m.p. 258–260°, identified as IVd (m.p. and mixed m.p. determination).

The light petroleum extract, on slow evaporation, gave colorless crystals (*ca.* 1.3 g.), m.p. 110°, identified as benzenesulfonanilide (m.p. and mixed m.p.).

The petroleum ether extract gave, on concentration, colorless crystals (*ca.* 1.5 g.), m.p. 177°, which were identified as IIIa (m.p. and mixed m.p.).

CAIRO, EGYPT

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

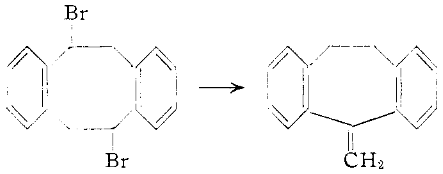
Cyclic Polyolefins. XXXVII. Ring Contraction in Dehydrobromination of 7-Bromo-1,2,5,6-dibenz-1,3,5-cycloöctatriene

BY ARTHUR C. COPE AND RONALD DEAN SMITH

RECEIVED MARCH 12, 1955

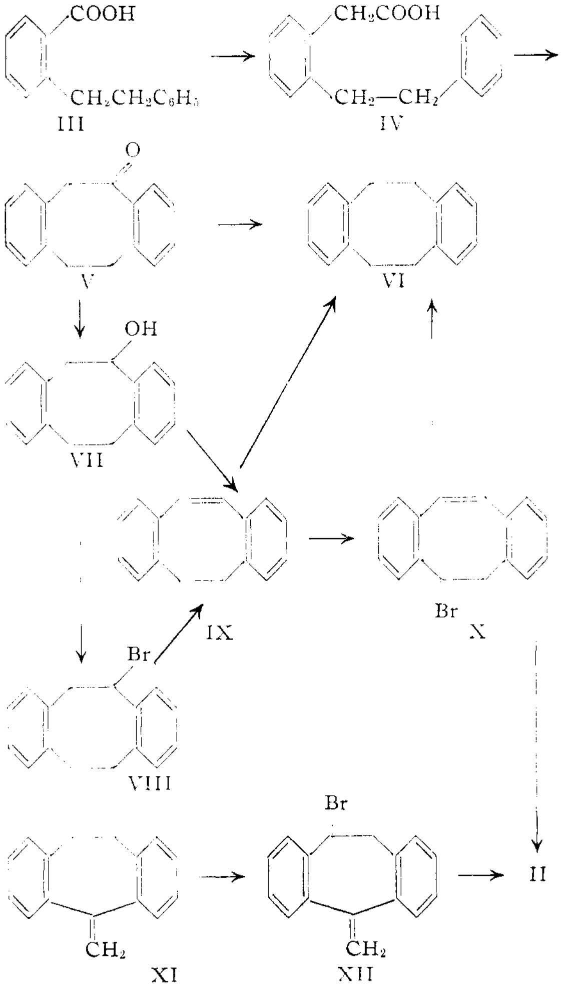
The dehydrobromination of 3-bromo-1,2,5,6-dibenz-1,5-cycloöctadiene (VIII) by α-picoline proceeds without rearrangement, forming 1,2,5,6-dibenz-1,3,5-cycloöctatriene (IX), while dehydrobromination of 7-bromo-1,2,5,6-dibenz-1,3,5-cyclooctatriene (X) occurs with molecular rearrangement to give 1-methylene-2,3,6,7-dibenzcycloheptatriene (II). 4-Bromo-1-methylene-2,3,6,7-dibenz-2,6-cycloheptadiene (XII) also gives II on dehydrobromination.

The rearrangement of 3,7-dibromo-1,2,5,6-dibenz-1,5-cycloöctadiene (I) to 1-methylene-2,3,6,7-dibenzcycloheptatriene (II) on dehydrobromination by amines was described in a previous communication.[1] This paper reports a study of the dehydrobromination of compounds related to I and II designed to determine the step at which molecular rearrangement occurs. 3-Bromo-1,2,5,6-dibenz-1,5-cycloöctadiene (VIII), 7-bromo-1,2,5,6-dibenz-1,3,5-cycloöctatriene (X), and 4-bromo-1-methylene-2,3,6,7-dibenz-2,6-cycloheptadiene (XII) were synthesized, and the structures of their dehydrobromination products were determined.



