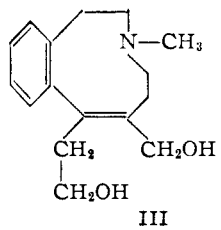
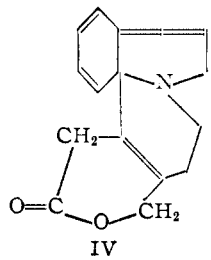
group.[4,5] Thus, des-N-methyl-apo-β-erythroidine, $C_{16}H_{17}NO_2$ (m.p. 167.5–169°, found C, 75.06; H, 6.71) gives formaldehyde on ozonolysis and shows a peak at 10.82 μ which is absent in its dihydro derivative, $C_{16}H_{19}NO_2$ (m.p. 130–130.5°, found C, 74.95; H, 7.71; —C—CH_3, 5.58). Likewise, the Hofmann degradation product of the dihydro derivative (found C, 74.92; H, 7.98) has a peak at 11.00 μ which is absent in its hydrogenation product, $C_{17}H_{23}NO_2$ (found C, 74.22; H, 8.46).

Structure I for β-erythroidine can be deduced from new evidence establishing III as the structure of the Hofmann degradation product of dihydro-β-erythroidinol.[3] This product undergoes slow hydrogenolysis of the allylic hydroxyl to yield a desoxy derivative, $C_{16}H_{23}NO$ (m.p. 89–90.5°, found C, 78.24; H, 9.36; —C—CH_3, 2.66). Further Hofmann degradation of the desoxy derivative gives an oil, $C_{17}H_{25}NO$ (found C, 78.48; H, 9.64), having peaks at 10.03 and 11.02 μ which are absent in the corresponding dihydro derivative, $C_{17}H_{27}NO$ (found C, 77.99; H, 10.50). This dihydro derivative, on a further Hofmann degradation, yields a nitrogen-free product, $C_{15}H_{20}O$ (found C, 82.78; H, 9.24) having peaks at 10.01 and 11.10 μ which are again absent in its hydrogenated derivative, $C_{15}H_{22}O$ (found C, 82.30; H, 10.19). Ozonolysis of this final hydrogenation product yields methyl ethyl ketone, whose identity is established by comparison of its 2,4-dinitrophenylhydrazone with an authentic sample. The presence of two —CH_2—CH_2— groups attached to the nitrogen supports the conclusion made previously with apo-β-erythroidine, and the isolation of methyl ethyl ketone shows the arrangement of the lactone ring with respect to the nitrogen.

Finally, when des-N-methyl-dihydro-β-erythroidinol (III) is subjected to exhaustive methylation without prior hydrogenation, a nitrogen-free product, $C_{15}H_{18}O_2$ (m.p. 84–86°, found C, 78.18; H, 7.58) results which readily gives a tetrahydro derivative, $C_{15}H_{22}O_2$ (found C, 76.79; H, 9.56). Permanganate oxidation of this tetrahydro derivative gives *o*-ethylbenzoic acid, identified by comparison of its infrared spectrum with that of an authentic sample, and establishes III as the correct structure.



III



IV

Since β-erythroidine serves as precursor for both II and III, structure I would appear to be the only logical possibility for it. This formulation shows for the first time the close chemical relationship between β-erythroidine and the other erythrina alkaloids.[6] Recent suggestions[7,8a,b] regarding the structure of β-erythroidine find no support in our experiments.[9]

(4) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. Sutherland, *J. Chem. Soc.*, 915 (1950).

(5) Because apo-β-erythroidine and certain of its derivatives show absorption in the 10 μ region, only the terminal methylene peak in the 11 μ region is informative for the Hofmann degradation products of this series.

(6) G. W. Kenner, H. G. Khorana and V. Prelog, *Helv. Chim. Acta*, **34**, 1969 (1951); M. Carmack, B. C. McKusick and V. Prelog, *ibid.*, **34**, 1601 (1951).

(7) C. Lapiére and R. Robinson, *Chem. and Ind.*, **30**, 650 (1951).

(8) (a) F. Koniuszy and K. Folkers, THIS JOURNAL, **73**, 333 (1951); (b) **72**, 5579 (1950).

