The Diamagnetic Anisotropy of a Borazine Ring. A Reply to Muszkat's Correction

Sir:

Muszkat[1] has given comments on our paper[2] in regard to the evaluation of diamagnetic anisotropy of a borazine ring. We were well aware of the difficulty in estimating $\chi_\perp$ of borazine and approximated it with that of isoelectronic benzene. This is a debatable problem to which Muszkat called our attention. However, we preferred the experimental $\chi_\perp$ of benzene to $\chi_\perp$ values of pyridine and other heterocycles calculated for a Kekulé-type structure by Pascal's additivity, because these compounds are not isoelectronic with borazine in a narrow sense (whereas *sym*-triazine, for instance, has 27 electrons in the 2s,2p orbitals of carbon or nitrogen and 3 electrons in the 1s orbitals of hydrogen, both borazine and benzene have 24 electrons in the 2s,2p orbitals of carbon, nitrogen, or boron and 6 electrons in the 1s orbitals of hydrogen) and also because Pascal's constant for nitrogen involves considerable complications in relation to bond types. Strictly speaking, one should take into account the exact shape and dimensions of bond orbitals occupied by electrons. In view of the lack of available data, we have made the bold assumption and hoped that, in spite of its approximate nature, our results would contribute to encourage future developments.

We further tried to confirm the adequacy of our assumption by estimation through Pascal's additivity rule taking into account constitutive correction constants. Muszkat's criticism is mainly directed to this point. Although our arguments are not convincing because of misprints involved and the approximate nature of Pascal's additivity rule, conclusions derived by us are not thereby altered. The magnetic susceptibility of boron trichloride, -62.0 (instead of -67.0), was taken from Landolt–Börnstein's Tables[3] rather than from the table compiled by Foëx.[4] This unfortunate error on our side must have made recalculation by Muszkat very difficult.

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(4) G. Foëx, "Constantes Sélectionnées. 7. Diamagnétisme et Paramagnétisme," Masson et Cie, Paris, 1957.

CHEMISTRY DEPARTMENT, NAGOYA UNIVERSITY MASAJI KUBO
CHIKUSA, NAGOYA, JAPAN
SHIONOGI PHARMACEUTICAL COMPANY HARUYUKI WATANABE
FUKUSHIMAKU, OSAKA, JAPAN
INSTITUTE OF SCIENTIFIC AND INDUSTRIAL RESEARCH
OSAKA UNIVERSITY KAZUO ITO
SAKAI, JAPAN

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Purine Deoxynucleosides. Synthesis of 9-(2′-Deoxy-α- and -β-D-ribofuranosyl and 2′-deoxy-α- and -β-D-ribopyranosyl)purines by the Fusion Method[1]

Sir:

A simple and superior procedure has been developed for the synthesis of purine 2′-deoxyribofuranosides and purine 2′-deoxyribopyranosides which is of considerable utility and overcomes many of the limitations found in earlier work.

Most previously recorded syntheses of purine 2′-deoxyribonucleosides *via* a purine and an appropriate carbohydrate derivative utilize a halosugar and a heavy metal (such as mercury or silver) salt to accomplish actual nucleoside formation.[2] This method is often characterized by inherent experimental difficulties and limitations including the arduous task of obtaining crystalline products due to purification problems. In view of these difficulties, numerous efforts have been made to devise new synthetic procedures for the preparation of purine 2′-deoxynucleosides. Schramm and co-workers[3] employed 2-deoxyribose in the presence of polyphosphoric acid for the direct synthesis of 2′-deoxyadenosine. This method, however, is of questionable preparative value since Carbon[4] has shown that under these conditions only a small yield of a mixture of at least six different deoxynucleosides was obtained.

A number of Japanese investigators[5–8] have reported the acid-catalyzed fusion of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose and related D-ribofuranose derivatives with various purines to provide the corresponding β-D-ribofuranosylpurines in variable yield. Although omitted from several recent reviews covering the synthesis of purine nucleosides,[2] this adaptation of the Helferich glycosidation procedure[9] now has been studied in our own laboratory and found to be of wide general application.[9a] This type of reaction has now been utilized for a most convenient preparation of 9-(2′-deoxy-α- and -β-D-ribofuranosyl)purines. When 1,3,5-tri-*O*-acetyl-2-deoxy-D-ribofuranose[10] was fused with various purines, a good yield of an anomeric mixture of the corresponding 9-(2′-deoxy-D-ribofuranosyl)purine was obtained. This method has the advantage of simplicity, and in most instances the deoxynucleosides were crystallized directly from the reaction mixture after deacetylation.

