Anal.—Calcd. for $C_{22}H_{24}O_{10}$: C, 58.92; H, 5.39. Found: C, 58.40; H, 5.63.

Decarboxylation.—One hundred milligrams of the acid was heated slowly to 250° with 0.4 Gm. of copper-bronze and 5 ml. of freshly distilled quinoline. Dry nitrogen was passed through the apparatus sweeping all evolved gases through a conventional carbon-hydrogen type train. The weight of carbon dioxide was found to be 10 mg. as compared to the calculated weight for carbon dioxide from one carboxyl group of 10.8 mg. Attempts to purify the main decarboxylation product were unsuccessful.

O-Methyl Corydine Methine.—One gram of corydine hydrochloride (Eastman Kodak Co.) was converted to the free base, then completely methylated with dimethyl sulfate according to Gadamer (14). The resulting impure O-methyl corydine methosulfate was digested with 30% sodium hydroxide solution for four hours to produce an oil as reported by Gadamer.

Picrate.—The picrate was prepared according to the conventional procedure, m. p. 182.5–184°. A mixed melting point with argemonine methine picrate showed a marked depression.

Methiodide.—The methiodide was prepared according to Gadamer's procedure (14). It sintered above 260°. A mixed melting point with argemonine methine methiodide gave a marked depression.

Corydine N-Free Compound.—The corydine methine methiodide was converted to the nitrogen-free compound according to Gadamer's procedure using a strong sodium hydroxide solution. A golden-yellow oil was obtained as reported. It could not be crystallized.

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2-Deoxystreptamine Derivatives

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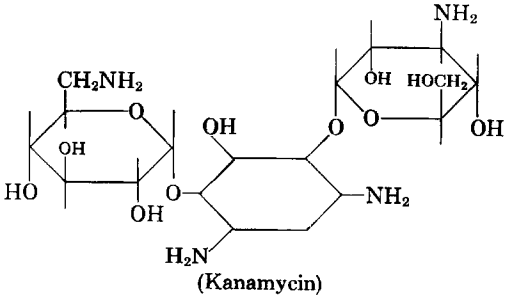
A group of N- and O-substituted 2-deoxystreptamine derivatives and their salts, represented by types I and II, have been synthesized for biological evaluation. Methods of their syntheses are discussed.

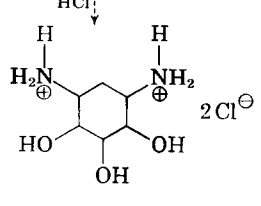
KANAMYCIN, discovered and characterized by Umezawa and co-workers (1, 2), is a water-soluble basic antibiotic which is active against many mycobacteria and Gram-positive and Gram-negative organisms. By boiling it for forty-five minutes in 6 *N* hydrochloric acid, kanamycin was hydrolyzed to 1,3-diamino-4,5,6-trihydroxycyclohexane (2-deoxystreptamine) dihydrochloride by Hooper and co-workers (3) while engaged in degradative studies which have led to an essentially complete structural elucidation for this important antibiotic (4).

It is noteworthy that several other antibiotics are known to contain 2-deoxystreptamine as a



(Kanamycin)

6N HCl | 45 min.



1,3-Diamino-4,5,6-trihydroxycyclohexane dihyodrochloride
(2-Deoxystreptamine) dihydrochloride

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structural component, including the neomycins (5, 6), hydroxymycin (7), kanamycin *B* (8), and paromomycin (9).

In the course of our search for new compounds having improved antimicrobial activity, fifteen N- and O-substituted 2-deoxystreptamine derivatives were synthesized for biological evaluation. These include acetyl and benzoyl derivatives, alkylated compounds resulting from the Leuckart reaction, and several Schiff bases. The latter were reduced catalytically and the products used in further alkylation or acylation reactions.

