COMMUNICATIONS TO THE EDITOR

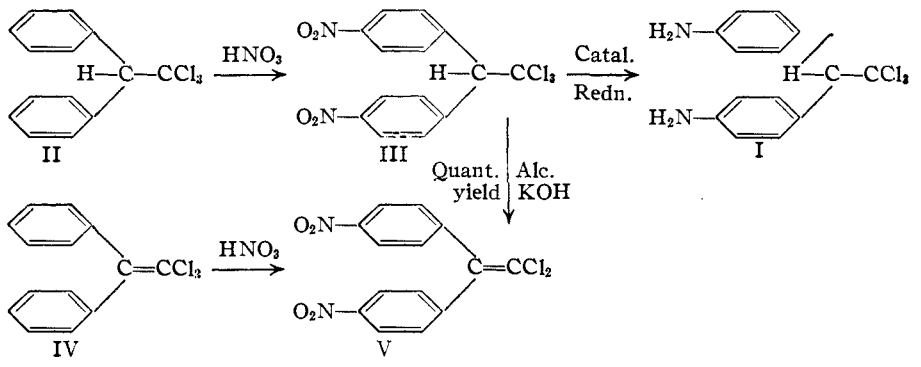
THE ANTITUBERCULAR ACTION OF 1,1,1-TRICHLORO-2,2-BIS-(*p*-AMINOPHENYL)-ETHANE

Sir:

In 1945 work was commenced at the Chemical Warfare Laboratories in Ottawa on the synthesis of the compound 1,1,1-trichloro-2,2-bis-(*p*-aminophenyl)-ethane (I).[1] It appeared from studies carried out on the Läuger hypothesis for the mechanism of action of DDT,[2] using fluorine analogs,[3,4] that this compound might possess marked antitubercular activity.

In view of similar work recently reported by Burger, Graef and Bailey,[5] we wish to report the progress of these researches at this time.

The synthesis of I seemed possible by the route



since the work of Lange and Zufall[6] showed that 1,1-dichloro-2,2-bis-(phenyl)-ethylene (IV) gave the compound 1,1-dichloro-2,2-bis-(*p*-nitrophenyl)-ethylene (V) as the main product of nitration.

The nitration of 1,1,1-trichloro-2,2-bis-(phenyl)-ethane (II) proceeded smoothly and a crystalline dinitro compound melting at 166–167° uncor. was isolated in good yield from the reaction mixture. This product was shown to be 1,1,1-trichloro-2,2-bis-(*p*-nitrophenyl)-ethane (III) by dehydrochlorination to V. The product from the dehydrochlorination proved to be identical with V prepared by the method of Lange and Zufall. Upon catalytic hydrogenation compound III took up six moles of hydrogen. The resulting amine was unstable in the crude form but was much more stable when purified by a procedure which will be described later. The substance crystallizes in the form of platelets melting with decomposition from 92–95° (uncor.) (calcd. for $C_{14}H_{13}N_2Cl_3$: N, 8.88. Found: N, 8.80). Repeated recrystallization of an analytically pure sample failed to raise the melting point or decrease the melting range. This is probably due to decomposition, with loss of hydrogen chloride, near the melting point.

In vitro tests on the activity of I showed that it gave complete inhibition of growth of *Mycobacterium tuberculosis* at dilutions of 1/100,000 and some inhibition at dilutions of 1/1,000,000. Transfer experiments showed that at dilutions of 1/100,000 the compound was bactericidal while at 1/1,000,000 it was bacteristatic. *In vivo* tests on the antitubercular activity of I, using the short assay of Feldman and Hinshaw,[7] showed remarkable control of experimentally induced tuberculosis in guinea pigs. The compound was fed at a level of 0.5% of the ration, this being the maximum well tolerated dose. The blood of guinea pigs fed this level of drug for a period of 56 days was found to contain an average of 1 mgm.% of I as determined by the method of Marshall.[8] This method has proven entirely satisfactory for the determination of I in biological material as well as in pure solution.

Full experimental details will be published later.