(9) Although the methylation and oxidation experiments on desmethoxy-β-erythroidine reported by Koniuszy and Folkers (ref. 8b) are not in accord with our formulation, we have repeated their experiments and, in our hands, phthalic acid was isolated in 36% yield as the only oxidation product. Since desmethoxy-β-erythroidine, to which we assign structure IV, would be expected to undergo Hofmann degradation under the conditions employed for methylation, phthalic acid is a rational product of oxidation.

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PHOSPHONOUS AND PHOSPHONIC CATION EXCHANGE RESINS

Sir:

Cation exchange resins available up to the present time have consisted of three major types—those in which sulfonic, carboxylic, or phenolic acid groups have served as the source of the exchangeable cations. There have now been developed in this laboratory phosphonous[1] and phosphonic[1] cation exchange resins which show certain desirable chemical characteristics that are not found in any of the older exchangers.

Figure 1 shows the titration curve as obtained in 1 *N* sodium chloride solution by the "Direct Titration" method of Gregor and Bregman,[2] for a phosphonic exchanger having a total capacity of 8.8 meq./g. dry resin. It can be seen that the first ionization occurs at a *p*H slightly higher than that of a sulfonic acid resin, while the second one is at a *p*H intermediate between the carboxylic and phenolic types.[2] The *pK* valuesin dicated from this curve compare favorably with those found by Rumpf and Chavane[3] for aliphatic phosphonic acids. The phosphonous resins show titration curves identical with the first portion of the phosphonic type.

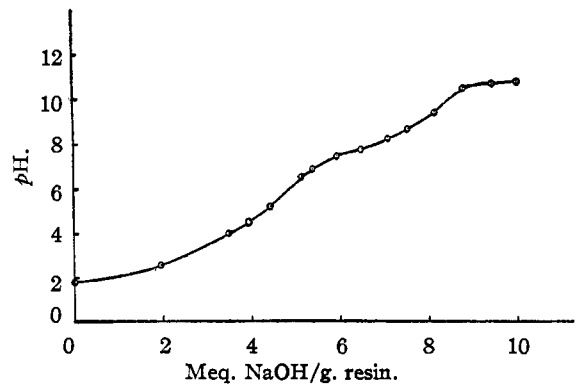

Fig. 1.—Titration curve of phosphonic acid cation exchange resin.

(1) Nomenclature follows that of Chemical Abstracts.

(2) H. P. Gregor, and J. I. Bregman, THIS JOURNAL, **70**, 2370 (1948).

(3) P. Rumpf, and V. Chavane, *Compt. rend.*, **224**, 919 (1947).

These resins are the first ones known to show a selectivity for sodium over potassium. This phenomenon and the subsequent inversion of the order of selectivity for the alkali cations as compared to sulfonic resins may be explained by a consideration of the polarizability of ionic groups and water as calculated by Teunissen and Bungenberg de Jong.[4] They found the order of polarizability to be: phosphate > water > sulfate. Since the order of polarizing ability of the alkali cations is Li > Na > K it would be expected that whereas in the sulfonic acid resins the volume sequence, as has been shown by Gregor, Gutoff and Bregman,[5] is Li > Na > K and consequently the order of preference for the alkali cations is K > Na > Li, in the case of the phosphonic resin the volume sequence should be K > Na > Li and the order of selectivity Li > Na > K. These volume and selectivity orders are in accord with values found in this laboratory for these resins and consequently the pressure-volume selectivity theory as expounded by Gregor[6] may be considered to apply to these systems when modified by the Teunissen–Bungenberg de Jong polarizability considerations. A detailed discussion of the experimental data together with the extension of this theory to carboxylic exchange resins will be given in a forthcoming paper.[7]

These resins show a volume increase of about 50% on going from the hydrogen to the sodium state. They are orange-yellow in the hydrogen state but show a striking color change to dark brown when placed in any of the alkali metal states.

Potential applications of phosphonous and phosphonic resins as a result of their unique properties include sodium depletion in physiological applications, rare earth separations, and use in mixed bed and reverse demineralization units.