I II

It has been shown that the reaction of 1,2,5,6-dibenz-1,5-cycloöctadiene (VI) with one molar equivalent of N-bromosuccinimide gives none of the monobromide VIII. Instead, a mixture of the dibromide I and unchanged VI is obtained.[2] Therefore, for the preparation of VIII, *o*-(β-phenylethyl)-benzoic acid (III) was converted to *o*-(β-phenylethyl)-phenylacetic acid (IV) by the Newman–Beal modification of the Arndt–Eistert sequence[3] in an overall yield of 53%. Cyclization of the acid IV to 1,2,5,6-dibenz-1,5-cycloöctadiene-3-one (V) was effected in 90–93% yield by polyphosphoric acid. To our knowledge this is the only reported case of a ring closure in good yield to an eight-membered cyclic ketone by polyphosphoric acid. The effect of the *ortho* substituted benzene ring in the acid IV on the ease of ring closure is remarkable, for the treatment of ε-phenylcaproic acid with polyphosphoric acid gives only small amounts of 1,2-benzcycloöct-1-ene-3-one.[4] The structure of the ketone V was established by its hydrogenation in the presence of a palladium catalyst to the known hydrocarbon VI.[2,5,6] Wolff–Kishner reduction of V also gave VI. Reduction of V with sodium borohydride afforded 1,2,5,6-dibenz-1,5-cycloöctadiene-3-ol (VII) in 97% yield. The bromide VIII was obtained in 91% yield on treatment of VII with anhydrous hydrogen bromide in benzene at 0°.



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[1] A. C. Cope and S. W. Fenton, THIS JOURNAL, **73**, 1673 (1951).

[2] A. C. Cope and S. W. Fenton, *ibid.*, **73**, 1668 (1951).

[3] M. S. Newman and P. F. Beal, *ibid.*, **72**, 5163 (1950).

[4] Unpublished observations of R. D. Smith and W. R. Moore.

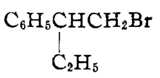
[5] W. Baker, R. Banks, D. R. Lyon and F. G. Mann, *J. Chem. Soc.*, 27 (1945).

[6] L. F. Fieser and M. M. Pechet, THIS JOURNAL, **68**, 2577 (1946).

Dehydrobromination of VIII by boiling α-picoline gave 1,2,5,6-dibenz-1,3,5-cycloöctatriene (IX) in 63% yield. Evidence that no rearrangement had occurred during the dehydrobromination was obtained from the catalytic hydrogenation of IX. The hydrocarbon IX absorbed 100% of one molar equivalent of hydrogen in the presence of a palladium-on-carbon catalyst, and the hydrocarbon VI was isolated in 89% yield. The hydrocarbon IX was also prepared in 63% yield by the dehydration of the alcohol VII with boric acid.

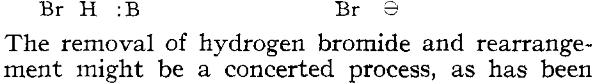
Treatment of IX with N-bromosuccinimide in carbon tetrachloride gave the bromide X in 79% yield as a rather unstable solid. The structure of X was established by its analysis and by catalytic hydrogenation to the hydrocarbon VI. Dehydrobromination of X by boiling α-picoline occurred with rearrangement to give II, whose structure was established by comparison with an authentic sample. Best results were obtained when the crude product of the bromination of IX was treated directly with α-picoline. The over-all yield of II from IX was 37% when X was not isolated.

The rearrangement of X on dehydrobromination can be regarded as proceeding through the removal of hydrogen bromide by an α-elimination.[7] The dehydrohalogenation of 1-halo-2,2-diarylethylenes to form diarylacetylenes is a well known example of α-elimination and rearrangement,[8] but differs from the present case in that β-elimination of hydrogen halide is clearly impossible. In the case of X, which contains hydrogen atoms β to the bromine atom, the removal of hydrogen bromide by the more common β-elimination process might be expected. However, examples of α-elimination in halides containing β-hydrogen atoms are known. The dehydrobromination of XIII by potassium amide or sodium amide in boiling xylene has been reported to give all[9] or some[10] of the olefin XIV arising from α-elimination and rearrangement.

