and 39 were negative, and compounds 5, 17, 34 and 38 were active. In view of our prime interest in compounds which would function orally as depressors of motor activity, it was established that compound 11, the 5-methyl-3-(4-pyridylethyl)-oxazolidine-2,4-dione showed a 30% depression of motor activity when evaluated orally at 50 mg./kg.

Experimental[13]

The many reactants prepared for this work which were not available commercially and which were previously described, have been gathered in Table III.

3-Aza-1-oxaspiro[4,4]nonane-2,4-dione.—A mixture of 3.6 g. (0.157 mole) of sodium metal in 38 ml. of methanol and 20.2 g. (0.172 mole) of diethyl carbonate was heated under reflux, a solution of 19.4 g. (0.15 mole) of 1-hydroxycyclopentane carboxamide in 50 ml. of hot methanol added, and heating continued for 4 hr. The methanol was removed and the residue was dissolved in 100 ml. of water and filtered. The filtrate was washed with two 50-ml. portions of ether and then aerated to remove the dissolved ether. After acidification with concentrated hydrochloric acid (13 ml.) and standing 16 hr., the product was separated, washed with water and dried, yielding 11.89 g., m.p. 132–133°. On extraction of the filtrate with four 50-ml. portions of ether, an additional 3.7 g., m.p. 132–133°, was obtained; total yield 67%.

Anal. Calcd. for $C_7H_9NO_3$: C, 54.2; H, 5.9; N, 9.0. Found: C, 54.4; H, 5.7; N, 8.7.

3-Aza-1-oxaspiro-8-methyl[4,5]decane-2,4-dione (2 Isomers).—The pair of stereoisomers was prepared as above from 18.5 g. (0.118 mole) of 1-hydroxy-4-methylcyclohexane carboxamide (mixture of isomers). In the final acidification step (careful addition of 3 *N* hydrochloric acid) the point of separation of the two isomers was taken as that point at which further acid addition gave a semi-permanent cloudiness which did not clear in a few seconds by crystallization to the hard needles of the high melting isomer. This isomer was filtered off, washed with water, and dried, yielding 9.9 g. (46%), m.p. 107–108° (form A), unchanged by recrystallization from ethyl acetate–hexane.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 59.2; H, 7.1; N, 8.0.

On complete acidification of the filtrate, 3.2 g. (15%) of the low melting isomer was obtained, m.p. 76–79° (form B), unchanged by recrystallization from hexane.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 59.4; H, 7.3; N, 7.8.

Pyridylethylated Oxazolidinediones (Compounds of Table I).—Equivalent amounts of the oxazolidinedione and the vinylpyridine were heated at 150° for 2 hr. If the residue solidified on cooling, it was triturated with hexane (in cases of compounds 41, 48 and 49, it was necessary to use *cold* hexane). The crude product was then dissolved in dilute hydrochloric acid, the solution washed with ether, and the product, precipitated on the addition of excess sodium bicarbonate solution, was filtered, washed with water, dried and recrystallized.

With compounds 29 and 34, the residue solidified on triturating with ether. Compound 29 was then worked up as above and compound 34 was recrystallized directly.

Compounds 1 and 3, water-soluble solids, were extracted from the aqueous solution with ether, the ether evaporated and the products recrystallized. Compound 5 was triturated with water, filtered, washed with water, dried and recrystallized.

Liquid residues were dissolved in dilute hydrochloric acid, the acid solutions washed with ether, the products extracted with benzene, the benzene evaporated and the products distilled under reduced pressures. In most cases where the boiling points anticipated would require a bath temperature high enough to reverse the reaction, purification was effected by short path distillation. In some cases (compounds 7, 11, 15, 30 and 32) the structures were characterized by the preparation of hydrochlorides or picrates.

Methiodides were prepared in the usual manner (compounds 2, 4, 6 and 35).

Acknowledgment.—The authors wish to thank Dr. G. Ungar and his staff for the pharmacologic results of the screening of the compounds.

YONKERS, NEW YORK

(13) Descriptive data shown in the tables are not reproduced in the Experimental section.

