The residue was taken up in water and extracted repeatedly with ether. The aqueous solution was acidified with 1.0 ml. of 0.98 *N* hydrochloric acid. The precipitated solid was extracted into ether. After drying, the ether solution was evaporated and there remained 194 mg. of crystalline solid (72% yield). This was recrystallized from 4 ml. of 50% ethanol to yield 160 mg. of β-anilino-α,α-dimethylhydrocinnamic acid, m.p. 167–169°, neutralization equivalent 265 (calcd. 269).

GENEVA, N. Y. RECEIVED DECEMBER 21, 1950

[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

A Synthesis of Crotonoside[1]

BY JOHN DAVOLL[2]

Treatment of 2,6-diamino-9-β-D-ribofuranosylpurine with nitrous acid yields 9-β-D-ribofuranosylisoguanine, identical with the natural nucleoside, crotonoside.

In 1932, Cherbuliez and Bernhard[3] isolated from croton beans (*Croton tiglium* L.) a purine derivative which they named crotonoside, and showed to yield isoguanine and D-ribose on hydrolysis with dilute mineral acid. The identification of the sugar as D-ribose was later confirmed by Spies and Drake.[4] Falconer, Gulland and Story's[5] findings that the ultraviolet absorption spectrum of crotonoside closely resembles that of 9-methylisoguanine, and that treatment of crotonoside with nitrous acid gives a ribosylxanthine with an absorption spectrum resembling that of xanthosine and 9-methylxanthine, indicate that the point of attachment of the sugar in crotonoside is position 9. However, a definite identification of the deaminated crotonoside with xanthosine was not made, and no information has so far been available on the size of the lactol ring or the configuration at the sugar-purine link in crotonoside, although the similarity of its optical rotation to that of guanosine indicated that it was probably a β-ribofuranosylpurine.

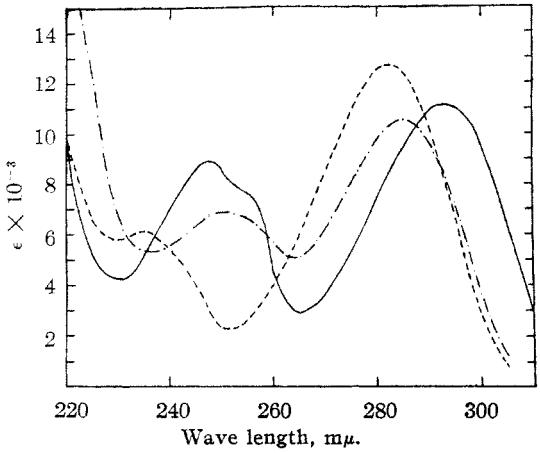

Fig. 1.—Ultraviolet absorption spectra of crotonoside, 22.9 mg. per liter: ———, water; - - - - - - -, 0.05 *N* HCl; -·-·-·-·-, 0.05 *N* NaOH.

Spies[6] has shown that isoguanine is resistant to deamination with nitrous acid, and Bendich[7] has observed that treatment of 2,6-diaminopurine with an excess of nitrous acid leads only to isoguanine, not to xanthine. This suggested that treatment of the 2,6-diamino-9-glycosylpurines reported recently[8] with nitrous acid might yield 9-glycosylisoguanines, and this proved to be the case. Treatment of 2,6-diamino-9-β-D-glucopyranosylpurine with nitrous acid for five minutes at 50° gave 9-β-D-glucopyranosylisoguanine in 55% yield. This compound has previously been prepared by treatment of 9-tetraacetyl-β-D-glucopyranosyl-2-methylsulfonyladenine with sodium hydroxide.[9] Similarly, 2,6-diamino-9-β-D-ribofuranosylpurine was converted to 9-β-D-ribofuranosylisoguanine in 57% yield.

