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]

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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

$$\underset{\text{tail}}{CH_3COCH_2CH_2}\overset{+}{N}(CH_3)_3\ X^- \qquad \text{(I)}$$

cationic head

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, $CH_3SCH_2CH_2\text{-}CH_2N^{-+}$, 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 $CH_3CH_2CH_2CH_2CH_2N^{-+}$, 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

(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).

TABLE I

Compound	Analyses: Calcd. I	Calcd. N	Calcd. S	Found I	Found N	Found S	M.p., °C.[b] or b.p. (mm.)	$n^{25}D$	Rel. pharm. activity[a]
$CH_3S(CH_2)_3Br$	[c]		18.96	[c]		18.73	75–77(18)	1.5204	
$CH_3S(CH_2)_3N(CH_3)_2$		10.51			10.22		60–62(15)	1.4605	
$CH_3S(CH_2)_3N(C_2H_5)_2$		8.68			8.68		91(19)	1.4608	
$C_2H_5S(CH_2)_2N(CH_3)_2$		10.51			9.94		66(20)	1.4658	
$C_2H_5S(CH_2)_3N(CH_3)_2$		9.51			9.13		78–80(15)	1.4620	
n-$C_3H_7S(CH_2)_3N(CH_3)_2$		8.69	19.88		8.45	20.40	92–94(17)	1.4629	
i-$C_3H_7S(CH_2)_3N(CH_3)_2$		8.69	19.88		8.46	20.68	81–84(17)		
$C_6H_5CH_2S(CH_2)_3N(CH_3)_2$		6.69	15.31		6.63	15.98	119(2)		
$CH_3S(CH_2)_3NC_4H_8$[d]		8.79	20.13		8.80	20.00	105–106(16)	1.4900	
$CH_3S(CH_2)_3NC_5H_{10}$[e]		8.08	18.49		8.16	18.50	114–116(16)	1.4950	
$CH_3SO(CH_2)_3N(CH_3)_2$		9.40			9.20		97–98(1.8)	1.4810	
$C_2H_5SO(CH_2)_2N(CH_3)_2$		9.40			8.97		98–100(2.2)	1.4798	
$CH_3SO(CH_2)_3N(CH_3)_2 \cdot HCl$		7.54	17.25		7.52	17.14	152–153		
$CH_3S(CH_2)_3N(CH_3)_3I$[f]	46.12		11.65	45.95		11.52	223–225		285
$C_2H_5S(CH_2)_2N(CH_3)_3I$[g]	46.12		11.65	45.80		12.08	215–216		16
$CH_3S(CH_2)_3N(CH_3)_2(C_2H_5)I$	43.87		11.08	43.9		11.01	146.5–148		5
$CH_3S(CH_2)_3N(CH_3)(C_2H_5)_2I$	41.85		10.57	42.2		10.29	90–92		
$CH_3S(CH_2)_3N(CH_3)_2C_6H_5CH_2Cl$	[h]		12.33	[h]		12.17	128–129.5		Inact.
$C_2H_5S(CH_2)_3N(CH_3)_3I$	43.81		11.08	44.10		11.23	134–136		
n-$C_3H_7S(CH_2)_3N(CH_3)_3I$	41.85		10.57	42.5		10.06	86–88.5		7.5
i-$C_3H_7S(CH_2)_3N(CH_3)_3I$	41.85		10.57	42.20		10.59	157–158		10
$C_6H_5CH_2S(CH_2)_3N(CH_3)_3I$	36.12		9.12	36.1		9.45	124–126		
$CH_3S(CH_2)_3C_4H_8 \cdot CH_3I$[i]	42.13		10.64	41.0		10.40	140–143		2.5
$CH_3S(CH_2)_3C_5H_{10} \cdot CH_3I$[e]	40.25		10.13	40.7		8.94	79–92		0.4
$CH_3S(CH_2)_3C_5H_5NBr$[j]	[j]		12.91	[j]		12.79	97–98		2.5
$I(CH_3)_2S(CH_2)_3N(CH_3)_3I$[k]	60.85		7.67	60.23		7.90	243–246		<2
$CH_3SO(CH_2)_3N(CH_3)_3I$[l]	43.58	4.81		43.55	4.89		191–192		4
$C_2H_5SO(CH_2)_2N(CH_3)_3I$[m]	43.58		10.99	43.30		11.15	176–182		<2

[a] Muscarinic activity with isolated tortoise auricle (amyltrimethylammonium = 100); for details see ref. 4. [b] Corrected. [c] Calcd.: Br, 47.26. Found: Br, 47.35. [d] C_4H_8 pyrrolidyl. [e] C_5H_{10} piperidyl. [f] Ref. 6; m. p. 217° dec. [g] W. Schneider, *Ann.*, **386**, 332 (1912); m.p. 216.5° dec. [h] Calcd.: Cl, 13.64. Found: Cl, 13.48. [i] C_5H_5N pyridinium. [j] Calcd.: Br, 32.20. Found: Br, 32.10. [k] Ref. 6; m.p. 246° dec. [l] P. Karrer, N. J. Antia and R. Schwyzer, *Helv. Chim. Acta*, **34**, 1392 (1951); m.p. 188–189.° [m] W. Schneider, *Ann.*, **386**, 332 (1912); m.p. 168°.

and discussion of the structure–activity relationships is presented elsewhere.[4]

The experimental section contains typical preparations used for the majority of the compounds reported. No attempt was made to obtain optimum yields as in many cases only one run was made.

