1.07 g. (0.01 mole) of imidazoleacetonitrile and 0.1 g. of platinum oxide were added. After shaking for 30 hr., 390 ml. of hydrogen was consumed (calcd. 445 ml.). The reaction mixture was adsorbed on Dowex 50, eluted with 4*N* hydrochloric acid, and the eluate evaporated under diminished pressure. The crude crystalline product obtained (1.0 g.) was recrystallized from ethanol and melted at 247–248°. When mixed with a sample of histamine dihydrochloride of m.p. 247–248°, the m.p. was 247–248°.

*4(or 5)-(2-Aminoethyl)-1-β* D-*ribofuranosylimidazole (histamine riboside) dihydrochloride* (VII). *Catalytic reduction of imidazoleacetonitrile riboside.* The concentrated aqueous solution "A" (about 50 ml.) was acidified with 0.5 ml. of concd. sulfuric acid and shaken with hydrogen with addition of 0.6 g. of platinum oxide in two portions. The amount of absorbed hydrogen varied between 360 and 450 ml. (calcd. 890 ml.). Hydrolysis of a sample of the crude reduced solution by heating with 2*N* hydrochloric acid at 150° and chromatography (solvent as before, Pauly[14] test) showed the presence of histamine and imidazoleacetic acid (formed by acid hydrolysis of the cyano group) in about equal amounts.

The reduced solution, after removing most of the sulfuric acid with barium hydroxide, was filtered through a column of Dowex 50 $H^+$ and eluted with 2*N* hydrochloric acid. Evaporation of a typical sample, which had absorbed 360 ml. of hydrogen, gave 2.36 g. of a crystalline product. The theoretical yield, calculated from hydrogen absorption, was 2.56 g. of histamine riboside dihydrochloride.

Recrystallization from water-ethanol gave colorless crystals of m.p. 174–175° (Kofler stage).They are soluble in water, sparingly soluble in ethanol, acetone, or ethyl acetate.

*Anal.* Calcd. for $C_{10}H_{17}N_3O_4 \cdot 2$ HCl: C, 37.99; H, 6.06; N, 13.29; Cl, 22.43. Found: C, 37.65; H, 6.09; N, 13.25; Cl, 22.30.

*Acknowledgment.* This work was supported by a grant from the National Science Foundation. It is a pleasure to thank Drs. H. Tabor and H. G. Fletcher, Jr., for helpful discussions; Dr. H. Tabor for urinary imidazoleacetic acid riboside; Drs. H. G. Fletcher, Jr., and R. K. Ness for a supply of tribenzoylribose; Dr. W. C. Alford and Mr. H. G. McCann and their staff for the microanalyses; and Mr. W. Jones for the infrared absorption spectra.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ARIZONA]

# Structure of Soil Humic Acid. II. Some Copper Oxide Oxidation Products[1-3]

GISELE GREENE AND CORNELIUS STEELINK

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The oxidation of soil humic acid with aqueous alkaline cupric oxide produced a mixture of phenolic aldehydes and acids. A paper chromatographic analysis of the mixture revealed the presence of vanillin, *p*-hydroxybenzaldehyde, syringaldehyde, *p*-hydroxybenzoic acid, vanillic acid, 3,5-dihydroxybenzoic acid, and *m*-hydroxybenzoic acid. Samples of humic acid taken from three widely separated geographic regions all yielded the same products on degradation.

The co-occurrence of a resorcinol derivative (3,5-dihydroxybenzoic acid) with guaiacyl derivatives (vanillin, syringaldehyde, *etc.*) has not been previously reported in the studies of humic acid, and its presence cannot be rationalized on the basis of the commonly accepted theory that lignin is the precursor of soil humic acid. Many plant polyphenols and microbiological metabolites are structural derivatives of resorcinol, however, and occur in the zones of humification. The possible role of these substances in humic acid biosynthesis is discussed in the light of these experimental results.

Humic acid is a dark brown polymeric substance which occurs in the organic matter of soils and composts. It may contain 0–4% fixed nitrogen and be chelated to a variety of metallic ions in the soil. The presence of phenolic hydroxyl and carboxyl groups has been established, but little is known about the chemical structure of this acid.

