The pK_1 value of glycyl-L-valine is intermediate, and it is difficult to say whether this represents the ionization of a more basic amide hydrogen than that of glycylglycine, a more acid proton from the hydration sphere of the divalent nickel ion than that of glycylsarcosine or glycylproline, or a mixture of both. The inductive effect of the valyl residue should make the removal of the amide hydrogen more difficult. In any event it is clear that for glycyl-L-valine the ionization of the amide hydrogen is significantly suppressed, with no concurrent change in metal binding capacity, by comparison with all the other compounds containing ionizable amide hydrogens. Examination of molecular models indicates that the chelation to the oxygen of the amide bond is not restricted in glycylvaline, whereas chelation to the amide nitrogen is sterically hindered. The normal log k_1 value and the high value of pK_1 are thus consistent with the postulate, originally made for cupric ion,[3] that the initial chelating point is the amide oxygen with a transfer to the amide nitrogen on titration of the amide hydrogen.

It is difficult to reconcile the observation that, at equimolar or higher ratios of peptide to nickel(II) ion, 2 additional equivalents per metal ion are titrated in triglycine and 3 in tetraglycine, with any postulate other than ionization of peptide hydrogens. If the ionizations were due to the formation of a hydroxo complex, it would not be expected that a greater number of ionizations occur for tetraglycine, for its nickel complex should be the more extensively chelated, thereby reducing the number of sites on the metal ion available for the formation of the hydroxo complex.

The successive ionization constants pK_1 and pK_2 for glycylglycine, glycylvaline, valylglycine and glycylglycine ethyl ester are approximately statistical. For glycinamide, triglycine and tetraglycine the successive ionization constants are markedly less than statistical, the ionization is accompanied by an increasing yellow color, and in the case of tetraglycine a definite time interval is required for the attainment of equilibrium. These facts imply that a profound molecular rearrangement occurs on the titration of the amide hydrogens for these three compounds; apparently a change in configuration of the nickel(II) ion from octahedral to planar. Thus after the peptide ionizations tetraglycine wraps around the four corners of the plane with a nitrogen at each corner forming an equimolar complex even in solutions with a tetraglycine to nickel(II) ratio greater than unity.

The curves of Fig. 2 graphically illustrate that the binding of tetraglycine is greater for copper than for nickel, as is indicated by the larger value of log k_1 for copper in Table I. However, because of the less than statistical ionizations of the Ni(II)–tetraglycine complex, the buffer capacity is extraordinarily high, the curves of Fig. 2 cross and the last equivalent is titrated at a lower pH for the nickel than for the copper complex, which shows a "normal" spacing between the successive pK's. Thus in the last two rows of Table I, K_3 is 16 times greater for the nickel complex, even though k_1 is 25 times greater for the copper complex. This reversal is consistent with the suggestion that a change in configuration has occurred in the tetraglycine complex of nickel upon the ionization of the peptide hydrogens. In the series diglycine, triglycine, tetraglycine, the values of pK_1 tend to increase for copper(II)[2] and decrease for nickel(II) ion.

Glycinamide apparently is also able to induce the planar configuration in nickel(II) ion with the ionization of two amide hydrogens. However, the intensity of the spectra is considerably less than for tri- or tetraglycine. All of these spectra are similar to that reported for the planar 1:2 nickel(II) complex of 2,3-dimethyl-2,3-diaminobutane where the molar extinction coefficient is 64 at 434 mμ.[10]

Glycylglycine does not give the less than statistical ionizations or the yellow color, indicating that the planar configuration is not attained in this case. Unlike the complex of glycinamide, the complex of glycylglycine has additional coördinating groups of apparently sufficient strength to maintain the octahedral field. The observation of a similar situation in glycylglycine ethyl ester indicates that these additional coördinating ligands need not be charged to maintain an octahedral configuration.

Acknowledgments.—The authors thank Dr. Walter L. Koltun and Miss Reta Roth for the gift of glycylsarcosine. We also thank Dr. Frank R. N. Gurd for interesting discussions.

CAMBRIDGE 38, MASSACHUSETTS

(10) F. Basolo, Y. T. Chen and R. K. Murmann, THIS JOURNAL, **76**, 956 (1954).

