The product was recrystallized from *n*-pentane to yield 0.77 g. (47%) of (−)-α-lipoic acid as blunt yellow needles, m.p. 47–52°, $[\alpha]^{23.8}D$ −63° (*c* 1.6, benzene). The (−)-α-lipoic acid was recrystallized again from *n*-pentane, m.p. 50–53°. Its infrared spectrum (4% in carbon tetrachloride, 0.127-mm. path) was identical to that of (+)-α-lipoic acid[3] and of DL-α-lipoic acid.[4] Its activity in enzymatic POF assays was 39% of that of DL-α-lipoic acid.[21] *Anal.* Calcd. for $C_8H_{14}O_2S_2$: C, 46.55; H, 6.84; S, 31.05; neut. equiv., 206. Found: C, 46.37; H, 6.90; S, 30.63; neut. equiv., 200.

B. **From DL-α-Lipoic Acid.**—In the preparation of (+)-α-lipoic acid (−)-cinchonidine salt described above, the filtrate remaining after removal of the crystalline salt from the original reaction mixture was reduced in volume by stages by distillation under reduced pressure at 35°. At each stage, additional crystalline material which formed by cooling the solution to −18° was removed by filtration. There finally remained 4.5 g. of a yellow sirup which did not crystallize, $[\alpha]^{24.7}D$ −79.6° (*c* 1, ethyl alcohol). The sirup was treated with 50 ml. of 5% hydrochloric acid, and the mixture extracted three times with ether. The ether extract was washed five times with water and dried over sodium sulfate in the cold. Removal of drying agent and ether left a yellow solid. Recrystallization of the solid from *n*-pentane yielded 2.29 g. of (−)-α-lipoic acid as yellow leaflets, m.p. 57–59°, $[\alpha]^{24.4}D$ −50° (*c* 1, benzene). Its activity in the POF assay[20] was 26% of that of DL-α-lipoic acid.[22]

DL-α-Lipoic Acid-S_2^{35} (VIII).—A solution of 1.015 mg. (50 mc.) of elemental sulfur-35 in 2.9 ml. of benzene[23] was transferred from a sealed tube to a 500-ml. round-bottomed flask using 75 ml. of benzene for rinsing. A 1.75-g. (0.0545 gram atom) portion of elemental sulfur (USP precipitated) was added to the solution, which was then heated to dissolve the sulfur in the benzene. The benzene was then distilled to leave crystalline elemental sulfur containing 50 mc. of sulfur-35. A 13.1-g. (0.0545 mole) portion of sodium sulfide ($Na_2S \cdot 9H_2O$) and 125 ml. of 95% ethyl alcohol were added and the mixture stirred and refluxed under nitrogen to form a yellow-brown solution. To this refluxing solution was added during the course of three hours, a cold solution prepared by adding 7.3 ml. of 5.82 *N* sodium hydroxide solution (0.0425 mole of NaOH) to a cold solution of 9.29 g. (0.0436 mole) of DL-6,8-dichloroöctanoic acid in 140 ml. of absolute ethyl alcohol. After another 30 minutes of refluxing, about one-half of the alcohol was distilled, and a solution of 1.75 g. (0.0436 mole) of sodium hydroxide in 100 ml. of water was added. The mixture was refluxed under nitrogen for 15 minutes to decompose complex sulfides. The reaction mixture was then cooled, acidified with 140 ml. of 5% hydrochloric acid and extracted four times with a total of 500 ml. of benzene. The benzene was washed four times with saturated sodium chloride solution and dried over anhydrous sodium sulfate in the cold. After removal of drying agent and benzene, the remaining oil was distilled in a small vapor bath still under reduced pressure (0.2 mm.) and vapor temperature up to 180°, to give a yellow oil which crystallized. The crystals were recrystallized from *n*-pentane to yield 4.05 g. (45%) of DL-α-lipoic acid-S_2^{35} as yellow prisms, m.p. 59–60°. Its specific activity, determined by combustion to barium sulfate, was approximately 4 mc./g. (theoretical specific activity, 4.4 mc./g.). Its infrared spectrum (4% in carbon tetrachloride, 0.127-mm. path) was identical with that of DL-α-lipoic acid.[4] Its assay for POF activity was 109% of that of DL-α-lipoic acid.