Oxidative degradation[4-8] of humic acid yields a variety of phenols, phenolic aldehydes and phenolic acids, all of which can be obtained from lignin by the same chemical treatment. Although the bulk of the chemical evidence seems to favor the lignin-origin theory[9] for the biosynthesis of humic acid, recent work[2] in this laboratory indicates other possibilities. From a potassium hydroxide fusion of soil humic acid, we were able to isolate resorcinol, a phenol associated with breakdown products of plant polyphenols other than lignin, as well as with breakdown products of microbiological metabolites. To further investigate the nature of the phenolic degradation products, we decided to employ the mild oxidative technique of Pearl.[10a,b] The disadvantage of the potassium hydroxide fusion is that

(1) Presented at the 140th Meeting of the American Chemical Society, Chicago, Ill., September 7, 1961.

(2) The first paper in this series: J. W. Berry, A. Ho, H. E. Nordby, and C. Steelink, *Sci. Proc. Royal Dublin Soc.*, Series A, Vol. 1, 59–69 (1960).

(3) Abstracted from the master's thesis of Gisele Green, University of Arizona, 1961. This research was supported by the National Institutes of Health through Grant # RG-6058. Grateful acknowledgment is hereby made to the donors of this fund.

(4) J. M. Bremner, *J. Soil Sci.*, **5**, 214 (1954).

(5) S. S. Dragunov, N. N. Zhelokhovtseva, and E. I. Strelkeve, *Pochvovedenie (Pedology)* 409, (1948) (*C.A.*, **44**, 6995).

(6) G. C. Esh and S. S. Guha-Sircar, *J. Indian Chem. Soc.*, **17**, 326–331 (1940).

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(8) M. Schnitzler and J. R. Wright, *Can. J. Soil Sci.*, **39**, 44 (1959).

(9) W. Flaig, U. Schobinger, and H. Deuel, *Chem. Ber.*, **92**, 1973–82 (1959).

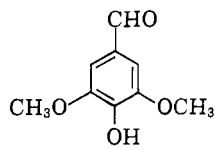
(10) (a) I. A. Pearl and D. L. Beyer, *J. Am. Chem. Soc.*, **76**, 6106 (1954); (b) *J. Am. Chem. Soc.*, **74**, 614 (1952).

many significant structural features of the original molecule are destroyed by the drastic conditions.

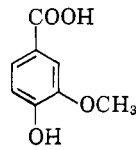
The present work reports the results of the cupric oxide–sodium hydroxide[10a,b] oxidation of soil humic acid.

## RESULTS

Humic acid,[11] extracted from a podzol-B soil sample taken from a Mendocino County (California) forest, was hydrolyzed with 2*N* hydrochloric acid to remove carbohydrate and mineral material. The residue from this hydrolysis was then oxidized with an aqueous mixture of sodium hydroxide and cupric oxide in a high-pressure stirring autoclave at 170° for three hours. The reaction mixture was successively extracted with ethyl ether at *p*H 6.5, *p*H 3.0, and *p*H 1.0. A chromatographic and spectrophotometric analysis of the ether extracts established the presence of the following compounds: vanillin (I), p-hydroxybenzaldehyde (II), syringaldehyde (III), vanillic acid (IV), *p*-hydroxybenzoic acid (V), *m*-hydroxybenzoic acid (VI), and 3,5-dihydroxybenzoic acid (VII).



III



V

The yields (see Table I) were low, but were comparable to those obtained by the analogous oxidation of lignin. As such they can be assumed to represent significant structural elements in the parent molecule. The data in Table I represent minimum concentrations, as the oxidation procedure itself destroys some of the aldehyde[7] and the successive chromatographic purifications entail some loss of final product. In addition to the compounds listed above, two well defined bands (Table II) appeared, which could not be unequivocally identified.

To eliminate the possibility that soil sampling technique or local impurities may have rendered the results of the experiments with the California sample spurious, we obtained humic acid material from two other sources. An analysis was carried out on a commercial low-nitrogen low-ash humic acid from Switzerland (supplied by FLUKA, Buchs, S. G. Switzerland); the results (Table I) indicated that the degradation products were the same as in the California sample, although the concentrations differed somewhat. A qualitative analysis was carried out on a sample obtained from a podzol-B soil from the Cheshire region in England[12]; the same compounds as described above were also detected in the degradation mixture.