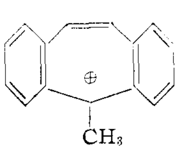

$$C_6H_5\underset{\displaystyle C_2H_5}{\underset{|}{C}}HCH_2Br$$
XIII

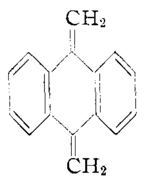
$C_6H_5CH{=}CHC_2H_5$
XIV

The occurrence of a small amount of α-elimination in the dehydrohalogenation of *n*-octyl halides by potassium amide has also been demonstrated.[11] Dehydrobromination of X by a reaction path involving α-elimination and rearrangement is shown in the equation



The removal of hydrogen bromide and rearrangement might be a concerted process, as has been shown to be the case in the α-eliminations of *n*-octyl halides.[11] An alternate mechanism for dehydrobromination of X consists of primary ionization of the bromine, followed by rearrangement of the intermediate secondary carbonium ion to the much more stable tropylium-type ion XV and loss of a proton forming II. This mechanism of rearrangement affords a possible explanation of the fact that the bromide VIII is dehydrobrominated without rearrangement, for in this case the driving force provided by formation of a tropylium-type ion would be absent.


XV


XVI

The rearrangement of X on dehydrobromination prompted a study of the reaction of the bromide XII with base, for if a similar rearrangement occurred, 9,10-dihydro-9,10-dimethyleneanthracene (XVI) would be formed. The properties of the hydrocarbon XVI have been predicted from molecular orbital calculations,[12] but the compound has not yet been prepared. The bromide XII was obtained in 59% yield on treatment of 1-methylene-2,3,6,7-dibenz-2,6-cycloheptadiene (XI) with N-bromosuccinimide and benzoyl peroxide in carbon tetrachloride. The crude bromide was not purified but was treated directly with α-picoline. The hydrocarbon II was isolated in 56% yield; hence no rearrangement occurred during the dehydrobromination of XII.

Experimental[13]

o-(β-**Phenylethyl**)-**phenylacetic Acid** (IV).—A mixture of 45.2 g. (0.2 mole) of *o*-(β-phenylethyl)-benzoic acid (III)[1] and 43 ml. (72.3 g., 0.61 mole) of thionyl chloride was heated under reflux on a steam-bath for 3 hours. Excess thionyl chloride was removed by distillation under reduced pressure. Final traces of thionyl chloride were removed by adding to the residue and distilling under reduced pressure two 10-ml. portions of dry benzene. The residual acid chloride was dissolved in 100 ml. of dry ether and added at 0° to a stirred solution of 0.5 mole (determined by titration) of diazomethane[14] in 1500 ml. of dry ether. A brisk evolution of nitrogen occurred, and the resultant solution was allowed to warm to room temperature. After the solution had stood for 15 hours, ether and excess diazomethane were removed under reduced pressure. The residue of diazoketone was dissolved in 600 ml. of dry *t*-butyl alcohol, and the resulting solution was arranged for stirring under reflux. A solution of 1 g. of dried silver benzoate[3] in 10 ml. of purified triethylamine[15] was added to the stirred solution of diazoketone during a period of 2 hours. Nitrogen evolution began after a short induction period and continued with mild evolution of heat. Cooling with a pan of water was occasionally necessary to control the rate of gas evolution. By the end of the addition, nitrogen evolution had ceased and 90% of

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[7] C. R. Hauser, THIS JOURNAL, **62**, 933 (1940).

[8] W. P. Buttenberg, *Ann.*, **279**, 327 (1894); G. H. Coleman and R. D. Maxwell, THIS JOURNAL, **56**, 132 (1934); G. H. Coleman, W. H. Holst and R. D. Maxwell, *ibid.*, **58**, 2310 (1936).

