11β,17α,21-Trihydroxy-1,5-pregnadiene-3,20-dione 21-Acetate (XIII).—11β,17α,21-Trihydroxy-1,4-pregnadiene-3,-20-dione 21-acetate (10 g.) was suspended in 100 ml. of dioxane and 80 ml. of acetic acid. A solution of 2.3 g. of bromine in 10 ml. of acetic acid was added, and the mixture allowed to stand at room temperature for 50 minutes. At that time, another 0.4 g. of bromine in 2 ml. of acetic acid was added. After an additional 15 minutes, all of the steroid had dissolved, and the solution had become decolorized to a light yellow. It was poured into 1.5 l. of ice-water; the resulting solid was filtered, washed to neutral and air-dried. This crude material had a positive Beilstein test and showed $\epsilon_{244}^{\mathrm{EtOH}}$ 12,600. Since purification of this solid proved difficult, it was used as such.

A solution of 2.5 l. of ethanol and 500 ml. of water was heated to boiling, 10 g. of zinc powder was added, and then the entire bromination product. Further 10-g. portions of zinc were added, at 15-minute intervals, up to a total of 120 g. Aliquots were taken out at intervals, and their ultraviolet spectrum determined. The high-intensity maximum migrated to lower wave lengths, until, after three hours, it reached a terminal 227.5 mμ. The reaction was interrupted, the solution filtered, and the zinc washed thoroughly with hot ethanol. Concentration to dryness gave a yellow amorphous material, which was chromatographed on 300 g. of Florisil. The first eluates with benzene–ether (3:1) gave 1.4 g. of crystals of m.p. 195–205°, having the same spectroscopic properties as the analytical sample. Later eluates were progressively more contaminated with the 1,4-isomer VII, and set aside for recycling.

An analytical sample was prepared by recrystallization from wet isopropyl ether. It had m.p. 200–207°, $\epsilon_{224}^{\mathrm{EtOH}}$ 11,800; $[\alpha]^{25}\mathrm{D}$ +187.9° (dioxane); λ^{Nujol} at 2.98, 5.72, 5.82, 6.04, 6.20(sh) and 8.20 μ.

Anal. Calcd. for $C_{23}H_{30}O_6 \cdot {}^1/_2\, H_2O$: C, 67.15; H, 7.54. Found: C, 67.00; H, 7.52.

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-Δ^1,5^-pregnadiene-3,20-dione 21-Acetate (XVII).—21-Acetoxy-17α-hydroxy-16α-methyl-9β,11β-epoxy-$\Delta^{1,4}$-pregnadiene-3,20-dione (XIV) (3.61 g.) was dissolved in 490 ml. of carbon tetrachloride and 430 ml. of chlorobenzene. The vessel was swept with argon, 10.8 ml. of 10% pyridine–methylene chloride and 910 mg. of N-bromosuccinimide were added and the resulting solution was refluxed with strong concomitant illumination for 45 minutes. It then was cooled, partitioned between methylene chloride and water, and the organic layer was dried and concentrated *in vacuo*. Crystallization from acetone–hexane gave 3.5 of crude XV, m.p. 165–175° dec., which was converted directly to fluorohydrin XVI as follows. It was dissolved in 5 ml. of chloroform, cooled to −25° and added to 240 ml. of a hydrofluoric acid solution[23] (containing 312 mg./ml. of hydrogen fluoride in a 2:1 tetrahydrofuran–chloroform mixture) previously cooled to −70°. The solution was stirred at 0° for five hours, poured into excess sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed to neutrality and concentrated to incipient crystallization. Filtration gave 1.96 g., m.p. 165–167°, of XVI. The latter was dissolved in 600 ml. of ethanol and 100 ml. of water, 20 g. of zinc powder was added, and the mixture was stirred at room temperature for three hours. It was filtered and allowed to concentrate to dryness under a draft. The residual oil was chromatographed on silica gel. Eluates with benzene–ether (3:1) furnished 357 mg. of the desired XVII. An analytical sample, from ethyl acetate, had m.p. 191–193° dec., ϵ_{220} 14,800.

Anal. Calcd. for $C_{24}H_{31}O_6F \cdot EtOAc$: C, 64.35; H, 7.52. Found: C, 64.81; H, 7.26.

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[23] R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, THIS JOURNAL, **78**, 4956 (1956).

BLOOMFIELD, N. J.

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

Preparation and Reactions of Quaternary Ammonium Salts Derived from *cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran Ditosylate

BY ARTHUR C. COPE AND EDWARD E. SCHWEIZER

RECEIVED AUGUST 29, 1958

The isolation of 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane methobromide (VI, R = CH_3) (50%) from the product obtained from dimethylamine and *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I) demonstrates the existence of the corresponding quaternary tosylate (II, R = CH_3) in the initial reaction mixture. The reaction also yields a significant amount of trimethylamine, formed by alkylation of dimethylamine by the quaternary tosylate. The reaction of the ditosylate I with other secondary amines followed by successive treatment with a basic ion exchange resin and hydrobromic acid yields quaternary ammonium bromides containing the 8-oxa-3-azabicyclo[3.2.1]octane ring system (IX and XI), and 2,5-bis-(N-aminomethyl)-tetrahydrofuran derivatives (VIII and X). The Hofmann degradations of the quaternary hydroxides prepared from IX and XI were studied.

The reaction of secondary amines with *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I) has been shown[1] to result in closure of a six-membered heterocyclic ring with the elimination of an alkyl group of the secondary amine, forming N-alkyl derivatives of 8-oxa-3-azabicyclo[3.2.1]-octane (III). The expected diamines IV also were formed.

The formation of intermediate cyclic quaternary salts II was postulated, followed by alkylation of the secondary amines (present in excess), forming the tosylates of the tertiary amines V and N-alkyl derivatives of 8-oxa-3-azabicyclo[3.2.1]octane (III).

This view now has been substantiated by the isolation of trimethylamine hydrobromide and 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane methobromide (VI, R = CH_3) from the reaction of I with dimethylamine and by demonstrating that the reaction of the quaternary tosylate II (R = CH_3) with dimethylamine yields 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane (III, R = CH_3).