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

10-(Dialkylaminoalkyl)-pyrido[3,2-b][1,4]benzothiazine (1-Azaphenothiazine) and Related Compounds

BY HARRY L. YALE AND FRANCIS SOWINSKI

RECEIVED NOVEMBER 8, 1957

1-Azaphenothiazine has been prepared *via* the Smiles rearrangement of 2′-(3-nitro-2-pyridylthio)-acetanilide. 8-Chloro-1-azaphenothiazine was prepared similarly from 5′-chloro-2′-(3-nitropyridylthio)-acetanilide. Reaction between these two azaphenothiazine derivatives and various dialkylaminoalkyl chlorides in xylene, using sodamide as the condensing agent, led to a series of 10-dialkylaminoalkyl derivatives, which were converted to mono- and dihydrochlorides, as well as salts with oxalic acid.

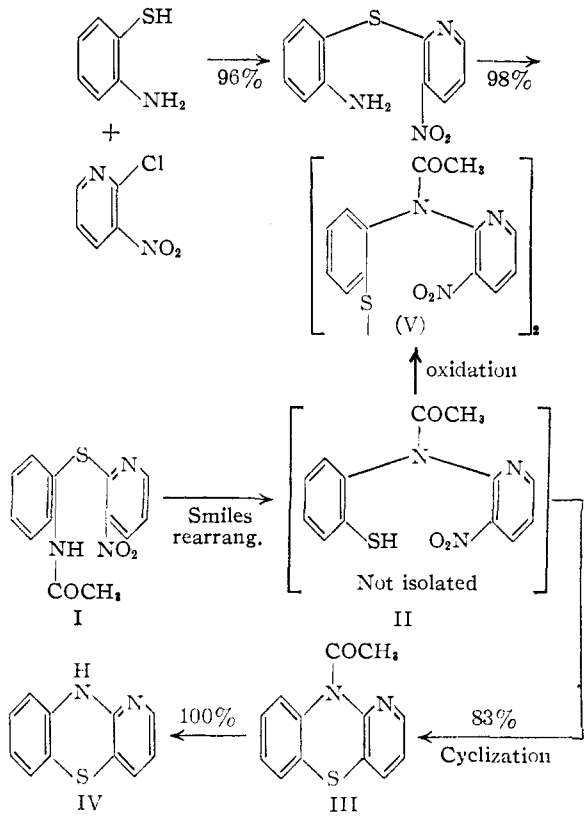
In our studies with substituted phenothiazines[1,2] and the relation of their structure to pharmacological activity, we thought it of interest to synthesize pyrido[3,2-b][1,4]benzothiazine (1-azaphenothiazine) and 8-chloropyrido[3,2-b][1,4]benzothiazine (8-chloro-1-azaphenothiazine) and their 10-dialkylaminoalkyl derivatives. These compounds have shown interesting pharmacological properties and several are now undergoing clinical evaluation.

1-Azaphenothiazine and 8-chloro-1-azaphenothiazine are new compounds; a few mono- and dinitro- and mono- and diamino-substituted 3- and 4-azaphenothiazines are known.[3,4]

The synthesis of 1-azaphenothiazine is outlined below and has, as its critical step, the Smiles rearrangement[5] of 2′-(3-nitro-2-pyridylthio)-acetanilide (I). Again, as reported in our previous paper[2] we prefer the rearrangement procedure involving the use of one equivalent of alkali in a mixture of acetone and ethanol; this makes possible the isolation of the intermediate 10-acetyl-1-azaphenothia-

(1) H. L. Yale, THIS JOURNAL, **77**, 2270 (1955).
(2) H. L. Yale, F. Sowinski and J. Bernstein, *ibid.*, **79**, 4375 (1957).
(3) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945).
(4) T. Takahashi and E. Yoshii, *Pharm. Bull. (Japan)*, **2**, 382 (1954).
(5) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181, 1263 (1935).

zine (III). Subsequent to isolation, III is subjected to an acid hydrolysis to give 1-azaphenothiazine (IV) in 83% over-all yield. When two equivalents of alkali are used in the rearrangement step, thus leading directly to IV, the yield of IV is 25%.