Acknowledgments.—We are indebted to Mrs. Sonia Schorr Sloan and Dr. C. W. de Fiebre for carrying out enzymatic POF assays, to Mrs. Doris H. Hahn and Miss Naomi E. Schlichter for infrared spectral data and to Dr. J. H. Peterson for specific radioactivity determinations.

WILMINGTON, DELAWARE

(21) The optical rotation and POF assay values for this sample of (−)-α-lipoic acid indicated that it contained 15–20% of (+)-α-lipoic acid.

(22) The optical rotation and POF assay values for this sample of (−)-α-lipoic acid were not in good agreement but indicated that the sample contained 13–22% of (+)-α-lipoic acid.

(23) Elemental sulfur-35 was obtained from Oak Ridge National Laboratory.

[CONTRIBUTION FROM THE PRODUCTS DEVELOPMENT LABORATORIES, PARKE, DAVIS & CO.]

Chloramphenicol. 2,4,8-Substituted-1-aza-3,7-dioxabicyclo[3.3.0]octanes

BY WILLIAM H. EDGERTON,[1] JAMES R. FISHER AND GEORGE W. MOERSCH

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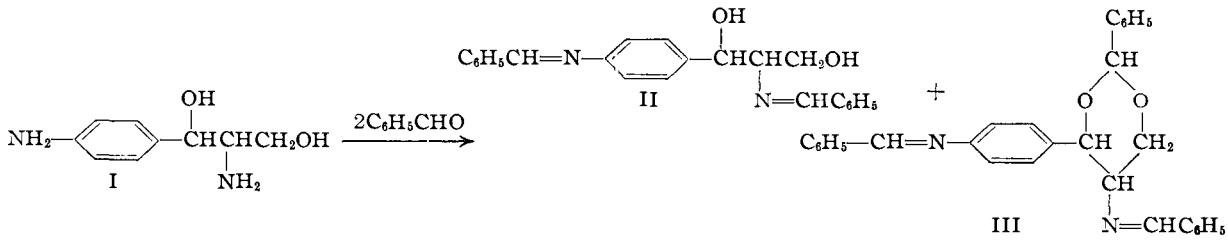
A series of 1-aza-3,7-dioxabicyclo[3.3.0]octanes derived from the chloramphenicol skeleton was prepared. A novel series of isomers, believed related by a *cis–trans* relationship, was isolated and characterized. The structure of a by-product previously reported from the reaction of benzaldehyde with L-*threo*-2-amino-1-(*p*-aminophenyl)-1,3-propanediol was demonstrated to be L-*threo*-4-(*p*-benzylideneaminophenyl)-2,8-diphenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane.

During the preparation of L-*threo*-2-benzylideneamino-1-(*p*-benzylideneaminophenyl)-1,3-propanediol (II) by treating benzaldehyde with L-*threo*-2-amino-1-(*p*-aminophenyl)-1,3-propanediol (I) in refluxing ethanol, a by-product was obtained which was reported to be a cyclic tribenzylidene derivative with a 1,3-dioxane structure (III).[2] This assumption was made on the ease of preparation and the ready decomposition of the compound to the known dibenzylidene derivative II. Subsequent study of this by-product has proved it to be L-*threo*-4-(*p*-benzylideneamino-