An aqueous solution of the products from the reaction of I with pure dimethylamine in dry tetrahydrofuran was passed through a basic ion exchange resin. The expected 2,5-bis-(dimethylaminomethyl)-tetrahydrofuran (IV, R = CH_3) and 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane (III, R = CH_3) were isolated by ether extraction of the effluent in 2 and 22% yields, respectively. The aqueous solution was concentrated by distillation in order to remove and collect the excess dimethylamine and any trimethylamine produced by alkylation. Neutralization of the concentrate with hydrobromic acid and evaporation to dryness gave the quaternary bromide VI (R = CH_3) in 50%

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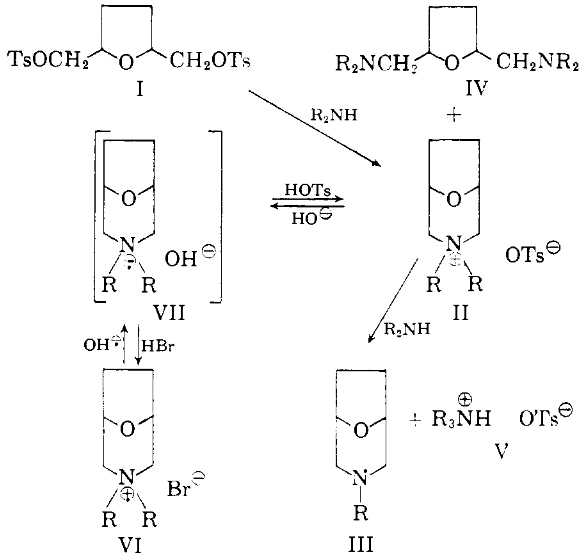
[1] A. C. Cope and B. C. Anderson, THIS JOURNAL, **77**, 995 (1955).



yield. The distillate containing dimethylamine and trimethylamine was treated with *p*-toluenesulfonyl chloride and sodium hydroxide. The reaction mixture was concentrated under reduced pressure and upon neutralization of the distillate with hydrobromic acid trimethylamine hydrobromide was obtained in a yield corresponding to 23% of the amount of the amine III (R = CH_3) that was isolated.

The quaternary tosylate II (R = CH_3) was prepared in 97% yield from the quaternary bromide VI (R = CH_3) *via* the quaternary hydroxide VII (R = CH_3). Reaction of the quaternary tosylate with an equivalent amount of dimethylamine in dry tetrahydrofuran gave 54% of the 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane (III, R = CH_3), thus definitely establishing the occurrence of the alkylation reaction.

In order to determine the scope of the transalkylation reaction in which a carbon–nitrogen bond of the quaternary tosylate is broken and excess secondary amine is alkylated, the reaction of the ditosylate I with two other secondary amines was studied.

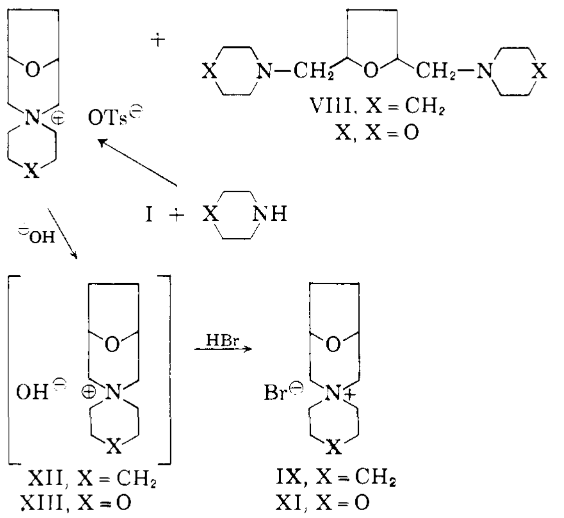
Piperidine and I in dry tetrahydrofuran, after treatment with basic ion exchange resin and hydrobromic acid, yielded spiro[8-oxa-3-azabicyclo[3.2.1]-octane-3,1′-piperidinium] bromide (IX) (78%) and 2,5-bis-(N-piperidylmethyl)-tetrahydrofuran (VIII) (4%).

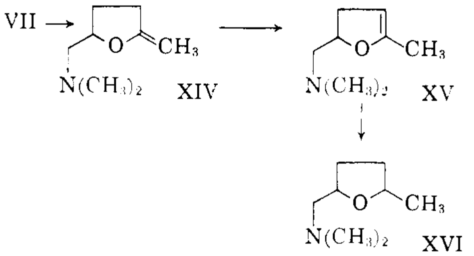
Similarly the reaction of morpholine with I afforded 70% of spiro[8-oxa-3-azabicyclo[3.2.1]-octane-3,1′-morpholinium] bromide (XI) and 8% of 2,5-bis-(N-morpholinomethyl)-tetrahydrofuran-(X).

In neither of these reactions of I with cyclic secondary amines was there any indication of alkylation of the secondary amine by the quaternary salt.

The thermal decompositions of the quaternary hydroxides VII (R = CH_3), XII and XIII were studied in order to substantiate the structures assigned, and, in the cases of XII and XIII, to determine which hydrogen atom β to the amine function would be eliminated.

The Hofmann degradation of VII afforded 2-methylene-5-(N-dimethylaminomethyl)-tetrahydrofuran (XIV) in 60% yield. The infrared spectrum of XIV had peaks at 788, 1597 and 1670 cm.$^{-1}$ which have been described by Meakins[2] as characteristic of 2-methylenetetrahydrofuran.





When XIV was heated at 105–110° for 48 hr. it was isomerized in 46% yield to 2-methyl-5-(dimethylaminomethyl)-4,5-dihydrofuran (XV). Paul and Tchelitcheff[3] observed a similar isomerization in the thermal conversion of 2-methylenetetrahydrofuran to 2-methyl-4,5-dihydrofuran. The peaks in the infrared spectrum of 2-methyl-4,5-dihydrofuran observed by Meakins[2] at 715 and 1674 cm.$^{-1}$ were present in the spectrum of XV. Catalytic reduction of XV gave *cis*-2-methyl-5-(dimethylaminomethyl)-tetrahydrofuran (XVI), which formed a methiodide that was shown to be identical to the methiodide of an authentic sample prepared by allowing one equivalent of N-bromosuccinimide to react with 2,5-dimethylfuran, then treating with dimethylamine and catalytic reduction.

The thermal decomposition of XII gave 71% of a mixture of amines. Fractional distillation of this mixture gave 3-(4-pentenyl)-8-oxa-3-azabicyclo[3.2.1]octane (XVII) (28%), 2-methylene-5-(N-piperidinomethyl)-tetrahydrofuran (XVIII) (8%) and a mixture of XVII and XVIII (14%). The infrared spectrum of the mixture of XVII and XVIII indicated that some XVIII isomerized to 2-methyl-5-(N-piperidinomethyl)-4,5-dihydrofuran (XIX) during the distillation. Catalytic hydrogenation of XVII gave 3-*n*-amyl-8-oxa-3-

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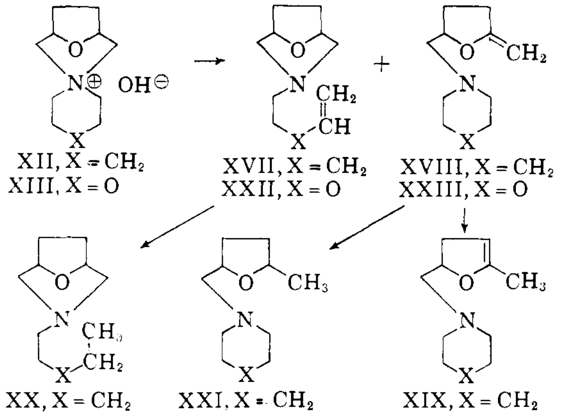
[2] G. D. Meakins, *J. Chem. Soc.*, 4170 (1953).

