benzene–petroleum ether gave material which melted constantly at 165–166° (micro-block).

Anal. Calcd. for $CH_3N_3(C_7H_5O)_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.58; H, 5.15; N, 15.63.

This substance exhibited two maxima in the ultraviolet at 2450 Å. with E_M 32,000 and 2750 Å. with E_M 32,000 in methanol solution.

The data obtained on this oxidation product were in agreement with a dibenzoylquinidine, but the melting point was lower than that reported in the literature (m. p. 215°; Korndörfer, *Arch Pharm.*, **241**, 449 [1903]). Accordingly, a 28.7-mg. sample was dissolved in 3.0 cc. of concentrated hydrochloric acid and the solution was refluxed for ninety minutes. The hydrolysis solution was diluted with water and extracted with ether. Evaporation of the ether extracts left a crystalline residue of practically pure benzoic acid; yield, 23.7 mg. The residual acid aqueous solution was evaporated to dryness to give a crystalline residue which was dissolved in 3.0 cc. of water. Addition of 2.0 cc. of saturated aqueous picric acid caused a crystalline precipitate to separate. The picrate was recrystallized once from hot water; yield, 25.9 mg., m. p. 335–336° (micro-block). Admixture with authentic guanidine picrate (m. p. 335–336°) did not alter the melting point of the product.

Anal. Calcd. for $CH_5N_3 \cdot C_6H_3N_3O_7$: C, 29.17; H, 2.80; N, 29.17. Found: C, 29.33; H, 3.10; N, 29.39.

The oxidation product is thus established to be dibenzoylguanidine. The yield of dibenzoylguanidine from heptabenzoylstreptidine would be 28% if one dibenzoylguanido moiety were present in the latter molecule, or 56% if both guanido groups were di-benzoylated. The yields of dibenzoylguanidine obtained in three oxidation experiments were 48, 30 and 43%, respectively.

Dodecabenzoyldihydrostreptomycin.—Benzoylation of 2.80 g. of dihydrostreptomycin trihydrochloride, using the conditions described above for streptomycin, gave 5.82 g. of buff-colored benzoylated dihydrostreptomycin. Chromatographic purification of 5.5 g. gave a first-eluate fraction in the form of a white amorphous powder weighing 0.5 g., $[\alpha]^{25}D$ +51° (*c*, 1.78 in chloroform).

Anal. Calcd. for $C_{21}H_{29}N_7O_{12}(C_7H_5O)_{12}$: C, 68.81; H, 4.90; N, 5.35. Found: C, 68.40; H, 5.25; N, 5.66.

Heptabenzoylstreptidine from Dodecabenzoyldihydrostreptomycin.—A 347-mg. sample of dodecabenzoyldihydrostreptomycin was dissolved in 6.62 cc. of chloroform and 0.16 cc. of 30% hydrogen bromide in glacial acetic acid was added. The solution was allowed to stand overnight, then diluted with chloroform and extracted with water and aqueous sodium bicarbonate. The chloroform solution was dried, evaporated to dryness, and the residue was dissolved in 0.5 cc. of benzene and 2.5 cc. of methanol. On standing, there was deposited 101 mg. of crystalline precipitate. Recrystallization of the precipitate from benzene–acetone and from benzene–methanol gave 22 mg. of white crystals of heptabenzoylstreptidine which melted at 256–258°, and showed $[\alpha]^{32}D$ +54° (*c*, 0.98 in chloroform). There was no change in the melting point of this material when mixed with heptabenzoylstreptidine (m. p. 256–258°) obtained from undecabenzoylstreptomycin.

Acknowledgment.—The authors wish to express their thanks to Dr. N. R. Trenner and his associates for carrying out ultraviolet and infrared absorption measurements, to Dr. J. B. Conn and his associates for molecular weight determinations, and to Mr. R. Boos and his associates for the microanalyses.

Summary

Streptomycin was benzoylated to give undecabenzoylstreptomycin, which was degraded by alkali to maltol and by hydrogen bromide to heptabenzoylstreptidine.

Dihydrostreptomycin was also benzoylated to give dodecabenzoyldihydrostreptomycin, which was likewise cleaved by hydrogen bromide to give heptabenzoylstreptidine.

Heptabenzoylstreptidine was further characterized by acetyl and anisoyl derivatives and by conversion to octabenzoylstreptidine. A hexabenzoylstreptidine and a monobenzoylstreptidine were also characterized. Hydrolysis of octabenzoyl-, heptabenzoyl- and octaacetylstreptidine yielded streptidine, showing that acylation and hydrolysis reactions involved no change in the structure of streptidine.