(1) Research Reports, Chemical Warfare Laboratories, Department of National Defense (army), Ottawa, Canada.

(2) P. Läuger, H. Martin and P. Müller, *Helv. Chim. Acta*, **27**, 892 (1944).

(3) S. Kirkwood and J. R. Dacey, *Can. J. Research*, **24B**, 69 (1946).

(4) S. Kirkwood and P. H. Phillips, *J. Pharmacol. and Exp. Therap.*, **87**, 375 (1946).

(5) A. Burger, E. Graef and M. S. Bailey, THIS JOURNAL, **68**, 1725 (1946).

(6) K. Lange and A. Zufall, *Ann.*, **271**, 1 (1893).

(7) W. H. Feldman and H. C. Hinshaw, *Am. Rev. Tuberc.*, **51**, 582 (1945).

(8) E. K. Marshall, *Proc. Soc. Exptl. Biol. Med.*, **36**, 422 (1937).

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RECEIVED SEPTEMBER 26, 1946

STREPTOMYCES ANTIBIOTICS. XI. THE STRUCTURE OF TETRAACETYLBISDESOXYSTREPTOBIOSAMINE

Sir:

Treatment of ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal[1] with Raney nickel catalyst gave tetraacetylbisdesoxystreptobiosamine[1] and tetraacetyldesoxystreptobiosamine (m. p. 166–167°, $[\alpha]^{25}D$ −81° (*c*, 1.04 in chloroform). *Anal.* Calcd. for $C_{13}H_{21}NO_8(CH_3CO)_4$:

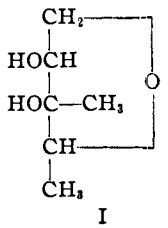
(1) (a) Kuehl, Flynn, Brink and Folkers, THIS JOURNAL, **68**, 2096 (1946); (b) Hooper, Klemm, Polglase and Wolfrom, *ibid.*, **68**, 2120 (1946).

C, 51.32; H, 6.77; N, 2.85; CH_3CO, 35.0. Found: C, 51.29; H, 6.94; N, 2.81; CH_3CO, 33.6). The additional oxygen atom of the latter product is present as a glycosidic hydroxyl group, as shown by the preparation of pentaacetyldesoxystreptobiosamine (m. p. 111–112°, $[\alpha]^{25}D$ −132° (*c*, 0.62 in chloroform)) and methyl tetraacetyldesoxystreptobiosaminide (m. p. 179–180.5°, $[\alpha]^{25}D$ −129° (*c*, 0.925 in chloroform)).

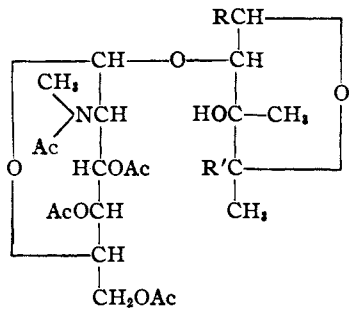
Acid hydrolysis of tetraacetylbisdesoxystreptobiosamine yielded N-methyl-L-glucosamine[2] and bisdesoxystreptose (m. p. 90–91°, $[\alpha]^{25}D$ +32° (*c*, 0.975 in chloroform). *Anal.* Calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.16; 2C—CH_3, 22.7; mol. wt., 132. Found: C, 54.63; H, 8.93; C—CH_3, 19.4; mol. wt., 141). Bisdesoxystreptose gave a bis-*p*-nitrobenzoate, m. p. 141–142°.

Bisdesoxystreptose was oxidized with one mole of periodic acid, and the product hydrolyzed with acid. Treatment of the solution with excess amounts of substituted hydrazines gave osazones of biacetyl. The derivatives prepared were the phenylosazone,[3] m. p. 247–249°; 5,6-dimethyl-2,3-diphenylosatetrazine,[4] m. p. 153–155°; the *p*-bromophenylosazone, m. p. 210–215°; and the *p*-nitrophenylosazone,[5] m. p. 312–316°.