[3] R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 520 (1950).

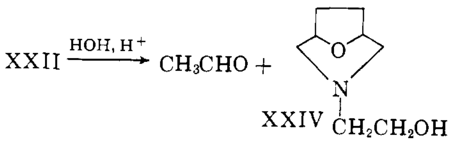


azabicyclo[3.2.1]octane (XX), which formed a perchlorate identical (infrared spectra, melting points and mixed melting point) to the perchlorate of an authentic sample prepared from I and *n*-amylamine.

Attempts to prepare crystalline derivatives of XVIII and XIX were unsuccessful, but catalytic hydrogenation of XVIII gave 2-methyl-5-(N-piperidinomethyl)-tetrahydrofuran (XXI), which was converted to the methiodide, identical to the methiodide of an authentic sample of XXI prepared from 2,5-dimethylfuran in a manner similar to the one used for the preparation of the authentic sample of XVI.

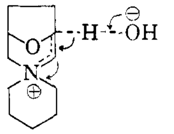
The Hofmann decomposition of XIII yielded 57% of N-(2-vinyloxyethyl)-8-oxa-3-azabicyclo-[3.2.1]octane (XXII). The bands characteristic of the methylenetetrahydrofuran structure[2] were absent in the infrared spectrum of XXII, indicating that no 2-methylene-5-(N-morpholinomethyl)-tetrahydrofuran (XXIII) was present.

Upon heating XXII in an acidic solution containing dimedon, 49% of acetaldehyde dimethone anhydride and 92% of N-(2-hydroxyethyl)-8-oxa-3-azabicyclo[3.2.1]octane (XXIV) were isolated. Compound XXIV and its picrate were found to be identical with authentic samples.[4]

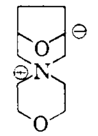


In the Hofmann decomposition of compound XII, β-hydrogen atoms at two different positions are attacked. Attack on the β-hydrogen atom of the piperidine ring leads to compound XVII while attack on the tertiary β-hydrogen atom of the tetrahydrofuran nucleus leads to the formation of compound XVIII. Since the tertiary β-hydrogen atom of the tetrahydrofuran ring would be expected to be more "acidic" than the β-hydrogen atoms in the piperidine ring, it is somewhat surprising that compound XVIII is not formed as the major product. On the other hand, it would be expected that the tertiary and secondary β-hydrogen atoms in compound XIII would be of comparable acidity and therefore on this basis compounds XXII and XXIII might be formed in the ratio of the number of hydrogen atoms in the respective β-positions or 2:1. However, compound XXII is the exclusive product of the decomposition of XIII, indicating that some factor in addition to the acidity of the β-hydrogen atoms directs the course of the reaction.

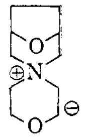
Models show that both compounds XII and XIII can form the necessary coplanar *trans* configuration for elimination initiated by attack on the tertiary β-hydrogen atoms. A possible explanation lies in a consideration of the possible transition states in the elimination reaction leading to XVIII. If the mechanism is E2 it is necessary to propose a transition state approximated by XXV in which a partial double bond is formed at a bridgehead carbon atom. This at once appears to be unfavorable since such a structure approaches a violation of Bredt's rule, which applies rather rigorously in small-ring systems. This unfavorable structure of the transition state may indeed direct the course of the reaction so that in one case the less acidic β-hydrogen atom is eliminated preferentially, and in the other case only one of two nearly equally acidic β-hydrogen atoms is eliminated. In a consideration of the E1cb mechanism one finds that both the intermediate carbanion XXVI leading to XXIII and the carbanion XXVII leading to XXII have the seat of the negative charge adjacent to an ethereal oxygen atom, so that similar inductive effects influence the stabilities of these two ions.



XXV



XXVI



XXVII

It is clear that β-hydrogen atom acidity is important in these decompositions. In the decomposition of compound XII some of the olefin resulting from the abstraction of the more acidic β-hydrogen atom is formed in spite of the fact that there is some factor inhibiting the formation of the 2-methylenetetrahydrofuran derivatives, while once the disparity in the acidity of the β-hydrogen atoms is reduced, as in compound XIII, no 2-methylenetetrahydrofuran derivative is formed.

Experimental[5]

Reaction of *cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran Ditosylate with Dimethylamine.—In a 1.5-l. dry, stainless steel reaction vessel, cooled in an ice–water-bath, were placed 44.06 g. of 2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I) and 700 ml. of dry tetrahydrofuran. A solution of 9.15 g. of dry dimethylamine in 25 ml. of dry tetrahydrofuran was added, and the vessel was immediately sealed, rocked and heated at 150° for 45 hr. After cooling, the product mixture was poured into 250 ml. of water and the resulting solution was concentrated to approximately 275 ml. under 16 mm. pressure with a bath temperature below 60°. Upon cooling, 0.77 g. (2%) of the ditosylate I was deposited and separated by filtration. The filtrate was passed through 250 ml. of wet basic ion exchange resin (Amberlite IRA-400). The resin was washed with distilled water until the effluent was neutral to litmus, and the water solution was extracted continuously with ether for 3 days. The ethereal extract was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue

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(4) A. C. Cope and W. N. Baxter, THIS JOURNAL, **77**, 393 (1955).

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

was distilled through a semi-micro column yielding 2.81 g. (22%) of 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane (III, R = CH_3), boiling below 65° (23 mm.), and 0.37 g. (2%) of 2,5-bis-(dimethylaminomethyl)-tetrahydrofuran (IV, R = CH_3), b.p. 114° (23 mm.). A redistilled sample of III had b.p. 66° (23 mm.), $n^{25}\text{D}$ 1.4659 (lit.[1] b.p. 55° at 12 mm., $n^{25}\text{D}$ 1.4663) and IV had b.p. 117° (23 mm.), $n^{25}\text{D}$ 1.4507 (lit.[1] b.p. 105° at 12 mm., $n^{25}\text{D}$ 1.4484).

The aqueous layer from the ether extraction was concentrated under reduced pressure to approximately 550 ml. with a bath temperature below 69°, and the distillate was collected in a Dry Ice–acetone-cooled trap. The residue was neutralized to *p*H 7 with 41.4 ml. of 1.71 *N* hydrobromic acid. The resulting solution was evaporated to dryness and the residue was recrystallized from absolute methanol. 3-Methyl-8-oxa-3-azabicyclo[3.2.1]octane methobromide (VI, R = CH_3) was obtained in 50% yield (11.2 g.) and had m.p. 254–255° dec. An analytical sample was recrystallized from absolute ethanol and had m.p. 264.0–264.2° dec.