Heptabenzoylstreptidine gave more than one equivalent of dibenzoylguanidine upon chromic acid oxidation showing that streptobiosamine is linked to streptidine through an oxygen atom.

RAHWAY, N. J. RECEIVED FEBRUARY 14, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Streptomyces Antibiotics. XVIII. Structure of Streptomycin

BY FREDERICK A. KUEHL, JR., ROBERT L. PECK, CHARLES E. HOFFHINE, JR., AND KARL FOLKERS

The degradation of streptomycin to N,N′-dibenzoyldesoxystreptamine, and the oxidation of this degradation product to show that streptobiosamine is linked glycosidically at position 4 of streptidine, have been reported.[1]

The unbenzoylated functional group of heptabenzoylstreptidine[2] is attached to the carbon atom of streptidine which is linked glycosidically to streptobiosamine. This unbenzoylated functional group was considered to be a hydroxyl group because of the facile methanolysis[3] of streptomycin, and because of the formation of more than one mole of dibenzoylguanidine[2] per mole of heptabenzoylstreptidine upon chromic acid oxidation. Conclusive evidence excluding a nitrogen-atom linkage was obtained in the present study.

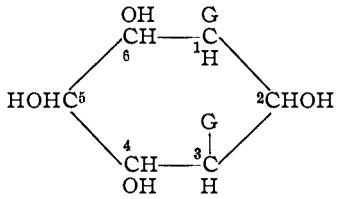
Streptidine and octabenzoylstreptidine[2] are optically inactive, showing that they are *meso* forms and have *cis* guanido groups; however, heptabenzoylstreptidine is optically active.[2] This optical activity proves that the unbenzoylated hy-

(1) Kuehl, Peck, Hoffhine, Peel and Folkers, THIS JOURNAL, **69**, 1234 (1947).

(2) Peck, Kuehl, Hoffhine, Peel and Folkers, *ibid.*, **70**, 2321 (1948).

(3) Brink, Kuehl and Folkers, *Science*, **102**, 2655 (1945); Brink, Kuehl, Flynn and Folkers, THIS JOURNAL, **68**, 2557 (1946).

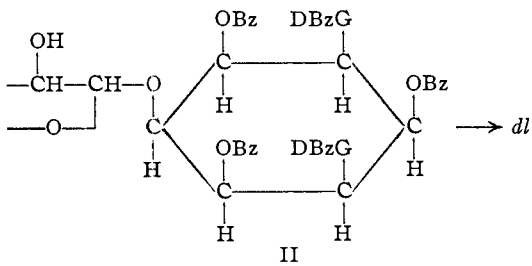
droxyl group in heptabenzoylstreptidine cannot be either at positions 2 or 5 of streptidine (I),



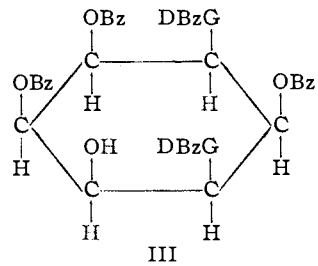
I, G = guanido

since these positions are in the plane of symmetry, and a heptabenzoylstreptidine with a free hydroxyl group at either position 2 or 5 would be optically inactive. The configuration of the groups about carbon atoms 4 and 6 is identical in streptidine and in the heptabenzoylstreptidine since there is no evidence of a Walden inversion in the formation of the latter compound. On the basis of these considerations of optical activity, the unbenzoylated hydroxyl group in heptabenzoylstreptidine is at position 4 (position 6 is equivalent).

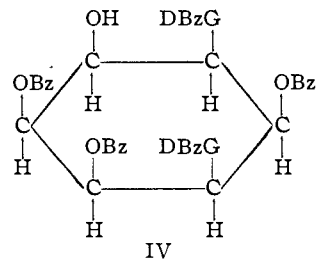
If streptobiosamine were linked glycosidically to position 5 of *meso*-streptidine, and if in the cleavage reaction an acyl group migrated from position 4 to position 5, such a migration might also be expected to occur from position 6 to result in a *dl*-heptabenzoylstreptidine. This hypothetical reaction is illustrated by the structures II, III, and IV, using one of the eight *meso* forms arbitrarily. The optical activity of the isolated heptabenzoylstreptidine eliminates such a rearrangement, unless an asymmetric rearrangement is considered possible.



