of I was recovered. Reactions 4, 5 and 6 are not satisfactory procedures and no details are given.

(b) **From IV, Reaction 7, Table I.**—A solution of 2 g. of bromine and 5 g. of IV in 100 ml. of carbon tetrachloride was placed in a Vycor flask and irradiated at 75–80° by four 8-watt ultraviolet tubes for 17 hours. The solvent and unreacted bromine were removed at the water pump and the residue taken up in boiling dibutyl ether. This gave, on cooling and filtering, 2.55 g. (50%) of II, m.p. and mixture m.p. 199–201°.

(c) **From Tetraphenylallene.**—The oxidation of 2 g. of tetraphenylallene by the procedure of Vorlander[5] gave 1.1 g. of II, m.p. and mixture m.p. 199–201°. Several attempts to isolate IV from this reaction were unsuccessful. However, a 30-second treatment of 2 g. of IV by Vorlander's oxidation procedure yielded 0.1 g. of II, m.p. and mixture m.p. 198–201°. An active hydrogen determination of II showed 0% enolization and 98% addition.

**Reduction of II.** (a) **By Lithium Aluminum Hydride.**—In the usual manner[18] 10 g. of II was reduced by 3 g. of lithium aluminum hydride to give 5.7 g. (57%) of V, m.p. 239–240°. *Anal.* Calcd. for $C_{27}H_{22}O_2$: C, 85.71; H, 5.82. Found: C, 85.41; H, 5.99.

(b) **By Isopropylmagnesium Bromide.**[19]—In the usual type of Grignard apparatus 10 g. of II reacted with 0.3 mole of isopropylmagnesium bromide[19] to produce 5.7 g. (57%) of V, m.p. and mixture m.p. 239–240°. The unsaturated nature of the effluent gas was demonstrated by its reaction with dilute aqueous potassium permanganate.

(c) **By Sodium Methoxide.**—A solution of 15 g. of II and 2.2 g. of sodium methoxide in 100 ml. of dioxane was heated at reflux for 2 hours. The solution was cooled and to it added 3 ml. of acetic acid and 150 ml. of water. The crystals separating were filtered and recrystallized from acetone–ethanol. This gave 14 g. (93%) of V, m.p. and mixture m.p. 239–240°.[20] Oxidation of 1 g. of V using 0.75 g. of chromic anhydride in 50 ml. of boiling acetic acid gave 0.56 g. (56%) of II, m.p. and mixture m.p. 199–201°. An active hydrogen determination of V showed 0.93 hydrogen per molecule.

**Preparation of IIIa and IIIb.**—Both compounds were prepared in the usual manner.[19] An excess of Grignard reagents was used in each case. The results are as follows: IIIa, 8.38 g. (89% yield) from 9.0 g. of II, m.p. 226–228°. *Anal.* Calcd. for $C_{28}H_{24}O_2$: C, 85.71; H, 6.38. Found: C, 85.76; H, 6.18. IIIb, 8.8 g. (70% yield) from 10.0 g. of II, m.p. 203–205°, mixture m.p. with II 175–185°. *Anal.* Calcd. for $C_{34}H_{28}O_2$: C, 87.15; H, 6.02. Found: C, 87.19; H, 6.36.

**Ring Opening of II.** (a) **By Potassium Hydroxide in Dioxane.**—A solution of 10 g. of II and 4 g. of potassium hydroxide in 100 ml. of 90% aqueous dioxane was heated at reflux with stirring for 3 hours. After the addition of 150 ml. of water and removal of 100 ml. of solvent at the water pump, the residue was extracted with benzene. The aqueous solution was boiled with Norite, filtered, cooled and acidified. The precipitate after filtering and drying was crystallized from benzene–petroleum ether. The product, O-benzhydrylbenzilic acid (VII), 7 g., has no definite m.p., but decomposes over the range 100–110°. *Anal.* Calcd. for $C_{27}H_{22}O_3$: C, 82.23; H, 5.58; neut. equiv., 394. Found: C, 82.60; H, 5.81; neut. equiv., 399. On heating with an aqueous acetic acid solution of hydrogen iodide, 2 g. of VII was cleaved to give 1 g. of IX, m.p. and mixture m.p. 144–146°, and 0.32 g. of X, m.p. 26°. Similarly 4 g. of VII was cleaved by hydrogen chloride to give 1.1 g. of VIII, m.p. and mixture m.p. 147–148°. The non-acidic fraction of this cleavage was not isolated.