The pentaacetyl product, which had been prepared previously by Hooper and co-workers (3), was hydrolyzed with concentrated ammonia solution to give 1,3-bisacetyl-2-deoxystreptamine (I) (Table I). Benzoylation of 2-deoxystreptamine base with benzoyl chloride gave the corresponding dibenzoyl derivative (II). The Schiff base IV, prepared quantitatively from benzaldehyde and 2-deoxystreptamine, was reduced with hydrogen in the presence of Raney nickel to produce III. The Schiff base V from *o*-methoxybenzaldehyde and 2-deoxystreptamine was made by following the same procedure employed for the preparation of IV. 1,3-Dibenzylidene-4,5,6-triacetyl-2-deoxystreptamine (VI) was prepared by acylation of IV in dry pyridine with acetic anhydride, refluxing the mixture for four hours. 1,3 - Diacetyl - 4,5,6 - phenylcarbamyl - 2 - deoxystreptamine (VII) was made from compound I by boiling the latter with phenyl isocyanate for seven minutes. When 2-deoxystreptamine was refluxed with *p*-nitrobenzoyl chloride (1:2 molar ratio) in pyridine for ten minutes, a tetra-*p*-nitrobenzoyl product was isolated. After instrumental studies, a provisional structure (1,3,4,6-tetra-*p*-nitrobenzoyl-2-deoxystreptamine) was assigned. The tetra-*p*-nitrobenzoyl product was then reduced to the tetra-*p*-aminobenzoyl derivative (VIII). 1,3-Dibenzyl-1,3-dimethyl-2-deoxystreptamine (IX) was prepared by refluxing III with formaldehyde in the presence of formic acid (Leuckart reaction). When compound III was caused to react with an excess of phenyl isocyanate, 1,3 - dibenzyl - 1,3,4,5,6 - pentaphenylcarbamyl-2-deoxystreptamine (X) resulted.

Compound XI (Table II) was prepared by the condensation of 2-deoxystreptamine and isobutyraldehyde in ethanol, followed by reduction of the product with hydrogen over Raney nickel and acidification to obtain the hydrochloride. When 2-deoxystreptamine was refluxed with formic acid and formaldehyde (1:4 molar ratio) compound XIII was isolated as the hydrochloride salt, which was then acetylated to give compound XII. Compound V was treated with ethanolic hydrogen chloride to obtain the corresponding salt. 1,3 - Guanyl - 2 - deoxystreptamine sulfate (XV) was made from the 2-deoxystreptamine and 2-methylisothiourea sulfate in aqueous solution.

EXPERIMENTAL

Synthesis.[1]—*1,3 - Bis - acetyl - 2 - deoxystreptamine* (I).—Pentaacetyl-2-deoxystreptamine, 11.2 Gm. (0.035 mole); 29.9% ammonia, 11.0 Gm.; and 150 ml. distilled water were refluxed for one hour. The solution was evaporated nearly to dryness, diluted with 10 ml. methanol, and stirred until a crystalline deposit formed. The yield of white solid, m. p. 292–293°, was 4.5 Gm. (61%).

After recrystallization from dimethyl formamide, the product melted at 283–285°.

1,3 - Dibenzoyl - 2 - deoxystreptamine (II). — Eight grams (0.05 mole) of 2-deoxystreptamine was refluxed for ten minutes in 25 ml. of benzoyl chloride. The mixture was cooled to room temperature and 25 ml. of petroleum ether was added. The crystals were filtered off and washed twice with 15-ml. portions of petroleum ether, then successively with 20% sodium carbonate solution, water, and finally, with ether. The product was dried and a yield of 7.0 Gm. (55%), m. p. 292–300°, was observed. The high carbon analysis indicates the probable presence of impurity.

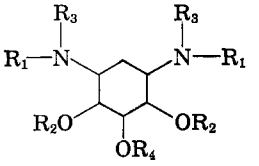
1,3-Dibenzylidene-2-deoxystreptamine (IV) *and 1,3-Dibenzyl-2-deoxystreptamine* (III).—2-Deoxystreptamine, 48.6 Gm. (0.3 mole) and 63.6 Gm. (0.6 mole) of benzaldehyde in 150 ml. of methanol were refluxed for ten minutes and then allowed to stand at room temperature for two hours. The mixture was evaporated to dryness under reduced pressure. The residue was dissolved in benzene and precipitated with petroleum ether. The yield of desired product was 85.0 Gm. (84.2%), m. p. 94–96°. The crystals were then reduced in alcohol, using Raney nickel as the catalyst. The yield was 84.5 Gm. (98.0%), m. p. 145–147°.

