Notes

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Derivatives of D-Glucaric Acid[1]

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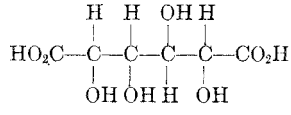
A general reaction of the glycaric acids is the formation of diamides by treatment of these acids with primary aliphatic amines.[2] These diamides are very labile to alkaline hydrolysis. In efforts to find diamides of D-glucaric acid,



less easily hydrolyzed by alkali, some aromatic diamides of D-glucaric acid have been synthesized. These derivatives were less labile to alkali and could be acetylated in good yields without hydrolysis of the amide linkage. This note describes the preparation of *p*-D-glucarotoluidide, 4′,4″-dihydroxy-D-glucaranilide, *p*-D-glucarotoluidide tetraacetate, 4′,4″-diacetoxy-D-glucaranilide tetraacetate.

EXPERIMENTAL[3]

Potassium acid glucarate. There were placed in an evaporating dish of suitable size, 800 g. of starch and 6.4 liters of nitric acid of specific gravity 1.100. The mixture was evaporated over a low flame in a fume hood to a volume of about 2 liters. The cooled solution was filtered and allowed to remain at 0° for 12 hr. Oxalic acid which crystallized out was separated by filtration, and the solution diluted with 2.4 l. of water; the solution was heated to boiling and neutralized to litmus with a saturated solution of potassium carbonate. The dark red solution was acidified to a pH of 4.5 with glacial acetic acid and evaporated to a volume of 1.5 l. The concentrated solution, which contained some crystals, was shaken with 800 ml. of 1:1 acetic acid solution. The precipitated product was collected, washed with several 200-ml. portions of 1:1 acetic acid solution, and purified by crystallization from hot water. The yield was 225 g. When sucrose was used, a yield of 34% based on sucrose was obtained. Analysis by conversion to the silver salt gave a purity of 97%.

Lactone of D-glucaric acid. To 460 g. (2 moles) of potassium acid D-glucarate there was added 500 ml. of distilled water containing 122 ml. of concentrated sulfuric acid. The mixture was allowed to stand until solution was complete. The solution was concentrated to a thick sirup under reduced pressure. The sirup was stirred with 4 l. of 95% alcohol, the potassium acid sulfate was separated in a Büchner funnel by filtration, and the solution concentrated as before. More potassium acid sulfate was removed by filtration. The sirup was dissolved in 500 ml. of distilled water and the solution again concentrated under reduced pressure to a sirup. The sirup was heated for 3 hr. on a boiling water bath under reduced pressure. The product was a slightly reddish sirup.

p-D-Glucarotoluidide (I). To 348 g. (2 moles) of D-glucaric acid lactone in 2 l. of boiling absolute alcohol in a 5-l. round bottom flask, there was added 500 g. (4.6 moles) of *p*-toluidine dissolved in 500 ml. of boiling absolute alcohol. Precipitation started immediately, and the mixture was stirred rapidly. After the addition of the *p*-toluidine, the mixture was stirred and heated to boiling until the mixture had concentrated to such a point that considerable bumping took place. The time required was 6 hr. The product was collected in a Büchner funnel and the crystals triturated with two successive 500 ml. portions of hot absolute alcohol and filtered. The product weighed 493 g., which represented a yield of 63% based on the lactone of D-glucaric acid. A sample for analysis was purified by crystallization from dioxane. Two recrystallizations gave a pure product which melted at 228°C.

Anal. Calcd. for $C_{20}H_{24}N$: C, 62.10; H, 6.20; N, 7.21. Found: C, 62.00; H, 6.40; N, 7.50.

4′,4″-Dihydroxy-D-glucaranilide (II). The procedure for the preparation of di-*p*-toluidide of D-glucaric acid was used in the preparation of this compound. The product was purified by recrystallization from hot water. The pure product melted at 290° C.