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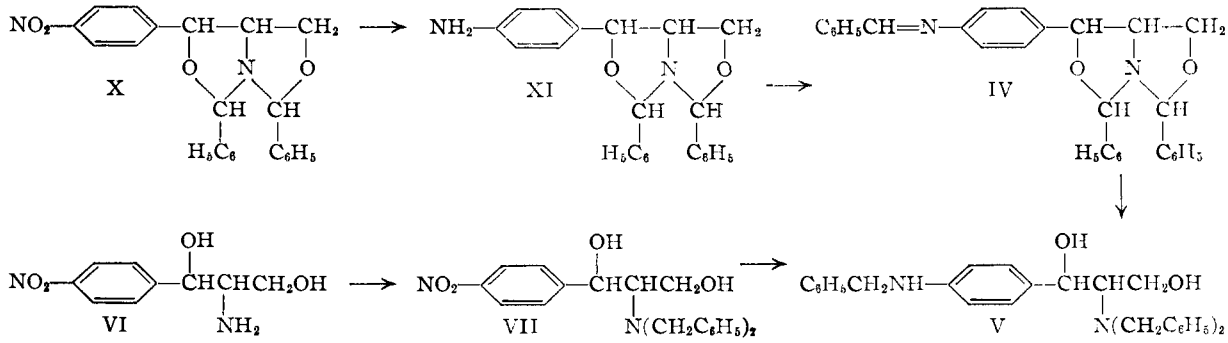
(2) W. H. Edgerton and J. R. Fisher, *J. Org. Chem.*, **19**, 593 (1954).



phenyl)-2,8-diphenyl-1-aza-3,7-dioxabicyclo[3.3.0]-octane (IV).

Hydrogenation of IV under less stringent conditions than those reported by Senkus[3] gave L-*threo*-1-(*p*-benzylaminophenyl)-2-dibenzylamino-1,3-propanediol (V). Although V could not be purified satisfactorily because of its labile nature, it was proved, by comparison of the infrared spectra, identical to a compound prepared by the reductive alkylation of L-*threo*-2-dibenzylamino-1-(*p*-nitrophenyl)-1,3-propanediol (VII).

L-*threo*-4-(*p*-nitrophenyl)-2,8-diphenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (X) was hydrogenated until three molar equivalents of hydrogen was absorbed. A 39% yield of the *p*-aminophenyl derivative XI was isolated. Examination of the other products of hydrogenation indicated that an abnormal reaction[4] had taken place with IV, II and L-*threo*-1-(*p*-aminophenyl)-2-benzylideneamino-1,3-propanediol being formed as well as the expected product XI. XI was benzalated to IV, thereby completing an alternate synthesis of IV.

An exhaustive hydrogenation of L-*threo*-2,4,8-triphenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (XII) resulted in extensive debenzylation with the isolation of primary amine as well as the monobenzyl and dibenzyl derivatives.[3]

The preparation of several 1-aza-3,7-dioxabicyclo[3.3.0]octanes[5] was successful, but it was noted that the 4-*p*-nitrophenyl (X) and 4-phenyl (XII) congeners could not be prepared by refluxing in ethanol as the parent member IV of the series was first isolated.[2] The reaction in benzene using a Dean and Stark[3,6] water trap resulted in good yields of the bicyclic products. Chloramphenicol[7] does not react with benzaldehyde under these conditions. The bicyclic compounds were formed also by treating the benzylidene derivatives with one mole of aldehyde under Dean and Stark conditions. Representatives of the D-*threo* and DL-*erythro* series were prepared in good yields. This is in accord with a suggestion by Bergmann[8] and was later confirmed by Pedrazzoli and Tricerri.[5] The configuration of the *erythro* series would lead one to expect that the *erythro* bicyclic compounds would form with difficulty.

Pedrazzoli and Tricerri[5] isolated a small quantity of by-product from the bicycloöctane formation to which they assigned a dioxane structure similar to III, largely on the basis of spectral data. No such by-product was found under the somewhat milder reaction conditions employed for the preparation of the bicycloöctanes of the present study. The infrared and ultraviolet curves of the bicycloöctanes of the normal series described in the present work agree quite well with those reported by the Italian workers.

The 4-phenyl-1-aza-3,7-dioxabicyclo[3.3.0]-octanes formed hydrochlorides which were stable in a dry atmosphere. Neutralization of the salts in ether–sodium carbonate solution yielded an isomeric compound as well as considerable amounts of decomposition products. The elemental analyses of the two isomers were alike, but the melting points, optical rotations (where present), X-ray diffraction patterns and infrared spectra were dissimilar. The prominent features of the infrared spectra of the *threo* isomers were the disappearance of a strong band at 8.3 to 8.95 μ and the appearance of a strong band at 10.34 to 10.42 μ. X and XA, respectively, were hydrolyzed with alcoholic hydrogen chloride to L-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol hydrochloride. The isolation of the same parent amine from both bicyclic isomers rejects any permanent alteration of the skeletal configuration either during formation of the bicyclic compound or during the formation of the isomer.

