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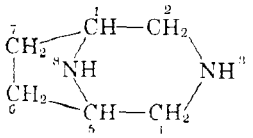
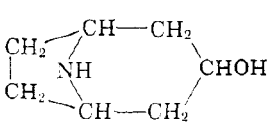
The preparation of 3,8-diazabicyclo[3.2.1]octane and some of its simple *N*-substituted derivatives is described.

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.

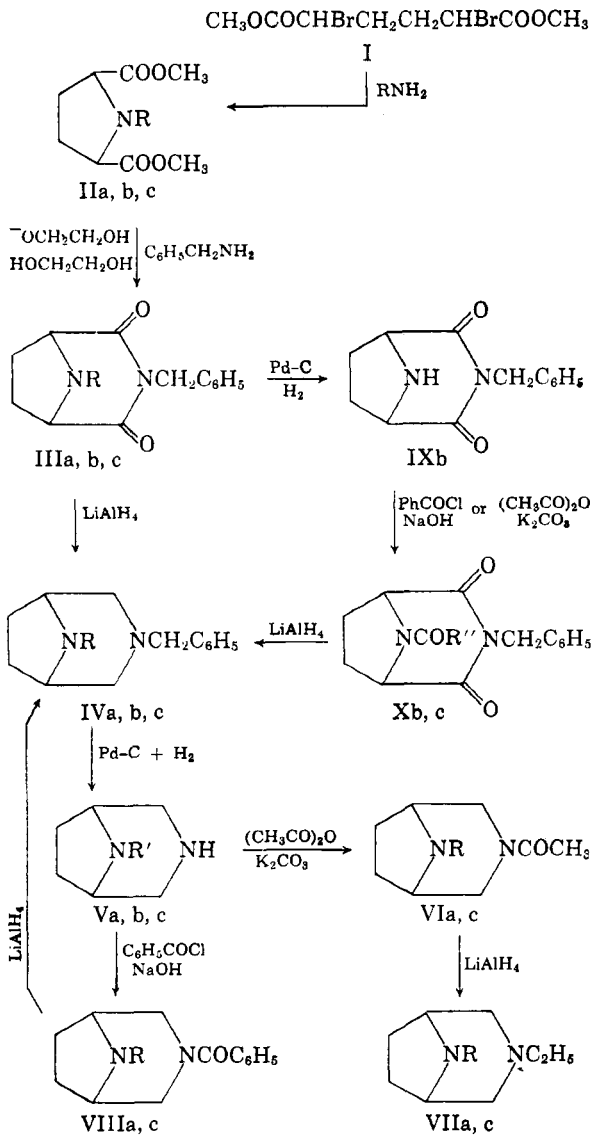
The esters of N—R pyrrolidine 2,5-dicarboxylic acids (II). The bromination of adipyl chloride followed by reaction with ethanol has been to shown give a mixture of isomers.[2] The higher-melting isomer (m.p., 66°) has been shown to be the *meso* form through its relatively facile conversion to the anhydride 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.**

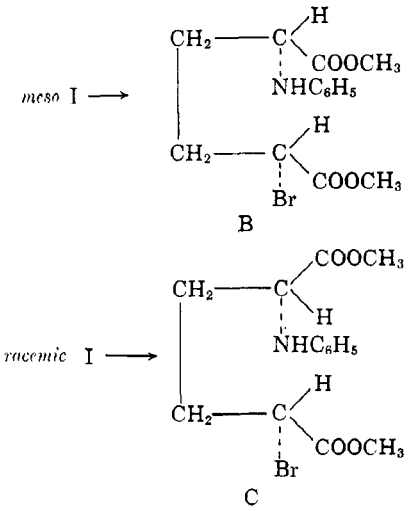


dure[2c] afforded the *meso* form, m.p., 76° and the racemic form, m.p., 13°. The latter, though analytically pure was probably not entirely homogeneous. As noted by Willstätter[2a] the lower melting form is partly converted to the higher by prolonged heating (as in distillation).