Anal. Calcd. for $C_{18}H_{20}O_8N_2$: C, 55.09; H, 5.13. Found: C, 55.26; H, 5.07.

p-D-Glucarotoluidide tetraacetate (III). There was placed in a 2 liter beaker 393 g. (1.01 moles) of di-*p*-toluidide of D-glucaric acid. To this was added 826 g. of pyridine and 806 g. (8 moles) of acetic anhydride. The mixture became very warm; the *p*-toluidine dissolved. The solution was allowed to remain for 20 hr. at room temperature. The solution was poured slowly into 3 l. of ice cold water with rapid stirring. After the mixture had been stirred for 6 hr., the granular precipitate was collected, dissolved in 2 l. of hot acetone, treated with Norite, filtered, and sufficient distilled water added to precipitate the product. The product weighed 446 g., a yield of 79% based on the di-*p*-toluidide of D-glucaric acid. A pure sample melted at 215° C.

Anal. Calcd. for $C_{28}H_{32}O_{10}N_2$: C, 60.42; H, 5.77; N, 5.03. Found: C, 60.68; H, 5.89; N, 5.27.

4′,4″-Diacetoxy-D-glucaranilide tetraacetate (IV). This compound was prepared from the di-*p*-hydroxyanilide of D-glucaric acid by the procedure described for the acetylation of (I). The product was purified by crystallization from alcohol. It melted at 193–4° C.

Anal. Calcd. for $C_{30}H_{32}O_{14}N_2$: C, 55.58; H, 5.00. Found: C, 55.81; H, 5.14.

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(1) This work was supported by a research grant AF33-(616)-409 from Wright Air Development Center.

(2) Dermer and King, *J. Org. Chem.*, **8**, 168 (1943).

(3) (a) All melting points were corrected: They were taken on a Fisher-Johns micro-hot stage.

(b) Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Chlorosulfonylation of 7-Hydroxy-4-methyl-8-acetylcoumarin and Its Methyl Ether

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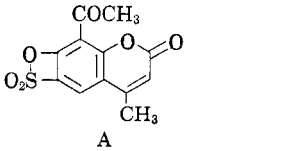
During the course of our investigations on the substitution reactions of benzopyrones, we had oc-

casion to study the chlorosulphonylation of 7-hydroxy-4-methyl-8-acetylcoumarin (I) and its methyl ether. When (I) was heated with one mole of chlorosulfonic acid at 100°, a monosulfonic acid (II) was obtained. Attempts to prove the position of the sulfonic acid group in (II) by bromination, nitration, hydrolysis, and oxidation failed to give definite products. However, the structure 7-hydroxy-4-methyl-8-acetylcoumarin-6-sulfonic acid was given to it by analogy with the sulfonation results of other 7-hydroxycoumarin derivatives.[1,2] Heating (I) with 2.5 moles of chlorosulfonic acid at 100° gave a disulfonic acid (III) and a crystalline neutral substance (IV) containing sulfur but no halogen.

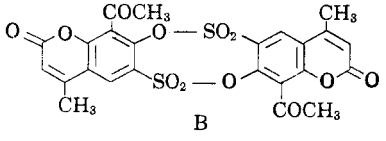
The disulfonic acid (III) was assigned the structure 7-hydroxy-4-methyl-8-acetylcoumarin-3,6-disulfonic acid. The substance (IV) did not give any coloration with alcoholic ferric chloride, whereas the original coumarin (I) gives a violet coloration. Further, the yield of (IV) was found to increase with an increase in the amount of chlorosulfonic acid used in the sulfonation. However, it could not be obtained by direct sulfonation of (II). A study of the properties of (IV) showed that it was quite stable in boiling water and could be crystallized in a pure state from benzene, alcohol, or dilute hydrochloric acid. It was nonacidic acid and did not form a sodium or a barium salt. It dissolved slowly in alkali and was also moderately soluble in sodium bicarbonate without effervescence. This solubility in weak alkalies may be attributed to the hydrolysis of the coumarin ring.