COMMUNICATIONS TO THE EDITOR

POTENTIAL HYPOSENSITIZING AGENTS AGAINST POISON IVY DERMATITIS. A NEW SYNTHESIS OF HYDROURUSHIOL (3-PENTADECYLCATECHOL)

Sir:

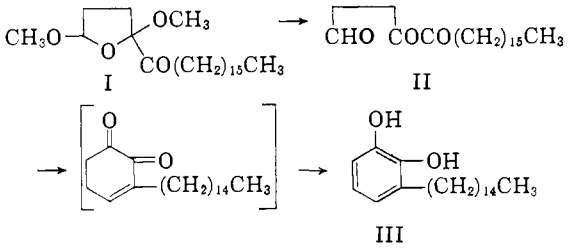
The high incidence each summer of dermatitis due to poison ivy and related members of the species *Rhus toxicodendron* continues to spur research toward improved prophylactic agents.[1] It has been established that the allergens of poison ivy are hydrourushiol and its unsaturated analogs.[2] Similar phenolic allergens are present in other members of the family Anacardiaceae, such as the oriental

(1) F. A. Stevens, *J. Am. Med. Assn.*, **127**, 912 (1945); G. E. Gaillard, *N. Y. State J. Med.*, **56**, 2255 (1956); A. M. Kligman, *A. M. A. Arch. Dermatol.*, **78**, 47 (1958); Anon., *Chem. Wk.*, **84**, 39 (June 27, 1959).

(2) C. R. Dawson, *Trans. N. Y. Acad. Sci.*, **18**, 427 (1956).

lac, cashew, mango and ginkgo trees.[2-4] Cross-sensitivity between hydrourushiol and the extracts of other members of the Anacardiaceae[3,5] has been demonstrated and hydrourushiol exhibits some advantages over the natural extracts in reducing immunologic sensitivity to *Rhus toxicodendron* dermatitis.[6]

We have been impressed by the ease with which certain furan derivatives are hydrolytically rearranged to form catechol. For example, Vargha and co-workers[7] reported the formation of catechol from the cleavage product of *p*-toluenesulfonyl 2-acetofuranoxime and Clauson-Kaas and co-workers[8] described the hydrolysis and spontaneous recyclization of 2-acetyl-2,5-dimethoxytetrahydrofuran dimethylketal to catechol. It appeared of interest, therefore, to synthesize some furanoid precursors of the catechol toxins which would hydrolyze *in vivo* to provide a low and lasting concentration of the allergen. This Communication describes the synthesis of 2-heptadecanoyl-2,5-dimethoxytetrahydrofuran (I) and its hydrolytic rearrangement to hydrourushiol (III) *in vitro*.



Methyl 2,5-dimethoxytetrahydrofuroate[9] upon treatment with hexadecylmagnesium bromide gave 29% of 2-heptadecanoyl-2,5-dimethoxytetrahydrofuran (I, b.p. 175–180°(0.05 mm.); calcd. for $C_{23}H_{44}O_4$: C, 71.83; H, 11.53. Found: C, 72.01; H, 11.50), dotriacontane (m.p. 70–71°; reported[10] m.p. 70.16°) and a mixture of 2,5-dimethoxytetrahydro-2-furyl-bis-hexadecylcarbinol and its dehydration product (b.p. 250–260°(0.05 mm.)).

Hydrolysis of compound I by refluxing for 2 hours with 0.1 *N* hydrochloric acid in 65% aqueous dioxane solution yielded 75% of 3,4-diketoheneicosaldehyde (II, m.p. 45–46° from pentane; calcd. for $C_{21}H_{38}O_3$: C, 74.51; H, 11.32. Found: C, 74.84; H, 11.33). It gave a negative ferric chloride test and deteriorated rapidly in the presence of moist air or when heated under reduced pressure.

When the time of hydrolysis was extended to 24 hours hydrourushiol (III, isolated as the lead salt[11] in 37% yield) was obtained as colorless, waxy crystals, m.p. 57–58° (reported[11] m.p. 57.5–58.5°). The infrared spectrum was identical with that of an authentic sample of hydrourushiol.[12]

(3) H. Keil, D. Wasserman and C. R. Dawson, *Ann. Allergy*, **4**, 268 (1946).

(4) B. Loev and C. R. Dawson, THIS JOURNAL, **80**, 643 (1958).

(5) H. Keil, D. Wasserman and C. R. Dawson, *Science*, **102**, 279 (1945); H. Keil, D. Wasserman and C. R. Dawson, *Ind. Med.*, **14**, 825 (1945).