TABLE I

ANALYSIS OF THE CALIFORNIA SAMPLE

| Compound | Degraded Residue, % | Fraction |
|---|---|---|
| Vanillin | 0.57 | C65 |
| *p*-Hydroxybenzaldehyde | 0.07 | C65 |
| Syringaldehyde | 0.05 | C65 |
| *m*-Hydroxybenzoic acid | 0.10 | C3 |
| *p*-Hydroxybenzoic acid | 0.05 | C3 |
| Vanillic acid | 0.41 | C3 |
| 3,5-Dihydroxybenzoic acid | 0.18 | C3 |
| ANALYSIS OF THE SWISS SAMPLE | | |
| *m*-Hydroxybenzoic acid | 0.08 | S3 |
| *p*-Hydroxybenzoic acid | 0.06 | S3 |
| Vanillic acid | 0.21 | S3 |
| 3,5-Dihydroxybenzoic acid | 0.21 | S3 |
| Vanillin | 0.01 | S65 |
| *p*-Hydroxybenzaldehyde | 0.01 | S65 |
| Syringaldehyde | Chromatographic evidence only | |

Pearl[10a,b] has pointed out that the yields from the cupric oxide oxidation procedure are very sensitive to reaction conditions. This might account, in part, for the variation in concentrations between the California and Swiss humic acids.

## DISCUSSION

This work constitutes the first report of the co-occurrence of lignin-derived products and resorcinol-derived products in the humic acid degradation mixture.[13] Although the total yield of identifiable product was low, the concentration of resorcinol-derived compounds was comparable to that of the guaiacyl-derived substances. It was assumed, therefore, that equal significance could be attached to the presence of both types of compounds.

The results indicate that lignin is not the only source material for humic acid synthesis, but that a variety of plant polyphenols could conceivably be incorporated into the final product. Also, on the basis of this evidence, one cannot exclude the intervention of microorganisms or the incorporation of their metabolites. Many such metabolites are structural derivatives of resorcinol and phloro-

(11) The term "humic acid," as used in this laboratory, refers to the alkali-soluble, acid and alcohol-insoluble fraction of the soil organic matter. Chemical uniformity of podzol-B humic acid is indicated by paper electrophoresis experiments, as reported by A. Burges at the VIIth Congress of the International Society of Soil Science, Madison, Wis., August 15, 1960.

(12) This sample was kindly provided by Professor Alan Burges, of the Department of Botany, University of Liverpool, England.

(13) The only previous report of the presence of resorcinol-derived compounds from a podzol-B forest soil was presented by D. E. Coffin, W. A. DeLong, and B. P. Wakentin at the VII Congress of the International Soil Science Society, Madison, Wis., 1960. These investigators found acids V, VI, and VII, as well as 2,4-dihydroxybenzoic acid. It is curious that they did not find any guaiacyl-derived compounds in their extracts. However, their soil extraction procedures differed markedly from those reported in this paper.

TABLE II

$R_f$ VALUES OF HUMIC ACID CONSTITUENTS (× 100)

| Substance[a] | Solv. 1 | Solv. 2 | PBW | Solv. D | U.V. | Color[b] / H.R.[c] | DSA[d] |
|---|---|---|---|---|---|---|---|
| Band 1, C | | | 35 | 91 | B-P | Y | Or |
| Band 1, S[b] | | | 35 | 91 | B-P | Y | Or |
| Vanillin | | | 35 | 90 | B-P | Y | Or |
| Band 2, C | | | 25 | 47 | P | Y | Y |
| Band 2, S | | | 25 | 47 | P | Y | Y |
| p-Hydroxybenzaldehyde | | | 25 | 48 | P | Y | Y |
| Band 3, C | | | 16 | 86 | P | Y | |
| Band 3, S | | | 14 | | P | Y | |
| Syringaldehyde | | | 15 | 85 | P | Y | |
| Band 4, C | 38 | 71 | | | P | | Y |
| Band 4, S | 37 | 70 | | | P | | Y |
| *p*-Hydroxybenzoic acid | 36 | 71 | | | P | | Y |
| Band 5, C | 40 | 83 | | | B-P | | Or |
| Band 5, S | 37 | 82 | | | B-P | | Or |
| Vanillic acid | 38 | 84 | | | B-P | | Or |
| Band 6, C | 38 | 23 | | | B | | Or-Br |
| Band 6, S | 38 | 25 | | | B | | Or-Br |
| 3,5-Dihydroxybenzoic acid | 38 | 23 | | | B | | Or-Br |
| Band 7, C | 40 | 66 | | | B-P | | Or-Y |
| Band 7, S | 35 | | | | B-P | | Or-Y |
| Band 8, C | 45 | 71 | | | B | | Y |
| Band 8, S | 41 | | | | B | | Y |
| Band 9, C | 55 | | | | B | | Y |
| Band 9, S | 55 | | | | B | | Y |
| *m*-Hydroxybenzoic acid | 55 | | | | B | | Y |