It is also of interest that while the yield of crude IV is 83%, it is still possible to isolate, in about 10% yield, 2,2′-(dithiodianilino)-bis-(3-nitropyridine) (V); this product occurs as an oxidation product of the intermediate thiol derivative II. Thus, to obtain optimum yields of 1-azaphenothiazine, the competing reaction to form V must be kept to a minimum. Hence, the reported failures[6] in the Smiles rearrangement may not have been due to failure in rearrangement, but rather to failure in the cyclization step.

The preparation of 8-chloro-1-azaphenothiazine followed the same sequence of reactions but utilized 2-amino-4-chlorobenzenethiol as the starting material.

The condensation of these two azaphenothiazine derivatives with several dialkylaminoalkyl chlorides led to a series of 10-dialkylaminoalkyl derivatives. These were obtained as viscous oils, distillable *in vacuo*, which formed crystalline mono- and dihydrochlorides as well as salts with oxalic acid. When the reaction was carried out with 1-dimethylamino-2-chloropropane, two isomeric products were obtained; these could be separated by fractional crystallization from acetonitrile of their monohydrochlorides into the less soluble, higher melting isomer, presumably 10-(2-dimethylamino-propyl)-1-azaphenothiazine, hydrochloride, which is the major product, and the more soluble, lower melting isomer, 10-(2-dimethylamino-1-methylethyl)-1-azaphenothiazine, hydrochloride.[7]

1-Azaphenothiazine was condensed with acrylonitrile, using Triton B as catalyst, to give 1-azaphenothiazinepropionitrile; the latter compound with lithium aluminum hydride gave 10-(3-aminopropyl)-1-azaphenothiazine.[2]

Acknowledgment.—The authors are grateful to Dr. J. Bernstein for his advice and coöperation during this investigation.

Experimental Part

1-Azaphenothiazine.—To a nitrogen-diffused solution of 250 g. (2.0 moles) of 2-aminobenzenethiol in 1 l. of methanol was added, first, a nitrogen-diffused solution of 132 g. (2.0 moles) of 85% potassium hydroxide in 1 l. of 95% ethanol, followed by 315 g. (2.0 moles) of 2-chloro-3-nitropyridine in 3 l. of warm methanol. The solid which separated was filtered to give 477.5 g. (96% yield) of 2-(*o*-aminophenylthio)-3-nitropyridine, m.p. 124–126°. *Anal.* Calcd. for $C_{11}H_9N_3O_2S$: C, 53.42; H, 3.66; N, 16.99; neut. equiv., 247.3. Found: C, 53.74; H, 3.92; N, 16.63; neut. equiv., 245. To 630 g. (2.55 moles) of 2-(*o*-aminophenylthio)-3-nitropyridine and 200 ml. of pyridine was added 2400 ml. of acetic anhydride; the mixture was heated on the steam-bath until solution occurred, then cooled to give 720 g. (98% yield) of 2′-(3-nitro-2-pyridylthio)-acetanilide, m.p. 141–142°. *Anal.* Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.96; H, 3.83. Found: C, 54.23; H, 3.79. To 44 g. (0.66 mole) of 85% potassium hydroxide in 350 ml. of ethanol and 12 l. of acetone was added, under nitrogen, 190 g. (0.66 mole) of the **acetanilide derivative**, the mixture was distilled rapidly, the residue was stirred with water and filtered to give 135 g. (83% yield) of 10-acetyl-1-azaphenothiazine, m.p. 150–153°. An analytical sample, from isopropyl alcohol, melted at 171–172°. *Anal.* Calcd. for $C_{13}H_{10}N_2OS$: C, 64.43; H, 4.16. Found: C, 64.70; H, 4.06. The crude **acetyl derivative**, 479 g. (2.0 moles), 4600 ml. of ethanol and 350 ml. of concd. hydrochloric acid was refluxed for one hour, concentrated from the steam-bath; the residue was cooled, treated with an excess of aqueous ammonia and the solid filtered. The damp solid was added to 8 l. of benzene; the benzene solution was dried under a separating still-head, filtered, and the filtrate concentrated to dryness to give a quantitative yield of 1-azaphenothiazine, m.p. 104–107°. An analytical sample, from hexane, melted at 112–114°.