The analytical data ruled out the possibility of a sulfone structure for IV. A reference to literature showed that the other common possibility during sulfonation with chlorosulfonic acid was the formation of cyclic esters of sulfonic acids. These are usually formed in the sulfonation of phenols if there are substituents in the *o*- or *p*-positions in the original phenol.[3]

The analytical results for IV were in close agreement with those required for a cyclic ester. The presence of the ketonic group in the latter was shown by the formation of a 2,4-dinitrophenylhydrazone. The absence of a ferric chloride coloration with IV therefore indicated that the OH group in it was probably involved in an ester formation in one of the following ways:



A



B

A molecular weight determination by the Rast method favored structure B for IV. Such bimolecular compounds containing two ester linkages are termed sulfonylides[3], and accordingly IV was assigned the structure 7-hydroxy-4-methyl-8-acetylcoumarin-6-sulfonic acid sulfonylide.

Sulfonation of I at higher temperatures led to a mixture of sulfonic acids. The methyl ether of I could not be sulfonated completely with one or two moles of chlorosulfonic acid at 60°, whereas at higher temperatures or with excess of the sulfonating agent, the sulfonation was accompanied by complete demethylation.

EXPERIMENTAL[4]

7-Hydroxy-4-methyl-8-acetylcoumarin-6-sulfonic acid (II). A mixture of 2 g. of 7-hydroxy-4-methyl-8-acetylcoumarin (I)[5] and 0.6 ml. (1 mole) of chlorosulfonic acid was protected from moisture and heated on a steam bath for 3 hr. The residue obtained on pouring the reaction mixture over ice weighed 400 mg. and was found to be the unreacted coumarin (I) by a mixed melting point determination. The filtrate after concentration was saturated with sodium chloride, when the sodium salt of (II) separated. The *S* benzylthiuronium derivative prepared from it was crystallized from dilute alcohol in yellowish plates, m.p. 212–214°.

Anal. Calcd. for $C_{20}H_{20}N_2O_7S_2$: N, 6.0. Found: N, 6.4.

The barium salt of (II) was prepared from the sodium salt by the addition of a solution of barium chloride. It was washed free from chloride, crystallized from water and dried at 130°.

Anal. Calcd. for $C_{24}H_{18}BaO_{14}S_2$: Ba, 18.8. Found: Ba, 18.5.

Sulfonation of 7-hydroxy-4-methyl-8-acetylcoumarin (I) *with excess of chlorosulfonic acid.* A mixture of 2 g. of (I) and 3 ml. of chlorosulfonic acid was heated on a steam bath for 2 hr. After cooling, the reaction mixture was poured over ice, when 400 mg. of a solid IV separated. It was washed free from acids and crystallized first from benzene and then from alcohol in colorless needles, m.p. 215–217°.

Anal. Calcd. for $C_{24}H_{16}O_{12}S_2$: C, 51.4; H, 2.85, S, 11.4. Mol. Wt.: 560. Found: C, 51.0, 51.3; H, 2.8, 3.1; S, 11.1. Mol. Wt. 519.

The 2,4-dinitrophenylhydrazone of IV was crystallized from alcohol in orange needles, m.p. 254–255°.

Anal. Calcd. for: $C_{36}H_{24}N_8O_{18}S_2$: N, 12.2. Found: N, 11.8.

The filtrate in the above experiment after removal of IV and concentration was saturated with sodium chloride when the sodium salt of (III) separated. The S-benzylthiuronium derivative from it was crystallized from dilute alcohol, m.p. 216–218°.

Anal. Calcd. for: $C_{28}H_{30}N_4O_{10}S_4$: N, 7.9. Found: N, 8.3.

The barium salt obtained from the sodium salt as before was crystallized from water and dried at 140°.

Anal. Calcd. for: $C_{12}H_{16}BaO_{10}S_2$: Ba, 26.8. Found: Ba, 26.1.