II



III



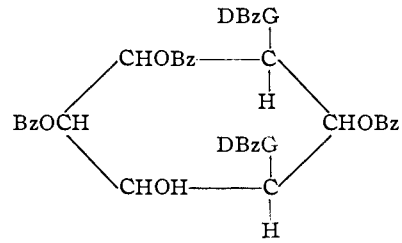
IV

DBzG = dibenzoylguanido
Bz = benzoyl-

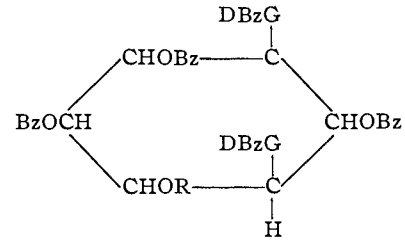
The determination of the position of the free hydroxyl group in heptabenzoylstreptidine by a series of degradative reactions led to a conclusion which is in agreement with that based on stereochemical considerations.

The most promising degradative method for locating the free hydroxy group appeared to be that of converting the >CHOH group to a $>CH_2$ group, because it seemed that the desoxy derivative would withstand the anticipated hydrolytic reactions.

Heptabenzoylstreptidine (V) reacted with methanesulfonyl chloride and toluenesulfonyl chloride to give mesylheptabenzoylstreptidine



V

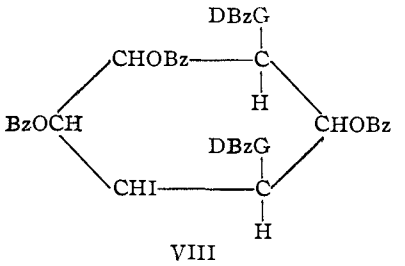


VI. R = CH_3SO_2—
VII. R = *p*-$CH_3C_6H_4SO_2$—

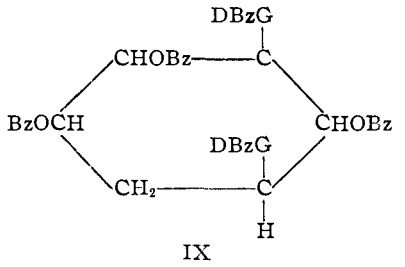
(VI) and tosylheptabenzoylstreptidine (VII), respectively. Mesyl derivatives of secondary alcohols in contrast to the corresponding tosyl derivatives have been reported[4] to react readily with sodium iodide to give the iodides. The mesyl derivative (VI) reacted with sodium iodide in acetone at 100° to give the iodoheptabenzoylstreptidine (VIII), and this mesyl derivative was used preparatively for this reaction. It was found later that the tosyl derivative (VII) also reacted readily with sodium iodide to give the iodo derivative (VIII). The formation of iodoheptabenzoylstreptidine constitutes conclusive evidence for an oxygen atom rather than a nitrogen atom linking streptidine to streptobiosamine.

Although iodoheptabenzoylstreptidine did not undergo hydrogenolysis over a palladium catalyst,

(4) Helferich and Gnuchtel, *Ber.*, **71B**, 712 (1938).



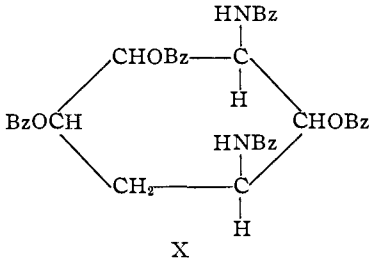
VIII



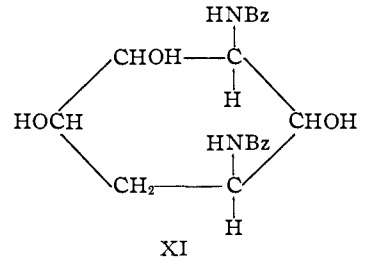
IX

the desired reduction product, heptabenzoyldesoxystreptidine (IX), was obtained when Raney nickel catalyst was used.

Heptabenzoyldesoxystreptidine (IX) was debenzoylated in methanol solution with barium methoxide. The resulting desoxystreptidine was then hydrolyzed to desoxystreptamine by baryta in the manner described for the conversion[5] of streptidine to streptamine. Desoxystreptamine was benzoylated to give pentabenzoyldesoxystreptamine (X), which was selectively debenzoylated in methanol solution with barium methoxide to N,N′-dibenzoyldesoxystreptamine (XI).