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Experimental

Dimethylaminopropyl Methyl Sulfide.—To 61 g. (0.5 mole) of dimethylaminopropyl chloride in 150 ml. of *t*-butyl alcohol was added 35 g. (0.5 mole) of sodium methylmercaptide and the mixture refluxed for four hours. The mixture was filtered and the filtrate distilled under reduced pressure to yield the sulfide (53%).

In a similar manner there were prepared diethylaminopropyl methyl sulfide (17%), dimethylaminoethyl ethyl sulfide (35%), dimethylaminopropyl ethyl sulfide (52%), dimethylaminopropyl *n*-propyl sulfide (33%), dimethylaminopropyl isopropyl sulfide (52%), benzyl dimethylaminopropyl sulfide (69%), 3-(1-pyrrolidyl)-propyl methyl sulfide (38%) and 3-(1-piperidyl)-propyl methyl sulfide (41%).

Dimethylaminopropyl Methyl Sulfoxide.—To a solution of 13.3 g. (0.1 mole) of dimethylaminopropyl methyl sulfide and 6 g. (0.1 mole) of acetic acid in 50 ml. of acetonitrile was added slowly, with cooling and shaking, a solution of 0.1 mole of peracetic acid prepared by dissolving the required amount of 40% per-acid in 25 ml. of acetonitrile. After standing at room temperature for one hour, the mixture was diluted with 100 ml. of benzene and 25 g. of powdered potassium hydroxide was added. After standing overnight the solid was filtered off and the filtrate distilled under reduced pressure. The sulfoxide (50% yield) is described in the table. A sample of the base was converted to the hydrochloride by treatment with ethereal hydrogen chloride.

Dimethylaminoethyl ethyl sulfoxide was prepared in a similar manner (45%).

Quaternary Ammonium Alkyl Sulfides and Sulfoxides.—To a solution of the aminosulfide or aminosulfoxide in benzene at room temperature was added 1.5 equivalents of the quaternizing agent (methyl iodide, ethyl iodide or benzyl chloride). After standing for one hour the mixture was filtered and the precipitate recrystallized from hot *n*-propyl alcohol. In some instances ether was added to the alcohol solution to complete the precipitation. The yields of the pure compound were variable.

1-Trimethylammonium-3-dimethylsulfoniumpropane Diiodide.—Dimethylaminopropyl methyl sulfide was refluxed for one hour with at least three equivalents of methyl iodide in *n*-propyl alcohol solution. The bis-quaternary salt was filtered off from the hot alcohol solution and washed with hot *n*-propyl alcohol. The yield was better than 90% of white crystalline product.

3-Bromopropyl Methyl Sulfide.—To 66.2 g. (0.63 mole) of 3-methylmercapto-1-propanol[5] was added with stirring and cooling 80 g. (0.295 mole) of phosphorus tribromide. When the addition was completed the reaction mixture was heated on a steam-bath for 30 minutes. After the heating period the mixture was cooled and poured into ice and water. The separated oily layer was washed successively with 10% ml. of 1% sodium carbonate solution and water. The oil

(4) A. M. Lands and C. J. Cavallito, *J. Pharmacol.*, **110**, 369 (1954).

(5) W. R. Kirner, THIS JOURNAL, **50**, 2446 (1928).

was taken up in benzene and dried over calcium chloride. After filtration and removal of benzene the residue was distilled under reduced pressure to give 45.1 g. (43%) of desired product.[6]

(6) W. Schneider, *Ann.*, **375**, 207 (1910), reported the preparation of this compound by a different procedure, but failed to isolate it from the reaction mixture.

1-(3-Methylmercaptopropyl)-pyridinium Bromide.—A solution of 22 g. (0.13 mole) of 3-bromopropyl methyl sulfide in 31.6 g. (0.4 mole) of pyridine was refluxed for five hours. The solid which formed was recrystallized several times with the least amount of hot *n*-propyl alcohol. The yield of pure product was 10 g. (31%).

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN CO.]

Sterols. XV.[1] Cortisone and Analogs. Part 1. 16α-Hydroxy and 16α,17α-Epoxy Analogs of Cortisone

BY PERCY L. JULIAN,[2] WAYNE COLE, EDWIN W. MEYER AND BERNARD M. REGAN

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The partial synthesis of 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione and 16α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16α-hydroxy-11-dehydrocorticosterone acetate) is described. The conversion of the key intermediate in this synthesis, 16β-bromocortisone acetate, into cortisone acetate by reductive dehalogenation is likewise detailed. 4,16-Pregnadiene-3,11,20-trione was obtained as a co-product in the preparation of 16α-hydroxy-11-dehydrocorticosterone acetate from the 16α,17α-epoxysteroid.

