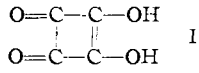
DIKETOCYCLOBUTENEDIOL

Sir:

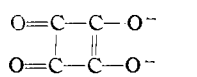
We wish to report a new cyclobutadienoacid derivative: diketocyclobutanediol (I)



I

Previously, Smutny and Roberts[1] and Blomquist and La Lancette[2] had reported on phenylcyclobutadienoquinone and diphenylcyclobutadienoquinone.

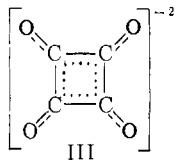
Compound I is a solid, white dibasic acid which has a pK_2 of 2.2 (pK$\sim$1) which is almost as strong as sulfuric acid (pK_2 of 1.5). The interesting anion (II) would be expected to have much resonance



II

stabilization since all four oxygen atoms should become equivalent through resonance.

The infrared spectrum of the potassium salt bears this out in that the carbonyl absorption of the solid free acid at 5.5 μ vanishes and in its stead a very intense broad absorption from 6.5 μ to 6.75 μ appears. This is in the accepted range for C—O vibration in acid salts and anions.[3] The C=C absorption also vanishes and thus the anion is best represented by the structure (III)



III

I was prepared by the aqueous hydrolysis of 1,3,3,-triethoxy-2-chloro-4,4-difluorocyclobutene[4] and also by the aqueous and acid hydrolysis of 1,2-diethoxy-3,3,4,4-tetrafluorocyclobutene.[5]

I was recrystallized from water and showed a decomposition point at about 293°. *Anal.* Calcd. for $C_4H_2O_4$: C, 42.11; H, 1.78 neut. equiv. 57.1. Found: C, 41.84; H, 1.86; neut. equiv. 57.9. The infrared spectrum of I showed a broad absorption at 4.3 μ characteristic of strong hydrogen bonding and chelation.[3] The carbonyl absorption occurred at 5.5 μ and the C=C conjugation system absorbed at 6.1 μ. This is expected since the proposed structure I should have strong hydrogen bonding. This also explains why the acid has such a high decomposition point. The ultraviolet absorption band was broad, $\lambda_{max}^{H_2O}$ 269.5 mμ ϵ = 37,000 showing the acid to be essentially completely ionized.

The acid in water solution gives an intense purple color with ferric chloride. It decolorizes bromine water, ceric nitrate and permanganate solutions. It also gives a very strong periodic acid test. The acid does not give the phenylhydrazine test and this is expected since the carbonyls are not ketonic but rather similar to acid carbonyls.

Investigation of the chemical and physical properties of I and its derivatives is being continued.

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RECEIVED MAY 1, 1959

(1) E. J. Smutny and J. D. Roberts, THIS JOURNAL, **77**, 3420 (1955).

(2) A. T. Blomquist and E. A. LaLancette, 135th meeting, American Chemical Society, Boston, Massachusetts, p. 54-O.

(3) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, p. 150.

(4) J. D. Park, C. M. Snow and J. R. Lacher, THIS JOURNAL, **73**, 234 (1951).

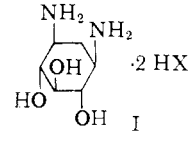
(5) J. D. Park, M. L. Sharrah and J. R. Lacher, *ibid.*, **71**, 2337 (1949).

PAROMOMYCIN. I. PAROMAMINE, A GLYCOSIDE OF D-GLUCOSAMINE[1]

Sir:

We wish to report the isolation and proof of structure of a glycoside of D-glucosamine derived from degradation of the antibiotic paromomycin.[2] Methanolysis of paromomycin hydrochloride in 0.32 N methanolic hydrogen chloride gave paromamine, isolated as its crystalline hydrochloride [*Anal.* Calcd. for $C_{12}H_{25}N_3O_7.3HCl\cdot{}^1/_2\ H_2O$ (441.8): C, 32.63; H, 6.62; N, 9.51; Cl, 24.08. Found: C, 32.36; H, 6.86; N, 9.65; Cl, 23.85; neutral equivalent, 157; $[\alpha]^{26}D$ +81.8° (c 1.0, H_2O)] and as its crystalline free base [*Anal.* Calcd. for $C_{12}H_{25}N_3O_7$ (323.4): C, 44.57; H, 7.79; N, 13.00. Found: C, 44,58; H, 7.97; N, 13.16; neut. equiv., 109; $[\alpha]^{26}D$ +114° (c 1.35, H_2O)]. From the mother liquors the amorphous anomeric mixture of methyl α- and β-paromobiosaminide dihydrochlorides was isolated [*Anal.* Calcd. for $C_{11}H_{21}N_2O_7(OCH_3)\cdot 2HCl\cdot{}^1/_2\ H_2O$ (406.3): C, 35.48; H, 6.70; N, 6.90; Cl, 17.45. Found: C, 35.87; H, 6.91; N, 6.71; Cl, 17.50; neutral equivalent, 209].