(b) **By Potassium Hydroxide in Ethylene Glycol.**—A solution of 7.5 g. of II and 28 g. of potassium hydroxide in 125 ml. of 75% ethylene glycol was heated with distillation of water to 195° over a one-hour period. After standing several days at room temperature, the solution was poured onto cracked ice. The solid separating was filtered and recrystallized from ethanol. It proved to be VI, 0.5 g., m.p. and mixture m.p. with prepared sample[21] 109–110°. The odor of X was quite pronounced, but no effort was made to isolate it or its accompanying product, benzophenone.[22]

(18) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947).

(19) In all the Grignard reactions it was necessary to use either toluene or dibutyl ether as a solvent because of the low solubility of II in diethyl ether.

(20) The ease with which II undergoes a Ponndorff reduction is consistent with our unsuccessful efforts to convert V to II by an Oppenauer oxidation. Treating V in boiling toluene for 3 hours with aluminum *t*-butoxide and a 15 molar excess of cyclohexanone resulted in a quantitative recovery of V.

(21) R. S. Tipson, M. A. Clapp and L. H. Cretcher, *J. Org. Chem.*, **12**, 133 (1947).

(22) D. Y. Curtin and S. Leskowitz, THIS JOURNAL, **73**, 2630 (1951), report that dibenzhydryl ether (VI) is readily cleaved by strong base into X and benzophenone.

EMORY UNIVERSITY, GEORGIA

---

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Aminoalcohols Containing the 8-Oxa-3-azabicyclo[3.2.1]octane Ring System and Their Benzoates

BY ARTHUR C. COPE AND WARREN N. BAXTER

RECEIVED JULY 28, 1954

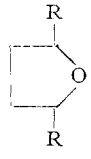
*cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran (III), prepared by reduction of 5-hydroxymethylfurfural or dimethyl tetrahydrofuran-*cis*-2,5-dicarboxylate, has been converted through the ditosylate II into a series of aminoalcohols containing the 8-oxa-3-azabicyclo[3.2.1]octane ring system (V–XI, Table I). The aminoalcohols were prepared from the ditosylate II and aminoalcohols containing a primary amino group. Benzoate hydrochlorides (Table II) and one tropate hydrochloride have been prepared from the bicyclic aminoalcohols and tested for pharmacological activity. Evidence confirming the structure of the aminoalcohols was obtained by synthesis of an identical authentic sample of N-(2-hydroxyethyl)-8-oxa-2-azabicyclo[3.2.1]octane (V) from 8-oxa-3-azabicyclo[3.2.1]octane (I) and ethylene oxide. The structure of I was verified by degradation through reaction of its N-benzoyl derivative XIII with phosphorus pentachloride to *cis*-2,5-bis-(chloromethyl)-tetrahydrofuran (XIV).

Newth and Wiggins[1] have shown that the bicyclic secondary amine, 8-oxa-3-azabicyclo[3.2.1]octane (I), is formed by reaction of the 2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate with m.p. 127.5–128° (which accordingly is the *cis* isomer) with ammonia in methanol. We have prepared a series of aminoalcohols containing the ring system present in I by reaction of the ditosylate II with seven aminoalcohols containing a primary amino group. It was of interest to determine the pharmacological activity of esters of these aminoalcohols, which have some features of structural similarity to scopolamine, the tropic acid ester of an aminoalcohol (scopine) which contains an ethylene oxide grouping.