A comparison of this compound with crotonoside was then made. The compounds were identical in melting point, optical rotation, R_f value on paper chromatograms, ultraviolet absorption spectra in water, 0.05 *N* hydrochloric acid or 0.05 *N* sodium hydroxide (Fig. 1), and in behavior toward sodium metaperiodate. Dr. Carl Clark, of the Physiology Department, Cornell University Medical College, determined the X-ray powder diffraction patterns (Table I) and infrared absorption spectra (Fig. 2) of anhydrous specimens of the natural and synthetic materials. The synthetic and natural samples show good general agreement, although the additional bands observed in the diffraction pattern and infrared absorption spectrum of the synthetic sample probably indicate the presence of a small quantity of impurity not detected by chemical methods. The decomposition points of the picrates were the same, and mixtures showed no depression. Mixtures of crotonoside and 9-β-D-ribofuranosylisoguanine showed a slight depression of melting point (one to two degrees), but since similar depressions were observed between different analytically pure preparations of the synthetic compound, this is not considered to indicate any difference in structure.

It is thus concluded that crotonoside may be fully described as 9-β-D-ribofuranosylisoguanine. Some of the properties of crotonoside, however,

(1) The author wishes to acknowledge the support of the National Cancer Institute of the United States Public Health Service and the Atomic Energy Commission, Contract AT(30-1)-910.

(2) Postdoctorate Fellow of the National Cancer Institute, United States Public Health Service.

(3) E. Cherbuliez and K. Bernhard, *Helv. Chim. Acta*, **15**, 464, 978 (1932).

(4) J. R. Spies and N. L. Drake, THIS JOURNAL, **57**, 774 (1935).

(5) R. Falconer, J. M. Gulland and L. F. Story, *J. Chem. Soc.*, 1784 (1939).

(6) J. R. Spies, THIS JOURNAL, **61**, 350 (1939).

(7) A. Bendich, unpublished.

(8) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951).

(9) K. J. M. Andrews, N. Anand, A. R. Todd and A. Topham, *J. Chem. Soc.*, 2490 (1949).

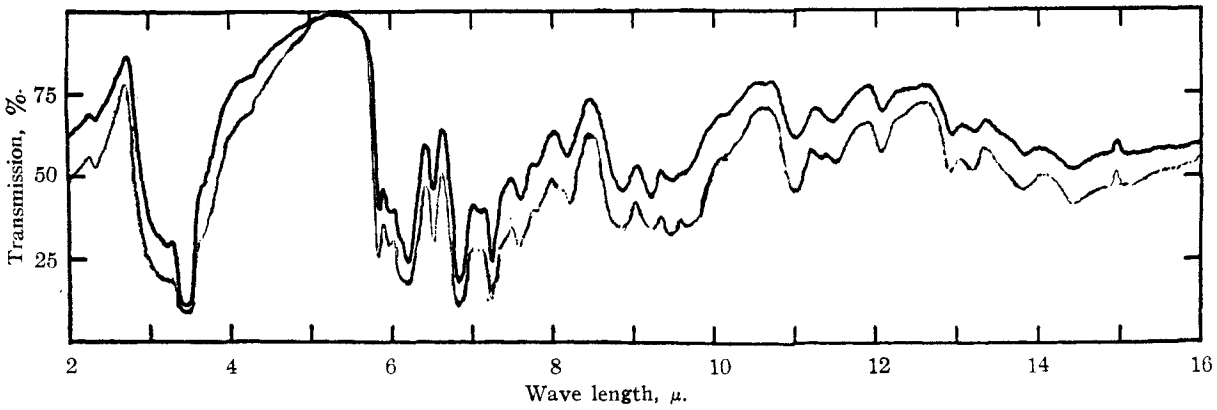

Fig. 2.—Infrared absorption spectra (mineral oil mull): ——, natural crotonoside; ——, 9-β-D-ribofuranosylisoguanine.