Anal. Calcd. for $C_8H_{16}BrNO$: C, 43.25; H, 7.26; Br, 35.98. Found: C, 43.53; H, 7.54; Br, 36.00.

p-Toluenesulfonyl chloride (36 g.) and 36 g. of sodium hydroxide were added to the distillate that had been collected in the trap. The mixture was shaken vigorously for 15 min. and allowed to stand for 15 min. The mixture was concentrated to one-half its original volume under reduced pressure, and the distillate was collected in a Dry Ice–acetone-cooled trap. The distillate was neutralized with hydrobromic acid and evaporated to dryness. The residue was recrystallized from ethanol, yielding 0.70 g. (corresponding to 23% of the amount of the yield of the amine III) of trimethylamine hydrobromide, m.p. 242.0–243.2°. Recrystallization from ethanol gave pure trimethylamine hydrobromide, m.p. 247.0–248.0°; mixed melting point with an authentic sample was 247.4–248.6°.

3-Methyl-8-oxa-3-azabicyclo[3.2.1]octane methiodide was prepared by adding an excess of methyl iodide to III and refluxing for 18 hr. The mixture was filtered and washed with absolute ethanol; a quantitative yield of the methiodide was obtained, m.p. 248.7–248.9° dec. Three recrystallizations from absolute ethanol gave an analytically pure sample, m.p. 250.8–251.2° dec.

Anal. Calcd. for $C_8H_{16}INO$: C, 35.70; H, 5.99; I, 47.16. Found: C, 36.01; H, 6.24; I, 47.34.

3-Methyl-8-oxa-3-azabicyclo[3.2.1]octane Methotosylate (II).—An aqueous solution of 5.85 g. of 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane methobromide (VI) was passed through 125 ml. of wet basic ion exchange resin (Amberlite IRA-400). The resin was washed with distilled water until the effluent was neutral to litmus, and the effluent was treated with an aqueous solution of 5.01 g. of *p*-toluenesulfonic acid. Upon evaporating to dryness under reduced pressure 8.05 g. (97.5%) of 3-methyl-8-oxa-3-azabicyclo-[3.2.1]octane methotosylate, m.p. 140.4–143.2°, was obtained as a white powder. An analytical sample was obtained by recrystallizing the salt three times from ethanol–acetone, m.p. 145.0–145.7°.

Anal. Calcd. for $C_{15}H_{23}NO_4S$: C, 57.48; H, 7.40; S, 10.23. Found: C, 57.52; H, 7.14; S, 10.10.

Reaction of Dimethylamine with 3-Methyl-8-oxa-3-azabicyclo[3.2.1]octane Methotosylate (II, R = CH_3).—3-Methyl-8-oxa-3-azabicyclo[3.2.1]octane methotosylate (5.0 g.) and a solution of 0.017 mole (by titration) of dimethylamine in dry tetrahydrofuran were heated at 150° and rocked in a stainless steel pressure vessel for 22 hr. The vessel was cooled, 50 ml. of distilled water was added and the solution was passed through 130 ml. of wet basic ion exchange resin (Amberlite IRA-400). The resin was washed with distilled water until the effluent was neutral, and the aqueous solution was extracted continuously with ether for 48 hr. After drying over anhydrous magnesium sulfate the ethereal extract was concentrated and the residue distilled, yielding 1.25 g. (58%) of 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane (III, R = CH_3), b.p. 58–61° (22 mm.), $n^{25}\text{D}$ 1.4646–1.4654. An attempt to isolate trimethylamine from the reaction mixture was unsuccessful.

Reaction of *cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran Ditosylate (I) with Piperidine.—In a 3-l. stainless steel hydrogenation vessel were placed 88.12 g. of 2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I), 1600 ml. of dry tetrahydrofuran and 34.9 g. of dry piperidine. The bomb was sealed and heated at 150° for 24.3 hr. with agitation by rocking. After cooling, the reaction mixture was poured into 400 ml. of water and the tetrahydrofuran was removed by distillation at atmospheric pressure. The aqueous solution was passed through 1300 ml. of wet basic ion exchange resin (Amberlite IRA-400) and the resin was washed with distilled water until the effluent was neutral. The aqueous solution was extracted continuously with ether for 48 hr.

The aqueous layer was neutralized to *p*H 7.0 with hydrobromic acid and evaporated to dryness under reduced pressure at a temperature of less than 50°. The residue was recrystallized from acetone–ethanol, and 38.0 g. (73%) of spiro[8-oxa-3-azabicyclo[3.2.1]octane-3,1′-piperidinium] bromide (IX) was obtained, m.p. 249.8–250.6°. An additional 2.8 g. (5%) of product, m.p. 249.0–250.6°, was recovered by concentration of the mother liquor. Recrystallization from acetone–alcohol gave an analytical sample, m.p. 251.6–252.1° dec.

Anal. Calcd. for $C_{11}H_{20}BrNO$: C, 50.39; H, 7.69; Br, 30.48. Found: C, 50.53; H, 7.69; Br, 30.21.

The ethereal extract was dried over anhydrous magnesium sulfate, filtered, and concentrated. Distillation of the residue through a 30 × 0.8-cm. column with a spinning band rotating at approximately 1200 r.p.m. gave 2.17 g. (4%) of 2,5-bis-(N-piperidylmethyl)-tetrahydrofuran (VIII), b.p. 108–113° (0.06 mm.), $n^{25}\text{D}$ 1.4912–1.4917. An analytical sample was distilled over sodium under dry nitrogen and had b.p. 114° (0.05 mm.), $n^{25}\text{D}$ 1.4918.

Anal. Calcd. for $C_{16}H_{30}N_2O$: C, 72.13; H, 11.35; N, 10.52. Found: C, 72.35; H, 11.22; N, 10.69.

2,5-Bis-(N-piperidylmethyl)-tetrahydrofuran dimethiodide was prepared by adding 4.0 g. of methyl iodide to 3.5 g. of VIII in 100 ml. of absolute methanol. The solution was stirred for 1 hr. and refluxed with stirring for 1.5 hr. Upon cooling, the reaction mixture deposited 5.01 g. (70%) of 2,5-bis-(N-piperidylmethyl)-tetrahydrofuran dimethiodide, m.p. 284.6–285.0°. An analytical sample was obtained by recrystallization from absolute methanol, m.p. 284.2–285.2°.

Anal. Calcd. for $C_{18}H_{36}I_2N_2O$: C, 39.28; H, 6.60; I, 46.12. Found: C, 39.02; H, 6.66; I, 45.86.

