[CONTRIBUTION FROM THE CHANDLER LABORATORY OF COLUMBIA UNIVERSITY]

Synthesis in the Colchicine Field. The Preparation and Reactions of Dimethyl 2,3,4-Trimethoxybenzosuber-5-ene-6,7-dicarboxylate

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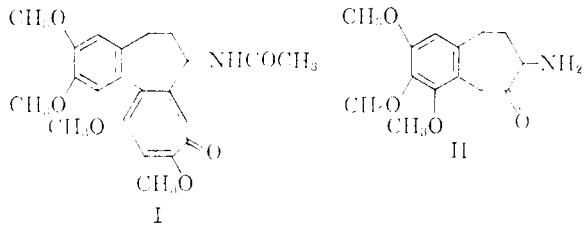
Dimethyl 2,3,4-trimethoxybenzosuber-5-ene-6,7-dicarboxylate was synthesized as an intermediate in a projected synthesis of colchicine. From the reactions of this compound and the examination of stereo models, it is concluded that the compound exists predominantly in one of the two possible conformations that the ring system may assume.

The total synthesis of colchicine (I) has recently been reported by two independent groups.[3,4] Both of these syntheses have followed the path

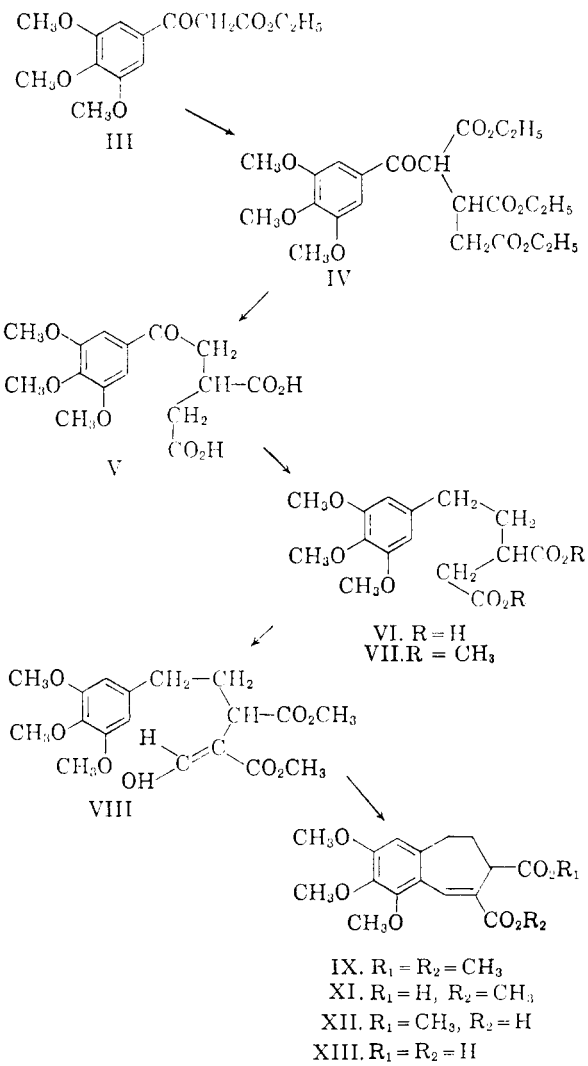


I II

of constructing the A—B ring system of colchicine before elaborating the carbon skeleton of ring C. The choice of such a sequence is based in part on the known susceptibility of tropolonoid systems to rearrangement[5] and, therefore, this most labile portion of the molecule is introduced only in the ultimate synthetic steps. This report is concerned with some of the results of a projected synthesis of colchicine which was directed along this general pathway.

Our initial aim at the outset of this work was to prepare the amino ketone II, the synthesis of which has since been reported by Buchanan and Sutherland.[6] To this end the following scheme was employed. 3,4,5-Trimethoxybenzoyl chloride was condensed with ethyl acetoacetate using sodium hydride as catalyst.[7]

Aminolysis of the condensation product produced ethyl 3,4,5-trimethoxybenzoylacetate[7] (III) which underwent addition to diethyl maleate in the presence of base. The Michael product IV, was a viscous red oil and it was hydrolyzed and decarboxylated to V without further purification. The ketonic carbonyl of V, was removed by catalytic



III IV V VI. R = H VII. R = CH_3 VIII

IX. $R_1 = R_2 = CH_3$
XI. $R_1 = H$, $R_2 = CH_3$
XII. $R_1 = CH_3$, $R_2 = H$
XIII. $R_1 = R_2 = H$

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(2) Abstracted from the Ph.D. thesis of David J. Goldsmith, Columbia University, 1958. The author is happy to acknowledge with thanks the guidance of Professor Gilbert Stork during the course of this research.