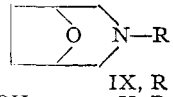
(1) F. H. Newth and L. F. Wiggins, *J. Chem. Soc.*, 155 (1948).

The intermediate from which the new aminoalcohols were prepared, *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran (III), was obtained most readily by the method used by Haworth, Jones and Wiggins[2]: catalytic hydrogenation of 5-hydroxymethylfurfural (obtained by heating sucrose with dilute acids[3]). Alternately, III was prepared from potassium acid saccharate, which was first converted to furan-2,5-dicarboxylic acid[4] and dimethyl furan-2,5-dicarboxylate.[2] Hydrogenation of dimethyl furan-2,5-dicarboxylate in the presence of Raney nickel yielded dimethyl tetrahydrofuran-*cis*-2,5-dicarboxylate (IV, 71%). Hydrogenation of IV in the presence of copper chromite formed *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran (III) in 46% yield, while reduction of the ester IV with lithium aluminum hydride yielded 74% of the same product III. The glycol III from all three sources formed the crystalline ditosylate II, m.p. 128.2–130°, in 83–90% yield. There was no evidence for the presence of the lower melting *trans* form[5] in any of the preparations.

The aminoalcohols V–XI (Table I) were prepared in yields of 50–64% by heating the ditosylate II with two molar equivalents of each of the aminoalcohols containing primary amino groups attached to the hydroxyalkyl groups present in formulas V–XI. The reactants were heated under pressure in a stainless steel vessel at 135–140° for 30 hours in tetrahydrofuran as a solvent. The picrates listed in Table I were prepared from the aminoalcohols as crystalline derivatives, as were two methiodides.



II, R = $-CH_2OSO_2C_6H_4CH_3$-*p*
III, R = $-CH_2OH$
IV, R = $-COOCH_3$
XIV, R = $-CH_2Cl$



I, R = H
V, R = $-CH_2CH_2OH$
VI, R = $-CH_2CH_2CH_2OH$
VII, R = $-CH(CH_3)CH_2OH$
VIII, R = $-CH_2CH(CH_3)OH$
IX, R = $-C(CH_3)_2CH_2OH$
X, R = $-CH(C_2H_5)CH_2OH$
XI, R = $-CH_2C(CH_3)_2OH$
XII, R = $-CH_2CH_2CH_2Cl$
XIII, R = $COC_6H_5$

Evidence supporting the structures of the aminoalcohols V–XI was obtained by an independent synthesis of V from 8-oxa-3-azabicyclo[3.2.1]-octane (I) and ethylene oxide. The two samples of I had identical infrared spectra and formed identical picrates. The structure of I had been assigned by Newth and Wiggins[1] on the basis of its empirical formula, method of preparation, and the fact that the compound was saturated and contained a secondary amino group. In the present work evidence confirming the structure of I was obtained by converting it to the N-benzoyl derivative XIII, which on reaction with phosphorus pentachloride formed the known *cis*-2,5-bis-(chloromethyl)-tetrahydrofuran (XIV), identical with a sample prepared from III and thionyl chloride.[1]

(2) W. N. Haworth, W. G. M. Jones and L. F. Wiggins, *ibid.*, 1 (1945).

(3) See W. N. Haworth and W. G. M. Jones, *ibid.*, 667 (1944).

(4) I. K. Phelps and W. J. Hale, *Am. Chem. J.*, **25**, 445 (1901).

(5) See D. J. C. Wood and L. F. Wiggins, *Nature*, **164**, 402 (1949); L. F. Wiggins and D. J. C. Wood, *J. Chem. Soc.*, 1566 (1950).

