyrrolidine[11] with benzylamine in butanol in the presence of sodium carbonate[14] was also unsuccessful.

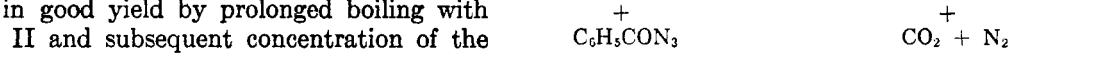
The desired products were obtained as shown in the following reaction scheme.



2,5-*cis*-Dicarbethoxy-N-benzylpyrrolidine (I)[10] was debenzylated with hydrogen and palladium to the still unknown 2,5-dicarbethoxy-*cis*-pyrrolidine. Pyrrolidine-*cis*-2,5-dicarboxylic acid (III) was isolated in good yield by prolonged boiling with water of II and subsequent concentration of the solution.

It was not possible to obtain the acid III by an even mild acid or alkaline hydrolysis, perhaps because of the instability of the pyrrolidine ring under the experimental conditions used. The separation of the product from the inorganic salts represented a further difficulty due to its high water solubility accompanied by a practically complete insolubility in alcohol owing to its structure of internal salt. The acid III was converted at low temperature by a known method[15] into the corresponding N-carbobenzyloxy derivative (IV). The latter, refluxed with acetic anhydride, gave a product the analytical data of which correspond to those of the internal anhydride of N-carbobenzyloxypyrrolidine-2,5-dicarboxylic acid (V). This structure was confirmed by the infrared spectrum and by the chemical behavior of the product, as reported in the experimental part.

The anhydride V in benzene solution reacted with ammonia or primary amines to give the monoamides (VI), which were not isolated in a pure state [except for VIa (R = H)]. By refluxing VI with acetic anhydride the 8-carbobenzyloxy-3,8-diazabicyclo[3.2.1]octane-2,4-diones (VII) were obtained, which could be easily purified by distillation or recrystallization. 3-Phenyl-8-carbobenzyloxy-3,8-diazabicyclo[3.2.1]octane-2,4-dione (VIId) was also obtained by treating benzoic acid azide with the anhydride V.[16]



The subsequent reaction of VII with lithium aluminum hydride in ethyl ether led with satisfactory yield to the 8-methyl-3,8-diazabicyclooctanes (VIII) by simultaneous reduction of the two carboxy groups at 2 and 4 to methylene groups and of the N-carbobenzyloxy group to NCH_3 and benzyl alcohol.[17]

(10) J. von Braun and J. Seeman, *Ber.*, **56**, 1840 (1923).
(11) G. Cignarella and G. G. Nathansohn, *Gazzetta Chimica Italiana*, in press.
(12) G. Y. Lesher and A. R. Surrey, *J. Am. Chem. Soc.*, **77**, 636 (1955).
(13) E. Renk and C. A. Grob, *Helv. Chim. Acta*, **37**, 2119 (1954).
(14) A. G. Anderson, Jr., W. F. Harrison, R. G. Anderson, and A. G. Osborne, *J. Am. Chem. Soc.*, **81**, 1255 (1959).
(15) Houben, *Die Methoden der organischen Chemie*, 11/2, p. 344.
(16) M. Aeberli and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 470 (1948).

The compound VIIIa (R = H), owing to the ether insolubility of the 2,4-dione VIIa, is more easily obtained by hydrogenolysis of 3-benzyl-8-methyl-3,8-diazabicyclooctane (VIIIe).

3,8-Diazabicyclooctanes are fluids (compound VIIId solidified on standing, m.p. 45–47°) with the characteristic smell of aliphatic amines. When exposed to air, they show a tendency to absorb carbon dioxide. Their solubility decreases with the length of the alkyl chain. The compounds were characterized through the dipicrates (although compound VIIId gave a monopicrate) and dihydrochlorides. These latter are very hygroscopic but can be easily purified by treatment with acetone; VIIa, however, gives a stable dihydrochloride. With methyl iodide in ether solution it is possible to quaternarize only one nitrogen atom even using an excess of reagent.

VIIIa (R = H), when treated with an equimolecular amount of methyl iodide gives a product having m.p. 225° and the empirical formula $C_8H_{17}N_2I$, which can be attributed both to 3,8-dimethyl-3,8-diazabicyclo[3.2.1]octane hydroiodide and to 8-methyl-3,8-diazabicyclo[3.2.1]octane methyl iodide (IX). The presence of a secondary acetylable nitrogen is in accordance with the structure of IX. From the ethereal mother liquors of IX by further addition of methyl iodide a product with m.p. 290–297° was isolated which was identical with the methyl iodide derivative of VIIIb (R = CH_3). In consideration of the properties of VIIIa and VIIIb, it is suggested that the salification occurs on the nitrogen atom at position 8.