Anal. Calcd. for $C_{11}H_8N_2S$: C, 65.97; H, 4.04; N, 13.99. Found: C, 66.00; H, 4.00; N, 14.16.

Isolation of 2,2′-(2,2′-Dithiodianilino)-bis-(3-nitropyridine) from the Smiles Rearrangement.—The aqueous filtrate from the crude 10-acetyl-1-azaphenothiazine (see above) when kept several days deposited 12 g. of a dark crystalline solid. This solid, 50 ml. of ethanol and 5 ml. of concd. hydrochloric acid were refluxed 4 hours, cooled and the solid filtered; a recrystallization from acetonitrile gave the product, m.p. 195–197°.

Anal. Calcd. for $C_{22}H_{16}N_6O_4S_2$: C, 53.64; H, 3.27; N, 17.06. Found: C, 53.22; H, 3.45; N, 16.48.

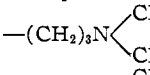
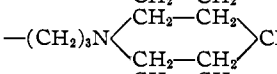
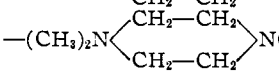
8-Chloro-1-azaphenothiazine.—To 59.2 g. (0.30 mole) of 2-amino-4-chlorobenzenethiol hydrochloride in 250 ml. of methanol was added, under nitrogen, a solution of 39.6 g. (0.60 mole) of 85% potassium hydroxide in 300 ml. of ethanol, followed by 47.6 g. of 2-chloro-3-nitropyridine in 400 ml. of warm methanol. As described above, there was obtained 58.5 g. (69% yield) of 2-(2-amino-4-chlorophenylthio)-3-nitropyridine, m.p. 137–138°. An analytical sample, from isopropyl alcohol, melted at 138.0–138.5°. *Anal.* Calcd. for $C_{11}H_8ClN_3O_2S$: C, 46.90; H, 2.86. Found:

(6) R. Baltzly, M. Harfenist and F. J. Webb, THIS JOURNAL, **68**, 2673 (1946). For a review of the Smiles rearrangement, see J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 369 (1951), and J. F. Bunnett and T. Okamoto, THIS JOURNAL, **78**, 5363 (1956).

(7) From the observations of P. Charpentier, *et al.*, *Compt. rend.*, **225**, 306 (1947); **232**, 415 (1951); and N. D. Edge and W. R. Wragg, *J. Pharm. Pharmacol.*, **5**, 279 (1953), the reaction of phenothiazine with 1-dimethylamino-2-chloropropane leads to two isomers. The isomer formed in the larger quantity has the 2-dimethylaminopropyl side chain and can be separated from the isomeric product with the 2-dimethylamino-1-methylethyl side chain by fraction crystallization of their hydrochlorides.

TABLE I

10-SUBSTITUTED PYRIDO[3,2-b][1,4]BENZOTHIAZINES

Side chain	Mol. formula	Base Yield, %	Boiling point, °C.	Mm.	Analysis, % Calcd. C	H	N	Found C	H	N
$-(CH_2)_2CN$	$C_{14}H_{11}N_3S$[a]	72					16.58			16.47
$-(CH_2)_3NH_2$	$C_{14}H_{15}N_3S$[b]	91								
$-(CH_2)_2N(CH_3)_2$	$C_{15}H_{17}N_3S$	71	183–185	0.5			15.48			15.23
$-(CH_2)_3N(CH_3)_2$	$C_{16}H_{19}N_3S$	80	195–198	0.5	67.33	6.70	14.72	67.49	6.44	14.81
$-CH_2-C(CH_3)HN(CH_3)_2$	$C_{16}H_{19}N_3S$[c]	58	171–174	0.4			14.72			14.85
$C(CH_3)H-CH_2N(CH_3)_2$	$C_{16}H_{19}N_3S$									
$-CH_2-CHOH-CH_2N(C_2H_5)_2$[d]	$C_{18}H_{23}N_3OS$	49	208–212	0.8			12.75			12.53
$-(CH_2)_3N$ 	$C_{18}H_{21}N_3S$	45	203–206	0.5	69.41	6.79		68.75	5.77	
$-(CH_2)_3N$ 	$C_{19}H_{23}N_3S$	68	234–238	0.4			12.91			12.68
$-(CH_3)_2N$ 	$C_{19}H_{24}N_4S$	65	224–226	0.4	67.02	7.10		67.02	7.13	

[a] m.p. 122–123°. [b] Not distilled. [c] No effort was made to separate the two isomeric bases during distillation. [d] On keeping, the base crystallized, m. p. 80–82°.