In our hands, the reaction of aniline with *meso*-dimethyl α,α'-dibromoadipate without solvent as described by Hill and Maynard was most unsatisfactory. Using suitable diluents *N*-phenylpyrrolidine-2,5-dicarboxylic esters were obtained in 70% yield. By a combination of fractional crystallization and chromatography this product was separated cleanly into the *cis* and *trans* isomers, melting points 56.5° and 88.5°, respectively, and in the proportion of 3:1. Under the same conditions, the racemic form of I afforded only a 10% yield of IIa[4] and this material was composed of the *cis* and *trans* forms in approximately equal proportion.

(4) The bulk of the product was polymeric material.

These observations are not easily explained by epimerization. *Cis* and *trans* IIa are individually stable under the conditions of the reaction.[5] Epimerization of I under the influence of aniline would be possible but this would not account for the yields and proportions. Neither does epimerization of the presumptive intermediates B and C lead to an acceptable rationalization. The following



argument appears to us the most attractive. Normal SN_2 displacement by aniline with *meso* I should give the *threo* isomer B and with *racemic* I the *erythro* isomer C. In the absence of substantial hindrance (as with tetramethylene bromide) the consequent internal displacement would proceed faster than intermolecular displacements and would give pyrrolidines in high yield. Both B and C, however, are rather heavily hindered. Examination of models reveals that there is some difficulty in bringing the nitrogen into approximation with the bromine-bearing carbon in the favored position opposite the bromine. This difficulty is apprec ably more pronounced in C than in B.[6] This accounts for the predominant polymerization starting with racemic I and for the very considerable loss from polymerization in both cases. The formation of *trans-II* from *meso*-I and of *cis*-II from *racemic* I could be due to concurrent operation of the process involved in retention of configuration in displace-

(5) This observation on IIa may not be transferable to IIb and IIc. The amines used in the preparation of these compounds (benzylamine and ethylamine) being more basic than aniline should be more effective in causing epimerization. There is a further point that may have some bearing on the proportion of isomers formed. Whereas the *trans* form of pyrrolidine 2,5-dicarboxylic acid would be expected to be slightly more stable than the *cis* form, this should not hold for derivatives having bulky groups on the nitrogen. Here in the *cis* series the *N*-substituent could occupy a position *trans* to both of the groups at 2 and 5 while in the *trans* series this is impossible. Thus, if IIb and IIc did epimerize, the *cis* series could be favored.

(6) The considerations on the hindrance factors of the *N*-substituted pyrrolidine dicarboxylic esters[5] hold also for the transition states leading thereto from B and C.