(3) E. E. van Tamelen, T. A. Spencer, Jr., D. S. Allen, Jr., and R. L. Orvis, *J. Am. Chem. Soc.*, **81**, 6341 (1959).

(4) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, and A. Eschenmoser, *Angew. Chem.*, **71**, 637 (1959).

(5) For a recent review of tropolone chemistry, see T. Nozoe in D. Ginsburg, "Non-Benzenoid Aromatic Compounds," Interscience Publishers, New York, N. Y., 1959, p. 339.

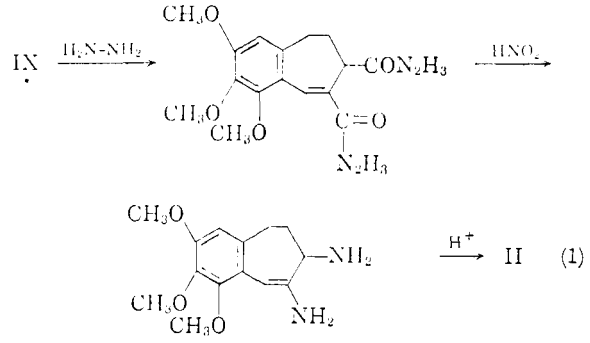
(6) G. L. Buchanan and J. K. Sutherland, *J. Chem. Soc.*, 2334 (1957).

(7) A previously reported preparation of the product of this reaction, ethyl 3,4,5-trimethoxybenzoylacetoacetate, using sodium ethoxide in ethanol as the catalyst [J. Koo, *J. Am. Chem. Soc.*, **75**, 720 (1953)] gave yields of less than 60% in our hands. Considerable quantities of ethyl 3,4,5-trimethoxybenzoate were always obtained. The modified procedure, however, gave essentially quantitative yields of the desired β-keto ester.

hydrogenation and the reduced diacid VI, was esterified with diazomethane to yield VII.

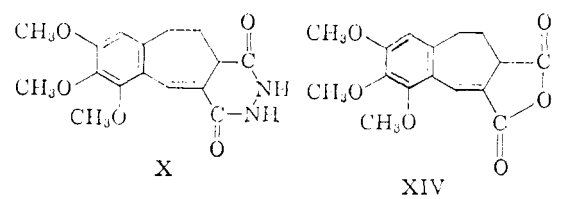
The formation of benzosuber-2-ene-3-carboxylic esters by condensation of substituted γ-phenylvaleric esters with oxalic or formic esters followed by acid catalyzed cyclization has been reported.[7,8] These procedures were applied to VII to yield initially the formyl ester VIII as a dark red oil. Treatment of VIII with polyphosphoric acid gave dimethyl 2,3,4-trimethoxybenzosuber-5-ene-6,7-dicarboxylate (IX). The expected bicyclic structure was consistent with both the ultraviolet spectrum and with the infrared spectrum which showed bands in the carbonyl region attributible to both saturated and unsaturated carbomethoxyl groups.

It was hoped that IX could be converted to the desired amino ketone *via* the pathway summarized in equation (I). Such a course, however,



(1)

could not be followed. The reaction of the diester IX with an excess of hydrazine hydrate in ethanol produced a high melting solid which was insoluble in dilute hydrochloric acid. Analysis of this product showed that only a single molecule of hydrazine had been incorporated and that both ester functions had been replaced. Although succinic acid and its derivatives easily form dihydrazides, both phthalic and maleic acids readily react with hydrazine to form cyclic monohydrazides.[9] From inspection of models it appears that the internuclear separation of the two carboxyl groups of IX closely approaches that of phthalic acid in one of the possible conformations that the compound may assume. If this conformation is the preferred one (*vide infra*) it is not surprising that the reaction product of IX with hydrazine is the cyclic monohydrazide X.