	Salts							
$C_{14}H_{11}N_3S\cdot HCl$[a]	46	172–173 d.	58.02	4.17	14.50	57.92	4.33	14.33
$C_{14}H_{15}N_3S\cdot(COOH)_2$[b,c]	40	191–192 d.	55.31	4.93	12.09	55.44	4.67	11.91
$C_{15}H_{17}N_3S\cdot HCl$[d]	75	196–197	58.59	5.90	13.65	59.03	5.66	13.64
$C_{16}H_{19}N_3S\cdot HCl$[e,f]	87	152-154	59.70	6.26	13.05	59.60	5.96	12.98
$C_{16}H_{19}N_3S\cdot HCl$[d,g,h]	48	222–223	59.70	6.26	13.05	59.36	6.65	13.04
$C_{16}H_{19}N_3S\cdot HCl$[d]	9	165–167	59.70	6.26	13.05	59.46	6.08	13.31
$C_{18}H_{22}N_3OS\cdot(COOH)_2$	64	155–156	57.26	6.00	10.01	57.15	6.05	10.13
$C_{18}H_{21}N_3S\cdot HCl$[i]	57	180–181	62.14	6.37	12.07	62.07	6.30	11.90
$C_{19}H_{23}N_3S\cdot HCl$[i]	40	179.5–180.5	63.05	6.68	11.61	63.10	6.41	11.56
$C_{19}H_{24}N_4S\cdot HCl$[d]	67	168–169	60.50	6.68	14.86	60.13	6.71	14.61

[a] Recrystallized from acetone. [b] Recrystallized from water. [c] The base gave a mixture of mono- and dihydrochloride, which could not be separated. [d] Recrystallized from acetonitrile. [e] Recrystallized from chlorobenzene. [f] Dihydrochloride, m.p. 205–206°, recrystallized from acetonitrile. *Anal.* Calcd. for $C_{16}H_{19}N_3S\cdot 2HCl$: Cl, 19.77; N, 11.72. Found: Cl, 19.74; N, 11.52. Salt with one mole of oxalic acid, m.p. 201–202°, recrystallized from water. *Anal.* Calcd. for $C_{18}H_{19}N_3S\cdot(COOH)_2$: C, 57.58; H, 5.63; N, 11.19. Found: C, 58.10; H, 5.52; N, 11.01. [g] Salt with one mole of oxalic acid, m.p. 185–187°, recrystallized from absolute alcohol. *Anal.* Calcd. for $C_{16}H_{19}N_3S\cdot(COOH)_2$: C, 57.58; H, 5.64; N, 11.20. Found: C, 57.88; H, 5.37; N, 10.91. [h] These two hydrochlorides were obtained from a mixture of the two corresponding bases. [i] Recrystallized from dry methyl ethyl ketone.

TABLE II

8-CHLORO-10-SUBSTITUTED PYRIDO[3,2-b][1,4]BENZOTHIAZINES

Side chain	Mol. formula	Base Yield, %	B.p. °C.	Mm.	Nitrogen, % Calcd.	Found
$-(CH_2)_2N(CH_3)_2$	$C_{16}H_{16}ClN_3S$	47	186–189	0.4	13.74	13.49
$-(CH_2)_3N(CH_3)_2$[aa]	$C_{16}H_{18}ClN_3S$		189–192	0.2		

	Salts							
Mol. formula	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	N	Found C	H	N
$C_{15}H_{16}ClN_3S\cdot HCl$[bb]	64	172–173	52.63	5.00	12.27	52.38	4.81	12.25
$C_{16}H_{18}ClN_3S\cdot HCl$[cc]	43	182–183	53.93	5.37	11.79	54.34	5.36	11.52

[aa] A considerable proportion of unreacted nucleus codistilled with this base. The base was dissolved in boiling acetonitrile (5.5 ml./g.), the solution was cooled, filtered from the nucleus, and the filtrate used directly for the preparation of the hydrochloride. [bb] Chlorobenzene. [cc] Acetonitrile.