[a] C = California sample; S = Swiss sample. [b] B = blue; P = purple; Y = yellow; Or = orange; Br = brown. [c] Hydrazine reagent. [d] Diazotized sulfanilic acid.

gulicinol[14]; in addition, some molds have been shown to yield humic acid-like substances in laboratory tests.[15] However, it is highly improbable that soil microorganisms could be the sole formers of humic acid, in view of the preponderances of guaiacyl-derived compounds in the degradation mixtures.[16]

The results of this work would support the speculations of Davies, Coulson, and Lewis[17] and Kononova and Aleksandrova[15] that podzol humic acid is largely derived from plant phenols (including lignin) and compounds of microbiological origin. Copolymerization of these substances in the presence of ferric iron and phenoloxidases would result in the formation of an iron-humate complex, such as found in podzol-B horizons. A model for such a copolymer has been proposed by Kukharenko.[18]

Although this study was not primarily concerned with the incorporation of nitrogen into the humic acid molecule, certain results do have a bearing on this process. Some investigators[19] prefer to think of "pure" humic acid as nitrogen-free. In acid podzol soil, the nitrogen content is very low. Under other soil environments and *p*H conditions, it could conceivably incorporate nitrogen. Thus Bremner[20] has shown that lignin and humic acid will oxidatively fix nitrogen, while Brusset and Charpin[21] have shown that catechol, resorcinol, and pyrogallol will form humic-type substances with ammonia under oxidative conditions. It is significant that the phenols tested by Charpin and Brusset were exactly those which were found in our degradation mixtures.

It has been proposed that semiquinones or semiquinone-free radicals[22] are the active intermediates in the formation of humic acids; similar intermediates have been proposed for the polymerization of guaiacyl substances into lignin.[23,24,25] In

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(16) A. C. Neish, "Annual Review of Plant Physiology," Machlis and Briggs, editors, Vol. 2, Annual Reviews, Palo Alto, Calif. (1960).

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(18) T. A. Kukharenko and T. E. Vnedenskoya, *Khim. i Teknol. Topliva*, 6, 25–34 (1956); *Chem. Abstr.*, 50, 16005.

(19) A. Burges, *Sci. Proc. Royal Dublin Soc.*, Series A, Vol. 1, 53–59 (1960).

(20) J. M. Bremner, *J. Agric. Sci.*, 48, 352 (1956).

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(22) W. Flaig, *Sci. Proc. Royal Dublin Soc.*, Series A, Vol. I, 149–161 (1960).

(23) K. Freudenberg, *Angew. Chem.*, 68, 84 (1956).

(24) The existence of stable semi-quinone free radicals in lignin and humic acid has been recently reported by R. U. Rex in *Nature*, 188, 1186 (1960), who assumed that these intermediates are trapped in the macro-molecule. His studies were based on electron paramagnetic resonance measurements of alkaline solutions of lignin and humic acid.

(25) Unpublished work with solid humic acid samples in this laboratory shows significant concentration of organic free radicals based on electron paramagnetic resonance measurements.

the presence of amino acids or ammonia, these intermediates could readily react to form nitrogeneous derivatives. Thus, from soils of low carbon/nitrogen ratios, one could expect to find nitrogen containing humic acid, which would yield on potassium hydroxide fusion compounds such as indole and its derivatives. This has been reported by Flaig[26] for dark-earth humic acids, after the latter have been separated from protein material.

Thus, the results of degradative studies have shown the presence of two types of phenol derivatives in the humic acid molecule: guaiacyl and resorcinol. Their presence can be rationalized on the basis of a copolymerization process of a variety of plant and microbiological phenols, under oxidative conditions. It is obvious that nitrogen is not an essential part of humic acid, but may become an important constituent under changing soil environment. Further structural investigations are necessary before a more definitive explanation of the humification process can be advanced.

## EXPERIMENTAL

*Extraction and hydrolysis.* The extraction of humic acid from the soil with dilute aqueous base, and the subsequent acid hydrolysis procedure, have been previously described.[2] The water-insoluble residue from the acid hydrolysis was used in this study.

*Anal.* California Sample: C, 47.80; H, 3.90; N, 0.64; Ash, 16.4. Swiss Sample: C, 62.22; H, 4.95; N, 0.35; Ash, 2.29. English Sample: C, 52.77; H, 3.62; N, 0.51; Ash, 1.63.