Five of the primary and secondary alcohols listed in Table I were converted into benzoate hydrochlorides (Table II) by treatment with benzoyl chloride in chloroform at the reflux temperature for periods of four to seven days. Under these conditions the tertiary alcohol XI failed to form an ester. However, the lithium alkoxide prepared from XI and *n*-butyllithium in ether reacted with benzoyl chloride to form the benzoate, which was isolated as the free base (Table II). The aminoalcohol VI also was converted into the tropic acid ester by first preparing the chloride XII from VI and thionyl chloride, and then treating XII with sodium tropate.[6] The structure of the tropic acid ester, which was isolated as the hydrochloride, was confirmed by saponification to tropic acid and the aminoalcohol VI.

## Pharmacological

We are indebted to Drs. Karl H. Beyer and V. G. Vernier of the Sharp and Dohme Division, Merck and Co., Inc., for preliminary pharmacological study of the hydrochlorides of the benzoic acid esters of the aminoalcohols V–IX and XI, and the hydrochloride of the tropic acid ester of VI. The toxicities of these compounds, determined by intravenous administration to mice, are listed in the last column of Table II. The benzoate hydrochlorides of V–IX produced no pupillary dilatation in the mouse at one-half or one-quarter of the intravenous $LD_{50}$ dose. The benzoate hydrochloride of XI showed minimal and the tropate hydrochloride of VI moderate pupillary dilatation at one-half but not at one-quarter of the intravenous $LD_{50}$ dose, and in both instances the effect was short-lasting. The benzoate hydrochlorides of VII, VIII and IX in concentrations corresponding to 1% of the free bases produced local anesthesia of the rabbits' cornea with durations of approximately 13, 56 and 30 minutes, respectively.

## Experimental[7]

*cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran (III). (a).—A solution of 127 g. of 5-hydroxymethylfurfural[3] in 500 ml. of ether was hydrogenated in the presence of 15 g. of commercial Raney nickel catalyst at 160° and 2000 p.s.i. during a period of 20 hours. The yield of III was 118 g. (89%), b.p. 105° (0.25 mm.), $n^{25}D$ 1.4766.

(b).—Furan-2,5-dicarboxylic acid was prepared[4] and esterified with methanol[2] by procedures previously described. A solution of 33 g. of dimethyl furan-2,5-dicarboxylate, m.p. 109.4–110.4°, in 300 ml. of methanol was hydrogenated in the presence of 5 g. of commercial Raney nickel at 90° and 1100 p.s.i. in a period of 20 hours. The solution was filtered and on cooling yielded 6 g. (18%) of the original ester, dimethyl furan-2,5-dicarboxylate. Concentration followed by distillation through a semi-micro column yielded 23.8 g. (71%) of dimethyl tetrahydrofuran-*cis*-2,5-dicarboxylate (IV), b.p. 81–83° (0.1 mm.), $n^{25}D$ 1.4511–1.4529. This ester has been prepared previously by esterification of the corresponding acid.[2] The ester IV (50 g.) was hydrogenated at 240° and 2000 p.s.i. in a period of 10 hours in the presence of 8 g. of copper chromite. Distillation of the product under reduced pressure separated 11 g. of a polymeric residue from 25 g. of volatile material, which was heated under reflux overnight with 20 g. of barium hydroxide octahydrate in 200 ml. of water. The mixture was extracted continuously with methylene chloride for 36 hours,

(6) A. Blankaert, *Festschrift Emil C. Barell*, 284 (1936); *C. A.*, **31**, 2675 (1937), prepared a series of tropic acid esters in this manner.