TABLE I

PHYSICAL AND ANALYTICAL DATA ON COMPOUNDS OF CHART 1

Compound No.	M.P.[a]	Yield, %[b]	Crystallizing Solvent[c]	Empirical Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
IIa (*cis*)	56.5	50	EP	$C_{14}H_{17}NO_4$	63.9	64.0	6.4	6.3	5.3	5.4
IIa (*trans*)	88.5	16	EH	$C_{14}H_{17}NO_4$	63.9	63.8	6.4	6.4	5.3	5.3
IIIa	116.5	42	Ac	$C_{19}H_{18}N_2O_2$	74.5	74.6	5.9	5.8	9.2	9.2
IVa	69–71[d]	95[h]	EH	$C_{19}H_{22}N_2$	82.0	81.9	8.0	7.7	10.1	10.2
IVa picrate	163–164		A	$C_{25}H_{25}N_5O_7$	59.2	58.8	4.9	4.8		
Va	323 dec.	80	AÆ	$C_{12}H_{16}N_2 \cdot HCl$	64.1	64.1	7.6	7.4	12.5	12.6
VIa	136	65	BH	$C_{14}H_{18}N_2O$	73.0	73.3	7.8	7.8	12.2	12.0
VIIa	209 dec.	78	A	$C_{14}H_{18}N_2 \cdot 2HCl$	58.1	58.0	7.6	7.7		
VIIIa	131–132	62	BH	$C_{19}H_{20}N_2O$	78.1	78.2	6.9	6.7	9.6	9.6
IIb	148–152[e]	68		$C_{15}H_{19}NO_4$	65.0	64.7	6.9	7.0		
IIIb	189.5	58	A	$C_{20}H_{20}N_2O_2 \cdot HCl$	67.3	67.2	5.9	5.7	8.2	8.2
IVb	55–57[d]	91[i]	HP	$C_{20}H_{24}N_2$	82.2	82.2	8.2	8.0	9.6	9.5
	229 dec.		AE	$C_{20}H_{24}N_2 \cdot 2HCl$	65.8	65.6	7.1	7.1		
Vb	*ca.* 280 dec.	95	MÆ	$C_6H_{16}N_2 \cdot 2HCl \cdot H_2O$[f]	35.5	35.9	7.9	7.7	13.8	14.1
				$C_6H_{16}N_2 \cdot 2HCl \cdot {}^1/_2H_2O$[g]	37.1	37.2	7.7	7.7	14.4	14.3
Vb di-picrate	285 dec.		A	$C_{18}H_{18}N_8O_{14}$	37.9	37.5	3.2	3.2	19.7	20.0
IXb	216–218	95	AE	$C_{13}H_{14}N_2O_2 \cdot HCl$	58.5	58.4	5.6	5.6	10.5	10.5
Xb	121–123	62	BH	$C_{20}H_{18}N_2O_3$	71.9	71.7	5.4	5.2	8.4	8.4
Xc	109	59	BH	$C_{15}H_{16}N_2O_3$	66.2	65.9	5.9	6.0	10.3	10.1
IIc	193–194[e]	45		$C_{10}H_{17}NO_4$	55.8	56.0	7.9	8.0	6.5	6.5
IIIc	56.5–58	26	EP	$C_{15}H_{18}N_2O_2$	69.8	69.8	7.0	6.8		
									Cl	Cl
IVc	233	72[k]	A	$C_{16}H_{22}N_2 \cdot 2HCl$	59.4	59.7	7.9	7.9	23.4	23.0
Vc	275 dec.	93	M	$C_8H_{16}N_2 \cdot 2HCl$	45.1	45.3	8.5	8.4		
VIc	229–230	67	AE	$C_{10}H_{18}N_2O \cdot HCl$	54.9	54.9	8.8	8.8		
VIIc	310 dec.	90	AE	$C_{10}H_{20}N_2 \cdot 2HCl$	49.8	49.8	9.2	9.2		
VIIIc	263 dec.	60	AE	$C_{15}H_{20}N_2O \cdot HCl$	64.2	63.7	7.5	7.5		

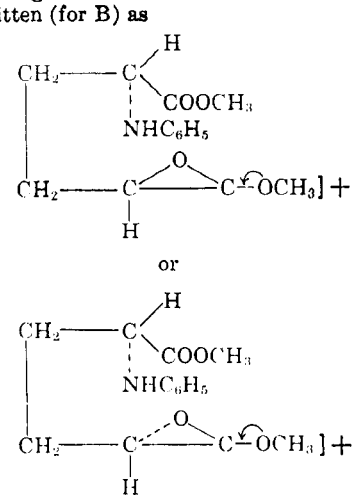
[a] All melting points corrected. [b] Yields calculated on basis of analytically pure product isolated. [c] A = abs. ethanol; Æ = ethyl acetate; Ac = acetone; E = abs. ether; B = benzene; H = hexane; M = methanol; P = pentane. [d] Sublimed in high vacuum (*ca.* 0.02 mm.) after crystallization. [e] B.p. at 1–2 mm. pressure. [f] Dried *in vacuo* four hours at 100°. [g] Dried *in vacuo* forty hours at 140°. [h] Yield by reduction of IIIa. By reduction of VIIIa the yield was 84%. [i] Yield of reduction of IIIb. By reduction of Xb the yield was 58%. [k] Yield by reduction of IIIc. By reduction of Xc the yield was 26%. By reduction of VIIIc the yield was 80%.