These data show that bisdesoxystreptose is a 3,4 - dihydroxy - 2,3 - dimethyltetrahydrofuran (structure I). The compound formed an acidic complex with boric acid, indicating that the hydroxyl groups have the *cis* configuration. Structure II represents tetraacetylbisdesoxystreptobiosamine. The presence of a free tertiary hydroxyl group in streptobiosamine derivatives has been indicated.[1a,6] Periodate oxidations of N-acetylbisdesoxystreptobiosamine[1] indicate a pyranose ring structure for the methylamino hexose moiety. The primary rapid reaction appeared to be with one mole of periodate, and neither formic acid nor formaldehyde could be isolated.

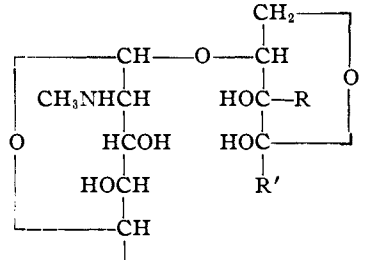


I

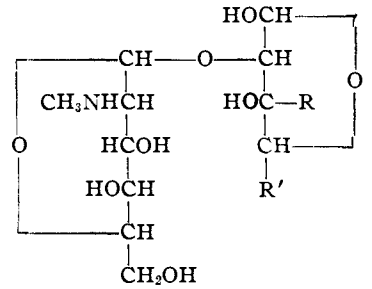


II, R, R′ = H
III, R = OH, R′ = H
IV, R = H, R′ = OH

Tetraacetyldesoxystreptobiosamine would have either structure III or IV. On the basis of structure II for tetraacetylbisdesoxystreptobiosamine, structures V, VI, VII and VIII may now be written for streptobiosamine.



V, R = —CHO, R′ = —CH_3
VI, R = —CH_3, R′ = —CHO



VII, R = —CH_3, R′ = —CHO
VIII, R = —CHO, R′ = —CH_3

Other degradations, to be published shortly,[7] will demonstrate which of these formulas is correct.

(2) Kuehl, Flynn, Holly, Mozingo and Folkers, THIS JOURNAL, **68**, 536 (1946).
(3) Neuberg and Reinfurth, *Biochem. Z.*, **148**, 563 (1923).
(4) H. v. Pechmann, *Ber.*, **21**, 2751 (1888).
(5) Hirsch, *Biochem. Z.*, **131**, 184 (1922); Neuberg and Kobel. *ibid.*, **160**, 255 (1925).
(6) Brink, Kuehl, Flynn and Folkers, THIS JOURNAL, in press.
(7) Kuehl, Flynn, Brink and Folkers, *ibid.*, in press.

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RECEIVED OCTOBER 15, 1946

2,3-DICHLORO-1,4-DIOXANE

Sir:

We have made two interesting and previously unrecorded observations in our study of the chlorination of dioxane.[1-7]

Repeated contact of 2,3-dichloro-1,4-dioxane (made from technical or purified[8] dioxane) with the skin, or inhalation of its vapor, quickly produces vertigo, nausea, headache, and inflamed eyes. These symptoms persist for several days: the inhalation of ammonia gives partial relief.

The uncatalyzed[1-6] chlorination of dioxane proceeded without mishap. When the chlorination was catalyzed by stannic chloride,[7] the reaction proceeded satisfactorily for about sixteen hours

(1) Böeseken, Tellegen and Henriquez, *Rec. trav. chim.*, **50**, 909 (1931).
(2) Summerbell and Christ, THIS JOURNAL, **54**, 3777 (1932).
(3) Baker, *J. Chem. Soc.*, 2666 (1932).
(4) Butler and Cretcher, THIS JOURNAL, **54**, 2987 (1932).
(5) Wilson, Baker and Shannon, *J. Chem. Soc.*, 1598 (1933).
(6) Böeseken, Tellegen and Henriquez, THIS JOURNAL, **55**, 1284 (1933).
(7) Kucera and Carpenter, *ibid.*, **57**, 2346 (1935).
(8) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, pp. 368–369.