TABLE I

X-RAY POWDER PATTERN DATA FOR CROTONOSIDE (ANHYDROUS)

d = spacing of crystal planes; I/I_1 = intensity ratio of each band to the strongest; b = broad band

Natural		Synthetic	
d(Å.)	I/I_1	d(Å.)	I/I_1
9.05	0.2	9.10	0.2
8.35	.1	8.25	.1
7.33	.01	7.27	.01
6.67	.01		
6.20	.08b	6.31b	0.03
		5.72	.03
5.34	0.01	5.30	.02
4.79	.2b	4.76	.4
4.54	.4b	4.52	.3
4.40	.01b	4.36	.3
		4.15b	.05
		3.72b	.05
3.62b	0.01		
3.36b	1.0	3.32b	1.0
3.11b	0.01	3.08b	0.01
2.91b	0.01	2.89b	.03
		2.62b	.01
		2.38b	.01

were found to differ somewhat from those previously reported. The optical rotations of the natural and synthetic materials ($[\alpha]^{26}D$ −71° and −72.5°, respectively, in 0.1 N sodium hydroxide) were considerably higher than the values previously recorded for crotonoside: $[\alpha]^{25}D$ −60.38°[3] and $[\alpha]^{20}D$ −60.2°[5] in 0.1 N sodium hydroxide. The ultraviolet absorption spectra were in fair agreement with those of Falconer, *et al.*,[5] but the curves were shifted 9–13 mμ toward the longer wave lengths, and the extinction coefficients were considerably higher. A previously unrecorded, small maximum was observed at 235 mμ in 0.05 N hydrochloric acid.

An attempt was made to deaminate crotonoside under the conditions described by Falconer, *et al.*,[5] but the product, isolated through the lead salt, did not crystallize on seeding with xanthosine, and showed only general absorption in the range 220–300 mμ, indicating that destruction of the purine ring system had occurred.

On treatment with sodium metaperiodate under the conditions described by Lythgoe and Todd[10] for the oxidation of glycosylpurines, natural and synthetic specimens of crotonoside rapidly consumed one mole of oxidant per mole, as expected for a ribofuranosylpurine structure. The dialdehyde produced then underwent further oxidation at a slower rate, and similar behavior was observed with 9-β-D-glucopyranosylisoguanine after the initial rapid consumption of two moles of oxidant per mole. Of a number of other glycosylpurines examined, none showed as rapid an oxidation of the resultant dialdehyde, although some further uptake of periodate usually occurred. The results are presented in Table II. Although the exact nature of the further oxidation was not investigated, the purine moiety is probably not attacked, since the free purines consumed negligible amounts of periodate, and in the oxidation of crotonoside little change occurred in the ultraviolet absorption spectrum during the reaction.

TABLE II

OXIDATION OF GLYCOSYLPURINES AND PURINES (3–4 MG. PER ML.) WITH AQUEOUS SODIUM METAPERIODATE (*ca.* 100% EXCESS) AT 25°

Substance	Periodate consumed, moles of oxidant per mole 6 hr.	48 hr.	144 hr.
Inosine	0.95	0.97	0.98
Adenosine	.96	1.02	1.14
2-Acetamido-6-amino-9-β-D-ribofuranosylpurine	.95	0.97	1.17
Xanthosine	1.08	1.14	1.26
Guanosine	0.94	1.02	1.32
2,6-Diamino-9-β-D-ribofuranosylpurine[a]	1.02	1.25	1.44
Crotonoside (natural or synthetic)	1.00	1.37	1.78
9-β-D-Glucopyranosylisoguanine	1.99	2.24	2.76
Adenine	..	..	0.01
2,6-Diaminopurine[b]	..	..	0.08
Isoguanine sulfate	..	..	0.04

[a] Dialdehyde separated quantitatively as an amorphous or microcrystalline powder. [b] A precipitate of 2,6-diaminopurine periodate was collected and the periodate removed in this form estimated separately.

Experimental

Melting points were determined on a heated microscope stage and are uncorrected. All evaporations were carried out at 10–20 mm. pressure. The ultraviolet absorption spectra were determined on a Beckman spectrophotometer, model DU.