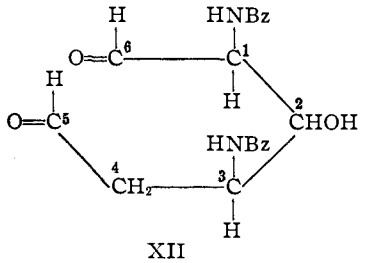


X

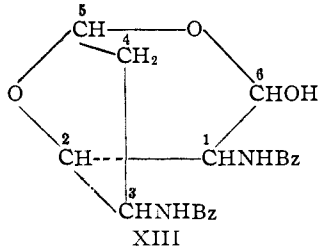


XI

Titration of N,N′-dibenzoyldesoxystreptamine with sodium periodate showed the consumption of one mole of periodate in seventeen hours and no further reaction in forty hours. The oxidation product was readily isolable as a crystalline compound which had a composition in agreement with that for α,γ-dibenzamido-β-hydroxyadipaldehyde (XII). The sharply defined consumption of one

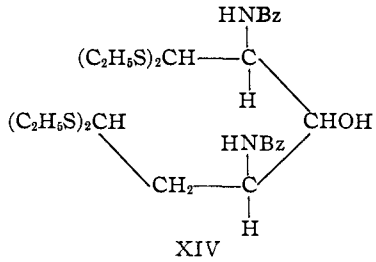


XII



XIII

mole of periodate was shown by treating the N,N′-dibenzoyldesoxystreptamine with excess periodate in aqueous solution, whereupon the same oxidation product crystallized directly from the solution after several days. In connection with the possibility that the aldehyde oxidation product actually has the cyclized structure XIII, the infrared absorption spectrum of the oxidation product was examined and a band for the aldehydic carbonyl group was not found. Only bands at 2.82, 6.38, 6.20 and 6.53 μ were observed Furthermore, the product exhibited a stability which is more compatible with structure XIII than the free aldehyde structure XII. The potential dialdehydic nature of the oxidation product was demonstrated, however, by the reaction of the compound with ethyl mercaptan and hydrogen chloride to give a crystalline derivative of the composition $C_{28}H_{40}N_2O_8S_4$; this derivative corresponds to structure XIV.

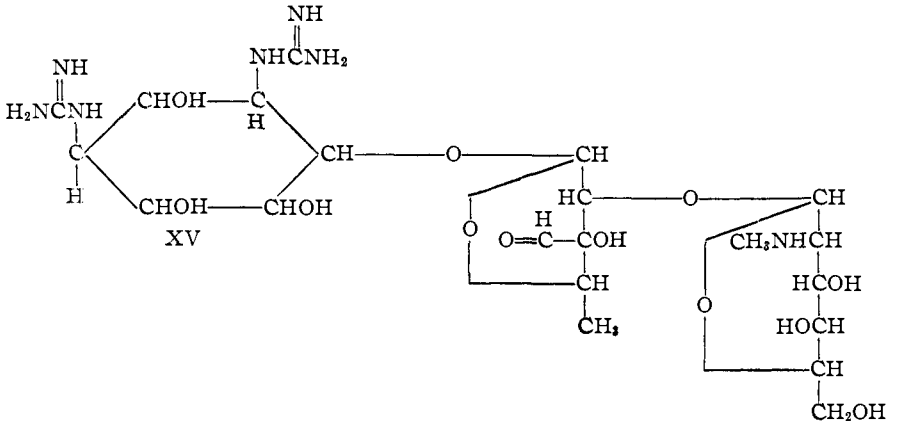


XIV

If the methylene group were positions 2 or 5 in desoxystreptamine, an aldehyde corresponding to structure XII or XIII could not have been formed. Thus, desoxystreptamine has the methylene group in position 4, and on the basis of the partial structure of streptomycin previously proposed,[6] the linkage of streptobiosamine to streptidine may be represented by structure XV. Structure XV for

(5) Peck, Hoffhine, Peel, Graber, Holly, Mozingo and Folkers, THIS JOURNAL, **68**, 776 (1946).

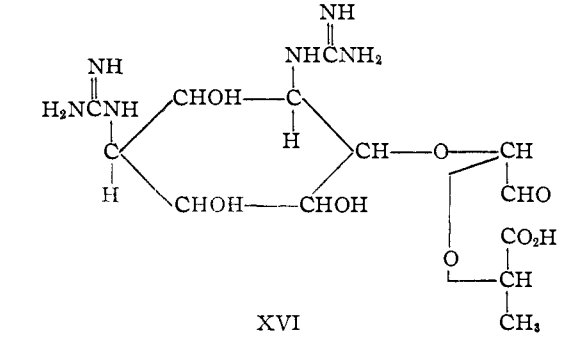
(6) Kuehl, Flynn, Brink and Folkers, *ibid.*, **68**, 2679 (1946).