5-Ethyl-2,8-diphenyl-1-aza-3,7-dioxabicyclo-[3.3.0]octane (XIV) was prepared in two isomeric forms whose infrared spectra resemble those of the 4-phenyl series in the points mentioned. The yield of the A isomer was much better in the 5-ethyl series due to less decomposition. No optical rotation was present in these compounds. Preliminary attempts to separate optical isomers of XIII by an activated lactose column[9] and by forming diastereoisomeric salts were unsuccessful. 5-Ethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (XV) was prepared, but no isomeric compound could be isolated from the hydrochloride.

(3) M. Senkus, THIS JOURNAL, **67**, 1515 (1945).

(4) This reaction is similar to that previously reported in reference 2. The fact that the reduction was limited to the absorption of three molar equivalents of hydrogen explains the isolation of the benzylidene compounds which are apparently in equilibrium in the reaction mixture.

(5) Since the completion of this work, several members of this series have been reported by A. Pedrazzoli and S. Tricerri, *Helv. Chim. Acta*, **39**, 965 (1956); M. Nagawa and B. Shimizu, *Ann. Rept. Takamine Lab.*, **7**, 1 (1955), as well as W. H. Edgerton and J. R. Fisher, U. S. Patent 2,777,854 (January 15, 1957). These previously reported compounds are enumerated in Table I.

(6) Dean and Stark, *Ind. Eng. Chem.*, **12**, 486 (1920).

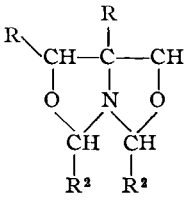
(7) Chloramphenicol is the generic name of the antibiotic for which the trademark of Parke, Davis & Co., is "Chloromycetin."

(8) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953).

(9) N. J. Leonard and W. J. Middleton, THIS JOURNAL, **74**, 5114 (1952).