Four grams of 6-chloropurine[11] and 10 g. of 1,3,5-tri-*O*-acetyl-2-deoxy-D-ribofuranose[10] were heated together to 127° in a preheated oil bath. Then a catalytic amount (75 mg.) of chloroacetic acid was added, and the temperature was maintained at 127° (oil bath temperature) for approximately 3 min. The acetic acid then was rapidly removed *in vacuo* and the melt was allowed to cool. The crude melt was dissolved in 30 ml. of hot methanol, and the solution was filtered to remove unreacted 6-chloropurine. The filtrate was treated with methanolic ammonia at 0° for 12 hr. After evaporation, the resulting residue was dissolved in hot ethyl acetate which on cooling yielded 2.6 g. of a crude anomeric mixture of crystalline nucleosides, m.p. 135–142°. Fractional crystallization from ethyl acetate containing a small volume of methanol gave 1.5 g. of fine needles[12] of 6-chloro-9-(2′-deoxy-α-D-ribo-

(1) Supported by research grants CY-4008(C4) and CA 04008-06 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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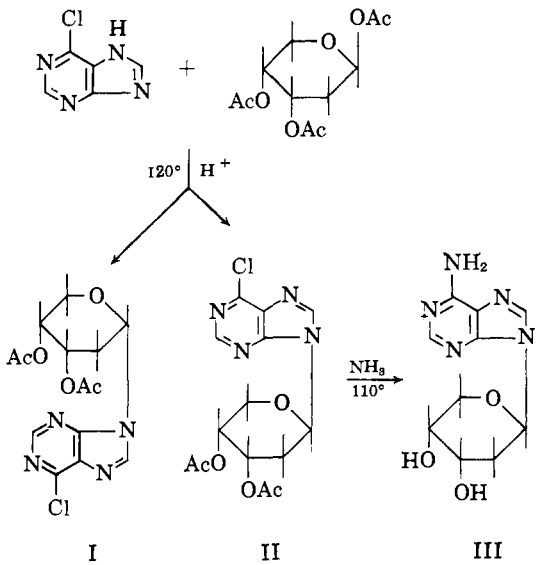
(6) T. Simadate, *ibid.*, **82**, 1268 (1961).
(7) T. Simadate, Y. Ishido, and T. Sato, *ibid.*, **82**, 938 (1961).
(8) Y. Ishido and T. Sato, *Bull. Chem. Soc. Japan*, **34**, 347, 1374 (1961).
(9) B. Helferich and E. S. Hillebrecht, *Chem. Ber.*, **66**, 378 (1933).
(9a) NOTE ADDED IN PROOF.—For recent application of the fusion method to nucleoside syntheses, see W. W. Lee, A. P. Martinez, G. L. Tong, and L. Goodman, *Chem. Ind.* (London), 2007 (1963).
(10) H. Venner and H. Zinner, *Chem. Ber.*, **93**, 137 (1960). A new and improved synthesis of this compound will be reported later.
(11) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954); see also A. G. Beaman and R. K. Robins, *J. Appl. Chem.* (London), **12**, 432 (1962).
(12) Correct analyses for carbon, hydrogen, and nitrogen have been obtained for all 2-deoxy-α- and -β-D-ribofuranosyl- and ribopyranosyl purines prepared.

furanosyl)purine, m.p. 155–156°, which shows $[\alpha]^{25}D$ +61.1° (H_2O), $\lambda_{max}^{H_2O}$ 263.5 mμ (ε 10,000), infrared bands 9.22 and 12.25 μ (lit.[13] m.p. 150–152°, $[\alpha]^{25}D$ +60.0° (H_2O), $\lambda_{max}^{H_2O}$ 264 mμ (ε 8869)). The concentrated filtrate gave 0.6 g. of 6-chloro-9-(2′-deoxy-β-D-ribofuranosyl)purine which was recrystallized from a small volume of ethyl acetate to yield 0.45 g. of colorless needles,[12] m.p. 144–145°, $[\alpha]^{25}D$ −10.8° (methanol), infrared bands at 8.77 and 10.75 μ, $\lambda_{max}^{H_2O}$ 264 mμ (ε 10,000) (lit.[13] m.p. 142–145°, $[\alpha]^{26}D$ −11.0° (methanol), $\lambda_{max}^{H_2O}$ 264 mμ (ε 8930)). These α- and β-anomers were readily distinguished on the basis of characteristic infrared bands.[13]

Similar acid-catalyzed fusion of purine[14] (2.77 g.) and 1,3,5-tri-*O*-acetyl-2-deoxy-D-ribofuranose[10] (12 g.) at 135–145° (30 min.) followed by deacetylation with methanolic ammonia gave a sirup which deposited crystals of crude nucleoside (1.7 g., mostly β-anomer), m.p. 171–174°, from methanol. The methanolic filtrate gave an additional 1.1 g. of crystalline nucleoside, m.p. 120–130° (largely α-anomer). The identification of these products as the α- and β-anomers of 9-(2′-deoxy-D-ribofuranosyl)purine was readily made in each case after an additional recrystallization by comparison of data recorded for these compounds prepared by another route.[13]

This general synthetic procedure has been found to be applicable equally well to the preparation of purine



2′-deoxy-D-ribopyranosides. This represents the first example of the preparation of a purine pyranosyl nucleoside by the fusion procedure.