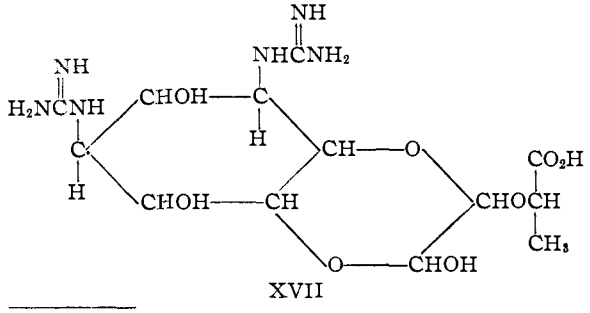
XV

streptomycin possesses a free formyl group. This group might also exist in hemiacetal form as a result of intramolecular cyclization.

Other workers[7] have treated streptomycin in aqueous solution with excess periodate, and obtained an oxidation product which yielded streptidine, glyoxal and an unidentified acid upon mild hydrolysis. They interpreted this result as strongly indicating that streptobiosamine is attached at carbon atom 5, although attachment at carbon atom 4 could not be entirely disregarded. On the basis of structure XV for streptomycin, perhaps the periodate oxidation data might be explained by intermediary formation of a product of structure XVI as the combined result of oxidation and hydrolytic reactions. Our experience has shown that streptose derivatives oxidize rapidly and streptidine oxidizes very slowly. Cyclization o the aldehydic product (XVI) might give the six-membered hemiacetal (XVII) which could be



XVI



XVII

(7) Carter, Loo and Skell, *J. Biol. Chem.*, **168**, 401 (1947).

sufficiently stable to block oxidation of the streptidine nucleus.

Experimental

Mesylheptabenzoylstreptidine.—A solution of 1.543 g. of heptabenzoylstreptidine in 20 ml. of pyridine was cooled to 5° and treated with 1.5 ml. of methanesulfonyl chloride. After remaining at 5° for fourteen hours, the reaction mixture was treated dropwise with 1 ml. of water at 5° to decompose the excess reagent. This mixture was poured into water, and the resulting oily suspension was extracted three times with chloroform. The combined chloroform extract was washed successively with dilute hydrochloric acid, sodium bicarbonate solution and water. The residue obtained from the dried chloroform solution was dissolved in 3 ml. of chloroform and at the boiling point of the solution was treated dropwise with methanol. Crystallization began quickly and after the mixture was cooled in ice-water for several hours, 1.520 g. of mesylheptabenzoylstreptidine was obtained, m. p. 241–242°. This product melted at 241.5–242° after a second recrystallization from the same solvent mixture; $(\alpha)^{25}D$ +18° (*c*, 0.8 in chloroform).

Anal. Calcd. for $C_{58}H_{48}N_6O_{13}S$: C, 65.16; H, 4.53; N, 7.85; S, 2.99. Found: C, 65.40; H, 4.29; N, 8.15 S, 2.46.

Iodoheptabenzoylstreptidine from Mesylheptabenzoylstreptidine.—A solution of 2.831 g. of mesylheptabenzoylstreptidine and 7 g. of dry sodium iodide in 50 ml. of anhydrous acetone was heated in a sealed tube for two hours at 100°. The acetone was removed *in vacuo*, and the yellow residue was shaken with a mixture of 50 ml. of water and 50 ml. of chloroform. The water layer was extracted three times with chloroform. The combined chloroform extract was washed successively with dilute sodium bicarbonate solution, sodium thiosulfate, water, and then dried over anhydrous magnesium sulfate. The colorless chloroform residue, 2.932 g., was dissolved in 5 ml. of chloroform and treated with 25 ml. of methanol. This solution yielded 2.542 g. of iodoheptabenzoylstreptidine, m. p. 153–154°, $(\alpha)^{25}D$ +23° (*c*, 0.08 in chloroform). Further recrystallization from the same solvent mixture did not alter the melting point.

Anal. Calcd. for $C_{57}H_{45}N_6O_{10}I$: C, 62.18; H, 4.12; I, 11.54. Found: C, 61.88; H, 4.05; I, 11.83.

Tosylheptabenzoylstreptidine.—A mixture of 275 mg. of heptabenzoylstreptidine, 115 mg. of tosyl chloride and 1.5 ml. of pyridine was allowed to stand in the cold room overnight. The clear solution was mixed with 10 ml. of cold water and allowed to stand for thirty minutes. The precipitated material was extracted with chloroform, and the chloroform solution was washed, dried over magnesium sulfate, and evaporated to dryness. The residue was crystallized from benzene–methanol; yield, 190 mg.; m. p. 200–203° (micro-block); $(\alpha)^{25}D$ +33° (*c*, 3.43 in chloroform).

Anal. Calcd. for $C_{64}H_{52}N_6O_{13}S$: C, 67.12; H, 4.58; N, 7.34; S, 2.80. Found: C, 67.40; H, 4.76; N, 7.47; S, 2.92.