*Oxidation.* To 185 ml. of water were added 37.3 g. of sodium hydroxide and 51.9 g. cupric sulfate. This slurry was transferred to a high speed stirring autoclave (200 ml. capacity); humic acid hydrolysate (6.13 g.) was then added to the mixture. The autoclave was flushed with nitrogen for several minutes and then heated to 170°C. and maintained at that temperature for 3 hr. (The Swiss sample was held at 170° for 5 hr.) After the reaction mixture had cooled to 90°, it was rapidly filtered. The aqueous alkaline solution was then subjected to fractionation as outlined below.

*Fractionation.* The filtrate from the oxidation mixture was adjusted to *p*H 6.5 with sulfuric acid and then extracted with ethyl ether in a continuous extractor for 24 hr. The ether extract was dried over magnesium sulfate and subsequently reduced to a small volume of viscous liquid by vacuum distillation. The residual liquid was finally dried in a vacuum dessicator and set aside for chromatographic studies.

The aqueous solution remaining from the above was adjusted to *p*H 3.0. A brown precipitate resulted, which was filtered and weighed. The clear filtrate at *p*H 3.0 was then extracted with ethyl ether as above; the dried ether extract was also set aside for chromatographic studies.

A similar procedure was carried out for the *p*H 1.0 fraction. The results of the oxidation and fractionation procedures are summarized in Table III.

*Chromatographic analysis.* The identification of all seven bands was made by analysis of chromatographic and spectrophotometric evidence as shown below.

The three separate ether extracts, at *p*H 6.5, *p*H 3.0, and *p*H 1.0 were analyzed by standard descending paper chromatographic methods. The aldehydes were completely contained in the *p*H 6.5 extract. A total of eleven solvent systems was necessary for the final separation; the four most effective systems are shown in Table II. Since relatively high temperatures were common in our laboratories, the $R_f$ values were consistently higher than corresponding literature values. Hence, authentic samples were used for co-chromatography with humic acid bands.

Abbreviations for the solvent system used in Table II and elsewhere are as follows: Solvent 1,[27] isopropyl alcohol-concentrated ammonia-water (8:1:1); Solvent 2,[27] benzene-propionic acid-water (2:2:1); PBW,[27] petroleum ether (b.p. 100–120°)-normal butyl ether-water (6:1:1); Solvent D,[28] benzene-2% formic acid (10:1); HAc,[29] 5% aqueous

TABLE III

FRACTIONATION OF HUMIC ACID

| | Weight in Grams | |
|---|---|---|
| | California Sample | Swiss Sample |
| Original weight of hydrolyzed humic acid | 6.13 | 5.91 |
| Residue recovered at *p*H 3 | 1.35 | 2.05 |
| Residue recovered at *p*H 1 | 1.06 | 1.34 |
| Weight of water-soluble products | 3.72 | 2.52 |
| Ether-soluble fraction | | |
| at *p*H 6.5 | 0.103 | 0.047 |
| at *p*H 3 | 0.394 | 0.334 |
| at *p*H 1 | 0.630 | 0.770 |
| Total ether-solubles | 1.13 | 1.15 |
| Percentage of water soluble products | 30.4% | 45.5% |

TABLE IV

SPECTRA OF HUMIC ACID OXIDATION PRODUCTS

| Substance | 95% Ethanol $\lambda_{max}$ mμ | Ethanol-KOH $\lambda_{max}$ mμ |
|---|---|---|
| Band 1, C | 230, 278, 308 | 250, 350 |
| Band 1, S | 232, 280, 310 | 248, 347 |
| Vanillin | 232, 280, 310 | 250, 350 |
| Band 2, C | 283 | 240, 335 |
| Band 2, S | 280 | 240, 335 |
| p-Hydroxybenzaldehyde | 284 | 240, 335 |
| Band 3, C | 233, 305 | 251, 363 |
| Band 3, S | — | — |
| Syringaldehyde | 232, 310 | 253, 367 |
| Band 4, C | 255 | 280 |
| Band 4, S | 255 | 280 |
| p-Hydroxybenzoic acid | 255 | 280 |
| Band 5, C | 261, 292 | 297 |
| Band 5, S | 261, 292 | 295 |
| Vanillic acid | 260, 290 | 297 |
| Band 6, C | 250, 308 | 322 |
| Band 6, S | 250, 310 | 320 |
| 3,5-Dihydroxybenzoic acid | 250, 310 | 320 |
| Band 7, C | 225, 268, 310 | 223, 263, 312 |
| Band 7, S | 227, 270, 310 | 227, 265, 310 |
| Band 8, C | 215, 249, 320 | 215, 245, 310 |
| Band 8, S | 215, 247, 320 | 215, 245, 310 |
| Band 9, C | 235, 297 | 310 |
| Band 9, S | 237, 298 | 312 |
| m-Hydroxybenzoic acid | 235, 297 | 313 |

(26) W. Flaig and Th. Breyhan, *Z. Pflanzenernahrung, Dungung, Bodenkunde*, 75, 132 (1956).