(10) B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 592 (1944).

9-β-D-Glucopyranosylisoguanine.—A solution of 0.40 g. of 2,6-diamino-9-β-D-glucopyranosylpurine and 0.50 g. of sodium nitrite in 7 ml. of hot water was cooled to 50° and treated with 0.50 ml. of glacial acetic acid. The mixture was kept at 50° for five minutes, and the resulting clear brown solution diluted with 25 ml. of water. A solution of 1.50 g. of lead acetate trihydrate in 15 ml. of water was added, followed by 6 ml. of concentrated aqueous ammonia. The precipitate was collected by centrifugation, washed, and dissolved in 30 ml. of 20% acetic acid. The solution was treated with hydrogen sulfide, filtered, and the filtrate evaporated to dryness. Crystallization of the residue from 10 ml. of water, with Norit, gave 0.19 g. of small leaflets; a further 0.03 g. was obtained by concentration of the mother liquors; total yield 0.22 g. (55%). Recrystallization from water gave 0.15 g. of tiny colorless leaflets, m.p. 279–282° (dec.), with previous darkening above 270° (reported,[9] m.p. 265–270° (dec.)); $[\alpha]^{24}D$ −26° (*c* 1.01% in 0.1 *N* sodium hydroxide). On a paper chromatogram in a *n*-butanol–diethylene glycol–water mixture in an ammonia atmosphere,[11] the R_f value was 0.15.

Anal. Calcd. for $C_{11}H_{15}O_6N_5$: C, 42.16; H, 4.79; N, 22.35. Found: C, 42.00; H, 4.83; N, 22.45.

Crotonoside (Natural).—This was prepared from croton beans as described by Falconer, *et al.*,[5] and was purified by conversion to the picrate and regeneration by the use of an anion-exchange resin.[8] It formed needles and needle clusters, m.p. between 237 and 252° (dec.), depending on the rate of heating; $[\alpha]^{26}D$ −71° (*c* 1.06% in 0.1 *N* sodium hydroxide). The ultraviolet absorption spectra, at *c* = 22.9 mg. per liter, showed maxima as follows: In water, 247 mμ (ϵ_m 8,930) and 293 mμ (ϵ_m 11,100); in 0.05 *N* hydrochloric acid, 235 mμ (ϵ_m 6,140) and 283 mμ (ϵ_m 12,700); and in 0.05 *N* sodium hydroxide, 251 mμ (ϵ_m 6,890) and 285 mμ (ϵ_m 10,550). [Falconer, *et al.*,[5] gave the following maxima: In water, 235 mμ (ϵ_m 8,600) and 284 mμ (ϵ_m 9,100); in 0.05 *N* hydrochloric acid, 270 mμ (ϵ_m 10,500); and in 0.05 *N* sodium hydroxide, 240 mμ (ϵ_m 4,000) and 275 mμ (ϵ_m 7,400)]. On paper chromatography as described for the glucosylpurine, the compound gave one spot, R_f value 0.23.

Anal. Calcd. for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.45; H, 4.96; N, 24.72.

Picrate.—Prepared in aqueous solution and recrystallized from water, the picrate formed needles, decomposing at 212–225°.

9-β-D-Ribofuranosylisoguanine.—A solution of 0.30 g. of 2,6-diamino-9-β-D-ribofuranosylpurine and 0.45 g. of sodium nitrite in 5 ml. of hot water was cooled to 50° and treated with 0.45 ml. of glacial acetic acid. The resultant gelatinous mass was kept at 50° for five minutes, then diluted with 15 ml. of water, heated to give a clear solution, and the compound isolated through the lead salt exactly as described for the corresponding glucosylpurine; yield 0.172 g. (57%). The material was twice recrystallized from water, with Norit, to give 0.12 g. of minute needles and needle clusters. The compound had the same melting point as crotonoside at any given rate of heating; mixtures with crotonoside melted one to two degrees lower; $[\alpha]^{26}D$ −72.5° (*c* 0.73% in 0.1 *N* sodium hydroxide). The ultraviolet absorption spectra in water, 0.05 *N* hydrochloric acid and 0.05 *N* sodium hydroxide were indistinguishable from those of crotonoside under similar conditions. On paper chromatography as described for the glucosylpurine the compound gave one spot, R_f value 0.23.