(8) E. C. Horning and J. Koo, *J. Am. Chem. Soc.*, **78**, 5830 (1951).

(9) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IV[B], Elsevier Publishing Co., New York, N. Y., 1959.

Our attention was then turned to a possible stepwise degradation of the benzosuberenedicarboxylic ester. The two carbomethoxyl groups of X should differ in their susceptibility to nucleophilic attack. It was expected that the conjugated ester would be the less readily saponified of the two. This view was based on the assumption that conjugation of the methoxylated aromatic ring to the olefinic ester would render this carboxyl less easily attacked by an anionic reagent (*e.g.*, OH^-) than its saturated neighbor. When the diester was treated with one equivalent of potassium hydroxide, in methanol a monosaponification product was obtained.[10] That the structure of this monoacid was XII rather than the expected structure XI, was shown by the following spectroscopic evidence. The longer wave-length band (5.99 μ) in the carbonyl region of the infrared spectrum of X was shifted to higher wave length (6.10 μ) on monohydrolysis. The position of the absorption band attributible to the saturated ester group of IX was unchanged. In addition, treatment of the monoacid with oxalyl chloride afforded an acid chloride which displayed only a single carbonyl absorption band at 5.82 μ. These results are only compatible with the presence of an olefinic acid since the acid chloride of a saturated carboxylic acid would produce an absorption band at 5.6 μ.[11]

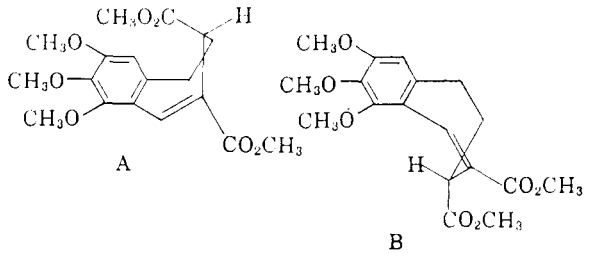
The finding that the unsaturated ester group is the more easily hydrolyzed of the two indicates that the double bond and the aromatic ring are not coplanar. On the basis of this conclusion it would be expected that the inductive effect of the double bond would render the conjugated carboxyl most susceptible to nucleophilic attack. Examination of Dreiding conformational models[12] shows that there is considerable angle strain associated with placing the ring and the double bond coplanar. Only two strain free conformations (A and B) of the benzosuber-2-ene system are possible,[13] and in both of these conformations the double bond lies out of the

(10) When the anhydride XIV was treated with potassium methoxide in methanol the same half hydrolysis product was obtained. This reaction proceeds to give the salt of the strongest acid possible; *i.e.*, the most stable base.

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., J. Wiley and Sons, Inc., New York, N. Y., 1958.

(12) W. Büchi, Glasapparatefabrik Flawil, Switzerland.

(13) α-Benzosuberone may exist in both boat and chair forms. In addition, the conformation in which the α-carbon and the ring are coplanar does not involve great angle strain. The nonbonded interactions which arise in this conformation, however, make it unfavorable with respect to others in which the carbonyl carbon is twisted out of the plane of the aromatic ring (*cf.* B. M. Wepster in W. Klyne and P. B. D. de la Mare, "Progress in Stereochemistry," Vol. 2, Academic Press Inc., New York, N. Y., 1958, p. 120). The benzosuber-2-ene system, in contrast, can only assume two *quasi*-boat conformations, A and B, in which the α-carbon is always out of the ring plane. Both of these conformations are rigid structures, and the conversion of one to the other is associated with great angle strain.