(27) R. J. Block, "Paper Chromatography and Paper Electrophoresis," 2nd ed., Academic Press, New York, 1958.

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(29) T. Anyos and C. Steelink, *Arch. Biochem. Biophysics*, 90, 63–67 (1960).

acetic acid. All the above developer ratios are volume for volume.

As the English humic acid reaction mixture was not quantitatively analyzed, the results of the analysis are not shown in Table II. However, all bands on the chromatograms of this mixture correspond exactly to those shown in Table II.

*Spectra.* In preparation for spectral measurements, the final purified eluates (from each chromatographic band described above) was half-banded on Whatman #1 paper; the band and blank cut from the other half of the paper were cut out and separately eluted with 70% ethanol. Spectral shifts in base were determined by adding three drops of 1*M* potassium hydroxide to the sample cuvette and the blank cuvette. Such shifts have been shown to be diagnostic in elucidating structural features.[30] The $\gamma_{max}$ values for the nine prominent bands are summarized in Table IV.

*Quantitative analysis.* The concentration of each compound listed in Table I was based on the amount of humic acid hydrolysate which reacted with cupric oxide-sodium hydroxide (water-soluble products). A quantitative estimation of each compound was obtained by comparing the optical density of its eluate (obtained from a known aliquot of the aqueous reaction solution) with the optical density of a standard solution of an authentic substance at the same wave length.

The determination of 3,5-dihydroxybenzoic acid illustrates the method used in this analysis. A 1.5-ml. aliquot of the ether extract was streaked on Whatman #1 paper. After development in solvent 1, the band at $R_f$ 0.38 was eluted; the eluate was concentrated and rechromatographed in solvent 2. The band at $R_f$ 0.23 was eluted; the eluate was half-banded on paper and developed in acetic acid. The band appearing at $R_f$ 0.60 in acetic acid solvent was cleanly separated from other bands, particularly vanillic and *p*-hydroxybenzoic acids. It was eluted (together with its blank) and the optical density of the eluate determined at 310 mμ in a Cary Recording Spectrophotometer. The optical density was compared to a standard curve which was derived from a solution of known concentration of 3,5-dihydroxybenzoic acid and which had been chromatographed in an identical manner to that described above.

All seven compounds obeyed Beer's Law in ethanol solution.

(30) O. Goldschmidt, *Anal. Chem.*, **26**, 1421 (1954).

TUCSON, ARIZ.

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[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES, U. S. VITAMIN & PHARMACEUTICAL CORP.]

# Pyridylethylbarbituric Acids

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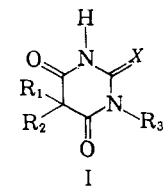
A series of 5-pyridylethylated barbituric acids has been synthesized and the effect of structure on ultraviolet absorption spectra and $pK_a$ noted. Several of these compounds markedly increased hexobarbital sleeping time.

For only a few basic structures has the relationship between structure and physiological activity been so extensively explored as for the barbiturates. Since Doran's recent review[1] many papers and patents[2] have evaluated new structural parameters including amino-substituted derivatives.[3] The 5-pyridylalkyl derivatives have, however, received scant attention, and have been limited to 5-picolyl substituents,[4,5] and 5-monosubstituted pyridylethyl derivatives.[6]

This study explores 5-pyridylethylated barbituric acids, which were varied[7] as shown for I. (Table I).



I

$R_1$ = 2-, 3-, and 4-picolyl-, [2-(2-, and 4-pyridyl)etyhl]-, [2-(5-ethyl-2-pyridyl)ethyl]-
$R_2$ = methyl and ethyl
$R_3$ = hydrogen, methyl, ethyl, allyl, butyl, and phenyl
$X$ = oxygen, sulfur, and imino

The requisite intermediates were obtained from the picolyl chloride and the substituted diethyl malonate,[4] or by pyridylethylation[8] of the malonate ester. These intermediate compounds are described in Table II.

(1) W. J. Doran, *Medicinal Chemistry*, Volume IV, Wiley, New York, 1959.

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