1,3 - Di - o - methoxybenzylidene - 3 - deoxystreptamine (V).—*o*-Methoxybenzaldehyde, 100.0 Gm. (0.74 mole) and 40 Gm. (0.25 mole) of 2-deoxystreptamine in 50 ml. of methanol were refluxed for forty-five minutes, cooled, and poured into 2 L. of ice water. Crystals formed on standing. The water was decanted. The residual crystals, after drying, were dissolved in benzene; the benzene solution was dried over Drierite, and the product was precipitated out by the addition of petroleum ether. A yield of 83.2 Gm. (84%), m. p. 186–188°, was obtained.

1,3 - Dibenzylidene - 4,5,6 - triacetyl - 2 - deoxystreptamine (VI).—1,3-Dibenzylidene-2-deoxystreptamine, 13.6 Gm. (0.04 mole), in 200 ml. of dry pyridine and 20 ml. of acetic anhydride was refluxed for four hours, during which time an orange solution formed. The mixture was cooled and 180 ml. of petroleum ether added. The resulting crystals were removed by filtration and washed twice with 30 ml. of petroleum ether. The product was

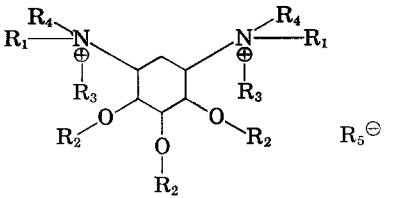
[1] Properties and analyses of the new compounds are shown in Tables I and II. All melting points are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York, N. Y.

TABLE I.—2-DEOXYSTREPTAMINES, TYPE I



No.	R_1	R_2	R_3	R_4	M. P., °C.	Yield %	Formula	Mol. Weight	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
I	CH_3CO	H	H	H	292–293	61	$C_{10}H_{18}N_2O_5$	246.26	48.77	48.90	7.36	7.46	11.37	11.72
II	C_6H_5CO	H	H	H	292–300	55	$C_{20}H_{22}N_2O_5$	370.40	64.85	66.23	5.98	6.12	7.56	7.71
III	$C_6H_5CH_2$	H	H	H	145–147	98	$C_{20}H_{26}N_2O_3$	342.43	70.15	69.91	7.65	7.85	8.18	8.19
IV	C_6H_5CH	H	...	H	79–80	84	$C_{20}H_{22}N_2O_3$	338.40	70.98	70.85	6.55	6.89	8.28	8.00
V	o-$H_3COC_6H_4CH$	H	...	H	186–188	84	$C_{22}H_{26}N_2O_5$	398.45	66.31	66.41	6.57	6.50	7.02	7.20
VI	C_6H_5CH	CH_3CO	...	CH_3CO	170–171	66	$C_{26}H_{28}N_2O_6$	464.52	67.22	67.66	6.07	6.19	6.03	6.26
VII	CH_3CO	C_6H_5NHCO	H	C_6H_5NHCO	293–295	90	$C_{31}H_{33}N_5O_8$	603.64	61.68	62.38	5.50	5.71	11.60	11.58
VIII	p-$H_2NC_6H_4CO$	p-$H_2NC_6H_4CO$	H	H	295–297	75	$C_{34}H_{34}N_6O_7$	638.68	63.93	64.63	5.36	5.38	13.15	13.35
IX	$C_6H_5CH_2$	H	CH_3	H	51–52	65	$C_{22}H_{30}N_2O_3$	370.49	71.32	70.23	8.16	8.02	7.56	7.30
X	$C_6H_5CH_2$	C_6H_5NHCO	C_6H_5NHCO	H	233–237	97	$C_{55}H_{51}N_7O_8$	938.06	70.42	70.32	5.48	5.43	10.45	10.55