Anal. Calcd. for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.38; H, 4.55; N, 24.96.

Prepared in aqueous solution and recrystallized from water, the picrate formed needles, decomposing at 210–225° alone or in admixture with crotonoside picrate.

Hydrolysis of the synthetic ribosylisoguanine with *N* hydrochloric acid for one hour at 100° gave isoguanine, identified by its ultraviolet absorption spectrum[12] and by paper chromatography.

Acknowledgment.—The author wishes to thank Dr. A. Bendich, of this Laboratory, for a sample of natural crotonoside; Dr. Carl Clark, of Cornell University Medical College, for determining the X-ray diffraction patterns and infrared absorption spectra of specimens of crotonoside; Mr. Roscoe C. Funk, Jr., for the microanalyses; and Dr. George Bosworth Brown for his interest in this work.

(11) E. Vischer and E. Chargaff, *J. Biol. Chem.*, **176**, 703 (1948).

(12) A. Bendich, J. F. Tinker and G. B. Brown, THIS JOURNAL, **70**, 3109 (1948).

NEW YORK, N. Y. RECEIVED JANUARY 26, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Small-Ring Compounds. VI. Cyclopropanol, Cyclopropyl Bromide and Cyclopropylamine

BY JOHN D. ROBERTS AND VAUGHAN C. CHAMBERS

Assignment by Cottle and co-workers of the cyclopropanol structure to one of the products of the reaction of ethylmagnesium bromide with epichlorohydrin has been verified by an independent synthesis from cyclopropylmagnesium chloride. Cyclopropyl acetate and *p*-toluenesulfonate have been prepared and characterized. Cyclopropyl bromide has been obtained from the reaction of silver cyclopropanecarboxylate with bromine. The von Braun reaction between N-cyclopropylbenzamide and phosphorus pentabromide was unsuccessful. The Beckmann rearrangement of cyclopropyl methyl ketoxime has been investigated as part of a synthesis of cyclopropylamine.

Cyclopropanol (I) has been reported by Cottle and co-workers[1] to be formed in the reaction of ethylmagnesium bromide with epichlorohydrin. Although the alcohol was not obtained pure, a large number of solid derivatives were prepared having the correct elemental analyses. The cyclopropanol structure was assigned indirectly on the basis of the non-identity of the compound and its derivatives with the known three-carbon alcohols as well as the rather facile formation of propionaldehyde on heating.[2]

In the present investigation, the preparation of I by the previously described method[1] has been duplicated and somewhat purer (halogen-free) product obtained by a slight modification of the isolation procedure. Analytically pure cyclopropanol was not obtained and, in agreement with earlier observations,[1] the material rearranged rather easily to propionaldehyde. The assignment of the cyclopropanol structure was verified by

(1) (a) J. K. Magrane and D. L. Cottle, THIS JOURNAL, **64**, 484 (1942); (b) G. W. Stahl and D. L. Cottle, *ibid.*, **65**, 1782 (1943).

(2) The work of Cottle and co-workers[1] seems to have been rather generally overlooked and the preparation and properties of cyclopropanol are not mentioned in recent books or reviews such as: P. Karrer, "Organic Chemistry," 4th English ed., Elsevier Publishing Company, Inc., New York, N. Y., 1950; G. M. Dyson, "A Manual of Organic Chemistry for Advanced Students," Vol. I, Longmans Green and Co., New York, N. Y., 1950; L. I. Smith, "Record of Chemical Progress," Kresge-Hooker Scientific Library, Detroit, Mich., Spring 1950 issue, p. 71.