ment processes.[7] This process is not normally competitive in displacements involving α-bromo esters although in displacements with the anions of α-bromo acids it is—the course of the reaction being dependent on the concentration of the competing hydroxide ion. We suspect that in the present instances such a process is able to compete owing to the diminution in the rates of the normally dominant process.[8]

The methyl esters of *N*-benzyl- and *N*-ethylpyrrolidine-2,5-dicarboxylic acids (IIb and IIc) could not be obtained in crystalline form. It was necessary therefore to employ the unseparated mixture of isomers on the assumption that these mixtures were reasonably comparable to IIa. This assumption was justified by the results since the imides IIIb and IIIc were obtained in acceptable yields.

The 3,8-diazabicyclo[3.2.1]octan-2,4-diones (III). The general conditions were worked out with the isolated *cis* and *trans* forms of IIa. Not only the cyclization but even the first step, formation of a monoamide, proved unexpectedly slow. From un-

(7) According to choice of notation the intermediate could be written (for B) as

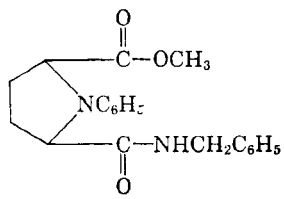


or

cf. S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, **64**, 2780 (1942). C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell Univ. Press, Ithaca, N. Y., 1953, pp. 382–383.

(8) It has been pointed out by a referee that formation of cross-products could have been due to exchange by iodide ion which was used in the preparation described below. In actual fact, use of iodide did not alter the yield or composition of the product but the very large amount of bromide liberated could have produced the same result.

catalyzed reactions in refluxing methanol virtually all of the starting materials were recovered. Even in the presence of methoxide catalyst 90% of the *trans* ester and 80% of the *cis* ester were unchanged. The procedure finally preferred was to heat IIa with benzylamine in ethylene glycol at reflux in the presence of alkoxide catalyst and to distill the reaction mixture *without removing the catalyst.* Under these conditions IIIa was obtained in 40% yield from *cis*-IIa and in 12% yield from *trans*-IIa. The behavior of the material during the distillation suggested that ring closure from the presumed intermediate D was being accomplished during this final heating. D is of course, not the only substance of this nature probably present. Through ester exchange glycol could replace methyl from the ester function giving rise to dimeric ester amides. Pyrolysis of diamide could also take place. Actually drastic heating of a plastic substance formed from *cis*- and *trans*- IIa and benzylamine without solvent also furnished IIIa albeit in poor yield (15% from the *cis* polymer, 5% from the *trans*).



D

The conversions of IIb and IIc to IIIb and IIIc were accomplished by the same technique. Although IIb was not sterically homogeneous (demonstrably, at least), the cyclization to IIIb was appreciably more efficient than in the *N*-phenyl series.[9]

The other processes indicated in Chart 1 proceeded smoothly. The lithium aluminum hydride reductions of amides and imides gave excellent yields with no indications of irregular cleavages. Some difficulty had been anticipated in the catalytic debenzylations because of the steric nature of the bicyclic system. In fact, the conversion of IIIb to IXb (debenzylation at the 8 position) proceeded at a normal rate. Debenzylation at the 3 position (IVa and IVc to Va and Vc) was exceptionally rapid. In the double hydrogenolysis of IVb to Vb the hydrogen absorption also suggested a very rapid reaction followed by one of moderate rate.

One incidental observation seems deserving of note. In a reaction of *cis*-IIa with benzylamine in methanol containing one equivalent of alkali, inadvertently as hydroxide, half of the ester was isolated as the disodium salt of the parent dicarboxylic acid. This is presumably to be attributed to a sterically favored intramolecular reaction of the monoanion first liberated by hydrolysis[10] and is further evidence in favor of the assigned configurations of these isomers.