Reaction of *cis*-2,5-Bis-(hydroxymethyl)-tetrahydrofuran Ditosylate (I) with Morpholine.—In a 1.5-l. stainless steel reaction vessel were placed 44.06 g. of 2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I), 730 ml. of dry tetrahydrofuran and 17.63 g. of dry morpholine. The vessel was heated at 150° for 50 hr. with rocking to provide agitation. After cooling, the reaction mixture was added to 300 ml. of water. The tetrahydrofuran was removed by distillation, and upon cooling the aqueous solution deposited 0.5 g. of the ditosylate I. After filtration the filtrate was passed through 400 ml. of Amberlite IRA-400 basic ion exchange resin and the resin was washed with distilled water until the effluent was neutral to litmus. The aqueous solution was extracted continuously with ether and with methylene chloride for 8 and 7 days, respectively. The aqueous layer was neutralized with hydrobromic acid and then evaporated to dryness under reduced pressure on a steam-cone. The residue was crystallized from absolute ethanol, yielding 18.5 g. (70.3%) of spiro[8-oxa-3-azabicyclo[3.2.1]-octane-3,1′-morpholinium] bromide (XI), m.p. 239.4–240.4°. An analytical sample was recrystallized from absolute ethanol, m.p. 244.0–244.5°.

Anal. Calcd. for $C_{10}H_{18}BrNO_2$: C, 45.46; H, 6.87; Br, 30.25. Found: C, 45.56; H, 6.97; Br, 30.09.

The ethereal extract was dried over anhydrous magnesium sulfate and concentrated. Fractionation of the residue through a semi-micro column gave 2.05 g. (8%) of 2,5-bis-(N-morpholinomethyl)-tetrahydrofuran (X), b.p. 128.0–130.5° (0.07 mm.), $n^{25}\text{D}$ 1.4903–1.4924. An analytical sample was redistilled through a semi-micro column over sodium in an atmosphere of dry nitrogen, b.p. 125.0° (0.19 mm.), $n^{25}\text{D}$ 1.4926.

Anal. Calcd. for $C_{14}H_{26}N_2O_3$: C, 62.19; H, 9.69; N, 10.36. Found: C, 61.86; H, 9.53; N, 10.53.

2,5-Bis-(N-morpholinomethyl)-tetrahydrofuran dimethiodide was prepared by refluxing a solution of 1.87 g. of X and an excess of methyl iodide in 250 ml. of dry methanol for 5 hr. The dimethiodide, 3.37 g. (88%), m.p. 263.4–

263.6°, crystallized upon cooling overnight. An analytical sample was recrystallized from absolute methanol, m.p. 266.4–266.8°.

Anal. Calcd. for $C_{16}H_{32}I_2N_2O_3$: C, 34.67; H, 5.82; I, 45.80. Found: C, 34.50; H, 5.93; I, 45.91.

Thermal Decomposition of 3-Methyl-8-oxa-3-azabicyclo[3.2.1]octane Methohydroxide (VII, R = CH_3).—3-Methyl-8-oxa-3-azabicyclo[3.2.1]octane methohydroxide was prepared by passing an aqueous solution of 10 g. of 3-methyl-8-oxa-3-azabicyclo[3.2.1]octane methobromide (VI, R = CH_3) through 200 ml. of wet basic ion exchange resin (Amberlite IRA-400). The resin was washed with distilled water until the effluent was neutral to litmus. The aqueous solution was evaporated to dryness under reduced pressure in an atmosphere of nitrogen at a bath temperature below 50°. Upon raising the temperature of the bath to 91° decomposition of the quaternary hydroxide was observed, and the temperature of the bath was raised slowly to 100°. The products were collected in a series of two traps: the first cooled with ice-water and the second with Dry Ice–acetone. The amine was extracted from the aqueous layer in the first trap with two 30-ml. portions of ether, and from the aqueous layer in the second trap with three 30-ml. portions of ether. The extracts were combined and dried over anhydrous magnesium sulfate, filtered, and concentrated. Distillation of the residue through a semi-micro column gave 3.79 g. (60%) of 2-methylene-5-(dimethylaminomethyl)-tetrahydrofuran (XIV), b.p. 40–46° (3.1 mm.). An analytical sample had b.p. 49–52° (3 mm.), $n^{25}D$ 1.4609.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.05; H, 10.87; N, 9.96.

2-Methylene-5-(dimethylaminomethyl)-tetrahydrofuran methiodide was prepared by adding an excess of methyl iodide to 0.24 g. of XIV. A solid formed instantly, and after 5 min. methanol was added. The solution was heated to boiling and absolute ether was introduced until a slight cloudiness appeared. Upon cooling, 0.29 g. (60%) of the methiodide, m.p. 145.9–149.4°, was deposited. Recrystallization from methanol–ether gave an analytical sample, m.p. 172.0–173.6°.

Anal. Calcd. for $C_9H_{18}INO$: C, 38.17; H, 6.41; I, 44.82. Found: C, 38.20; H, 6.59; I, 45.06.

Isomerization of 2-Methylene-5-(dimethylaminomethyl)-tetrahydrofuran (XIV).—Compound XIV (3.40 g.) was heated at 105–110° for 48 hr. and then distilled through a semi-micro column, yielding 1.55 g. (46%) of 2-methyl-5-(dimethylaminomethyl)-4,5-dihydrofuran (XV), b.p. 73–78° (27 mm.). An analytical sample was redistilled through a semi-micro column over sodium in a nitrogen atmosphere, b.p. 66.5° (24.6 mm.), $n^{25}D$ 1.4530.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.85; H, 10.48; N, 10.05.

2-Methyl-5-(dimethylaminomethyl)-4,5-dihydrofuran methiodide was prepared by adding an excess of methyl iodide to a solution of 0.30 g. of the amine in dry benzene and refluxing the solution for 1 hr. The methiodide precipitated upon cooling; 0.45 g. (75%), m.p. 135.0–136.4°. Repeated recrystallization from methanol–ether gave an analytical sample, m.p. 141.4–143.4°.

Anal. Calcd. for $C_9H_{18}INO$: C, 38.17; H, 6.41; I, 44.82. Found: C, 38.10; H, 6.60; I, 44.98.

2-Methyl-5-(dimethylaminomethyl)-tetrahydrofuran Methiodide.—Catalytic hydrogenation of an ethereal solution of 0.246 g. of 2-dimethylaminomethyl-5-methyl-4,5-dihydrofuran (XV) in the presence of Adams platinum catalyst resulted in the absorption of 103.5% of one molar equivalent of hydrogen in 10.5 hr. The mixture was filtered and the residue washed with ether. Excess methyl iodide was added and the solution was refluxed for 1 hr. 2-Methyl-5-(dimethylaminomethyl)-tetrahydrofuran methiodide was obtained in 79% yield (0.38 g.), m.p. 124–127°. On repeated recrystallization from methanol–ethyl acetate the methiodide was obtained as a colorless solid, m.p. 156.8–157.7°. Mixed melting point with an authentic sample, prepared by a reaction sequence described below beginning with 2,5-dimethylfuran, was 156.8–158.0°.