Iodoheptabenzoylstreptidine from Tosylheptabenzoylstreptidine.—A mixture of 378 mg. of tosylheptabenzoylstreptidine, 3.4 g. of sodium iodide and 15 ml. of acetone was sealed in a bomb tube and heated at 100° for two hours. The contents of the tube were evaporated and water was added to the residue. The mixture was extracted with chloroform, and the chloroform extracts were washed with water and a little aqueous sodium thio-

sulfate. The colorless chloroform solution was evaporated to a volume of 2 ml. and diluted with 10 ml. of methanol. The first crop of iodoheptabenzoylstreptidine weighed 148 mg. and melted at 149–152° (micro-block). The second crop weighed 120 mg. and melted at 149–152°. Recrystallization of the combined material gave iodoheptabenzoylstreptidine, m. p. 151–153°.

Anal. Calcd. for $C_{87}H_{45}N_6O_{10}I$: C, 62.18; H, 4.12; I, 11.54. Found: C, 61.91; H, 4.40; I, 10.77.

Heptabenzoyldesoxystreptidine.—A solution of 5.58 g. of iodoheptabenzoylstreptidine in 330 ml. of aqueous 80% dioxane was reduced catalytically for one hour at 40 lb. pressure in the presence of about 25 g. of Raney nickel catalyst. After removal of the catalyst the solution was concentrated *in vacuo* to *ca.* 10-ml. volume. This solution was extracted several times with chloroform and distillation of the chloroform gave a colorless glassy residue. The residue was dissolved in a small amount of chloroform and crystallization was aided by adding methanol. The yield of crystalline product was 4.437 g., m. p. 187–191°. A number of recrystallizations alternately from chloroform–methanol and ethyl acetate–methanol was required to obtain pure heptabenzoyldesoxystreptidine, m. p. 198–199°.

Anal. Calcd. for $C_{87}H_{46}N_6O_{10}$: C, 70.21; H, 4.76; N, 8.62. Found: C, 70.25; H, 4.76; N, 8.49.

Pentabenzoyldesoxystreptamine.—A suspension of 321 mg. of heptabenzoyldesoxystreptidine in 150 ml. of absolute methanol containing 5 ml. of 0.4 *N* methanolic barium methoxide was stirred overnight at room temperature. The resulting clear solution was treated with carbon dioxide and concentrated *in vacuo* to a residue. This residue was leached with 20 ml. of 50% methanol, and after removal of the solvent from the extract, 119 mg. of desoxystreptidine carbonate was obtained as a white powder. A solution of desoxystreptidine in 20 ml. of saturated baryta was boiled for twenty-three hours, and then concentrated to *ca.* 10-ml. volume. Excess hydrochloric acid was added, and the solution was concentrated to dryness. This residue of desoxystreptamine hydrochloride and barium chloride was leached with 30 ml. of boiling methanol. The methanol-soluble material was again leached with 10 ml. of hot methanol. Removal of the methanol gave crude desoxystreptamine hydrochloride which was benzoylated at 5° with 20 ml. of pyridine and 3 ml. of benzoyl chloride. After standing overnight, the reaction mixture yielded pentabenzoyldesoxystreptamine which was crystallized from chloroform–ether; yield, 67 mg., m. p. 293–294°. After two recrystallizations from the same solvent mixture, the pentabenzoyldesoxystreptamine melted at 298–299°.

Anal. Calcd. for $C_{41}H_{34}N_2O_8$: C, 72.12; H, 5.02; N, 4.10. Found: C, 72.37; H, 5.10; N, 4.19.

N,N′-Dibenzoyldesoxystreptamine.—A suspension of 43 mg. of pentabenzoyldesoxystreptamine in 25 ml. of absolute methanol containing 2 ml. of 0.4 *N* methanolic barium methoxide was shaken at room temperature for ten minutes. The resulting clear solution was maintained at a temperature of 5° for fourteen hours and then treated with carbon dioxide. The solvent was removed *in vacuo*, and the residue was leached with 5 ml. of hot 50% methanol. This methanol-soluble portion, after removal of the solvent, was again leached with 5 ml. of hot methanol, and 18 mg. of methanol-soluble material was obtained which was redissolved in 1 ml. of methanol. Ten milligrams of N,N′-dibenzoyldesoxystreptamine was obtained; m. p. 287–289°; $(\alpha)^{25}D$ −4° (*c*, 1.1 in 50% acetic acid). The melting point remained unchanged after a second recrystallization from acetone–water.

Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.50. Found: C, 64.72; H, 6.21; N, 7.80.

Titration of N,N′-Dibenzoyldesoxystreptamine with Sodium Periodate.—A 10.4-mg. sample was dissolved in 5 ml. of water and treated with 3.0 ml. of sodium periodate solution (1 ml. ≅ 6.355 ml. of 0.01 *N* arsenite solution); the total volume was adjusted to 10.0 ml. One-milliliter aliquots were removed and titrated periodically with 0.01 *N* standard arsenite solution. The data on the titration are given in Table I.

TABLE I

TITRATION OF N,N′-DIBENZOYLDESOXYSTREPTAMINE

Time in hours	0.01 *N* arsenite utilized	Moles of $NaIO_4$ consumed
17	0.580	1.03
21	.585	1.04
24	.580	1.03
41	.570	1.02

Oxidation of N,N′-Dibenzoyldesoxystreptamine to α,γ-Dibenzamido-β-hydroxyadipaldehyde.—A solution of 106.5 mg. of N,N′-dibenzoyldesoxystreptamine in 100 ml. of hot water was treated with 10.8 ml. of sodium periodate solution (1 ml. ≅ 5.67 mg. of $NaIO_4$). After forty hours, when titration indicated the consumption of 0.8 mole of oxidizing agent, the solution was concentrated *in vacuo* to a residue. Trituration of the residue with acetone gave 102 mg. of acetone-soluble material which was dissolved in 15 ml. of hot water. α,γ-Dibenzamido-β-hydroxyadipaldehyde crystallized from the aqueous solution; yield, 32 mg.; m. p. 148–149°; $(\alpha)^{25}D$ +12° (*c*, 1.0 in methanol) (initial). The melting point did not change upon recrystallization from acetone–water.

Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.18; H, 5.48; N, 7.60. Found: (sample dried at 100°) C, 65.37; H, 5.57; N, 7.57.

α,γ-Dibenzamido-β-hydroxyadipaldehyde Tetraethyl Mercaptal.—A suspension of 38 mg. of α,γ-dibenzamido-β-hydroxyadipaldehyde in 15 ml. of ethyl mercaptan was saturated with anhydrous hydrogen chloride. After shaking for fifteen minutes, the crystals dissolved and the clear solution was allowed to stand overnight at room temperature. The ethyl mercaptan was removed *in vacuo*, and the 64-mg. residue was dissolved in 5 ml. of ether. The ethereal solution was allowed to flow into a column containing 5 g. of acid-washed alumina. Elution of the alumina with 15 ml. of ether gave a residue which crystallized from benzene–petroleum ether; yield, 15 mg.; m. p. 143–144°. Further elution with 10 ml. of chloroform resulted in the isolation of 14 mg. of material, m. p. 146–146.5°. The melting point of α,γ-dibenzamido-β-hydroxyadipaldehyde tetraethyl mercaptal remained at 146–146.5° after repeated recrystallizations.

Anal. Calcd. for $C_{28}H_{40}N_2O_3S_4$: C, 57.79; H, 6.94; N, 4.81; S, 22.03. Found: C, 57.90; H, 6.82; N, 5.17; S, 22.40.

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Summary

Heptabenzoylstreptidine reacted with methane sulfonyl chloride and tosyl chloride to give mesylheptabenzoylstreptidine and tosylheptabenzoylstreptidine, respectively. Treatment of both the mesyl or tosyl derivatives with sodium iodide gave iodoheptabenzoylstreptidine. Hydrogenolysis of the iodo derivative gave heptabenzoyldesoxystreptidine, which was converted stepwise into pentabenzoyldesoxystreptamine and N,N′-dibenzoyldesoxystreptamine.

Oxidation of N,N′-dibenzoyldesoxystreptamine with sodium periodate gave α,γ-dibenzamido-β-

hydroxyadipaldehyde. The adipaldehyde derivative was also characterized as the tetraethyl mercaptal.

These results show that streptobiosamine is linked glycosidically at position 4 of streptidine.