(7) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.

and the extracts were dried over magnesium sulfate and concentrated. Fractionation of the residue through a semi-micro column yielded 17.2 g. (46%) of 2,5-bis-(hydroxymethyl)-tetrahydrofuran (III), b.p. 95° (0.04 mm.). Tetrahydrofuran-2,5-dicarboxylic acid (5.0 g., 12%) was isolated from the alkaline aqueous solution by the method described by Haworth, Jones and Wiggins.[2]

Dimethyl tetrahydrofuran *cis*-2,5-dicarboxylate (IV) also was reduced by adding a solution of 19 g. of the ester in 50 ml. of tetrahydrofuran dropwise during a period of 1 hour with stirring to 8 g. of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was stirred for 1 hour after the addition was completed, after which moist tetrahydrofuran was added to decompose excess lithium aluminum hydride, and the mixture was heated briefly with an excess of 10% sodium hydroxide solution to dissolve aluminum salts. The mixture was filtered to separate a small insoluble residue, and the filtrate was concentrated to remove tetrahydrofuran. The aqueous concentrate was extracted continuously with methylene chloride for 48 hours, and the extract was dried over magnesium sulfate. Concentration followed by distillation of the residue through a semi-micro column yielded 9.7 g. (74%) of III, b.p. 104° (0.1 mm.) $n^{25}D$ 1.4750–1.4768. The alkaline aqueous solution from which III had been extracted was acidified with hydrochloric acid and evaporated to dryness. Extraction with acetone followed by concentration of the extract and crystallization of the residue from ether–petroleum ether yielded 2.8 g. (15%) of tetrahydrofuran *cis*-2,5-dicarboxylic acid, m.p. 125.7–126.8°.

*cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran (III) prepared by the three methods described above was converted to the ditosylate by a modification of the procedure described by Newth and Wiggins.[1] Solutions of III and of *p*-toluenesulfonyl chloride (a 50% excess of two molar equivalents) in pyridine were cooled to 0°, mixed and stirred without further cooling for 3 hours. The mixture was poured into water and the solid ditosylate II that separated was collected and recrystallized from ethanol. Yields of II were 83–90%, m.p. 128.2–130°.

**Preparation of the Bicyclic Aminoalcohols V–XI.**—*cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran ditosylate (II) (30–90 g.) was treated with two molar equivalents of each of the seven aminoalcohols containing a primary amino group attached to the hydroxylalkyl groups in V–XI. The reactants were heated in 500 ml. of dry tetrahydrofuran at 135–140° in a 1.5-l. stainless steel hydrogenation bomb for 30 hours, with shaking. The mixtures were cooled, 35 g. of barium hydroxide octahydrate and 300 ml. of water were added, and most of the tetrahydrofuran was removed by heating on a steam-bath for 1 hour. The aqueous concentrates were cooled, filtered and extracted continuously with methylene chloride for 36 hours. The extracts were dried over magnesium sulfate, concentrated and the residues were fractionated through a semi-micro column, yielding the aminoalcohols listed in Table I.

The picrates listed in Table I were prepared by adding a saturated ethereal solution of picric acid to solutions of the aminoalcohols in ether until no further precipitation occurred. They were recrystallized to constant melting point from mixtures of absolute ethanol and ether. The two methiodides described in the footnotes of Table I were prepared in 29% yield by heating the aminoalcohols with a 4–6 molar excess of methyl iodide in methanol or benzene for 2–4 days and were recrystallized from absolute ethanol.

**Benzoate Hydrochlorides.**—The benzoate hydrochlorides listed in Table II (except for the tertiary alcohol ester) were prepared by heating 4.0–6.5 g. of the aminoalcohols listed in Table I with 10 g. of benzoyl chloride in 100–125 ml. of chloroform under reflux protected from atmospheric moisture for 4 days (for the primary alcohols) or 7 days (for the secondary alcohols). Cyclohexane was added in each case and the chloroform was removed by distillation, after which the solid hydrochlorides were collected on a filter and recrystallized to constant melting point from the solvents noted in Table II.