C, 47.27; H, 2.89. The following products were obtained as described above for 1-azaphenothiazine:

5′-Chloro-2′-(3-nitro-2-pyridylthio)-acetanilide (97% yield), m.p. 176–177°. *Anal.* Calcd. for $C_{13}H_{10}ClN_3O_3S$: N, 12.98. Found: N, 12.96.

10-Acetyl-8-chloro-1-azaphenothiazine (89% yield), m.p. 189–190°. *Anal.* Calcd. for $C_{13}H_9ClN_2OS$: C, 56.41; H, 3.27. Found: C, 56.27; H, 3.32.

8-Chloro-1-azaphenothiazine (86% yield), m.p. 207–208°. *Anal.* Calcd for $C_{11}H_7ClN_2S$: C, 56.28; H, 3.00. Found: C, 56.44; H, 3.09.

The example below is typical of the condensation of a 1-azaphenothiazine with a dialkylaminoalkyl chloride.

10-(3-Dimethylaminopropyl)-1-azaphenothiazine Hydrochloride.—A mixture of 200 g. (1.0 mole) of 1-azaphenothiazine, 47 g. (1.2 moles) of sodamide, 3.5 l. of dry xylene and 133.7 g. (1.1 mole) of 3-dimethylaminopropyl chloride was stirred and refluxed for 24 hours, filtered, the filtrate concentrated and the residue distilled to give 228.5 g. (80% yield) of 10-(3-dimethylaminopropyl)-1-azaphenothiazine, b.p. 195–198° (0.5 mm.). To a solution of 228.5 g. of the *base* in 550 ml. of dry acetonitrile was added 192 ml. of a 3.8 *N* solution of hydrogen chloride in ether; the product was filtered and recrystallized from chlorobenzene to give 225.8 g. (87% yield) of product, m.p. 152–154°.

10-(2-Hydroxy-3-diethylaminopropyl)-1-azaphenothiazine Oxalate.—A mixture of 20 g. (0.1 mole) of 1-azaphenothiazine, 4.3 g. (0.11 mole) of sodamide and 500 ml. of dry toluene was stirred and refluxed for 8 hours, cooled, and treated with a solution of 14.2 g. (0.11 mole) of 1,2-epoxy-3-diethylaminopropane in 50 ml. of dry toluene. The mixture was refluxed for 8 hours, filtered, and the filtrate concentrated. The residual oil was dissolved in 200 ml. of chloroform and the chloroform solution extracted with three 100-

ml. portions of 5% hydrochloric acid. The acid extracts were treated with an excess of 10% aqueous potassium hydroxide, and extracted with chloroform; the chloroform extracts were dried, concentrated and distilled to give 16.1 g. of **10-(2-hydroxy-3-diethylaminopropyl)-1-azaphenothiazine.** The *base*, 11.5 g. (0.035 mole), 12.6 g. (0.14 mole) of anhydrous oxalic acid and 200 ml. of methyl ethyl ketone was refluxed until a clear solution formed: the oxalate separated from the cooled solution.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO., LEDERLE LABORATORIES]

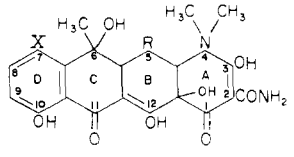
Chemistry of the Tetracycline Antibiotics.[1] I. Quaternary Derivatives

BY JAMES H. BOOTHE, GUIDO E. BONVICINO, COY W. WALLER, JOSEPH P. PETISI, RAYMOND W. WILKINSON AND ROBERT B. BROSCHARD

RECEIVED NOVEMBER 11, 1957

The quaternary methiodides of the antibiotics tetracycline and chlorotetracycline have been prepared and some of their chemical properties are described. In general the quaternary compounds are more reactive and less stable than the corresponding tertiary amines. The quaternary amines are reduced with extreme ease to the dedimethylaminotetracyclines.