[9] P. Amagat, *Bull. soc. chim. France*, [4] **49**, 1410 (1931).

[10] C. R. Hauser, P. S. Skell, R. D. Bright and W. B. Renfrow, THIS JOURNAL, **69**, 589 (1947).

[11] D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor and C. R. Hauser, *ibid.*, **74**, 5599 (1952).

[12] A. Pullman, G. Berthier and B. Pullman, *Bull. soc. chim. France*, 450 (1948); A. Pullman, B. Pullman, E. D. Bergmann, G. Berthier, E. Fischer, D. Ginsburg and Y. Hirshberg, *ibid.*, 707 (1951); G. Berthier, M. Mayot and B. Pullman, *J. phys. radium*, **12**, 717 (1951).

[13] Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses and for infrared spectra, which were determined in potassium bromide pellets at 1% concentration with a Baird Double Beam Infrared Recording Spectrometer, Model B, fitted with a sodium chloride prism.

[14] F. Arndt, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

[15] J. C. Sauer, THIS JOURNAL, **69**, 2444 (1947).

the theoretical amount of gas had been collected. The mixture was next heated under reflux for 1 hour, then allowed to stand 15 hours. The solution was treated with 50 ml. of water and filtered with Celite. The solvent and triethylamine were distilled under reduced pressure. For removal of the last traces of *t*-butyl alcohol, 100 ml. of benzene was added and distilled under reduced pressure. The residue was dissolved in 250 ml. of ether, and this solution was washed with water, 10% hydrochloric acid solution, saturated sodium bicarbonate solution, and water. The solution was dried over anhydrous magnesium sulfate and concentrated. Distillation of the residue yielded 39.2 g. (66%) of crude *t*-butyl *o*-(β-phenylethyl)-phenylacetate, b.p. 170–172° (1.5 mm.).

For preparation of the acid IV, the crude *t*-butyl ester (21.9 g.) and *p*-toluenesulfonic acid monohydrate (1.0 g.) were heated under reflux for 2 hours in 100 ml. of benzene. The benzene solution was washed three times with water to remove the toluenesulfonic acid, and then the benzene was distilled under reduced pressure. The solid residue was dissolved in boiling hexane, treated with Norit, and allowed to crystallize. There was obtained as colorless prisms 15.1 g. (85%) of IV, m.p. 92–93°. An analytical sample recrystallized from benzene–hexane and sublimed at 160° (0.7 mm.) melted at 92.2–93.2°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6 71; equiv. wt., 240. Found: C, 79.95; H, 6.60; equiv. wt., 236.

1,2,5,6-Dibenz-1,5-cycloöctadiene-3-one (V).—The acid IV (5.00 g., 0.0208 mole) was dissolved in 250 g. of hot polyphosphoric acid. The resulting yellow solution was heated on a steam-bath with stirring for 2 hours. The cooled solution was added to 600 ml. of ice-water; the white solid which separated was collected on a filter and washed with 10% sodium carbonate solution and water. The dried product was crystallized from methanol–water to give 4.30 g. (93%) of the ketone V as colorless needles melting at 92–95°. An analytical sample prepared by two recrystallizations from methanol and sublimation at 130° (0.5 mm.) melted at 95.2–96.5°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.56; H, 6.52.

A solution of 0.090 g. of V in 15 ml. of glacial acetic acid was hydrogenated at atmospheric pressure and room temperature in the presence of 0.05 g. of 10% palladium-on-carbon.[16] After 13 hours 96% of two molar equivalents of hydrogen had been absorbed. The catalyst was separated by filtration, and the solvent was distilled under reduced pressure. The residue was dissolved in 10 ml. of ether, and the resulting solution was washed with saturated sodium bicarbonate solution and water. Evaporation of the ether left a solid residue, which was sublimed at 120° (0.2 mm.). Three recrystallizations of the sublimate from 95% ethanol gave 0.023 g. of 1,2,5,6-dibenz-1,5-cycloöctadiene (VI) as colorless prisms melting at 109.2–109.8° (lit. 109.4–109.9°,[2] 108.5°,[5] 108.5 – 110°[6]). Mixed melting point with an authentic sample[2] of VI was 109–109.8°, and the infrared spectra of the two samples were identical.