The tertiary alcohol XI failed to form a benzoate under the conditions described above. A solution of 4.6 g. of XI in 50 ml. of dry ether was cooled to −20° (protected from atmospheric moisture) and stirred while 2.3 molar equivalents of *n*-butyllithium in 50 ml. of ether was added during a period of 30 minutes. The mixture was stirred for 1 hour at room temperature, and then was cooled to −20°

TABLE I

N-HYDROXYALKYL-8-OXA-3-AZABICYCLO[3.2.1]OCTANES

| Formula | Yield, % | Boiling point, °C. | Mm. | $n^{25}D$ | $d^{25}_4$ | Formula | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found | Nitrogen, % Calcd. | Found | M.p., °C. | Picrate Formula | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| V[a] | 64 | 94 | 1.0 | 1.4894 | 1.0881 | $C_8H_{15}NO_2$ | 61.12 | 61.10 | 9.62 | 9.71 | 8.91 | 9.11 | 169.7–170.7 | $C_{14}H_{18}N_4O_9$ | 43.53 | 43.60 | 4.69 | 4.88 | 14.50 | 14.41 |
| VI[b] | 60 | 96 | 0.15 | 1.4884 | 1.0669 | $C_9H_{17}NO_2$ | 63.13 | 63.15 | 10.01 | 9.98 | 8.18 | 8.29 | 159.2–160.4 | $C_{15}H_{20}N_4O_9$ | 45.00 | 45.24 | 5.04 | 5.27 | 14.00 | 13.72 |
| VII | 50 | 73 | .08 | 1.4856 | 1.0721 | $C_9H_{17}NO_2$ | 63.13 | 63.17 | 10.01 | 10.13 | 8.18 | 8.15 | 139.5–140.6 | $C_{15}H_{20}N_4O_9$ | 45.00 | 45.16 | 5.04 | 5.31 | 14.00 | 13.90 |
| VIII | 52 | 65 | .09 | 1.4775 | 1.0489 | $C_9H_{17}NO_2$ | 63.13 | 63.43 | 10.01 | 10.02 | 8.18 | 8.48 | 139.4–140.6 | $C_{15}H_{20}N_4O_9$ | 45.00 | 45.10 | 5.04 | 5.22 | 14.00 | 13.87 |
| IX | 53 | 80–83 | .08 | [c] | ..... | $C_{10}H_{19}NO_2$ | 64.83 | 64.79 | 10.34 | 10.28 | 7.56 | 7.71 | 184.8–186.6 | $C_{16}H_{22}N_4O_9$ | 46.37 | 46.30 | 5.35 | 5.58 | 13.52 | 13.40 |
| X | 33 | 88 | .11 | 1.4855 | 1.0489 | $C_{10}H_{19}NO_2$ | 64.83 | 65.03 | 10.34 | 10.33 | 7.56 | 7.60 | 185.1–188.1 | $C_{15}H_{22}N_4O_9$ | 46.37 | 46.34 | 5.35 | 5.43 | 13.52 | 13.69 |
| XI | 63 | 70 | .04 | 1.4771[d] | 1.0303 | $C_{10}H_{19}NO_2$ | 64.83 | 64.58 | 10.34 | 10.24 | 7.56 | 7.81 | 148.7–150.2 | $C_{16}H_{22}N_4O_9$ | 46.37 | 46.27 | 5.35 | 5.42 | 13.52 | 13.29 |

[a] Methiodide, m.p. 113.5–115.9°. Calcd. for $C_9H_{18}INO_2$: C, 36.13; H, 6.06; I, 42.43. Found: C, 35.97; H, 6.18; I, 42.70. [b] Methiodide, m.p. 203.7–204.3°. Calcd. for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44; I, 40.53. Found: C 38.44; H, 6.69; I, 40.74. [c] Solidified and was recrystallized from petroleum ether; m.p. 35.1–36.8°. [d] Solidified, m.p. 29.3–31.6°.