The pharmacological data on these compounds and on other homologs of piperazine not described in this paper will be published elsewhere by Maffii and co-workers.

EXPERIMENTAL

cis-2,5-Dicarbethoxy-N-benzylpyrrolidine (I) was prepared from ethyl *meso*-α,α-dibromoadipate,[18] m.p. 65–66°, and benzylamine by modifying the Braun and Seeman's method.[8] A solution of 500 g. of ethyl *meso*-α,α-dibromoadipate (1.39 moles) in 1500 ml. of benzene was heated to reflux, then heating was discontinued and 500 ml. of benzylamine (490 g., 4.58 moles) were added under stirring in 1 hr. The exothermic reaction was sufficient to keep the internal temperature at 83–85°. At the end of the addition (in the meantime an abundant precipitate of benzylamine hydrobromide separated) the reaction mass was refluxed under stirring for 24 hr. The solution was cooled, the hydrobromide was filtered off and washed with benzene, and the benzene solution was evaporated under reduced pressure. The oily residue was distilled under 0.3 mm. and the fraction having b.p. 145–148° was collected; yield 350 g. of I (82.5% of th.). A sample was converted into the hydrochloride with hydrogen chloride in ether solution; after recrystallization from ethanol the m.p. was 123–125°.

Anal. Calcd. for $C_{17}H_{24}ClNO_4$: N, 4.10; Cl, 10.30. Found: N, 4.24; Cl, 10.28.

(17) P. Karrer and B. J. R. Nicolaus, *Helv. Chim. Acta*, 35, 1581 (1952).

(18) P. C. Guhe and D. K. Sankoson *Org. Syntheses*, Coll. Vol. III, 623 (1955).

cis-2,5-Dicarbethoxypyrrolidine (II). A solution of 60 g. of I in 600 ml. of absolute ethanol was hydrogenated under 20 atm. at 40° in the presence of 9 g. of 10% palladium-on-charcoal. The reaction was complete in about 2 hr. After spontaneous cooling to room temperature, the catalyst was filtered off, and the alcohol solution was evaporated under reduced pressure. The oily residue was distilled and 38 g. of *cis*-2,5-dicarbethoxypyrrolidine (II) (90%) were collected at 95–96° under 0.3 mm. pressure. The analysis was carried out on a twice distilled sample.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.81; H, 7.9. Found: C, 56.01; H, 7.78.

The hydrochloride obtained in ether solution with gaseous hydrogen chloride was crystallized from ether-alcohol mixture, m.p. 134–135°.

Anal. Calcd. for $C_{10}H_{18}ClNO_4$: N, 5.55; Cl, 16.5. Found: N, 5.36; Cl, 16.8.

cis-Pyrrolidine-2,5-dicarboxylic acid (III). A suspension of 200 g. of II in 8 l. of water was refluxed under stirring for 25–30 hr. The resulting clear, slightly yellowish solution was concentrated under reduced pressure until an abundant crystalline mass separated. After standing one night at 0° the solution was filtered, the solids were washed with 95% ethanol and the filtrate was evaporated to dryness *in vacuo* at 80°; yield 98 g. of III, m.p. 260–261°. The mother liquors after further concentration gave an additional 12 g. of III, m.p. 260–261°, with a total yield of 74.5%. A sample was crystallized from water for analytical purposes.

Anal. Calcd. for $C_6H_9NO_4$: C, 45.34; H, 5.73; N, 8.81. Found: C, 45.51; H, 5.90; N, 8.70.

Acidimetric assay 99.8%. With copper acetate in aqueous solution a copper salt was obtained, recrystallized from water and dried *in vacuo* at 80°, m.p. >300°.

Anal. Calcd. for $C_6H_7CuNO_4 \cdot {}^1/_2H_2O$: C, 31.3; H, 3.48; N, 6.09; Cu, 27.1. Found: C, 31.35; H, 3.54; N, 6.39; Cu, 27.4.

cis-N-Carbobenzyloxypyrrolidine-2,5-dicarboxylic acid (IV). To 420 ml. of 2*N* sodium hydroxide cooled to −8/−10°, 67 g. of *cis*-pyrrolidine-2,5-dicarboxylic acid (0.42 mole) were added. To this solution 73 g. of benzyl chlorocarbonate (0.43 mole) and 210 ml. of 2*N* sodium hydroxide were added in 30 min. with strong stirring and cooling. After stirring for 2 hr. at room temperature the unchanged chlorocarbonate was extracted with ethyl ether and the aqueous solution, cooled on ice was acidified to Congo Red with hydrochloric acid. The thick separated oil was thoroughly extracted with ethyl ether. After drying over sodium sulfate and evaporation of the solvent the white pasty residue became solid after standing some hours *in vacuo*. Yield 94 g. of IV (70% of th.), m.p. 125–127°. After recrystallization from water and drying at 60° *in vacuo* the melting point rose to 127–128°.