2-Methyl-5-(dimethylaminomethyl)-furan.—In a dry, three-necked, 500-ml. flask, equipped with a thermometer and an oil-sealed stirrer, was placed a solution of 20.7 g. of freshly distilled 2,5-dimethylfuran and 110 ml. of dry benzene. Commercial N-bromosuccinimide (38.1 g.) was added in small portions. As soon as the exothermic reaction began, the flask was cooled with an ice-bath, and the temperature of the reaction mixture was maintained at 30–40° by regulating the rate of addition of N-bromosuccinimide. After the addition had been completed the mixture was stirred for 0.5 hr. without cooling. The mixture was filtered, and the residue was washed with three 25-ml. portions of dry benzene. The filtrate was treated with a large excess of dimethylamine and allowed to stand for 2 hr. with intermittent shaking, after which 200 ml. of 10% aqueous sodium hydroxide was added. After shaking the solution vigorously it was extracted continuously for 18 hr. with benzene, and the benzene extract was concentrated under reduced pressure. The residue was distilled under reduced pressure through a semi-micro column; 14.5 g. (49%) of 2-methyl-5-(dimethylaminomethyl)-furan was obtained, b.p. 58–64° (17 mm.), $n^{25}D$ 1.4569–1.4613. A redistilled sample had b.p. 64° (17 mm.), $n^{25}D$ 1.4613; reported[6] b.p. 68–70° (25 mm.), $n^{25}D$ 1.4620.

2-Methyl-5-(dimethylaminomethyl)-furan hydrochloride was prepared in 97% yield according to the procedure of Holdren and Nixon.[6] After recrystallization from ethanol–acetone the salt had m.p. 160.4–161.4°, reported[6] m.p. 158.0–158.5° (uncor.).

***cis*-2-Methyl-5-(dimethylaminomethyl)-tetrahydrofuran (XVI).**—Catalytic hydrogenation of 10 g. of 2-methyl-5-(dimethylaminomethyl)-furan in 100 ml. of absolute methanol in the presence of one teaspoonful of Raney nickel at 1500 p.s.i. and a temperature of 150° required 6 hr. The mixture was filtered, and the catalyst was washed with absolute methanol. The methanolic solution was concentrated, and the residue was distilled through a semi-micro column under reduced pressure. *cis*-2-Methyl-5-(dimethylaminomethyl)-tetrahydrofuran (XVI) was obtained in 63% yield (6.47 g.), b.p. 55–56° (12 mm.), $n^{25}D$ 1.4307–1.4313. An analytical sample was redistilled through a semi-micro column over sodium in an atmosphere of dry nitrogen, b.p. 68.5° (23 mm.), $n^{25}D$ 1.4314.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78. Found: C, 67.37; H, 12.11; N, 10.02.

***cis*-2-Methyl-5-(dimethylaminomethyl)-tetrahydrofuran methiodide** was prepared by refluxing a solution of 0.5 g. of XVI in 100 ml. of dry ether with an excess of methyl iodide for 10 min. Upon cooling, 0.85 g. (85%) of the methiodide separated, m.p. 155.8°. An analytical sample recrystallized from methanol–ethyl acetate had m.p. 157.5–158.5°.

Anal. Calcd. for $C_9H_{20}INO$: C, 37.90; H, 7.07; I, 44.51. Found: C, 37.90; H, 6.80; I, 44.59.

Thermal Decomposition of Spiro[8-oxa-3-azabicyclo[3.2.1]octane-3,1′-piperidinium] Hydroxide (XII).—Spiro[8-oxa-3-azabicyclo[3.2.1]-octane-3,1′-piperidinium] hydroxide was prepared by passing an aqueous solution of 17.02 g. of spiro-[8-oxa-3-azabicyclo[3.2.1]octane-3,1′-piperidinium] bromide (IX) through 130 ml. of wet basic ion exchange resin (Amberlite IRA-400). The resin was washed with distilled water until the effluent was neutral to litmus and the aqueous solution was concentrated under reduced pressure at a bath temperature of less than 60° in an atmosphere of dry nitrogen until XII started to crystallize. The quaternary hydroxide started to decompose at 75° as the temperature of the bath was raised slowly to 160°. The decomposition products were collected in two traps, one cooled with ice-water and the second with Dry Ice–acetone. The two layers were separated and the amine mixture, 8.32 g. (71%), $n^{25}D$ 1.4824, was dissolved in ether and dried over anhydrous magnesium sulfate. The mixture was filtered and then concentrated under reduced pressure. After a short path distillation (recovery of the amine mixture was 6.80 g. (82%), b.p. 66–74° at 0.75 mm., $n^{25}D$ 1.4820) the mixture was redistilled through a 30 × 0.5-cm. spinning band column. Three fractions were collected: (1) 3.26 g. (28%) of 3-(4-pentenyl)-8-oxa-3-azabicyclo[3.2.1]octane (XVII), b.p. 33–37.5° (0.09 mm.), $n^{25}D$ 1.4749–1.4762; (2) 1.62 g. (14%) of a mixture of XVII, XVIII and XIX, b.p. 35–43° (0.08 mm.), $n^{25}D$ 1.4767–1.4868; (3) 1.00 g. (8.5%) of 2-methylene-5-(N-piperidinomethyl)-tetrahydrofuran (XVIII), b.p. 38–44° (0.08 mm.), $n^{25}D$ 1.4875–1.4886.

3-(4-Pentenyl)-8-oxa-3-azabicyclo[3.2.1]octane (XVII) was purified by redistilling a sample from a similar prepara-

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[6] R. F. Holdren and R. M. Hixon, THIS JOURNAL, **68**, 1198 (1946).

tion through a 30 × 0.5-cm. spinning band column over sodium in an atmosphere of dry nitrogen. Pure XVII had b.p. 70° (0.65 mm.), n^{25}D 1.4756.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 73.17; H, 10.82; N, 7.87.

3-(4-Pentenyl)-8-oxa-3-azabicyclo[3.2.1]octane perchlorate was prepared by adding 0.22 g. of 70% perchloric acid to a solution of 0.2 g. of XVII in dry ether. A quantitative amount of the amine perchlorate, m.p. 118.0–119.7°, was obtained. Recrystallization from ethyl acetate–ether gave an analytical sample, m.p. 124.7–126.4°.

Anal. Calcd. for $C_{11}H_{20}NO_5Cl$: C, 46.89; H, 7.16; N, 4.97. Found: C, 47.20; H, 7.13; N, 5.03.

2-Methylene-5-(N-piperidinomethyl)-tetrahydrofuran (XVIII) with b.p. 38° (0.09 mm.) and n^{25}D 1.4882 was analyzed. Attempts to prepare crystalline derivatives of XVIII were unsuccessful.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.94; H, 10.66; N, 7.75.

3-*n*-Amyl-8-oxa-3-azabicyclo[3.2.1]octane Perchlorate.—Hydrogenation of 3-(4-pentenyl)-8-oxa-3-azabicyclo[3.2.1]octane (XVII) in an ethereal solution in the presence of Adams platinum catalyst required 9.5 hr. with the absorption of 105% of one molar equivalent of hydrogen. A slight excess of 70% perchloric acid was added to the filtered ethereal solution, and 3-*n*-amyl-8-oxa-3-azabicyclo[3.2.1]octane perchlorate was obtained in 93% yield, m.p. 122.1–123.2°. After recrystallization from ethyl acetate–ether the perchlorate had m.p. 123.0–124.0°. The mixed melting point with an authentic sample prepared from *n*-amylamine and I showed no depression.