The ketone V (0.50 g., 0.00225 mole) was added to a solution of 1 g. of potassium hydroxide and 1.5 ml. of 85% hydrazine hydrate in 10 ml. of diethylene glycol. After the mixture had been heated under reflux for 2 hours, water and excess hydrazine were distilled until the temperature of the reaction mixture reached 200°. The solution was heated under reflux at 190–200° for 3 hours, allowed to cool, and added to 80 ml. of water. After the mixture had been acidified with hydrochloric acid, the white solid was collected and dried. Sublimation and crystallization from 95% ethanol afforded 0.35 g. (75%) of VI, m.p. 109.2–109.7°, which was identical with an authentic sample (mixed m.p. and comparison of infrared spectra).

1,2,5,6-Dibenz-1,5-cycloöctadiene-3-ol (VII).—To a stirred solution of V (10.0 g., 0.045 mole) in 150 ml. of methanol was added dropwise during 15 minutes a solution of 1.5 g. of sodium borohydride in 50 ml. of methanol containing three drops of 6 *N* sodium hydroxide solution. Stirring was continued for 2 hours, and then the solution was added to 1 l. of water. The *p*H of the aqueous phase was adjusted to 5 by the addition of 10% sulfuric acid solution, and the solid was extracted with ether. The ether extract was washed with saturated sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate and concentrated. Crystallization of the residue from benzene–ligroin afforded 9.80 g. (97%) of the alcohol VII as colorless needles which melted at 114.2–115.5°. An analytical sample recrystallized from ethanol–water melted at 114.8–115.8°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.81; H, 7.00.

3-Bromo-1,2,5,6-dibenz-1,5-cycloöctadiene (VIII).—The alcohol VII (1.80 g., 0.008 mole) was dissolved in 25 ml. of benzene. The resulting solution was cooled in an ice-bath and saturated with anhydrous hydrogen bromide. After the solution had remained at 0° for 2 hours, it was washed with water until the washings were no longer acid. Benzene was removed by distillation under reduced pressure, and the solid residue was crystallized from benzene–hexane to give 2.10 g. (91%) of the bromide VIII, m.p. 123–124.8°. An analytical sample was recrystallized from benzene–hexane to give VIII as colorless needles which melted at 123.8–124.8°.

Anal. Calcd. for $C_{16}H_{15}Br$: C, 66.91; H, 5.27; Br, 27.83. Found: C, 67.08; H, 5.42; Br, 27.65.

1,2,5,6-Dibenz-1,3,5-cycloöctatriene (IX) (a).—A mixture of 0.50 g. (0.00223 mole) of VII and 0.80 g. (0.013 mole) of boric acid was placed in a short-path distillation apparatus. The heating block temperature was gradually raised to 205° while the pressure was slowly reduced to 0.5 mm. These final conditions were maintained for 30 minutes. The solid distillate was crystallized from 95% ethanol to give 0.29 g. (63%) of the hydrocarbon IX as colorless prisms melting at 53.6–54.4°.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.24; H, 7.00.

Hydrogenation of 0.125 g. of IX in 15 ml. of glacial acetic acid in the presence of 0.04 g. of 10% palladium-on-carbon catalyst at atmospheric pressure and room temperature was complete in 10 minutes, and required 101% of one molar equivalent of hydrogen. The catalyst was removed by filtration, and the solvent was distilled under reduced pressure. The solid residue was crystallized from 95% ethanol to give 0.112 g. (89%) of VI, m.p. 105–109.6°. Recrystallization from 95% ethanol raised the melting point to 109.1–109.7°. The identity of the hydrogenation product with VI was proved by a mixed melting point with an authentic sample and comparison of infrared spectra.