Anal. Calcd. for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.12; N, 4.77. Found: C, 57.19; H, 5.20; N, 4.77.

N-Carbobenzyloxypyrrolidine-2,5-dicarboxylic acid anhydride (V). A mixture of 79 g. of IV and 360 ml. of acetic anhydride was refluxed for 1 hr. The solvent was removed and the residue was allowed to stand under 1 mm. pressure at 140° for 1 hr. The temperature was adjusted to 50–60° and the residual solid was taken up with 100 ml. of anhydrous ethyl acetate. After filtering, washing with cold ethyl acetate and drying *in vacuo* at 60°, 58.1 g. of V (78%) melting at 166–168° were obtained. A sample crystallized from benzene or acetone showed m.p. 170–171°.

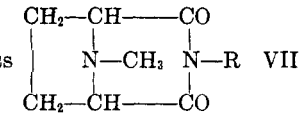
Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.07; H, 4.76; N, 5.08. Found: C, 61.15; H, 4.83; N, 5.05.

In the infrared spectrum the product showed bands at 1820–1750 cm.$^{-1}$, attributable to an anhydride, and a band at 1705 cm.$^{-1}$, which may be attributed to a group >N—COOR. At room temperature it is insoluble in weak alkali and gives the starting product IV by boiling in a water-acetone solution.

3-Substituted 8-carbobenzyloxy-3,8-diazabicyclooctane-(3,2,1)-2,4-diones (VII). *General procedure.* To a solution of

TABLE I

METHYL-3,8-DIAZABICYCLOOCTANE-2,4-DIONES

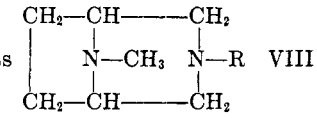


VII

Compound	R	Formula	Yield, %, V–VII	B.P., 0.3 mm.	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
VIIa	H	$C_{14}H_{14}N_2O_4$	50.4	—	124–125	61.31	61.39	5.10	5.18	10.22	10.22
VIIb	CH_3	$C_{15}H_{16}N_2O_4$	60	170–172	50–51	62.49	62.36	5.59	5.44	9.72	9.55
VIIc	n-C_4H_9	$C_{18}H_{22}N_2O_4$	63	192–194	—	65.43	65.36	6.66	6.80	8.48	8.59
VIId	—C_6H_5	$C_{20}H_{18}N_2O_4$	45	—	148–149	68.57	68.70	5.14	5.24	8.00	7.98
VIIe	—$CH_2C_6H_5$	$C_{21}H_{20}N_2O_4$	64	—	83–84	69.21	69.07	5.53	5.64	7.69	7.57

TABLE II

8-METHYL-3,8-DIAZABICYCLOCYCLOOCTANES



VIII

Compound	R	Formula	B.P.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
VIIIa	H	$C_7H_{14}N_2$	193–198 (760 mm.)	89[a]	—	—	—	—	22.22	22.03[b]
VIIIb	CH_3	$C_8H_{16}N_2$	50–52 (8 mm.)	57	—	—	—	—	20.00	19.81[b]
VIIIc	n-C_4H_9	$C_{11}H_{22}N_2$	54–55 (0.3 mm.)	61	72.52	72.23	12.09	12.14	15.38	15.10[b]
VIIId	C_6H_5	$C_{13}H_{18}N_2$	104–105 (0.3 mm.)[c]	64	77.22	76.90	8.91	9.08	13.86	13.90
VIIIe	$CH_2C_6H_5$	$C_{14}H_{20}N_2$	88–90 (0.3 mm.)	70	77.77	77.68	9.26	9.27	12.96	12.82

[a] Yield of the hydrogenolysis of VIIIe. [b] Acidimetric assay. [c] M.p. 45–46°.