(4) P. H. Teunissen and H. G. Bungenberg de Jong, *Kolloid Beihefte*, **48**, 80 (1938).
(5) H. P. Gregor, Fradelle Gutoff, and J. I. Bregman, *J. Colloid Science*, **6**, 3, 245 (1951).
(6) H. P. Gregor, THIS JOURNAL, **73**, 642 (1951).
(7) J. I. Bregman, and Y. Murata, in preparation.

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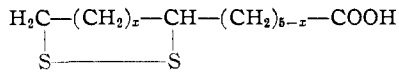
RECEIVED JANUARY 17, 1952

STRUCTURE OF PROTOGEN-A

Sir:

An unidentified growth factor for *Tetrahymena geleii* was first described in 1944 by Kidder and Dewey.[1] Using the test described by these workers it was found that several substances would produce a response in the organism.[2] These factors were called the "protogens."[2,3] The isolation of the sulfur-containing compound protogen-B from liver was described recently.[3] This compound (I) upon titration with sodium hydroxide was found to have a molecular weight corresponding to about 230 on the basis of one carboxyl group per molecule. Elementary analysis indicated the presence of 8 carbon and 2 sulfur atoms. When saponified with an excess of sodium hydroxide, I was converted to another compound (II) which gave a positive nitroprusside reaction and which contained one –SH group as indicated by titration with iodine. Reduction of I with sodium borohydride yielded a third compound (III) which contained two –SH groups as shown by iodine titration. Mild oxidation readily converted III to a disulfide (IV) as indicated by the disappearance of the nitroprusside reaction and by its reappearance on treatment with cyanide. Protogen-A[3] also gave a nitroprusside reaction after treatment with cyanide. A band at 1040 cm.$^{-1}$, present in the infrared absorption spectrum of protogen-B and indicating a sulfoxide group, was absent from the spectra of IV and of protogen-A. Protogen-A and IV appeared to be identical as shown by biological activity, liquid–liquid countercurrent distribution, paper chromatography and infrared absorption spectra. The absence of C-methyl groups in I was indicated by a negative Kuhn–Roth determination. Upon treatment of I with Raney nickel,[4] octanoic acid was obtained and identified by means of its infrared absorption spectrum, its melting point, and the X-ray powder photograph of its S-benzylthiuronium salt. These findings showed the probability of the following structure for IV, I being presumed to be a



sulfoxide. By the use of molecular models, a stable ring could be constructed for $x = 2$. The name "thioctic acid" is proposed for this structure ($x = 2$), a sulfur-containing organic acid with 8 carbon atoms. The synthesis of DL-thioctic acid with biological activity corresponding to that of the "protogens"[2] and the "lipoic acids"[5] is described in another communication.[6] Numerical prefixes indicating the position of the carbon atom to which the secondary sulfur is attached may be used to designate compounds in this series with different values for x.

(1) G. W. Kidder and V. Dewey, *Biol. Bull.*, **87**, 121 (1944).
(2) E. L. R. Stokstad, *et al.*, *Arch. Biochem.*, **20**, 75 (1949).
(3) E. L. Patterson, *et al.*, THIS JOURNAL, **73**, 5919 (1951).
(4) R. Mozingo, *et al.*, *ibid.*, **65**, 1013 (1943).
(5) L. J. Reed, *et al.*, *Science*, **114**, 93 (1951).
(6) M. W. Bullock, *et al.*, THIS JOURNAL, **74**, 1868 (1952).

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RECEIVED DECEMBER 26, 1951

SYNTHESIS OF *DL*-THIOCTIC ACID

Sir:

Thioctic acid,[1] a compound with the biological activity of protogen, was synthesized as follows: furylacrolein was hydrogenated to 2-tetrahydrofurylpropanol (I) over Raney nickel.[2] I was converted to 2-tetrahydrofurylpropyl chloride (II) with thionyl chloride and II was converted to γ-(2-tetrahydrofuryl)-butyric acid (III).[3] III was converted to a mixture of 5-hydroxy-8-iodocaprylic

(1) J. A. Brockman, Jr., *et al.*, THIS JOURNAL, **74**, 1868 (1952).
(2) A. Hintz, *et al.*, *Ber.*, **76**, 676 (1943).
(3) H. Gilman and H. P. Hewlett, *Rec. Trav. Chim.*, **51**, 93 (1932).