nitrophenylhydrazone (m.p. 119.5–120.5°) was prepared from each acetal. Mixed melting points with an authentic sample[7] showed no depression.

Apparently this reduction is of general applicability. The orthoformic, orthoacetic, and orthovaleric ethyl esters, prepared from the nitriles, were converted to the corresponding acetals in good yields.

An article giving detailed results of our experiments will be submitted in the near future.

[7] *Cf.* C. D. Hurd and L. L. Gershbein, THIS JOURNAL, **69**, 2328 (1947).

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ACID TRANSFORMATION PRODUCTS OF LEUCOVORIN

Sir:

Communications from these laboratories[1] have described the synthesis of a formyltetrahydropteroylglutamic acid, leucovorin (I), with activity for *Leuconostoc citrovorum* 8081.[2] From our chemical studies on the pure crystalline vitamin, we have concluded that the probable structure of leucovorin is 5-formyl-5,6,7,8-tetrahydropteroylglutamic acid.[3] During this investigation we have isolated and characterized several acid transformation products of I.

At *p*H 1.3 or below, leucovorin yielded isoleucovorin chloride (II), repeatedly crystallized by solution in 12 *N* hydrochloric acid and dilution to 2 *N;* boat-shaped crystals; n_L, 1.508 ± 0.004; n_S, 1.84 ± 0.01; m.p. 250–251° (dec.). *Anal.* Calcd. for $C_{20}H_{22}N_7O_6Cl$: C, 48.8; H, 4.51; N, 19.9; Cl, 7.21; CHO, 5.90.[4] Found: C, 49.4; H, 4.73; N, 20.2; Cl, 7.32; CHO, 5.74 (corrected for 6% water, Karl Fischer titration). Crystallization of II at *p*H 2 yielded anhydroleucovorin-A (III), hair-like needles from 0.01 *N* hydrochloric acid; parallel extinction: n_S, 1.63; n_L, 1.87; oblique extinction (30°): n_S, 1.48; n_L, >1.90; m.p. (anhydrous form) 250–257° (dec.). *Anal.* Calcd. for $C_{20}H_{21}N_7O_6 \cdot 4H_2O$: C, 45.5; H, 5.42; N, 18.6; CHO,[4] 5.50; H_2O, 13.7. Found: C, 45.4; H, 5.44; N, 18.6; CHO, 5.68; H_2O, 13.4. II or III at *p*H 4 (hot) gave anhydroleucovorin-B (IV), tablets; n_S, >1.90; n_L, 1.57; anhydrous form, non-melting below 330°. *Anal.* Calcd. for $C_{20}H_{21}N_7O_6 \cdot 1/2H_2O$: C, 51.7; H, 4.78; N, 21.1; CHO,[4] 6.25; H_2O, 1.94. Found: C, 51.7; H, 4.68; N, 21.1; CHO, 6.22; H_2O, 1.6 (by Karl Fischer titration). In 0.1 *N* hydrochloric acid II, III and IV exhibit a maximum at 355 $m\mu$ ($T = 35 \pm 1\%$, 10 mg./liter); in anaerobic sodium hydroxide solution each is converted to leucovorin in high yield.

Chemical and physical evidence indicate that II, III and IV are representatives of a new class of tetrahydropteroylglutamic acid derivatives, in which an imidazoline or imidazolidine ring has been formed linking the N^5- and N^{10}-positions by a single carbon bridge derived from the formyl group. Such ring compounds may be intermediates involved in the synthesis of leucovorin.[1]

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[1] J. A. Brockman, Jr., *et al.*, THIS JOURNAL, **72**, 4325 (1950); B. Roth, *et al.*, *ibid.*, in preparation.

[2] H. E. Sauberlich and C. A. Baumann, *J. Biol. Chem.*, **176**, 165 (1948).

[3] W. Shive, *et al.*, proposed the structure 5-formyl-5,6,7,8-tetrahydropteroylglutamic acid for "folinic acid-SF"; 119th meeting, American Chemical Society, Boston, Mass., April, 1951.

[4] Formic acid is liberated by the drastic acid hydrolysis in the usual analysis for the formyl group.

CATION EXCHANGE EQUILIBRIA

Sir:

In a recent valuable paper on cation exchange equilibrium, Lowen and associated authors[1] discuss a paper by Krishnamoorthy, Davis, and Overstreet.[2] Apparently two misconceptions are involved in this discussion. (a) The authors state "It should be mentioned, however, that the arbitrary substitution of equivalent fraction for mole fraction in the resin phase, in the equilibrium expression given by these authors (which may possibly be justified on the basis of the statistical nature of the exchange of ions among resin sites), results in decreased apparent hysteresis and more nearly constant values of K_a."

It should be pointed out that the terms used in the equation derived by Davis for the paper in *Science* represent moles (or, statistically, ions) and not equivalents (or, statistically, individual charges). This situation is more clearly represented in a detailed paper by Davis.[3]

(b) The work reported in THIS JOURNAL involved basic cation–hydrogen ion exchanges. Both in the *Science* paper cited and in another paper by Davis[4] it is shown that the exchange "constant" is probably not invariant for exchanges involving hydrogen ions. The statistical theory applies only to completely dissociated ions, so that the ion-exchanger bond strength is not a function of the concentration (at least to a first approximation).

I should like to comment that probably all successful attempts to formulate theoretical ion exchange equations represent only approximately adequate working hypotheses, which may have considerable heuristic value in relation to physical intuition. It is doubtful that any such equations are completely adequate. We may except, of course, those expressed in terms of activities, but, as Lowen and his group point out, this result is unavoidable in view of the circular dependency of K_a and the a values.

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[1] W. K. Lowen, R. W. Stoenner, W. J. Argersinger, Jr., A. W. Davidson and D. N. Hume, THIS JOURNAL, **73**, 2666 (1951).

[2] C. Krishnamoorthy, L. E. Davis and R. Overstreet, *Science*, **108**, 439 (1948).

[3] L. E. Davis, *J. Colloid Science*, **5**, 71 (1949).

[4] L. E. Davis, *ibid.*, **5**, 107 (1950).