TABLE II.—2-DEOXYSTREPTAMINES, TYPE II



No.	R_1	R_2	R_3	R_4	R_5	M. P., ° C.	Yield, %	Formula	Mol. Weight	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found.	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
XI	$(CH_3)_2CHCH_2$	H	H	H	Cl	294–296	66	$C_{14}H_{32}Cl_2N_2O_3$	347.32	48.41	48.06	9.28	9.63	8.06	7.84	20.41	19.99
XII	CH_3	CH_3CO	CH_3	H	Cl	263–265	87	$C_{16}H_{32}Cl_2N_2O_7$[a]	435.35	44.14	44.85	7.40	7.43	6.43	6.47	16.29	16.75
XIII	CH_3	H	CH_3	H	Cl	263–265	79	$C_{10}H_{28}Cl_2N_2O_5$	327.25	36.70	36.57	8.62	8.58	8.56	8.70	21.66	21.77
XIV	o-$H_3COC_6H_4CH_2$	H	H	H	Cl	213–215	94	$C_{22}H_{32}Cl_2N_2O_5$	475.20	55.54	55.31	6.79	7.07	5.90	6.06	14.92	14.35
																Sulfur	
XV	H_2NCNH	H	H	H	$SO_4\ominus$	165–170	13	$C_8H_{20}N_6O_7S$	344.34	27.90	28.17	5.85	5.99	24.40	24.10	9.31	9.28

[a] One mole of water present.

recrystallized from a benzene-petroleum ether mixture, yield 12.2 Gm. (66%), m. p. 168–170°.

1,3 - Diacetyl - 4,5,6 - tri - phenylcarbamyl - 2-deoxystreptamine (VII).—1,3-Diacetyl-2-deoxystreptamine (I), 3.5 Gm. (0.014 mole) was dissolved in 400 ml. of dry pyridine. Phenyl isocyanate was added and the mixture was refluxed for seven minutes. The reaction mixture was cooled; the resulting crystals were removed by filtration and washed with 40 ml. of petroleum ether. Yield of dried product was 7.5 Gm. (90%), m. p. 293–295°.

1,3,4,6 - p - Aminobenzoyl - 2 - deoxystreptamine (VIII).—2-Deoxystreptamine, 16.2 Gm. (0.10 mole), 37.0 Gm. (0.20 mole) of *p*-nitrobenzoyl chloride, and 60 ml. of pyridine were refluxed for ten minutes. The solution was poured into 400 ml. water, filtered, and the impurities removed from the crude product by extracting with 300 ml. of hot ethylene glycol monomethylether. The yield of white crystals was 11.3 Gm. (30.0%), m. p. >310°. The tetra-*p*-nitrobenzoyl-2-deoxystreptamine thus obtained was reduced with hydrogen over Raney nickel at an initial pressure of 49 pounds. The product was recrystallized from methanol. The yield was 8.5 Gm. (75%), m. p. 295–297°.

1,3 - Dibenzyl - 1,3 - dimethyl - 2 - deoxystreptamine (IX).—1,3-Dibenzyl-2-deoxystreptamine (II), 11.4 Gm. (0.033 mole); 7.5 Gm. (0.088 mole) 35% formaldehyde; and 9.0 Gm. (0.17 mole) of 88% formic acid were refluxed for sixteen hours. Six milliliters of concentrated hydrochloric acid were added and the solution evaporated until a thick syrup was obtained. The product was dissolved in 150 ml. of water and made alkaline with 10% sodium hydroxide solution; the precipitate thus obtained was dissolved in ether, dried over anhydrous potassium carbonate, and the ether removed by distillation. A colorless oil was obtained which became a flaky solid on pumping at high vacuum for several hours. Yield was 8.0 Gm. (65%), m. p. 51–52°.