(9) Especially high efficiencies in these cyclizations cannot be expected if alkoxide ion catalysis is essential to cyclization of D. Recent work [J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 82, 665 (1960)] has shown that under conditions of alkoxide ion catalysis of the amidification of esters, considerable loss ensues due presumably to nucleophilic attack of alkoxide ion on the ester alkyl group.

EXPERIMENTAL

Data on analyses, physical properties and yields of the compounds of Chart 1 are presented in Table I. All melting points are corrected. Type procedures are given below in detail especially for the critical cyclization steps. The various samples of IVa, IVb, and IVc prepared by the alternative routes shown in Chart 1 were shown to be identical with those prepared by the main line of synthesis (m.p. and m.m.p.).

The empirical formulae in Table I refer to the characterized form (salt or base).

Dimethyl α,α'-dibromoadipate (I). Adipyl chloride was brominated by the conventional procedure[2,11] and added to methanol cooled in a Dry-Ice-acetone bath. After standing over-night at room temperature, the solid that precipitated was collected and washed with cold methanol, and recrystallized from methanol. The solid so obtained was the pure *meso* ester, m.p.,[8] 75–76°, yield 30%.

Anal. Calcd. for $C_8H_{12}Br_2O_4$: C, 28.9%; H, 3.6%. Found: C, 29.3%; H, 3.7%.

The original mother-liquor and the filtrate from the recrystallization were combined, concentrated and partitioned between ether and water. The ester layer was washed successively with bisulfite solution, sodium carbonate solution, and water and was dried over potassium carbonate. The ether was evaporated and the residual ester was distilled through a good fractionating column. In some runs considerable monobromo ester was isolated as a fore-run boiling from 155–170° at 16 mm. The main fraction of dibromo ester boiled at 170–181° at 16 mm. On refractionation a sharp cut boiling at 189–190° at 20 mm. was obtained. This material, on standing, partly solidified to a paste. The paste was dissolved in a mixture of ether-pentane (1:2) and the solution was blown down to small volume (*i.e.*, 200 cc. from 1500) with a stream of dry air. A further quantity of pure *meso* ester corresponding to 30% of the calculated yield was so obtained. No further amounts of this solid could be obtained from the mother-liquors. On evaporation of solvent the residual oil (about 6% of the calculated amount) solidified when cooled to −7° and remained solid up to 12.5–13°. It was not completely pure, however, since it thawed to a cloudy melt. No more of the *meso* isomer could be separated but the contaminants must have had similar composition as the substance was analytically "pure."

Dimethyl-N-phenylpyrrolidine 2,5-dicarboxylate (IIa). One-third mole (111 g.) of *meso*-I was dissolved in 250 cc. of dry benzene and 250 cc. of nitromethane. To the solution was added 124 g. (4/3 mole) of freshly distilled aniline and 1 g. of potassium iodide. The solution was refluxed with stirring for 16 hr., cooled, and poured into 1 l. of anhydrous ether. The precipitated aniline hydrobromide was filtered off, washed with ether and the solvents were removed *in vacuo* on a steam bath.

The oily residue was cooled, dissolved in 1 l. of ether and washed successively with five 300-cc. portions of ice cold 5*N* hydrochloric acid (to remove traces of aniline) and thrice with ice water. After drying over potassium carbonate, the ethereal layer was evaporated and distilled at 1 mm. pressure. The main portion of distillate boiled at 144–147° and weighed 77 g. After refractionation there was obtained 68 g. of a straw colored liquid boiling at 146–147° at 1 mm. This distillate was dissolved in 300 cc. of anhydrous ether and 300 cc. of hexane. On refrigeration, 27 g. of solid separated

(10) *Cf.* A. P. Phillips, *J. Am. Chem. Soc.*, 75, 4725 (1953).