(6) H. Keil, D. Wasserman and C. R. Dawson, *J. Allergy*, **16**, 275 (1945); W. Cutting and G. Read, *Stanford Med. Bull.*, **16**, 149 (1958).

(7) L. Vargha, J. Ramonczai and P. Bite, THIS JOURNAL, **70**, 371 (1948).

(8) J. T. Nielson, N. Elming and N. Clauson-Kaas, *Acta chem. scand.*, **9**, 9 (1955).

(9) N. Clauson-Kaas and F. Limborg, *ibid.*, **6**, 551 (1952).

(10) A. W. Ralston, C. N. Hoerr and L. T. Crews, *J. Org. Chem.*, **9**, 319 (1944).

(11) B. Loev and C. R. Dawson, THIS JOURNAL, **78**, 6095 (1956).

(12) B. Loev, Dissertation, Columbia University, 1952.

RESEARCH DIVISION
ETHICON, INC. WERNER R. BOEHME
SOMERVILLE, NEW JERSEY

RECEIVED NOVEMBER 30, 1959

INTERPRETATION OF THE KINETICS OF ACID CATALYZED REACTIONS IN MODERATELY CONCENTRATED AQUEOUS ACIDS[1]

Sir:

With reference to the idea[2] that transition states for some acid catalyzed reactions may contain *several* molecules of water, one might expect the rate law

$$\text{rate} = k_\psi[S] = \frac{k}{K_{SH^+}}[S]h_0 a_{H_2O}{}^u \frac{f_S f_{BH^+}}{f_B f_\pm} \qquad (1)$$

and that plots of ($\log k_\psi + H_0$) against $\log a_{H_2O}$ should be linear. Examination of published data on some fifty reactions in 1 to 10*M* hydrochloric, sulfuric and perchloric acids has shown that such plots[3] generally are linear. Figure 1 is an example. The slopes vary and are taken to define a new parameter, *w*, characteristic of the reaction.

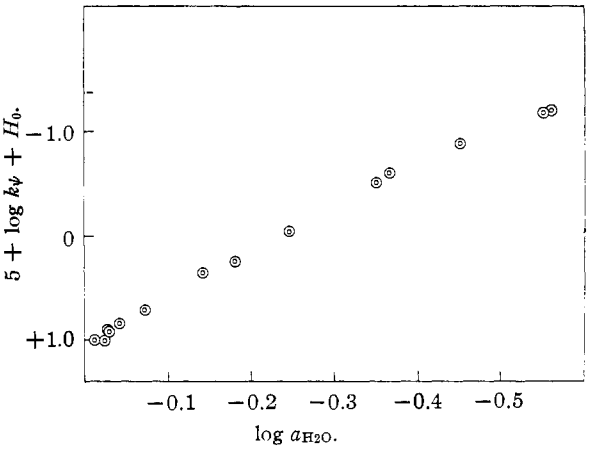


Fig. 1.—Hydrolysis of ethyl acetate in hydrochloric acid solutions; the slope, *w*, is 4.5; data of R. P. Bell, A. L. Dowding and J. A. Noble, *J. Chem. Soc.*, 3106 (1955).

The magnitude of *w* depends on the chemical function of water in the rate determining transition state. When no water is required for transformation of SH^+ to transition state, as in acetal hydrolyses, *w* is zero or a small negative value. When water acts as a nucleophile (hydrolysis of diethyl ether[4] or of carboxamides), *w* is about +2. When water functions as a proton transfer agent (enolization of acetophenone[5]), *w* is about + 5 to +7.

The size of *w* is thus indicative of mechanism. For example, *w* of *ca.* + 6 for γ-butyrolactone hydrolysis[6] shows that water acts as a proton

(1) Supported by the Office of Ordnance Research, U. S. Army, and by the National Science Foundation.

(2) J. A. Leisten, *Chemistry & Industry*, 397 (1959).

(3) When S is protonated to an appreciable extent at any acid concentration used, [$\log k\psi - \log [h_0/(h_0 + K_{SH^+})]$] is plotted against $\log a_{H_2O}$.

(4) J. Koskikallio and E. Whalley, *Can. J. Chem.*, **37**, 788 (1959).

(5) L. Zucker and L. P. Hammett, THIS JOURNAL, **61**, 2791 (1939).

(6) F. A. Long, F. B. Dunkle and W. F. McDevit, *J. Phys. Colloid Chem.*, **55**, 829 (1951).