TABLE I

1-AZA-3,7-DIOXABICYCLO[3.3.0]OCTANES



Cpd.[a]	R	R^1	R^2	Yield, %	M.p., °C.	$[\alpha]^{26}D$[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IV[e]	*p*-$C_6H_5CH{=}NC_6H_4$	H	C_6H_5	83	155	−34.6°(4%)	$C_{30}H_{26}N_2O_2$	80.69	80.84	5.87	5.92	6.29	6.68
IVA				46	178	+51(1.7%)			81.05		6.08		6.73
X[c,l]	*p*-$NO_2C_6H_4$	H	C_6H_5	57	97	−45.3(4%)	$C_{23}H_{20}N_2O_4$	71.12	71.41	5.19	5.28	7.21	7.01
XA				25	118	+28.2(4%)			71.01		5.40		7.24
XII[c]	C_6H_5	H	C_6H_5	77	77	−42.8(4%)	$C_{23}H_{21}NO_2$	80.44	80.59	6.17	6.02	4.05	4.13
XIIA				16	123	+23.8(4%)			80.83		6.12		4.22
XIII[d]	C_6H_5	H	C_6H_5	76	75	+45(2%)	$C_{23}H_{21}NO_2$	80.44	80.83	6.17	6.39		
XIIIA				39	123	−24(2%)			80.36		6.10		
XIV[e]	H	C_2H_5	C_6H_5	57	67		$C_{19}H_{21}NO_2$	77.26	77.07	7.16	7.10		
XIVA				85	55				76.80		7.36	4.74	4.75
XVI[c,l]	*p*-$NO_2C_6H_4$	H	C_6H_5	78	122		$C_{23}H_{20}N_2O_4$	71.12	71.42	5.19	5.46		
XVIA				46	112				70.80		5.16		
XVII[c]	*p*-$NO_2C_6H_4$	H	H	98	78	−38.5(2%)	$C_{11}H_{12}N_2O_4$	55.93	56.19	5.12	4.90		
XVIII[d,m]	C_6H_5	H	C_6H_{13}	85	198-204[g]	−21.1(2%)	$C_{23}H_{37}NO_2$	76.83	77.07	10.37	10.36		
XIX[d,l]	*p*-$NO_2C_6H_4$	H	C_6H_5	91	95	+45(2%)	$C_{23}H_{20}N_2O_4$	71.12	71.18	5.19	5.31		
XIXA				18	119	−28.8(2%)			71.04		5.47		
XX[f,l]	*p*-$NO_2C_6H_4$	H	C_6H_5	74	113		$C_{23}H_{20}N_2O_4$	71.12	71.28	5.19	5.27		
XXA				24	166				71.29		5.40	7.21	7.39
XXI[d]	*p*-$NO_2C_6H_4$	H	H	99	79	+37.5(2%)	$C_{11}H_{12}N_2O_4$	55.93	56.19	5.12	5.11		
XXII[d]	C_6H_5	H	H	79	138[h]	+20.5(2%)	$C_{11}H_{13}NO_2$	69.09	68.68	6.85	7.09		
XXIII[d]	C_6H_5	H	*p*-$NO_2C_6H_4$	87	157	+58(1.65%)	$C_{23}H_{19}N_3O_6$	63.73	63.76	4.42	4.30		
XXIV[d]	C_6H_5	H	*p*-$CH_3OC_6H_4$	81	131	+57.3(2%)	$C_{25}H_{25}NO_4$	74.42	74.32	6.25	6.20		
XXV[d,m]	*p*-$NO_2C_6H_4$	H	*p*-$CH_3OC_6H_4$	18	89	+53(2%)	$C_{25}H_{24}N_2O_6$	66.97	67.15	5.39	5.42	6.25	6.40
XXVI[d]	*p*-$NO_2C_6H_4$	H	*p*-$NO_2C_6H_4$	8	152	−46(0.5%)	$C_{22}H_{18}N_4O_8$	57.74	57.40	3.79	4.13	11.71	11.89
XXVII[e]	*p*-$NO_2C_6H_4$	H	H										
			p-$CH_3OC_6H_4$[i]	89	112	0(2%)	$C_{18}H_{18}N_2O_5$	63.15	63.16	5.30	5.02		
XXVIII[d]	*p*-$NO_2C_6H_4$	H	*p*-$CH_3OC_6H_4$[j]		98		$C_{24}H_{22}N_2O_5$	68.88	68.20	5.30	5.49	6.70	6.95
			C_6H_4										
XXIX[c,m]	*p*-$NO_2C_6H_4$	H	*i*-C_3H_7[k]		148	+29.2(1.2%)	$C_{20}H_{21}N_3O_6$	60.14	59.69	5.30	4.97	10.52	10.90
			p-$NO_2C_6H_4$										

[a] Isomeric series designated by A isolated from acid treatment. [b] In ethyl acetate. [c] L-*threo*. [d] D-*threo*. [e] DL-*erythro*. [f] DL-*threo*. [g] B.p. at 1.5 mm. [h] B.p. at 3.3 mm. [i] From the reaction of paraformaldehyde on the *p*-methoxybenzylidene derivative. [j] From benzaldehyde on the *p*-methoxybenzylidene derivative. [k] From *p*-nitrobenzaldehyde on the sopropyloxazolidine. [l] Pedrazzoli and Tricerri. [m] No isomer was isolated.

Although simple 1-aza-3,7-dioxabicyclo[3.3.0]-octanes have been reported previously by several investigators,[3] no isolation of isomers has been indicated. Isomeric oxazolidines have been reported[8,10] but with few details. The isomers here would seem to be related by *cis-trans* geometry at positions 2 and 8. In this event, the failure of XV to isomerize would be expected. Benzaldehyde and VI will not react by shaking in ether–sodium carbonate solution. The conversion of isomers, therefore, would seem to be concerned with salt formation since scission and reformation of the rings is not likely under the conditions employed.