27.5 g. of anhydride V (0.1 mole) in 300 ml. of anhydrous benzene a solution of 0.11 mole of amine in 50 ml. of benzene was added with cooling. The mixture was heated on a water bath for 20 min. and the solvent was removed under reduced pressure. The crude monoamide (VIb–d) was refluxed with five times its volume of acetic anhydride for 1–2 hr. The solvent was removed by distillation and the residual oil was kept under 1 mm. pressure at 130–140° for 1–2 hr. After spontaneous cooling to room temperature the solution was taken up with 200 ml. of an ether-benzene mixture (1:1). The clear solution was decanted from a small amount an insoluble oil and washed in a separatory funnel first with a 5% sodium bicarbonate solution and then with water. After drying over sodium sulfate and evaporation of the solvent the final product was purified by distillation (VIIb, c) or crystallization from methanol (VIId, e).

N-Carbobenzyloxypyrrolidine-2-carbamyl-5-carboxylic acid (VIa). In a benzene solution of 27.5 g. of anhydride (V) (0.1 mole) a stream of ammonia was bubbled with cooling to complete saturation. The benzene was evaporated under reduced pressure and the hygroscopic residue consisting of the ammonium salt of VIa was dissolved in water and cautiously acidified with 10% hydrochloric acid. An oil separated which rapidly became solid and was crystallized from water; yield 23.4 g. (80%), m.p. 179–181°.

Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.74; N, 9.58. Found: C, 57.49; H, 5.57; N, 9.64.

It was subsequently observed that VIa can be prepared with identical yield by adding the anhydride V to an aqueous 33% solution of ammonia at 0°C., filtering the undissolved impurities, evaporating *in vacuo* the excess ammonia, and acidifying at *p*H 4 with 10% hydrochloric acid.

8-Carbobenzyloxy-3,8-diazabicyclo[3.2.1]octane-2,4-dione (VIIa) was prepared according to the general method described for the 3-substituted derivatives. From 20 g. of amide acid VIa 11.8 g. (63%) of VIIa were obtained, which when crystallized from methanol melted at 124–125°.

3-Phenyl-8-carbobenzyloxy-3,8-diazabicyclo[3.2.1]octane-2,4-dione (VIId) (from anhydride V and benzoic acid azide). To a solution of 11 g. of benzoic acid azide[19] (0.075 mole) in 60 ml. of anhydrous pyridine a suspension of 20 g. of anhydride V (0.072 mole) in 60 ml. of pyridine was added under stirring. After the addition was complete, the internal temperature was gradually adjusted to 100–110° and the solution was heated for 1 hr. till the gaseous evolution subsided. The pyridine was evaporated *in vacuo* and the residue was taken up in ether. The solid was collected and treated with a small amount of water. The undissolved portion was recrystallized from methanol. A white crystalline product (9.1 g.) separated, m.p. 143–145°. The mixed melting point with an authentic sample gave no depression and the infrared spectrum was found to be identical with VIId, yield 39.7%.

3-Substituted 8-methyl-3,8-diazabicyclo[3.2.1]octanes (VIII) *General procedure.* One tenth mole of VII in 100 ml. of ethyl ether was added under vigorous stirring and cooling to 0° to a suspension of 19 g. of lithium aluminum hydride (0.5 mole) in 200 ml. of ether. At the end of the addition the reaction mass was mildy refluxed for 4–6 hr. It was then collected to 5° and with strong stirring cautiously decomposed with 50 ml. of water. After spontaneous cooling to room temperature the mixture was stirred for 1 hr. and filtered, thoroughly washing the inorganic salts with ether. The ether extracts were collected and dried over sodium sulfate. The separation of VIII from the benzyl alcohol formed in the reactions was effected by distilling under reduced pressure (VIIIb, d, e) or, if this were not possible because of the proximity of the boiling points (VIIIc) by precipitating with gaseous hydrogen chloride the dihydrochloride from the ether extracts and subsequently setting free the base with 50% potassium hydroxide.

8-Methyl-3,8-diazabicyclo[3.2.1]octane (VIIIa). A solution of 5.4 g. of 3-benzyl-8-methyl-3,8-diazabicyclo[3.2.1]octane (VIIId) in 100 ml. of absolute ethyl alcohol was hydrogenated under 20 atm. at 50° in the presence of 1 g. of

(19) T. Curtius, *Ber.*, **23**, 3023 (1890).