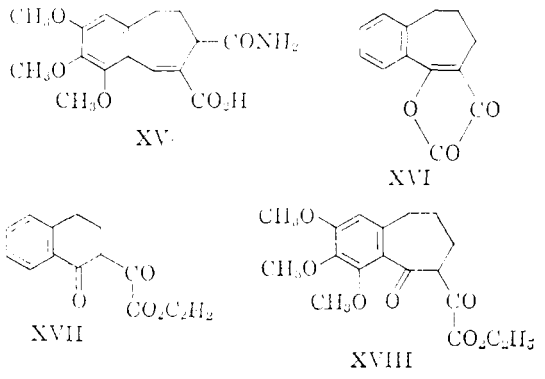


A B

plane of the aromatic ring by approximately 60°. In neither form, therefore, would resonance between the aromatic ring and the unsaturated ester be expected to contribute greatly to the properties of the molecule. Measurements from the models indicate that the carboxyl group of A lies closer to the aromatic nucleus than the preferred separation of aromatic rings in the crystal lattice.[14] B in contrast suffers from the lesser interaction of a hydrogen with the ring and would be expected, therefore, to be the favored conformational isomer. The finding that the diester (IX) forms a cyclic monohydrazide is in accord with this conclusion. More striking chemical evidence for the preference of conformation B was provided by the following. The diacid (XIII) was converted to the corresponding anhydride (XIV). When treated with warm aqueous ammonia the anhydride dissolved.[15] Careful neutralization of the basic solution produced a solid amino acid (presumably XV) which on standing for five to ten minutes in air at room temperature *completely reverted to the anhydride.* When the ammoniacal solution was acidified to *p*H 2 only the starting anhydride could be obtained. Since the anhydride is rapidly regenerated from the solid amino acid it seems reasonable to assume that this compound exists predominantly in the conformation in which the two carboxyl groups are closest.

It has been suggested by Gardner and Horton[16] that coplanarity of the aromatic ring and the double bond in a benzosuber-2-ene system is more easily achieved than in the corresponding dihydronaphthalene system. The basis of this suggestion is the finding that benzosuber-2-one reacts with ethyl oxalate to yield the enol lactone (XVI).

In contrast, α-tetralone gives only the glyoxalate (XVII).[17] An increase in resonance stabilization due to the greater ease of achieving coplanarity in XVI was suggested as the explanation for this difference in behavior between the two ketones. It appears, however, from inspection of conformational models that the dihydronaphthalene system is the more nearly planar of the two. The lack of enol lactone formation in XVII must then be attributible to an interaction of the *peri* groups in the transition state leading to lactonization. In agreement with this is the finding that 2,3,4-trimethoxybenzosuber-5-one forms only the simple glyoxalate (XVIII) in the analogous reaction.[16] In this case, the increased size of methoxyl over hydrogen causes an interference of the *peri* groups.



XV XVI XVII XVIII

EXPERIMENTAL[18]

3,4,5-Trimethoxybenzoyl chloride. 3,4,5-Trimethoxybenzoyl chloride was prepared from gallic acid by the procedure of Perkin and Weizmann.[19]

Ethyl 3,4,5-trimethoxybenzoylacetoacetate. The salt of acetoacetic ester was prepared by adding the ester (30 ml.) dropwise to a stirred suspension of sodium hydride (5.5 g.) in dry benzene (300 ml.). The system was kept under nitrogen and cooled in an ice bath. When all of the sodium hydride had reacted a solution of 3,4,5-trimethoxybenzoyl chloride (50 g.) in dry benzene (200 ml.) was added over 1 hr. The reaction was stirred overnight at room temperature. Absolute ethanol (50 ml.) was added to destroy any residual sodium hydride and, after 15 min. additional stirring, the benzene solution was extracted with cold 10% sodium hydroxide. Acidification of the aqueous solution with cold dilute hydrochloric acid precipitated an oil which solidified on standing. The crude product (70 g.) was used in the next reaction without further purification.

Ethyl 3,4,5-trimethoxybenzoylacetate (III). Ethyl 3,4,5-trimethoxybenzoylacetate was prepared according to the method of Koo.[19] From the above di-β-keto ester (60 g.) there was obtained an 80% yield (42 g.) of the benzoylacetate. Recrystallization from methanol gave plates: m.p. 93–94° (reported[19] m.p. 95°).

Triethyl α-(3,4,5-trimethoxybenzoyl)tricarbalyllate (IV). Sodium (2.3 g.) was dissolved in dry *t*-butyl alcohol (228 ml.). To this solution, under a nitrogen atmosphere, was added with stirring ethyl 3,4,5-trimethoxybenzoylacetate (65 g.). The mixture formed a gel which slowly dissolved on heating. When most of the gel had dissolved, diethyl maleate (42 ml.) was added, and the solution was refluxed for 2 hr. It was poured when cool into cold 10% potassium hydroxide (400 ml.) and extracted with ether. The aqueous solution was acidified with cold hydrochloric acid and the reddish oil which precipitated was taken up in ether. Removal of the ether after drying left a viscous red oil (81 g., 74%), which gave a deep red color with alcoholic ferric chloride.