Experimental[11,12]

1-Aza-3,7-dioxabicyclo[3.3.0]octanes.—A solution of one mole of aminoalcohol and a slight excess over two moles of aldehyde in benzene was heated at reflux over a Dean and Stark water trap for 10 to 15 hr. The theoretical amount of water was collected. The reaction mixture was filtered and evaporated *in vacuo*. The residue was recrystallized from aqueous ethanol to purity.

The benzylidene derivative of the aminoalcohol (with one mole of aldehyde) can be condensed under similar conditions.

L-*threo*-1-(*p*-Benzylaminophenyl)-2-dibenzylamino-1,3-propanediol Dihydrochloride (V). Method A.—A suspension of 13.4 g. (0.03 mole) of L-*threo*-4-(*p*-benzylideneaminophenyl)-2,8-diphenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (IV) in 75 ml. of ethanol was hydrogenated with 5% palladium-on-charcoal at three atmospheres and 40° for 20 hr. After removal of the catalyst, the colorless solution was evaporated *in vacuo*. An ether extract of the residue was treated with dry hydrogen chloride gas. The resulting white solid, 5.5 g. (34%), m.p. 103–105° dec., could not be purified because of its instability.

The salt was shaken in ether–sodium carbonate solution. The ether layer was separated, dried over anhydrous potassium carbonate and evaporated under a stream of dry air. A viscous sirup was recovered which could not be crystallized. The hydrochloride was formed in benzene with dry hydrogen chloride gas. After drying over phosphorus pentoxide and potassium hydroxide *in vacuo*, the solid melted at 115° dec.

Anal. Calcd. for $C_{30}H_{32}N_2O_2 \cdot 2HCl \cdot {}^1/_2H_2O$: C, 67.41; H, 6.60; N, 5.24. Found: C, 67.74; H, 6.93; N, 5.80.

Method B.—A solution of 7.95 g. (0.02 mole) of VII (below) in 100 ml. of ethanol was hydrogenated with platinum oxide at three atmospheres. Two grams of benzaldehyde and fresh catalyst were added and the hydrogenation was continued. After filtration and concentration, the residue was extracted with ether. The dried ether extract was acidified with dry hydrogen chloride gas to cause the separation of 7.5 g. (69%) of solid, m.p. 120–122° dec. This compound had an infrared spectrum identical with the product obtained by method A. This compound also can be synthesized by hydrogenation of IX.

Anal. Calcd. for $C_{30}H_{32}N_2O_2 \cdot 2HCl \cdot {}^1/_2H_2O$: C, 67.41; H, 6.60; N, 5.24. Found: C, 67.14; H, 7.04; N, 5.67.

L-*threo*-2-Dibenzylamino-1-(*p*-nitrophenyl)-1,3-propanediol (VII).—A solution of 42.4 g. (0.2 mole) of L-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol (VI) and 25.3 g. of benzyl chloride in 100 ml. of ethanol was heated at reflux for 4 hr.; 26 g. of benzyl chloride and 21.6 g. of anhydrous sodium carbonate were added along with 50 ml. of water. The mixture was heated at reflux with stirring for 20 hr. After the reaction mixture had been diluted with 100 ml. of water, the alcohol was evaporated and the remaining slurry extracted twice with 750-ml. portions of ether. After drying and evaporating the ether extract, 39.5 g. (44%) of yellow crystals remained, m.p. 142–145°. Recrystallization from ethyl acetate and then from isopropyl alcohol raised the melting point to 158–159°.

Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.17. Found: C, 70.25; H, 6.51.

L-*threo*-1-(*p*-Aminophenyl)-2-dibenzylamino-1,3-propanediol (VIII).—A suspension of 11.0 g. (0.028 mole) of VII in 100 ml. of ethanol was hydrogenated at three atmospheres with platinum oxide. After 15 minutes, the reaction mixture was filtered, concentrated and cooled to cause the separation of 7.5 g. (74%) of white solid, m.p. 138–139°. A sample was recrystallized from isopropyl alcohol, m.p. 142–143°.