Vigorous acid hydrolysis of paromamine (48% hydrobromic acid) yielded an optically inactive compound which was found to be identical with the hydrobromide of 1,3-diamino-4,5,6-trihydroxycyclohexane (I, X = Br) isolated from neomycin[3] and kanamycin.[4] Identity was established by infrared spectra and X-ray diffraction patterns as well as mixed melting point.



I

Less drastic hydrolytic conditions (refluxing 6 N hydrochloric acid for 3 hours) produced, in addition to I (X = Cl), an Elson–Morgan positive reducing sugar. The crystalline sugar proved to

(1) Since this paper was written, M. J. Bartos [*Ann. pharm. franç.*, **16**, 596 (1958)] has described a similar product called *pseudo*neamine, derived from the antibiotic hydroxymycin, which consists of D-glucosamine glycosidically linked to one of the hydroxyls on deoxystreptamine.

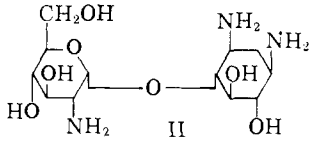
(2) Parke, Davis & Company, Belgian Patent 547,976 (October 12, 1956).

(3) B. E. Leach and C. M. Teeters, THIS JOURNAL, **74**, 3187 (1952).

(4) M. J. Cron, D. L. Johnson, F. N. Palermiti, Y. Perron, H. D. Taylor, D. F. Whitehead and I. R. Hooper, *ibid.*, **80**, 752 (1958).

be identical with D-glucosamine hydrochloride by infrared spectrum, X-ray diffraction, optical rotation and comparison of the salicylidene derivatives.

Since the crystalline N,N′,N″-triacetylparomamine [*Anal.* Calcd. for $C_{18}H_{31}N_3O_{10}$ (449.5): C, 48.10; H, 6.95; N, 9.35. Found: C, 48.04; H, 7.03; N, 9.37; $[\alpha]^{25}D$ +108° (*c* 1.0, H_2O); m.p. 300–306° dec.] consumes two moles of periodate[5] with the absence of formaldehyde formation, and paromamine gave negative reduction tests, the structural formula of the latter is represented as II.



II

Since the infrared spectra (KBr) of crystalline paromamine trihydrochloride and paromamine free base show absorption bands at 11.2, 11.91 μ and 11.06, 11.75 μ, respectively, no assignment of anomeric configuration is possible by this method.[6] However, since glucosamine is in the D-series and paromamine trihydrochloride has a high positive molecular rotation (+36,100), an α-D-glycosidic linkage is inferred. Data from methylation experiments described in a subsequent paper have more rigorously established this conclusion.

(5) R. W. Jeanloz and E. Forchielli, *J. Biol. Chem.*, **188**, 361 (1951).
(6) S. A. Barker, E. J. Bourne, M. Stacey and D. H. Whiffen, *J. Chem. Soc.*, 171 (1954); *cf.* "Methods of Biochemical Analysis," Vol. III, Interscience Publishers, Inc., New York, N. Y., 1956, p. 213.

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RECEIVED MAY 5, 1959

PAROMOMYCIN. II. PAROMOBIOSAMINE, A DIAMINOHEXOSYL-D-RIBOSE

Sir:

In the previous communication[1] methanolysis of the antibiotic paromomycin was reported to yield paromamine and the α- and β-anomers of methyl paromobiosaminide. This communication deals with preliminary structural studies on the disaccharide moiety, paromobiosamine.