(b).—A solution of 1.75 g. (0.0061 mole) of VIII in 40 ml. of freshly distilled α-picoline was heated under reflux in a nitrogen atmosphere for 100 hours. About 30 ml. of α-picoline was distilled, and the cooled residue was added to 150 ml. of 10% phosphoric acid solution. The mixture was extracted with ether. The ether extract was washed with water, saturated sodium bicarbonate solution, and water, and was dried over anhydrous magnesium sulfate. The ether was distilled, and the residue was sublimed at 90–100° (0.5 mm.). Crystallization of the sublimate from 95% ethanol gave 0.785 g. (63%) of the hydrocarbon IX melting at 53.6–54.6°. A mixed melting point with IX prepared by procedure (a) was 53–54°.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.06; H, 6.81.

A solution of 0.098 g. of IX, obtained from the dehydrobromination of VIII, in 10 ml. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 0.04 g. of 10% palladium-on-carbon catalyst. After 10 minutes 100% of one molar equivalent of hydrogen had been absorbed. The catalyst was removed by filtration, and the residue obtained by concentrating the filtrate was sublimed and crystallized from 95% ethanol to give 0.088 g. (89%) of the hydrocarbon VI melting at 107.4–109.8°. Recrystallization from 95% ethanol raised the melting point to 109.1–109.8°. The hydrocarbon VI from this source was identical with an authentic sample according to mixed melting point and comparison of infrared spectra.

7-Bromo-1,2,5,6-dibenz-1,3,5-cycloöctatriene (X).—A mixture of 0.317 g. (0.00154 mole) of IX, 0.295 g. (0.00166 mole) of N-bromosuccinimide and 15 ml. of carbon tetrachloride was heated under reflux for 1 hour. The cooled mixture was filtered to separate succinimide and concentrated under reduced pressure. The residue was dissolved in 10 ml. of petroleum ether (30–60°) and filtered to remove a small amount of succinimide. The filtrate was cooled in

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[16] E. R. Alexander and A. C. Cope, *Org. Syntheses*, **26**, 31 (1946).

an acetone–Dry Ice bath. The colorless crystals which separated were collected on a filter and dried to give 0.344 g. (79%) of the bromide X, m.p. 80–85° dec. An analytical sample recrystallized from petroleum ether (30–60°) melted at 82–86.5° dec.

Anal. Calcd. for $C_{16}H_{13}Br$: C, 67.38; H, 4.59; Br, 28.02. Found: C, 67.59; H, 4.75; Br, 27.79.

The bromide X (0.122 g.) dissolved in 15 ml. of cyclohexane was hydrogenated at atmospheric pressure and room temperature in the presence of 0.5 g. of palladium-on-carbon catalyst. After 11 hours 95% of two molar equivalents of hydrogen had been absorbed. The catalyst was separated by filtration and washed with hot cyclohexane. The filtrate and washings were combined and concentrated. The residue was sublimed at 100° (0.3 mm.). Recrystallization of the sublimate from 95% ethanol to constant melting point gave 0.020 g. of VI, m.p. 109–109.7°, which did not depress the melting point of an authentic sample. The infrared spectrum was identical with that of the authentic sample.

1-Methylene-2,3,6,7-dibenzcycloheptatriene (II).—The bromide X was prepared as above from 1.00 g. (0.00485 mole) of IX, 0.89 g. (0.005 mole) of N-bromosuccinimide and 25 ml. of carbon tetrachloride. Without purification the crude bromide obtained on evaporation of the carbon tetrachloride was dehydrobrominated with α-picoline in the manner described for the preparation of IX from VIII. The residue obtained on evaporation of the ether extract was sublimed at 125° (0.3 mm.). Recrystallization of the sublimate from 95% ethanol gave 0.364 g. (37% from IX) of II, m.p. 119–119.6°, which did not depress the melting point of an authentic sample.[1] The infrared spectra of the two samples were identical. Dehydrobromination of a purified sample of the bromide X gave essentially the same results.

Preparation and Dehydrobromination of 4-Bromo-1-methylene-2,3,6,7-dibenz-2,6-cycloheptadiene (XII).—A mixture of 0.337 g. (0.00164 mole) of 1-methylene-2,3,6,7-dibenz-2,6-cycloheptadiene (XI),[1] 0.303 g. (0.0017 mole) of N-bromosuccinimide, 0.01 g. of benzoyl peroxide and 15 ml. of carbon tetrachloride was heated under reflux for 2 hours. The hot solution was filtered to remove succinimide and concentrated under reduced pressure. The residue was treated with hot hexane and filtered; from the filtrate 0.276 g. (59%) of colorless prisms of XII crystallized, m.p. 85–117° dec. Recrystallization did not narrow the melting range.