2-Methyl-5-(N-piperidinomethyl)-tetrahydrofuran Methiodide.—Catalytic hydrogenation of an ethereal solution of 2-methylene-5-(N-piperidinomethyl)-tetrahydrofuran (XVIII) in the presence of Adams platinum catalyst required 9 hr. and 99.3% of one molar equivalent of hydrogen was absorbed. An excess of methyl iodide was added to the filtered solution, and the solution was refluxed for 1 hr. An amorphous solid precipitated. Upon recrystallization from acetone–ether a 31% yield of the methiodide, m.p. 112.8–114.0°, was obtained. Recrystallization from acetone–ether gave a pure sample, m.p. 115.0–116.2°. Mixed melting point with an authentic sample showed no depression.

Preparation of 3-*n*-Amyl-8-oxa-3-azabicyclo[3.2.1]octane (XX).—A solution of 19.0 g. of *cis*-2,5-bis-(hydroxymethyl)-tetrahydrofuran ditosylate (I) and 7.52 g. of *n*-amylamine in 400 ml. of dry tetrahydrofuran in a stainless steel pressure vessel was heated at 140° and rocked for 28 hr. The mixture was poured into 350 ml. of 17% aqueous sodium hydroxide, filtered, and extracted continuously with ether for 48 hr. The extract was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was distilled through a 30 × 0.8-cm. spinning band column, yielding 2.47 g. (31%) of 3-*n*-amyl-8-oxa-3-azabicyclo[3.2.1]octane (XX), b.p. 51–55° (0.45 mm.), n^{25}D 1.4610–1.4626. An analytical sample had b.p. 55° (0.45 mm.), n^{25}D 1.4625.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.81; H, 11.73; N, 7.83.

3-*n*-Amyl-8-oxa-3-azabicyclo[3.2.1]octane perchlorate was prepared by adding a slight excess of 70% perchloric acid in dry ether to an ethereal solution of XX and shaking the mixture vigorously until a solid precipitated. The perchlorate was recrystallized to a constant m.p. of 121.7–122.2° from ethyl acetate–ether.

Anal. Calcd. for $C_{11}H_{22}ClNO_5$: C, 46.55; H, 7.82; Cl, 12.50. Found: C, 46.55; H, 7.91; Cl, 12.48.

2-Methyl-5-(N-piperidinomethyl)-furan.—2-Bromomethyl-5-methylfuran was prepared as described above in the preparation of 2-methyl-5-(dimethylaminomethyl)-furan from 20.7 g. of 2,5-dimethylfuran and 38.1 g. of commercial N-bromosuccinimide. Upon the addition of 55 g. of dry piperidine a precipitate formed instantly. The mixture was shaken intermittently over a period of 5 min., 300 ml. of dry benzene was added, and the mixture was refluxed for 1.5 hr. The reaction mixture was poured into 400 ml. of 10% aqueous sodium hydroxide and stirred vigorously until solution was effected. The solution was extracted continuously with benzene for 36 hr., the benzene extract concentrated, and the residue distilled through a semi-micro column under reduced pressure, yielding 24 g. (62%) of 2-methyl-5-(N-piperidinomethyl)-furan, b.p. 58.2–64.0° (0.28 mm.), n^{25}D 1.4885–1.4938. An analytical sample had b.p. 54.0–54.5° (0.08 mm.), n^{25}D 1.4930; reported[6] b.p. 88–89° (6 mm.), n^{25}D 1.4960.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.81; H, 9.34; N, 8.08.

2-Methyl-5-(N-piperidinomethyl)-furan methiodide was prepared by adding a slight excess of methyl iodide to a solution of the amine in dry ether. The precipitate was recrystallized to a constant m.p. of 121.6–122.3° from acetone–ether.

Anal. Calcd. for $C_{12}H_{20}INO$: C, 44.87; H, 6.28; I, 39.51. Found: C, 44.64; H, 6.34; I, 39.32.

2-Methyl-5-(N-piperidinomethyl)-tetrahydrofuran (XXI).—Catalytic hydrogenation of 12.35 g. of 2-methyl-5-(N-piperidinomethyl)-furan in 120 ml. of dry methanol over one teaspoonful of Raney nickel catalyst required 5 hr. at 150° under a pressure of 1700 p.s.i. The reaction mixture was filtered and the catalyst was washed with three 25-ml. portions of methanol. The filtrate was concentrated, and the residue was distilled under reduced pressure through a semi-micro column, yielding 10.14 g. (81%) of 2-methyl-5-(N-piperidinomethyl)-tetrahydrofuran (XXI), b.p. 48.0–52.0° (0.07–0.18 mm.), n^{25}D 1.4655–1.4660. An analytical sample had b.p. 51.5° (0.16 mm.), n^{25}D 1.4655.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.32; H, 11.20; N, 7.69.

2-Methyl-5-(N-piperidinomethyl)-tetrahydrofuran methiodide was prepared by adding a slight excess of methyl iodide to a solution of the amine in dry ether. The precipitate was recrystallized to a constant m.p. of 116.0–117.0° from acetone–ether.

Anal. Calcd. for $C_{12}H_{24}INO$: C, 44.31; H, 7.43; I, 39.02. Found: C, 44.31; H, 7.48; I, 39.12.

Thermal Decomposition of Spiro[8-oxa-3-azabicyclo[3.2.1]octane-3,1′-morpholinium] Hydroxide (XIII).—An aqueous solution of 7.83 g. of spiro-[8-oxa-3-azabicyclo[3.2.1]octane-3,1′-morpholinium] bromide (XI) was passed through 100 ml. of wet basic ion exchange resin (Amberlite IRA-400). The resin was washed with distilled water until the effluent was neutral to litmus. The aqueous solution was evaporated to dryness under reduced pressure in an atmosphere of nitrogen at a bath temperature below 45°. The bath temperature was slowly raised to 230°; the product started to distil when the bath temperature reached 170° and was collected in two traps cooled with Dry Ice–acetone. The heavier amine layer was separated from the aqueous layer, and the aqueous layer was saturated with potassium hydroxide and extracted with two portions of ether. The amine layer and ether extracts were combined, concentrated, and the residue was distilled under reduced pressure through a semi-micro column yielding 3.11 g. (57%) of N-(2-vinyloxyethyl)-8-oxa-3-azabicyclo[3.2.1]octane (XXII), b.p. 55.0–56.5° (0.12 mm.), n^{25}D 1.4802–1.4814, d^{20}_4 1.032.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.71; H, 9.35; N, 7.53.

N-(2-Vinyloxyethyl)-8-oxa-3-azabicyclo[3.2.1]octane picrate was prepared in a quantitative yield by adding a saturated ethereal solution of picric acid to a solution of XXII in ether. Recrystallization from ethyl acetate gave an analytical sample, m.p. 126.7–127.7°.