1,3 - Dibenzyl - 1,3,4,5,6 - pentaphenylcarbamyl-2-deoxystreptamine (X).—1,3-dibenzyl-2-deoxystreptamine, 8.5 Gm. (0.03 mole) was mixed with 18.0 Gm. (0.15 mole) of phenyl isocyanate. The temperature of the reaction mixture rose to 40°; external heat was applied and the mixture was refluxed for ten minutes. The phenyl isocyanate was removed under reduced pressure. The remaining crystals were washed twice with 40-ml. portions of petroleum ether. Yield, 27.3 Gm. (97%), m. p. 233–237°.

1,3-Diisobutyl-2-deoxystreptamine Dihydrochloride (XI).—2-Deoxystreptamine, 16.2 Gm. (0.10 mole); 15.0 Gm. (0.21 mole) of isobutyraldehyde; and 50 ml. of absolute ethyl alcohol were refluxed for one hour. The solid was removed under reduced pressure and half of the crude product was reduced with hydrogen over Raney nickel at an initial pressure of 49 pounds. After filtration of the catalyst, the solution was evaporated to 30 ml., acidified with anhydrous hydrogen chloride in absolute ethanol, and this solution was finally diluted with 500 ml. of absolute ether to yield a crystalline product which was filtered, washed with ether, and dried in an oven. Yield of white solid was 11.4 Gm. (66%), m. p. 294–296°, with decomposition.

1,1,3,3 - Tetramethyl - 4,5,6 - triacetyl - 2 - deoxystreptamine Dihydrochloride (XII).—1,1,3,3-Tetramethyl-2-deoxystreptamine dihydrochloride (XIII), 11.6 Gm. (0.04 mole); 50 ml. of acetic anhydride; and 50 ml. of dry pyridine were refluxed for five hours. The mixture was chilled overnight, filtered, and the solid thus obtained was washed with acetone. The yield of light gray crystals was 14.5 Gm. (87%), m. p. 265–266°.

1,1,3,3 - Tetramethyl - 2 - deoxystreptamine Dihydrochloride (XIII).—2-Deoxystreptamine, 16.2 Gm. (0.10 mole); 51.0 Gm. (1.0 mole) of 88% formic acid; and 37.6 Gm. (0.44 mole) of 35% formaldehyde were refluxed for three hours. The mixture was acidified with 20 ml. concentrated hydrochloric acid and evaporated on the steam bath. The product was triturated with acetone, and finally boiled with 300 ml. absolute ethanol until crystallization occurred. The yield of nearly colorless crystals was 22.8 Gm. (78%), m. p. 263–265°, with previous softening at 105–110°, followed by resolidification (indicative of loss of water). Recrystallization of this material from 95% ethanol produced no change in melting point.

1,3 - Di - o - methoxybenzyl - 2 - deoxystreptamine Dihydrochloride (XIV).—To a 40.0-Gm. (0.1 mole) portion of 1,3-di-*o*-methoxybenzyl-2-deoxystreptamine in 100 ml. of ethanol solution was added 200 ml. of 50% ethanolic hydrochloride until a clear acidic mixture was obtained. To this mixture 1,000 ml. of ether was added. The reaction mixture was cooled, and the crystals which formed were removed by filtration; yield 44.6 Gm. (94%), m. p. 213–215°, of product.

1,3-Di-guanyl-2-deoxystreptamine Sulfate (XV)—To 11.34 Gm. (0.07 mole) of 2-deoxystreptamine was added, portionwise, 19.46 Gm. (0.07 mole) of 2-methylisothiourea sulfate in aqueous solution, 50 ml., over a period of twenty-four hours, maintaining the temperature at 70–75°. At this point, 1.1 Gm. more of 2-methylisothiourea was added, and the mixture was heated another twenty-four hours at the same temperature. It was then cooled to 0°, 50 ml. of acetone added, and filtered. The crystals which formed were washed three times with 1 *N* ammonia solution, 10 ml. acetone, and dried in high vacuum at 100°. Yield, 4.7 Gm. (13%), m. p. 165–170°.

Biological Activity.—None of the compounds described has been found to possess appreciable antimicrobial activity or noteworthy pharmacological properties in tests conducted to date.

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