(11) *Org. Syntheses*, Coll. Vol. III, 623 (1953).

which was collected and washed with hexane. Two types of crystal were present—long orange-yellow needles and clusters of colorless crystals. These were separated mechanically. The yellow type could not be purified completely by recrystallization. The colorless crystals (14 g.) were recrystallized from 50 cc. of ether and 300 cc. of hexane. The product weighed 13 g. and melted at 88.5°. This appears identical with the product reported by Hill and Maynard[8]: it is, in fact, the *trans* isomer.

Purification of the yellow crystals and separation of the mixture of isomers in the mother-liquors from the first crystallization was accomplished by chromatography on alumina. The ester mixture was added in 1:3 ether-pentane and the chromatogram was developed and eluted by the same solvent. A small amount of *trans* isomer came first, followed by pure *cis* isomer, melting at 56.5°. A total of 44 g. of the *cis* and 13 g. of the *trans* isomer was obtained.

In another run of the same size, the distillation was omitted, the residue, after removal of volatile material on the steam bath *in vacuo*, being dissolved in 300 cc. of benzene and 900 cc. of hexane. On refrigeration a tan colored mixture of the two isomers weighing 67 g. was obtained. This was chromatographed as before yielding 14 g. of the *trans* and 44 g. of the *cis* isomers.

3-Benzyl-8-phenyl-3,8-diazabicyclo[3.2.1]octan-2,4-dione (IIIa). One-third mole (88 g.) of *cis*-IIa was dissolved with warming in 500 cc. of freshly distilled ethylene glycol. To the resultant solution was added 40 g. (0.037 mole) of benzylamine and a sodium methoxide solution prepared from 4 g. of sodium and 50 cc. of methanol. The reaction mixture was heated under a Vigreux column (2 cm. × 60 cm.) connected above with a receiver for distillate. The reaction-mixture was heated gently and 72 cc. of methanol collected in the first 2 hr. Heating was then increased until glycol refluxed midway in the fractionating column and heating was so continued for 16 hr. The fractionating column was then removed and volatile material (glycol and benzylamine) was removed *in vacuo*.

The residue was transferred to a smaller flask and distilled at oil-pump vacuum[12] through a heated Vigreux column 2 × 20 cm. leading directly into a receiver with wide apertures. (This was necessary as the distillate solidified on cooling.) Distillation began when the bath temperature reached 200°. A bath temperature of 275° was necessary to drive over the last traces of distillate. The receiver at this point contained a mass of tan colored solid and a small quantity of dark-brown liquid. The entire distillate was dissolved in 250 cc. of hot acetone and the solution was allowed to cool. Crystallization began almost at once. After refrigeration over-night the deposited mass of feathery crystals was filtered and washed with cold acetone. It weighed 38.7 g. and melted at 166.5°. An additional portion of 4 g. (after recrystallization) was obtained from the mother-liquors.

3-Benzoyl-8-phenyl-3,8-diazabicyclo[3.2.1]octane (VIIIa). A portion (2.25 g., 0.01 mole) of the hydrochloride of Va was benzoylated by the Schotten-Baumann procedure giving 1.8 g. (after two recrystallizations from benzene-hexane) of the 3-benzoyl derivative, m.p., 131–132°.

Dimethyl N-benzylpyrrolidine-2,5-dicarboxylate (IIb). To a solution of 222 g. (0.67 mole) of *meso*-I in 800 cc. of dry benzene was added 225 cc. (2.1 moles) of benzylamine. The solution was stirred at room temperature for 24 hr. during which time much benzylamine hydrobromide precipitated. The mixture was then refluxed with stirring for 8 hr. cooled with stirring and diluted with 1 l. of anhydrous ether. The precipitated benzylamine hydrobromide was filtered off, washed with ether, and dried (wt., 241 g.). The combined filtrates were extracted with cold dilute sulfuric acid and the base was liberated from the acid extracts with sodium carbonate, taken into ether and dried over potassium carbonate. The ether was evaporated and the residual base was distilled at 1 mm. pressure. The main cut was refractionated giving 126 g. of oil boiling at 148–152° at 1 mm. This material could not be crystallized but was analytically pure.