The unresolved anomeric mixture of methyl paromobiosaminides was converted to the amorphous N,N′-dibenzoyl derivative [*Anal.* Calcd. for $C_{11}H_{19}N_2O_7(OCH_3)(COC_6H_5)_2$: C, 58.64; H, 6.06; N, 5.26. Found: C, 58.37; H, 6.25; N, 5.58] melting over a wide range (120–145°). Dilute acid hydrolysis followed by extraction, ion exchange treatment and carbon chromatography afforded a neutral colorless gum which corresponded to ribose in several paper chromatographic systems. Its infrared absorption spectrum in KBr[2] was identical to that of D-ribose. Since it exhibited a negative rotation $[\alpha]^{27}D$ −14° → −18° (18 hr.) the sugar is assigned to the D-series. Reduction with sodium borohydride afforded crystalline ribitol, m.p. 102–103°.

Vigorous acid hydrolysis of methyl paromobiosaminide (6 *N* hydrochloric acid) resulted in complete destruction of the ribose moiety and, following carbon chromatography, afforded an amorphous hygroscopic diaminohexose (paromose) $[\alpha]^{26}D$ +19° (*c* 1.0, H_2O; no mutarotation). Paromose is characterized as its crystalline dipicrate [*Anal.* Calcd. for $C_6H_{14}N_2O_4$ $(C_6H_3N_3O_7)_2$: C, 33.97; H, 3.17; N, 17.61; picric acid, 72. Found: C, 34.15; H, 3.40; N, 17.44; picric acid (via ultraviolet analysis), 70; $[\alpha]^{28}D$ +22° (*c* 0.5, H_2O)] which melted at 126–128° with decomposition. N,N′-Diacetylparomose formed a crystalline *p*-nitrophenylhydrazone (yellow needles) [*Anal.* Calcd. for $C_{16}H_{23}N_5O_7$: C, 48.36; H, 5.83; N, 17.63. Found: C, 48.42; H, 5.82; N, 17.53; $[\alpha]^{28}D$ + 5.9° (*c* 0.4, moist MeOH), m.p. 229–231° dec.]. N-Acetylation of paromose by the method of Roseman and Ludowieg[3] followed by sodium borohydride reduction yielded the crystalline dihydro N,N′-diacetyl derivative [*Anal.* Calcd. for $C_{10}H_{20}N_2O_6$: C, 45.45; H, 7.63; N, 10.60. Found: C, 45.29; H, 7.61; N, 10.50; $[\alpha]^{28}D$ −17.8° (*c* 4.0, 0.2 *M* *p*H 4.5 acetate buffer); m.p. 150.5–151.5°].

Dilute acid hydrolysis (0.5 *N* hydrochloric acid for 5 hours at 92°) of methyl paromobiosaminide produced, in addition to small amounts of starting material and paromose, the reducing disaccharide paromobiosamine which was isolated as the crystalline dihydrochloride [*Anal.* Calcd. for $C_{11}H_{22}N_2O_8 \cdot 2HCl \cdot CH_3OH$ (415.3): C, 34.71; H, 6.80; N, 6.75; Cl, 17.08. Found: C, 34.53; H, 7.13; N, 6.82; Cl, 16.84; neutral equivalent, 204; $[\alpha]^{27}D$ +25.5° (*c* 1.0, H_2O; no mutarotation)] and as the free base having a mutarotation value of +32° (*c* 1.0, H_2O). The ease of methanolysis (0.32 *N* HCl) of paromomycin to methyl paromobiosaminide which in turn can be hydrolysed with 0.5 *N* HCl to the free disaccharide, paromobiosamine, argues strongly in favor of a diaminohexosyl pentose rather than a pentosyl diaminohexose structure. Rinehart and Woo[4] arrive at the same conclusion with the neobiosamines but base their evidence on the detection of ribitol from hydrolysis of N,N′-dibenzoyldihydroneobiosamine C.

(1) T. H. Haskell, J. C. French and Q. R. Bartz, THIS JOURNAL, **81**, 3480 (1959).
(2) F. E. Resnik, L. S. Harrow, J. C. Holmes, M. E. Bill and F. L. Green, *Anal. Chem.*, **29**, 1874 (1957).
(3) S. Roseman and J. Ludowieg, THIS JOURNAL, **76**, 301 (1954).
(4) K. L. Rinehart, Jr., and P. W. K. Woo, *ibid.*, **80**, 6463 (1958).

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RECEIVED MAY 5, 1959

PAROMOMYCIN. III. THE STRUCTURE OF PAROMOBIOSAMINE

Sir:

The characterization of paromobiosamine as an *O*-(diaminohexosyl)-D-ribose was described in the previous communication.[1] This report concerns

(1) T. H. Haskell, J. C. French and Q. R. Bartz, THIS JOURNAL, **81**, 3481 (1959).