TABLE III

ADDITION SALTS OF COMPOUNDS VIII

R	Formula	M.P.			Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
			Dihydrochlorides					
H	$C_7H_{16}N_2Cl_2$	314–315 (dec.)[a]			14.07	14.13	35.57	35.59
CH_3	$C_8H_{18}N_2Cl_2$	260–262[b]			13.14	13.05	33.6	33.4
n-C_4H_9	$C_{11}H_{24}N_2Cl_2$	245–247[b]			10.98	11.05	27.86	27.69
C_6H_5	$C_{13}H_{20}N_2Cl_2$	180–182[c]			10.18	10.30	25.81	25.74
$CH_2C_6H_5$	$C_{14}H_{22}N_2Cl_2$	213–215[b]			9.68	9.58	24.58	24.25
			Methyl Iodides					
H	$C_8H_{17}N_2I$	224–225			10.44	10.55	47.38	47.25
CH_3	$C_9H_{19}N_2I$	290–292			9.93	9.98	45.03	44.75
n-C_4H_9	$C_{12}H_{25}N_2I$	218–220			8.64	8.51	39.14	38.95
C_6H_5	$C_{14}H_{21}N_2I$	262–264			8.14	7.98	36.92	36.79
$CH_2C_6H_5$	$C_{15}H_{23}N_2I$	250–251			7.82	7.78	35.47	35.25
			Dipicrates					
H	$C_{19}H_{20}N_8O_{14}$	247–250	39.04	39.15	3.42	3.48	19.18	18.90
CH_3	$C_{20}H_{22}N_8O_{14}$	242–245	40.01	40.06	3.68	3.85	18.74	18.71
n-C_4H_9	$C_{23}H_{28}N_8O_{14}$	220–222	43.12	43.15	4.37	4.35	17.5	17.45
C_6H_5	$C_{19}H_{21}N_5O_7$[e]	172–174	52.9	52.85	4.87	5.01	16.26	16.19
$CH_2C_6H_5$	$C_{26}H_{26}N_8O_{14}$	228–230	46.3	46.52	3.86	4.00	16.62	16.62

[a] Crystallized from 80% ethanol. [b] Washed with acetone. [c] Crystallized from ethanol. [d] Crystallized from 80% alcohol. [e] Monopicrate.

palladium-on-charcoal. After 2 hr. the temperature was allowed to decrease to room temperature, the catalyst was filtered and the solution was distilled at atmospheric pressure collecting the fraction boiling at 193–198°; yield 2.8 g. (89%). The product was hygroscopic, quickly absorbed carbon dioxide and was characterized through the dihydrochloride, the dipicrate, and the methyl iodide. Analyses and melting points are given in Tables II and III.

8-Methyl-3,8-diazabicyclo[3.2.1]octane methyliodide (IX). To a solution of 1 g. of 8-methyl-3,8-diazabicyclo[3.2.1]-octane in 10 ml. of anhydrous ether 1 g. of methyl iodide (0.44 ml.) was added with cooling. The temperature was maintained at room temperature for 2 hr., the separated product was filtered and 1.3 g. of crystals melting at 222–224° were obtained. After crystallization from ethyl alcohol they melted at 224–225°.

Anal. Calcd. for $C_8H_{19}N_2I$: N, 10.44; I, 47.38. Found: N, 10.55; I, 47.25. Tertiary N calcd.: 522. Found: 5.15.

The ethereal mother liquors of IX were treated with 0.2 ml. of methyl iodide and allowed to stand one night in a refrigerator. The product which separated (1.15 g.) melted at 288–290°. A sample recrystallized from ethanol (m.p. (290–292°) did not depress the melting point in admixture with a sample of 3,8-dimethyl-3,8-diazabicyclo[3.2.1]octane methyl iodide.

Acknowledgment. The authors gratefully acknowledge the help of Prof. R. Fusco in discussing this work, and of Mr. A. Restelli for the microanalytical data.

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Synthesis and Properties of 3-Methylpurines[1]

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Received June 17, 1960

3-Methylpurines are obtained by desulfuration of appropriate mono- and dithio intermediates. However, the synthesis of 3-methylpurine itself failed. The 3-methylated derivatives, which possess a fixed double bond at position 1,2, exhibit a large bathochromic shift of λ_{max} and R_f values, *smaller* than those of the nonmethylated mother substances. The 3-methyl derivative of 6,8-dihydroxypurine is slowly converted into 3-methyluric acid by xanthine oxidase, whereas 3-methyl-8-hydroxypurine is not attacked.

In recent studies on the mechanism of enzymatic oxidation of purines, 3-methylated derivatives have played a major role, because the substituent in the 3-position imposes on the pyrimidine moiety a fixed distribution of double bonds and thus prevents structural changes from taking place in the activated enzyme–substrate complex.[3] In this

(1) This work was supported in part by grant No. RG-6631 from the National Institutes of Health.

(2) Part of a Ph.D. thesis, submitted to the Faculty of Science, The Hebrew University, Jerusalem, 1960.

(3) F. Bergmann, H. Kwietny, G. Levin, and D. J. Brown, *J. Am. Chem. Soc.*, **82**, 598 (1960).