During investigations of the chemistry and of the preparation of derivatives of the tetracycline antibiotics, the conversion of the tertiary amine which occurs in these compounds to a quaternary amine was studied. This is a report on the formation and subsequent reactions of these quaternary compounds.



tetracycline, X = R = H; chlorotetracycline, X = Cl, R = H; oxytetracycline, X = H, R = OH

The first attempts to quaternize these antibiotics were by heating with methyl iodide at 95° in a sealed vessel using tetrahydrofuran as a solvent. Each of the three antibiotics chlorotetracycline, tetracycline and oxytetracycline reacted differently. Chlorotetracycline yielded the corresponding methiodide in good yield, but tetracycline was dehydrated at the 5a–6-position. No pure product was isolated from this reaction, but the ultraviolet absorption spectra showed conclusively that the product was an anhydrotetracycline[2] derivative. Because of its insolubility in tetrahydrofuran, oxytetracycline was allowed to react using 1,2-dimethoxyethane as a solvent. The only recognizable product from this reaction was tetramethylammonium iodide. This probably resulted from an initial quaternization of the antibiotic followed by elimination of trimethylamine which then further reacted with methyl iodide.

A more practical method of preparing the methiodides of tetracycline and chlorotetracycline is to allow the reaction to proceed at room temperature for about a week during which time the methiodides slowly crystallize. Quaternization experiments on oxytetracycline again demonstrated the instability of oxytetracycline methiodide, even at room temperature. A solution of oxytetracycline and excess methyl iodide in methyl Cellosolve at room temperature yielded tetramethylammonium iodide as a white crystalline deposit. The dark filtrate from the tetramethylammonium iodide was not worked up further; however, this reaction is discussed in some detail by Conover.[3]

The methiodides are readily converted to the corresponding betaines (III) by raising the *p*H of their solutions to about 4–5. The betaines are crystalline compounds which are somewhat unstable even as solids especially in the presence of light at room temperature. They can be stored satisfactorily at 5° in the dark for several months, but always have a slight odor of trimethylamine. The betaines can be reconverted to the quaternary salts by treatment with strong acids such as hydriodic acid.

These quaternary derivatives are relatively inactive as antibacterial agents as compared to the antibiotics from which they are prepared.

The quaternary derivative of chlorotetracycline is more labile in neutral or alkaline solution than chlorotetracycline; for example in 0.1 *M* sodium borate the latter compound is fairly stable while its methiodide breaks down rapidly. Also under alkaline conditions which would convert chlorotetracycline to isochlorotetracycline,[4] much more extensive changes occur with the methiodide. If oxygen is carefully excluded, the mild alkaline treatment of chlorotetracycline methiodide yields dedimethylaminoaureomycinic acid (VII, X = Cl).[5] The treatment of chlorotetracycline with 5 *N* sodium hydroxide to yield dedimethylaminoaureomycinic acid already has been described.[5] This transformation involves at least three separate steps, and the probable sequence is as follows: (1) the cleavage of the C ring to form the phthalide, isochlorotetracycline[4]; (2) a Hofmann-type elimination of dimethylamine to form a double bond at position 4–4a; and (3) cleavage of the B ring be-

(1) The trademarks of the American Cyanamid Co. for chlorotetracycline and tetracycline are Aureomycin and Achromycin, respectively, and the trademarks of Charles Pfizer and Co. for oxytetracycline and tetracycline are Terramycin and Tetracyn, respectively.

(2) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, THIS JOURNAL, **74**, 4981 (1952).

(3) L. H. Conover, Symposium on Antibiotics and Mould Metabolites, The Chemical Society, Special Publication No. 5, 1956, pp. 72–74.

(4) C. W. Waller, B. L. Hutchings, C. F. Wolf, A. A. Goldman, R. W. Broschard and J. H. Williams, THIS JOURNAL, **74**, 4981 (1952).

(5) C. W. Waller, B. L. Hutchings, A. A. Goldman, C. F. Wolf, R. W. Broschard and J. H. Williams, *ibid.*, **74**, 4979 (1952).