RAHWAY, N. J. RECEIVED FEBRUARY 14, 1948

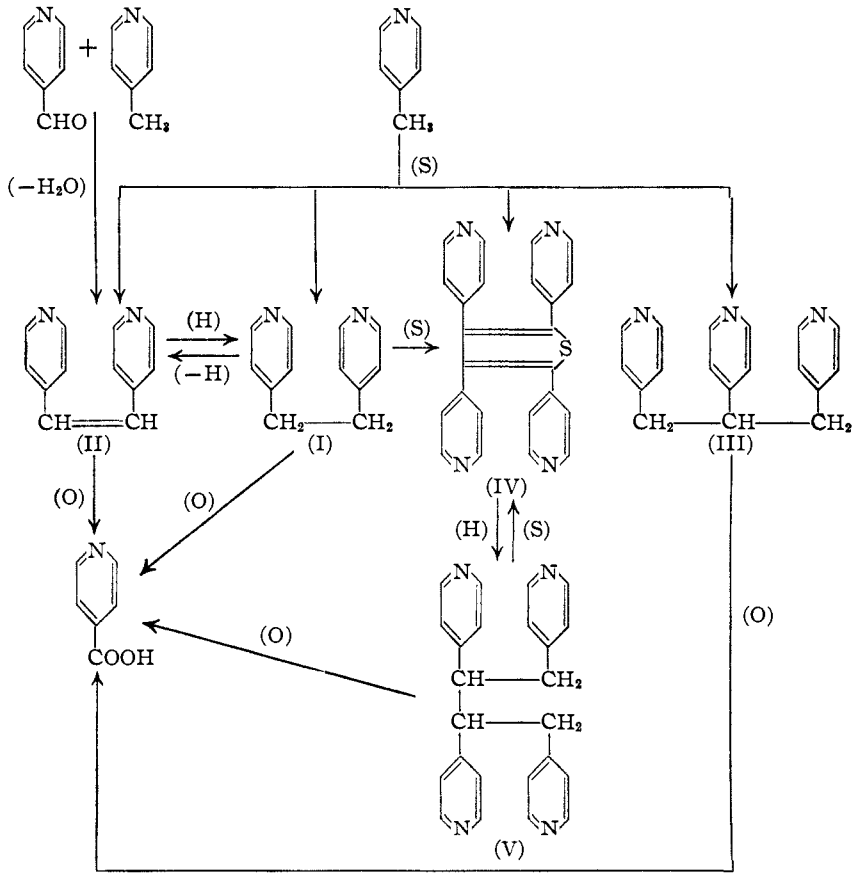
[CONTRIBUTION FROM KOPPERS CO., INC., MULTIPLE FELLOWSHIP ON TAR SYNTHETICS, MELLON INSTITUTE]

Action of Sulfur on Certain Pyridine and Quinoline Derivatives. I. Action of Sulfur on 4-Picoline

BY HELEN I. THAYER AND B. B. CORSON

The dehydropolymerizing action of sulfur on the picolines has not been previously noted, but certain examples of this action have been recorded in the methylbenzene series. For example, it is known that sulfur converts toluene to stilbene and tetraphenylthiophene, and xylenes to dimethylstilbenes and dimethylbenzyls.[1]

This paper describes the synthesis of several higher molecular weight bases from 4-picoline by the action of sulfur. Five products were obtained: hydrogen sulfide, 1,2-di-(4-pyridyl)-ethane (I), 1,2-di-(4-pyridyl)-ethylene (II), 1,2,3-tri-(4-pyridyl)-propane (III) and 2,3,4,5-tetra-(4-pyridyl)-thiophene (IV). In the absence of sodium hydroxide the yield of tetrapyridylthiophene (IV) was negligible, but it was the main product (85–90% yield) when the reaction mixture contained a catalytic amount of sodium hydroxide and the final reaction temperature was in the vicinity of 300°. In general, the presence of sodium hydroxide favored the production of the unsaturated compounds of dipyridylethylene (II) and tetrapyridylthiophene (IV) at the expense of the saturated compounds of dipyridylethane (I) and tripyridylpropane (III). The product-distribution was also affected by temperature, length of reaction time, and sulfur–picoline ratio.



At the lower temperatures, sulfur-free compounds (I, II, and III) resulted, whereas at the higher temperatures the main product was the sulfur-containing tetrapyridylthiophene (IV). These results are similar to those of Aronstein and von Nierop,[1] who treated toluene with sulfur at 200° and 250–300° to obtain stilbene and tetraphenylthiophene, respectively. Likewise, Oddo and Raffa[2] obtained the sulfur-free compound 3,3′-biindole by treating indole with sulfur at 115–125° and sulfur-containing products at higher reaction temperatures.

The structures of I and II were established as follows: (1) oxidation of these compounds to isonicotinic acid; (2) hydrogenation of II to I; (3) dehydrogenation of I to II; and (4) the synthesis of 1,2-di-(4-pyridyl)-ethylene (II) by the condensation of 4-pyridylaldehyde with 4-pico-

(1) Aronstein and von Nierop, *Rec. trav. chim.*, **21**, 448 (1902).

(2) Oddo and Raffa, *Gazz. chim. ital.*, **69**, 562 (1939).