(14) D. J. Cram, N. L. Allinger, and H. Steinberg, *J. Am. Chem. Soc.*, **76**, 6132 (1954).

(15) This procedure when applied to phthalic anhydride [E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1791 (1925)] readily yields phthalamic acid.

(16) P. D. Gardner and W. J. Horton, *J. Am. Chem. Soc.*, **75**, 4976 (1953).

(17) W. E. Bachman, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(18) Melting points are uncorrected. Analyses were performed by Schwartzkopf Microanalytical Laboratories, Woodside, New York.

(19) W. H. Perkin and C. Weizmann, *J. Chem. Soc.*, **89**, 1649 (1909).

β-Carboxy-γ-keto-γ-(3,4,5-trimethoxyphenyl)valeric acid (V). The triester IV (110 g.) was refluxed 15 hr. with 3 *N* hydrochloric acid (500 ml.). When cool, the dark aqueous solution was extracted with ether. The ether was dried and removed, leaving a dark red oil. This was triturated with ether and a light yellow solid separated. The solid acid was filtered and washed several times with cold ether. The dried material was a pale yellow powder (45 g., 57%). Recrystallization from ether gave fine needles: m.p. 153–158°; λ^{KBr} 5.9, 6.0 μ.

Anal. Calcd. for $C_{15}H_{18}O_8$: C, 55.21; H, 5.56. Found: C, 54.91; H, 5.49.

β-Carboxy-γ-(3,4,5-trimethoxyphenyl)valeric acid (VI). Reduction of V was carried out on the Parr apparatus by shaking a solution of the acid (45 g.) in glacial acetic acid (150 ml.) with 10% palladium on charcoal catalyst (5 g.). The shaking was continued for 3.5 hr. at 60° and an initial pressure of 60 lb. of hydrogen. Removal of the solvent and the catalyst left a clear oil which solidified on standing and was crystallized from water to yield powdery white crystals (37 g., 86%): m.p. 142–245°; λ^{KBr} 5.90, 5.95 μ.

Anal. Calcd. for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46. Found: C, 57.62; H, 6.49.

Methyl β-carbomethoxy-δ-(3,4,5-trimethoxyphenyl)valerate (VII). The diester was obtained from treatment of VI with either diazomethane (75% yield) or with methanol and sulfuric acid (87% yield). Crystallization from ether–petroleum ether (b.p. 30–60°) afforded colorless prisms: m.p. 55–58°, λ^{CHCl_3} 5.81 μ.

Anal. Calcd. for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.91; H, 7.17.

Methyl α-formyl-β-carbomethoxy-δ-(3,4,5-trimethoxyphenyl)-valerate (VIII). Potassium (5 g.) was dissolved in dry methanol (50 ml.) and the alcohol removed *in vacuo*. The alkoxide was dried at 150° for 1 hr. at oil pump vacuum and when cool, the solid mass was covered with dry ether and broken up. An atmosphere of nitrogen was maintained throughout. With the temperature at −20° a solution of VII (32 g.) and methyl formate (15 ml.) in ether was added dropwise over 1 hr.[18] The reaction mixture was allowed to warm to room temperature and then stirred for 4 hr. Ice and water added and the layers separated. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. Evaporation of this acidic fraction left a red oil (12 g., 34% conversion) which produced a deep red color with alcoholic ferric chloride. The neutral fraction yielded the starting diester (15 g.).

Dimethyl 2,3,4-trimethoxybenzosuber-5-ene-6,7-dicarboxylate (IX). Polyphosphoric acid was prepared from phosphorus pentoxide (40 g.) and 85% phosphoric acid (40 ml.). This solution was added to the α-formyl ester VII (5.5 g.) and stirred for ½ hr. at room temperature during which time it became deeply red in color. Ice and water were then added and a gummy solid precipitated. It was extracted into ether and the ether washed with cold 10% potassium hydroxide. The ether was dried and evaporated, leaving an oily residue which crystallized to give a light yellow solid (3.5 g., 66%). Recrystallization from ether-petroleum ether gave colorless prisms: m.p. 72–74°; $\lambda_{max}^{C_2H_5OH}$ 235,310 mμ (ε = 18,000, 23,000); λ^{KBr} 5.87, 5.99 μ.