3,8-Dibenzyl-3,8-diazabicyclo[3.2.1]octan-2,4-dione hydrochloride (IIIb). This preparation was carried out according to the technique described for IIIa. Thirty grams of benzylamine, 74 g. of IIb, 500 cc. of ethylene glycol, and sodium methoxide from 5 g. of sodium were employed. The initial distillation yielded 80 g. boiling from 160–220° at 1 mm. This was refractionated giving 59 g. over the range 205–211° at 1 mm. This final distillate was dissolved in 500 cc. of abs. ethanol and acidified with 100 cc. of saturated ethanolic hydrogen chloride solution. On refrigeration a copious cream colored precipitate separated. This was recrystallized from hot ethanol giving 55 g. of colorless crystals.

3,8-Dibenzyl-3,8-diazabicyclo[3.2.1]octane (IVb). A dry ethereal solution of the base, IIIb was prepared from 8.9 g. (0.025 mole) of the hydrochloride. This was added dropwise to a slurry of 15.2 g. of lithium aluminum hydride in 1 l. of anhydrous ether. The reaction flask was equipped with a reflux condenser and a magnetic stirrer. Addition of the solution of the base was completed in about 30 min., after which, stirring was continued for 30 hr. An excess of 10% sodium hydroxide solution was then added cautiously and stirring was continued overnight. The inorganic salts were then allowed to settle. The supernatant solution was decanted through a filter and the salts were washed thoroughly with dry ether which was also passed through the filter.

The ethereal filtrate was evaporated and the oily residue was dissolved in 25 cc. of boiling hexane. On cooling to 0°, there was deposited 5.5 g. of an off-white, waxy solid that melted at 52–57°. This was recrystallized from pentane and then sublimed in high vacuum.

3,8-Diazabicyclo[3.2.1]octane dihydrochloride (Vb). A solution of 5.15 g. of the base IVb in 50 cc. of methanolic solution containing 5 cc. of saturated methanolic hydrogen chloride was reduced with 6 g. of 10% palladized charcoal. The first equivalent (17–18 mmoles) of hydrogen was absorbed within 2 min., the second equivalent at a moderate rate (total absorption, 35.5 mmoles). The solution was removed from the catalyst and evaporated *in vacuo* on a steam bath. The residue was dissolved in hot methanol and ethyl acetate was added to incipient turbidity. On standing overnight, 1.45 g. of colorless solid had separated. An equal amount was obtained from the mother-liquors on addition of ether. This solid appeared to be a monohydrate: it softened at 85° but reset and did not melt below 280°. After stringent drying, the composition agreed with that calculated for a hemihydrate. The base was further characterized as a dipicrate.

3-Benzyl-3,8-diazabicyclo[3.2.1]octan-2,4-dione hydrochloride (IXb). The hydrogenation of the dibenzylimide hydrochloride, IIIb, (9.3 g., 0.026 mole) in methanol with palladized charcoal proceeded smoothly. The solution was removed from the catalyst and concentrated to 25 cc. On addition of ether and cooling there was obtained 6.2 g. of crystalline solid, melting at 216–218°. The mother-liquors contained 0.4 g. of the same substance.

3-Benzyl-8-benzoyl-3,8-diazabicyclo[3.2.1]octan-2,4-dione (Xb). One-fortieth mole (6.7 g.) of the monobenzylimide, IXb, was benzoylated by the Schotten-Baumann method and the resultant 8-benzoyl derivative was crystallized from benzene-hexane. It melted at 121–123° with frothing. The mixed melting point with benzoic acid showed a 20° depression.

Two grams of this amide was reduced with lithium aluminum hydride (2 g.) in ether over a period of 24 hr. at reflux. The ethereal solution, after removal of inorganic material, was concentrated to 33 cc. and a little hexane was added. There was deposited 1 g. of a waxy solid melting at 54–56°, identical with the 3,8-dibenzyl-3,8-diazabicyclo[3.2.1]octane described previously (IVb).