Anal. Calcd. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23. Found: C, 75.99; H, 7.54.

L-*threo*-1-(*p*-Benzylideneaminophenyl)-2-dibenzylamino-1,3-propanediol (IX).—A solution of 3.0 g. (0.00825 mole) of VIII and 0.9 g. (0.0085 mole) of freshly distilled benzaldehyde in 75 ml. of ethanol was heated at reflux for 3 hr. Concentrating and cooling the solution resulted in 2.95 g. (79%) of yellow crystals, m.p. 136–137°.

Anal. Calcd. for $C_{30}H_{30}N_2O_2$: C, 79.97; H, 6.71. Found: C, 80.40; H, 6.89.

L-*threo*-4-(*p*-Aminophenyl)-2,8-diphenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (XI).—A suspension of 38.8 g. (0.1 mole) of L-*threo*-2,8-diphenyl-4-(*p*-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane (X) in 300 ml. of ethanol was hydrogenated with platinum oxide at low pressure until three-tenths of a mole of hydrogen was absorbed. The catalyst was removed from the warm reaction mixture by filtration and the clear solution was cooled to cause the separation of 18.5 g. of white solid, m.p. 88–90°. Recrystallization from ethanol yielded 4.0 g. of IV, m.p. 155–157°, and 14.0 g. (39%) of XI, m.p. 92–93° from 2,2,4-trimethylpentane.

The yellow sirup obtained by evaporating the mother liquor was allowed to react with benzaldehyde. Crystalline fractions identified as IV and L-*threo*-2-benzylideneamino-1-(*p*-benzylideneaminophenyl)-1,3-propanediol (II) were isolated from this reaction.

L-*threo*-4-(*p*-Benzylideneaminophenyl)-2,8-diphenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (IV).—A solution of 1.1 g. (0.003 mole) of XI and 0.33 ml. of benzaldehyde in 30 ml. of propanol-2 was heated at reflux for 1 hr. Cooling separated 1.2 g. (88%) of white crystals, m.p. 156–157°, which were identical to authentic IV.

Hydrogenation of L-*threo*-2,4,8-Triphenyl-1-aza-3,7-dioxabicyclo[3.3.0]octane (XII).—A solution of 17.2 g. (0.05 mole) of XII in 100 ml. of ethanol was hydrogenated at three atmospheres at 40° with 5% palladium-on-charcoal for 14 hr. After the catalyst had been removed by filtration, the solution was concentrated *in vacuo*. Trituration of the residue with carbon tetrachloride resulted in the isolation of 5.2 g. of L-*threo*-2-amino-1-phenyl-1,3-propanediol, m.p. 100–111°. Monobenzyl and dibenzyl derivatives of this base were isolated and identified by using techniques previously reported.[3]

Isomeric 1-Aza-3,7-dioxabicyclo[3.3.0]octanes.—The bicyclic compound was dissolved in a dry non-polar solvent such as ether. A dry stream of hydrogen chloride gas was bubbled through the solution until a granular precipitate had formed. The solid was separated quickly by filtration, washed with ether and pressed under a rubber dam. The solid was shaken thoroughly with excess ether–sodium bicarbonate solution. The ether extract was filtered to remove any insoluble residue, dried and concentrated *in vacuo*. The isomer was further separated from degradation products (usually monobenzalated base) either by direct recrystallization from methanol or extraction of the residue with hot 2,2,4-trimethylpentane. The desired compounds were then purified by recrystallization from acetone, ethanol or isooctane.

DETROIT, MICHIGAN

(10) G. E. McCasland and E. C. Horswill, THIS JOURNAL, **73**, 3923 (1951).

(11) Microanalytical data were supplied by Mr. C. E. Childs, Mr. E. Meyer and staff. Optical rotations, infrared data and X-ray diffraction patterns were determined and interpreted by Dr. J. M. Vandenbelt, Mr. R. B. Scott, Mr. E. J. Schoeb and Mrs. C. Spurlock.

(12) Melting points are uncorrected.