Anal. Calcd. for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 62.13; H, 6.39.

When the diester was treated with either 85% or 100% hydrazine hydrate in ethanol a crystalline solid was obtained which was insoluble in dilute hydrochloric acid and did not melt below 250°. Analysis of the crude material checked most closely with a cyclic monohydrazide.

Anal. Calcd. for $C_{16}H_{22}O_5N_4$: C, 54.84; H, 6.33; N, 15.99 (Dihydrazide). Calcd. for $C_{16}H_{18}O_5N_2$: C, 60.37; H, 5.70; N, 8.80 (Monohydrazide). Found: C, 59.40; H, 5.43; N, 8.95.

2,3,4-Trimethoxybenzosuber-5-ene-6,7-dicarboxylic acid (XIII). The dimethyl ester (IX) (0.9 g.) was heated with 10% aqueous sodium hydroxide (25 ml.) under reflux for 3.5 hr. Any remaining neutral material was extracted with ether and the aqueous solution was acidified with dilute hydrochloric acid. Extraction with ether followed by drying and evaporation of the organic layer yielded the solid diacid (0.7 g., 85%). Recrystallization from ethyl acetate–cyclohexane afforded powdery crystals, m.p. 180.5–182.5°, λ^{KBr} 5.89; 6.10 μ.

Anal. Calcd. for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.93; H, 5.53.

Methyl 6-carboxy-2,3,4-trimethoxybenzosuber-5-ene-7-carboxylate (XII). IX (2 g.) was dissolved in 50% methanol (2 ml.). This solution was dropped rapidly into 50% methanol (10 ml.) containing equivalent of sodium hydroxide (0.224 g.). The temperature was maintained at 50°. As soon as the addition was complete (5 min.), ice and water were added and the unchanged ester was extracted with ether. After acidification the half-acid ester was taken up in ether. Evaporation of the ethereal solution left a pale yellow oil which crystallized on standing. Recrystallization from ethyl acetate–cyclohexane afforded colorless material (0.6 g.): m.p. 166–167°; λ^{KBr} 5.85, 6.10 μ. Mixed m.p. with the diacid (XII), 160–165°.

7-Carbomethoxy-2,3,4-trimethoxybenzosuber-5-ene-6-carboxylyl chloride. The half acid ester (XII, 0.5 g.) was dissolved in benzene (2 ml.) and oxalyl chloride (1 ml.) added. After standing at room temperature for 4 hr. the excess oxyalyl chloride and benzene were removed *in vacuo*. Benzene was added and stripped off again to remove an residual reagent. The remaining yellow-green oil showed a single carbonyl peak at 5.82 μ in the infrared (carbon tetrachloride).

2,3,4-Trimethoxybenzosuber-5-ene-6,7-dicarboxylic anhydride (XIV). Acetic anhydride (2 ml.) was added to the cyclic diacid (XIII, 0.1 g.) and the solution refluxed for 2 hr. After standing overnight at room temperature the excess acetic anhydride was removed *in vacuo*. The residual oil was washed with acetic acid and the acid removed again *in vacuo*. A light yellow oil remained (0.1 g.) which crystallized on standing. The infrared spectrum showed absorption typical of an anhydride; 5.5 μ and 5.75 μ.

Refluxing the anhydride with methanol for 20 min. effected no change. When treated with sodium methoxide in methanol (slightly more than 1 equivalent) an acidic substance was obtained. The infrared spectrum of this acid was superimposable with that of XII and the two monoacids did not show a depression on mixed melting point.

Reaction of XIV *with ammonia.* The anhydride (0.1 g.) was added in portions to a stirred solution of aqueous ammonia at 50–60°. A clear yellowish solution was obtained. Careful neutralization with dilute hydrochloric acid afforded a solid material (0.1 g.) which was filtered and rapidly dried. The infrared spectrum showed strong hydrogen bonded absorption in the 3 μ region, weak carbonyl peaks attributable to the anhydride and a new broad band at 6 μ. On standing for 5–10 min. at room temperature the solid reverted to the anhydride with loss of ammonia as shown by the infrared spectrum. When acidification was carried to *p*H 2 the solid material obtained showed only anhydride absorption in the infrared.

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