8-Ethyl-3,8-diazabicyclo[3.2.1]octane (Vc). Seven grams (0.022 mole) of 3-benzyl-8-ethyl-3,8-diazabicyclo[3.2.1]oc-

(12) The pressure varied between 1 and 2 mm., variations being caused by release of volatile material.

tane dihydrochloride (IVc) was dissolved in 50 cc. of methanol and hydrogenated over 6 g. of 10% palladized charcoal. The absorption of hydrogen was essentially complete in 90 seconds. This is a reduction rate comparable with that found with benzyl alcohol and cyclohexene and is the most rapid the senior author has observed in an *N*-debenzylation except for the first step in the debenzylation of IVb to Vb. After removal from the catalyst, the solvent was evaporated *in vacuo* and the residue was recrystallized from methanol.

3-Acetyl-8-ethyl-3,8-diazabicyclo[3.2.1]octane (VIc). One-fiftieth mole (4.3 g.) of Vc dihydrochloride was placed in a flask and covered with 25 cc. of acetic anhydride. Three grams of potassium carbonate was added and the flask was heated, first on a steam bath, then cautiously with a free flame. There was considerable but not violent evolution of gas. As the reaction-mixture became rather thick from deposition of solid, 12 cc. more of acetic anhydride was added, and boiling was continued until the still-head, used as condenser, was thoroughly heated. Five grams more of potassium carbonate was then added and the mixture was refluxed a few minutes longer. The reaction-mixture was cooled, methanol was added to react with the excess anhydride, and volatile material was removed *in vacuo*. The residual material was diluted with water to about 50 cc. and concd. potassium hydroxide solution was added to *p*H 8. The solution was cooled and then made strongly alkaline. The solution (volume now about 80 cc.) was extracted thrice with 1:1 ether-benzene mixture (3 × 50 cc.). The third extract, when evaporated, was found to contain only 0.2 g. of oil.

The combined extracts were dissolved in 20 cc. of hexane and refrigerated, however, no crystals formed. The material was therefore converted to the hydrochloride which was crystallized from ethanol-ether mixture.

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[CONTRIBUTION FROM MIDWEST RESEARCH INSTITUTE]

Pyrimidines. II. Orotic Acid Analogs[1,2]

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The syntheses of all eight structural analogs of orotic acid which contain amino, hydroxy, and thio substituents at positions 2 and 6 are reported. The chlorination of orotic acid with phosphorus oxychloride and *N,N*-dimethylaniline yields 2,6-dichloro-4-pyrimidinecarboxylic acid. Previous structures proposed for this chlorination product have been shown to be in error. A practical, large-scale synthesis of orotic acid has been devised, and a new route to the useful synthetic intermediate, methyl 2,6-dihydroxy-4-pyrimidinecarboxylate is reported. Formamidine has been condensed with the sodium derivative of diethyloxalacetate to give 6-hydroxy-4-pyrimidinecarboxylic acid in good yield. Several novel reactions involving methyl 2,6-dichloro-4-pyrimidinecarboxylate and methyl 6-chloro-2-methylthio-4-pyrimidinecarboxylate have been studied.

The importance of orotic acid in pyrimidine nucleotide synthesis has been well established.[3] Derivatives such as 5-chloro-, 5-bromo-, and 5-fluoroorotic acid[4,5] have been shown to exhibit orotic acid antimetabolite activity in various biological systems. 6-Uracil methyl sulfone and 6-uracilsulfonamide, synthesized[6] as orotic acid antagonists, have exhibited significant antitumor activity[7-10] against several types of tumor growth. Other pyrimidines related to orotic acid have been shown to exhibit interesting antitumor properties.[11]

As part of a general program to investigate pyrimidines as potential anti-neoplastic agents[12] a synthetic study of simple orotic acid derivatives was undertaken in this laboratory. As a result of this effort all the structural isomers of 2,6-disubstituted 4-pyrimidinecarboxylic acid which contain

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(2) Presented in part before the Division of Medicinal Chemistry, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 1960.

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