The partial synthesis of cortisone acetate from 3α-acetoxy-16-pregnene-11,20-dione[3] has already been reported.[4,5] The present paper describes the essential experimental details of this synthesis, and specifically describes our preparation of the 16α,17α-epoxy analog of cortisone acetate, and its reduction products, 16α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16α-hydroxy-11-dehydrocorticosterone acetate) and 17α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (cortisone acetate).

For the synthesis of the epoxy analog, 3α-hydroxy-16α,17α-epoxypregnane-11,20-dione (I) may be represented, for this paper, as starting material. It was prepared in excellent yield by the alkaline peroxide epoxidation and hydrolysis of 3α-acetoxy-16-pregnene-11,20-dione.[3,6] Bromination of the epoxy steroid I at C-21, followed by acetolysis with potassium acetate, afforded the desired 3α-hydroxy-16α,17α-epoxy-21-acetoxypregnane-11,20-dione. The latter substance also was prepared in a more circuitous fashion by treating 3α-acetoxy-16α,17α-epoxypregnane-11,20-dione with hydrogen bromide in acetic acid to form the corresponding bromohydrin, then brominating this substance at C-21, followed by hydrolysis at C-3 with hydrogen bromide in methanol-benzene and finally introducing the necessary C-21 acetoxy group by a potassium acetate acetolysis. The resulting 3α-hydroxy-16α,17α-epoxy-21-acetoxypregnane-11,20-dione gave, upon oxidation with chromic acid in acetic acid–chloroform, 16α,17α-epoxy-21-acetoxypregnane-3,11,20-trione.[7] Our experience has shown that for preparation of the related bromohydrin, 16β-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione (II), it is more expedient to employ the crude oxidation product, since isolation of the 3,11,20-trione results in a substantial crystallization loss. Bromination of the bromohydrin II proceeded rapidly; however, attempts to recrystallize the resulting 4α-bromo derivative (III) proved unsuccessful. Therefore, the crude intermediate was converted in solution to the semicarbazone, which then was cleaved with pyruvic acid to give 16β-bromo-17α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16β-bromocortisone acetate (IV)), melting at 236–237°. The preparation, by total synthesis, of the *dl*-modification of this steroid recently has been reported.[8] Reaction of 16β-bromocortisone acetate with potassium acetate in acetone achieved the necessary dehydrobromination for formation of the 16α,17α-epoxy analog of cortisone acetate, 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione (V). The over-all yield in this conversion from II was 50%.

Reductive dehalogenation of 16β-bromocortisone acetate (IV) with a Raney nickel catalyst produced cortisone acetate (VIII). A similar reduction, the hydrogenolysis of 16β-bromo-4,5-dihydrocortisone acetate in the presence of palladium-on-calcium carbonate, has been reported by Kendall and coworkers.[7]

The 16α,17α-epoxy analog of cortisone acetate (V) also served as a convenient intermediate in the preparation of the hitherto undescribed 16α-hy-

(1) For paper XIV in this series, see W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

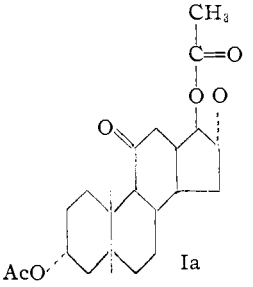
(2) The Julian Laboratories, Inc., Franklin Park, Ill.

(3) For preparation of this 16-dehydropregnane, see P. L. Julian and W. J. Karpel, U. S. Patent 2,671,794; R. U. Schock and W. J. Karpel, U. S. Patent 2,684,963; see also discussion in reference 5, particularly p. 199; see further W. R. Nes and H. L. Mason, THIS JOURNAL, **73**, 4765 (1951).

(4) Presented at the Symposium on Steroids of the 118th National Meeting of the American Chemical Society, Chicago, Ill., September 5, 1950.

(5) P. L. Julian, *et al.*, in G. Pincus, "Recent Progress in Hormone Research," Vol. VI, Academic Press, Inc., New York, N. Y., 1951, p. 195.

(6) The by-product originally reported as XXXIX in reference 5, p. 200, and formed in part by the action of perbenzoic acid on 3α-acetoxy-16-pregnene-11,20-dione, has since been found by two of us to have the structure of 3α-acetoxy-16α,17α-epoxy-17β-acetoxyetiocholan-11-one (Ia). A more detailed description of it and proof of its structure will appear later (P.L.J. and W.C.).



Ia

(7) *Cf.* F. B. Colton, W. R. Nes, D. A. Van Dorp, H. L. Mason and E. C. Kendall, *J. Biol. Chem.* **194**, 235 (1952).

(8) L. B. Barkley, M. S. Farrar, W. S. Knowles and H. Raffelson, THIS JOURNAL, **76**, 5017 (1954).