TABLE II

N-HYDROXYALKYL-8-OXA-3-AZABICYCLO[3.2.1]OCTANE BENZOATE HYDROCHLORIDES

| Benzoate hydrochloride of aminoalcohol formula | Yield, % | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Chlorine, % Calcd. | Chlorine, % Found | Intravenous toxicity in mice $LD_{50}$, mg./kg. |
|---|---|---|---|---|---|---|---|---|---|---|
| V | 75 | 193.2–195.3[a] | $C_{15}H_{20}ClNO_3$ | 60.50 | 60.49 | 6.77 | 6.85 | 11.90 | 11.66 | 113 |
| VI | 77 | 186.8–188.2[a] | $C_{16}H_{22}ClNO_3$ | 61.62 | 61.83 | 7.12 | 7.19 | 11.63 | 11.68 | 96 |
| VII | 72 | 132.7–134[a] | $C_{16}H_{22}ClNO_3$ | 61.62 | 61.78 | 7.12 | 7.24 | 11.63 | 11.40 | 89 |
| VIII | 56 | 159.6–161[a] | $C_{16}H_{22}ClNO_3$ | 61.62 | 61.59 | 7.12 | 7.24 | 11.63 | 11.93 | 113 |
| IX | 72 | 172.2–173.7[b] | $C_{17}H_{24}ClNO_3$ | 62.66 | 62.38 | 7.42 | 7.47 | 10.88 | 10.68 | 61 |
| XI[c] | 78 | 91.2–92.1 | $C_{17}H_{23}NO_3$ | 70.56 | 70.89 | 8.01 | 8.23 | 4.84[e] | 5.02[e] | 72 |
| VI[d] | | | | | | | | | | 142 |

[a] Recrystallized from methylene chloride–ether. [b] Recrystallized from methanol–ether. [c] Free base, recrystallized from 30–60° petroleum ether. [d] Tropic acid ester hydrochloride. [e] Nitrogen.

again. A solution of 10 ml. of benzoyl chloride in 100 ml. of dry ether was added in a period of 30 minutes, after which the mixture was heated under reflux for 2 hours, with stirring. The mixture was filtered, and the filtrate was saturated with hydrogen chloride. The solid hydrochloride was separated, dissolved in ice-water, and the solution was made basic by adding 50 ml. of 10% sodium hydroxide at 0°. The aminoester was extracted with three 100-ml. portions of ether, and the extracts were dried over magnesium sulfate and concentrated. The residue crystallized on cooling and was recrystallized to a constant m.p. of 91.2–92.1° from 30–60° petroleum ether (see Table II).

**N-(3-Chloropropyl)-8-oxa-3-azabicyclo[3.2.1]octane (XII).**—A solution of 2.8 g. of the aminoalcohol VI in 75 ml. of dry methylene chloride was saturated with hydrogen chloride, 6 g. of thionyl chloride was added, and the mixture was heated under reflux overnight. The mixture was concentrated and 100 ml. of ether was added to the residue, after which it was extracted with water and the aqueous extracts were made basic with 10% sodium hydroxide. The chloroalkylamine XII was extracted with ether and the extracts were dried over magnesium sulfate, concentrated and the residue was fractionated through a semi-micro column. The yield of XII was 1.95 g. (63%), b.p. 81° (0.35 mm.), $n^{25}D$ 1.4863, $d^{25}_4$ 1.0629.

*Anal.* Calcd. for $C_9H_{16}ClNO$: C, 56.98; H, 8.50; Cl, 18.69. Found: C, 56.93; H, 8.51; Cl, 18.43.

**N-(3-Hydroxypropyl)-8-oxa-3-azabicyclo[3.2.1]octane Tropate Hydrochloride.**—A mixture of 1.0 g. of the chloride XII, 5.0 g. of sodium tropate and 30 ml. of ethanol was heated under reflux for 2 days, after which it was concentrated. Sodium bicarbonate (25 ml. of a 5% solution) was added to the residue, and the aqueous suspension was extracted with methylene chloride. The extracts were dried over magnesium sulfate, filtered and saturated with hydrogen chloride. The crystals of the tropate hydrochloride that separated on adding ether and cooling were recrystallized from methylene chloride–ether and methanol–ether to a constant melting point of 164.1–165.5°; yield 0.93 g. (52%).