6-Chloropurine (1.54 g.) and 1,3,4-tri-*O*-acetyl-2-deoxy-β-D-ribopyranose[15,16] (2.60 g.) were thoroughly mixed and heated at 115–120° (oil bath) until a light yellow melt was obtained. Then *p*-toluenesulfonic acid (20 mg.) was added and the contents were heated at 120° *in vacuo* for 15 min. The residue was dissolved in 125 ml. of warm ethyl acetate and the solution was filtered to remove unreacted 6-chloropurine (0.20 g.). The ethyl acetate solution, after washing, was finally concentrated to a tan sirup. This sirup was dissolved in 50 ml. of absolute ethanol which, upon cooling, deposited 1.28 g. of a crystalline anomeric mixture of 6-chloro-9-(3′,4′-di-*O*-acetyl-2′-deoxy-α- and -β-D-ribopyranosyl)purines,[12] m.p. 178–184°. The ultraviolet absorption, $\lambda_{max}^{methanol}$ 263.5 mμ (ε 9900) is indicative of 9-substitution.[17,18] Separation of anomers was accomplished by fractional crystallization from absolute ethanol to give 0.88 g. of the more ethanol-insoluble isomer[12] (I), m.p. 206–207°, $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 8890), $\lambda_{max}^{pH\ 11}$ 264 mμ (ε 10700), $[\alpha]^{26}D$ +22.4° (*c* 0.75, acetone). The ethanolic filtrates were combined and evaporated to dryness. The solid residue was crystallized several times from methanol to yield 0.18 g. of white needles[12] (II), m.p. 149–150°, $[\alpha]^{26}D$ −28.3° (*c* 1.0, ethyl acetate).

The assignment of I as 6-chloro-9-(3′,4′-di-*O*-acetyl-2′-deoxy-α-D-ribopyranosyl)purine and II as 6-chloro-9-(3′,4′-di-*O*-acetyl-2′-deoxy-β-D-ribopyranosyl)purine is tentative as far as the anomeric configuration is concerned. Proton magnetic resonance spectra of I and II in $CDCl_3$ show clearly two acetylmethyl groups at δ 1.95 and 2.1, respectively. The presence of two protons at C-2 is indicated by the fact that the C-1 proton is split into two doublets in the δ 5.7–5.9 region. Treatment of 6-chloro-9-(3′,4′-di-*O*-acetyl-2′-deoxy-β-D-ribopyranosyl)purine (II, 400 mg.) with methanolic ammonia at 110° gave 210 mg. of crystalline 6-amino-9-(2′-deoxy-β-D-ribopyranosyl)purine (III). Recrystallization from methanol and water gave 120 mg. of pure[12] III, m.p. 266–267°, $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 17100), $\lambda_{max}^{pH\ 13}$ 258.5 mμ (ε 17100), $[\alpha]^{26}D$ −17.0° (*c* 0.6, water), R_f 0.26, R_{ad} 0.56 (*n*-butyl alcohol–water 86:14). Compound III was shown to be identical with a product assigned the structure 9-(2′-deoxy-β-D-ribopyranosyl)-adenine recently prepared[19] by the mercury salt procedure (lit.[19] m.p. 262–264°, $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 16,600), $\lambda_{max}^{pH\ 13}$ 259.5 mμ (ε 16,400), $[\alpha]^{20}D$ −17.8° (*c* 0.58, water), R_f 0.27, R_{ad} 0.60 (*n*-butyl alcohol–water 86:14). Acidic hydrolysis of III revealed the presence of adenine and 2-deoxy-D-ribose which were identified by paper chromatography in several solvent systems.

The direct attachment of the 2-deoxy-D-ribopyranosyl and 2-deoxy-D-ribofuranosyl functions to various purines and other related heterocycles by this simple procedure is presently under investigation in our laboratory.

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DEPARTMENT OF CHEMISTRY
ARIZONA STATE UNIVERSITY
TEMPE, ARIZONA
MORRIS J. ROBINS
WILLIAM A. BOWLES
ROLAND K. ROBINS

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The Direct Utilization of Glycals for the Preparation of Purine Deoxynucleosides[1]

Sir:

We wish to report the first recorded synthesis of a heterocyclic nucleoside by direct utilization of a glycal in an acid-catalyzed fusion reaction. This simple procedure avoids the necessity of synthesis of the usual 2-deoxy halosugar (often prepared from the glycal) and would appear to compete favorably with other known synthetic methods. The suggestion for the use of glycals in a direct alkylation of the purine ring was first made by Robins, *et al.*,[2] in a model study with

(1) Supported by research grants CY-4008(C4) and CA 04008-06 from the National Cancer Institute of the National Institutes of Health, Public Health Service.
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