For dehydrobromination the crude bromide XII was treated with 15 ml. of α-picoline by the procedure described above for the preparation of IX and II. Crystallization of the sublimed product from 95% ethanol gave 0.111 g. (56%) of the hydrocarbon II as colorless plates melting at 118.8–119.2°. Admixture with an authentic sample of II did not depress the melting point. The infrared spectrum was identical with that of an authentic sample of II.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

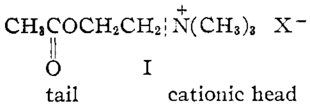
Quaternary Ammonium Alkyl Sulfide and Sulfoxide Cholinergic Agents

BY FRED. K. KIRCHNER, ALBERT E. SORIA AND CHESTER J. CAVALLITO[1]

RECEIVED APRIL 21, 1955

A number of monoquaternary ammonium alkyl sulfides and sulfoxides were prepared and found to have cholinergic activity. The activity is greater for the alkonium sulfides than for the sulfoxides and appears to be a function of the position of sulfur in the chain as well as of the nature of the cationic portion of the molecule.

Many homologs and analogs of acetylcholine (I) have been described and a summary of correlation of chemical structure with physiological activity has been prepared by Ing.[2] Although many variations have been made of the acetylcholine molecule which allow some correlation of size and shape of the molecules with physiological activity, relatively little work has been done to determine the effect of possible secondary bonding or dipole attracting forces present in the "tail" portion of the acetylcholine molecule. Welsh and Taub[3] showed



$$\underset{\underset{O}{\|}}{CH_3C}OCH_2CH_2\overset{+}{N}(CH_3)_3\ X^-$$

I

that 4-ketoamyltrimethylammonium chloride was an active cholinergic agent and suggested that the carbonyl group might serve as a structure providing secondary bonding (possibly hydrogen bonding) to the receptor site in addition in the bonding provided by the cationic "head."

The present work describes a group of quaternary ammonium alkyl sulfides and sulfoxides which has been found to show marked variations in cholinergic (muscarinic) activity with changes in the nature of secondary bonding or "electronic disturbing" structures in the "tail" portion of the molecule. Thus in the series $RSCH_2CH_2CH_2\overset{+}{N}(CH_3)_3$, cholinergic activity is high where R is methyl, but falls off sharply when R becomes ethyl, propyl or isopropyl (Table I). A shift in the relative position of the sulfur atom, as in $CH_3CH_2SCH_2CH_2\overset{+}{N}(CH_3)_3$, also results in a drop in activity. A glance at the sulfoxides shows that oxidation of the sulfur atom also brings about a decrease in activity.

In order to determine the influence of the cationic head upon activity in this series of thio ethers, a few compounds were made of the type, $CH_3SCH_2CH_2CH_2\overset{|}{\underset{|}{N}}-^{+}$, wherein distance between the nitrogen and sulfur atoms was kept constant but the substituents on the nitrogen were altered. As has been observed with the corresponding alkane derivatives of type $CH_3CH_2CH_2CH_2CH_2\overset{|}{\underset{|}{N}}-^{+}$, the presence of groups larger than methyl on the quaternary nitrogen results in a marked decrease in acetylcholine-like activity. However, the very sharp drop in activity observed with the ethyldimethylammonium analog in this thio ether series was somewhat unexpected. It is apparent in this series that not only are the small cationic head and optimum length of appendage structure factors in determining activity, but the nature and position of other atoms in this "tail" structure markedly influence the order of activity. A more complete evaluation

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(1) Irwin, Neisler and Co., Decatur, Ill.

(2) H. R. Ing, *Science*, **109**, 264 (1949).

(3) J. H. Welsh and R. Taub, *ibid.*, **112**, 467 (1950).