*Anal.* Calcd. for $C_{17}H_{24}ClNO_4$: C, 60.75; H, 7.37; Cl, 9.96. Found: C, 60.67; H, 7.42; Cl, 9.77.

The tropate hydrochloride was saponified by heating 0.129 g. with 1.5 ml. of a 20% solution of potassium hydroxide in aqueous methanol under reflux for 15 minutes. The mixture was cooled and acidified with concentrated hydrochloric acid. Tropic acid separated from the solution on standing in a yield of 0.039 g. (62%), m.p. 115.8–116.9°, raised to 116.5–117.8° by recrystallization from water. The acidic filtrate from which the tropic acid had been separated was made basic with potassium hydroxide and evaporated. The residue was extracted with acetone, and the extracts were dried over magnesium sulfate, concentrated and redissolved in ether. The ethereal solution was dried over magnesium sulfate and then treated with an ethereal solution of picric acid. The picrate of VI was obtained in a yield of 0.107 g. (71%), m.p. 158.2–158.9°, raised to 159.2–160.4° by recrystallization from methanol–ether (identical by mixed m.p. with an authentic sample).

**N-Benzoyl-8-oxa-3-azabicyclo[3.2.1]octane (XIII).**—8-Oxa-3-azabicyclo[3.2.1]octane (I) was prepared by the procedure of Newth and Wiggins.[1] A mixture of 2.5 g. of I, 8.0 g. of benzoyl chloride and 25 ml. of benzene was heated under reflux for 20 minutes. The solution was washed with 10% sodium bicarbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure to remove benzene and benzoyl chloride. The residue was again washed with 10% sodium bicarbonate and extracted with ether. The extracts were dried over magnesium sulfate, concentrated, and the residue was distilled through a semi-micro column, yielding 2.8 g. (58%) of the N-benzoyl derivative XIII, b.p. 154–157° (0.5 mm.). A redistilled analytical sample had b.p. 154° (0.5 mm.), $n^{25}D$ 1.5647, $d^{25}_4$ 1.1821.

*Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.87; H, 7.01; N, 6.43.

***cis*-2,5-Bis-(chloromethyl)-tetrahydrofuran (XIV).**—A mixture of 3.0 g. of the N-benzoyl derivative XIII and 5.6 g. of phosphorus pentachloride was heated in a bath at 160° for 1 hour, and then distilled under reduced pressure (b.p. 50–90° at 0.35 mm.) until a black decomposition product began to distil. The distillate was stirred with 30 ml. of cold water for 1 hour, after which the mixture was heated briefly on a steam-bath (to decompose phosphorus oxychloride). The mixture was cooled, extracted with ether, and the extracts were dried over magnesium sulfate and concentrated. Fractionation of the residue through a semi-micro column yielded 0.78 g. (33%) of the dichloride XIV, b.p. 76–77° (1.0 mm.), $n^{25}D$ 1.4812–1.4815. An authentic sample of the dichloride XIV was prepared from II and thionyl chloride in pyridine by the procedure of Newth and Wiggins[1] in 57% yield, $n^{25}D$ 1.4814. This sample of XIV and the sample prepared from XIII had infrared spectra that were identical within the limits of experimental error.

**N-(2-Hydroxyethyl)-8-oxa-2-azabicyclo[3.2.1]octane (V).**—A mixture of 1.5 g. of the secondary amine I, 0.58 g. of ethylene oxide and 0.24 g. of water was shaken and heated at 70° in a stainless steel pressure vessel for 8 hours. Distillation of the product yielded 1.15 g. (55%) of the aminoalcohol V, which after redistillation had b.p. 101° (0.7 mm.), $n^{25}D$ 1.4893. The infrared spectra of this sample of V and a sample prepared from the ditosylate II and ethanolamine were identical, and the two samples formed identical picrates (m.p. and mixed m.p. 169.5–170.6°).

CAMBRIDGE, MASSACHUSETTS