Anal. Calcd. for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.89; N, 13.59. Found: C, 46.67; H, 5.09; N, 13.73.

Acid Hydrolysis of N-(2-Vinyloxyethyl)-8-oxa-3-azabicyclo[3.2.1]octane (XXII).—To a solution of 3 ml. of concentrated sulfuric acid, 50 ml. of water, 100 ml. of ethanol and 8 g. of dimedon was added 2.1 g. of XXII. The solution was heated rapidly to 50°, when a strong odor of acetaldehyde was detected, and then allowed to stand at room temperature for 60 hr. Water (150 ml.) was added and the solution was allowed to stand for 2 hr. The white precipitate of acetaldehyde dimethone anhydride had m.p. 176.9–177.9°. Mixed melting point with an authentic sample was 177.6–178.6°.

The filtrate was extracted with eight 100-ml. portions of chloroform to remove the excess dimedon. The aqueous layer was made strongly basic with sodium hydroxide, and extracted continuously with ether for 36 hr. The extract was concentrated and 1.65 g. (92%) of N-(2-hydroxyethyl)-

8-oxa-3-azabicyclo[3.2.1]octane (XXIV), $n^{25}D$ 1.4848, was obtained. Distillation under reduced pressure through a semi-micro column gave 1.35 g. (75%) of XXIV, b.p. 54–59° (0.05–0.08 mm.), $n^{25}D$ 1.4901–1.4903; reported[4] b.p. 94° (1 mm.), $n^{25}D$ 1.4894. The picrate was obtained in 87% yield, m.p. 169.8–171.0°, by treating an ethereal solution of XXIV with an ethereal solution of picric acid. After recrystallization from ethanol it had m.p. 169.2–171.0°, and was found to be identical (mixed m.p.) to an authentic sample.[4]

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, THE UNIVERSITY OF NEW MEXICO, AND BIOMEDICAL RESEARCH GROUP,[3] LOS ALAMOS SCIENTIFIC LABORATORY, UNIVERSITY OF CALIFORNIA]

Liquid Scintillators. VI. 2-Aryl- and 2,7-Diarylfluorenes[1]

BY MARTIN D. BARNETT,[2] GUIDO H. DAUB, F. NEWTON HAYES AND DONALD G. OTT

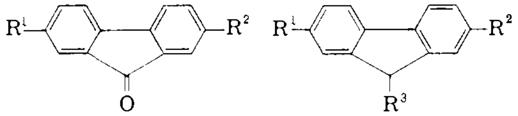
RECEIVED JANUARY 2, 1959

2-Phenylfluorene (II), 2-(4-biphenylyl)-fluorene (IX), 9-methyl-2-(4-biphenylyl)-fluorene (X), 2,7-diphenylfluorene (XVI) and 2,2′-bifluorene (VI) have been synthesized and screened as potential primary liquid scintillation solutes. Although the scintillation properties of II were inferior to those of *p*-terphenyl, the pulse-height values for VI, IX, X and XVI were greater than *p*-quaterphenyl at comparable concentrations. In addition, VI, IX and XVI were evaluated as secondary solutes and found to possess excellent scintillation characteristics.

In connection with work being carried out, in part, by the Biomedical Research Group of the Los Alamos Scientific Laboratory on the evaluation of organic compounds as solutes in liquid scintillation detector systems, it seemed of interest to investigate the liquid scintillation properties of fluorene analogs of *p*-terphenyl and *p*-quaterphenyl. These latter compounds have been shown to possess remarkable scintillation properties; however, the use of *p*-quaterphenyl has been severely curtailed by its low solubility in toluene. Accordingly, the synthesis of a number of 2-aryl- and 2,7-diaryl-substituted fluorenes was carried out in an effort to obtain a more soluble, completely conjugated aromatic system and to learn what effect, if any, the presence of a methylene bridge would have on the scintillation properties of the molecule.

The synthesis of 2-aryl-substituted fluorenes is complicated by the fact that the halogen atoms in 2-bromofluorene and 2-iodofluorene are relatively inert toward the usual reactions with magnesium or lithium metal. Thus, Miller and Bachman[4] report that 2-bromofluorene did not react with either magnesium or lithium in ether or boiling xylene, while Korczynski[5] was unable to couple two molecules of 2-iodofluorene using copper powder in a sealed tube at 300°. Another factor limiting the use of 2-fluorenylmetallic derivatives is the acidity of the methylene hydrogens in fluorene.

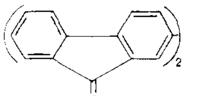
2-Phenylfluorenone (I) was prepared in four steps from 1,4-diphenylbutadiene[6] essentially according to the procedure described by Weizmann.[7] Reduction of I with hydrazine in a modified Wolff–Kishner reduction without alkali[8] afforded 2-phenylfluorene (II) in 76% yield.



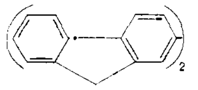
I, $R^1 = C_6H_5$, $R^2 = H$
IV, $R^1 = I$, $R^2 = H$
VIII, $R^1 = 4\text{-}C_6H_5C_6H_4$, $R^2 = H$
XV, $R^1 = R^2 = C_6H_5$
II, $R^1 = C_6H_5$, $R^2 = R^3 = H$
III, $R^1 = I$, $R^2 = R^3 = H$
IX, $R^1 = 4\text{-}C_6H_5C_6H_4$, $R^2 = R^3 = H$
X, $R^1 = 4\text{-}C_6H_5C_6H_4$, $R^2 = H$, $R^3 = CH_3$
XVI, $R^1 = R^2 = C_6H_5$, $R^3 = H$

Although 2-iodofluorene (III) is reported[5] to be inert in the Ullmann reaction, there is ample evidence[9] to indicate that the presence of an electron-withdrawing group in the molecule may enhance the reactivity of the iodine to coupling. Hence, 2-iodofluorene (III), prepared in 32% yield by the reaction of 2-fluorenediazonium chloride[10] with potassium iodide, was oxidized with sodium dichromate in glacial acetic acid to 2-iodofluorenone (IV) in 75% yield.

Heating the ketone IV in a sealed tube with copper bronze gave a 31% yield of 2,2′-bifluorenone (V) from which 2,2′-bifluorene (VI) was prepared in 82% yield by a modified Wolff–Kishner reduction without alkali. 2,2′-Bifluorene (VI) has been reported previously[11] as a possible product in the reduction of 2,7-dibromofluorene with hydrazine over palladium–calcium carbonate; however, no physical constants were given.



V



VI

The availability of *p*-quaterphenyl-2,2′-dicarboxylic acid (VII), prepared by the oxidation of

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(1) From the dissertation presented by Martin D. Barnett to the graduate faculty of The University of New Mexico in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Graduate Research Assistant under Los Alamos Contract SC-5 with The University of New Mexico.

(3) Work done in part under the auspices of the U. S. Atomic Energy Commission.

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