The free sulfonic acid (III) prepared the barium salt after crystallization from concentrated hydrochloric acid had m.p. 212–215° (dec.).

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(1) J. R. Merchant and R. C. Shah, *J. Ind. Chem. Soc.* **34**, 35 (1957).

(2) J. R. Merchant and R. C. Shah, unpublished results.

(3) C. M. Suter, *Organic Chemistry of Sulfur*, John Wiley and Sons, Inc. New York, 1944, p. 230.

(4) All melting points are corrected.

(5) D. B. Limaye, *Ber.*, **65**, 375 (1932).

In the above sulfonation, a maximum yield of 800 mg. of (IV) and a very small amount of (III) were obtained by heating 2 g. of (I) with 10 moles of chlorosulfonic acid at 100°.

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Sulfonation of Ethyl γ-Phenylbutyrate with Sulfuric Acid

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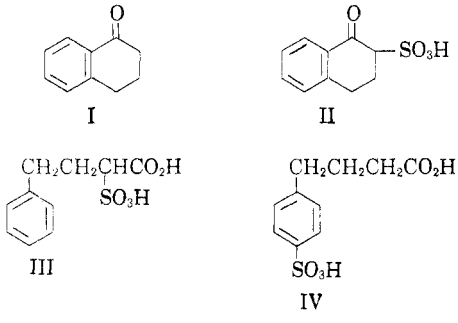
The direct sulfonation of phenylacetic acid with concentrated sulfuric acid,[1] chlorosulfonic acid,[2] and sulfur trioxide,[3] and of β-phenylpropionic acid with fuming sulfuric acid[4] all gave the corresponding ring substituted sulfophenylalkanoic acids.

Sulfonation of γ-phenylbutyric acid however failed to yield γ-(*p*-sulfophenyl)butyric acid (IV).[5,6] Instead, 50% yield of α-tetralone (I) was obtained when the sulfonation reagent was concentrated sulfuric acid,[5] and α-tetralonesulfonic acid (II) (78%) and γ-phenyl-α-sulfobutyric acid (III) (13%) were obtained when dioxane sulfur trioxide was the sulfonation agent.[6]



The present work shows that the action of excess 99% sulfuric acid on ethyl γ-phenylbutyrate at 60–65° gave predominately the ring substituted product, γ-(*p*-sulfophenyl)butyric acid (IV) isolated as its sodium salt. Small amounts of α-tetralone and acetaldehyde-sodium bisulfite adduct were the only by-products isolated.

Since addition of a solution of a simple ester (methyl benzoate) in 100% sulfuric acid to ice water did not result in hydrolysis,[7] it seems likely that the hydrolysis of the present ester took place during sulfonation, although the acid strength in the present case was only 99%. Formation of acetaldehyde can best be explained by oxidation of ethanol which became detached from the ester during sulfonation. Apparently, sulfonation of the benzene ring preceded the hydrolysis, otherwise excessive tetralone formation would ensue as in the case of γ-phenylbutyric acid. The implication is that under the experimental conditions used, ring sulfonation prevented the cyclization of γ-phenylbutyric acid.

(1) Hausman, German Patent **289,028**.
(2) Stewart, *J. Chem. Soc.*, **121**, 2555 (1922).
(3) Brust, *Rec. trav. chim.*, **47**, 153 (1928).
(4) Senderens and Aboulenc, *Compt. rend.* **186**, 1497 (1928).
(5) Krollpfeiffer and Schaefer, *Ber.*, **56**, 624 (1923).
(6) Truce and Olson, *J. Am. Chem. Soc.*, **75**, 1651 (1953).
(7) Treffers and Hammett, *J. Am. Chem. Soc.*, **59**, 1711 (1937).

EXPERIMENTAL[8]

Ethyl γ-phenylbutyrate. Ethyl γ-phenylbutyrate was prepared from 100 g. (0.58 mole) of γ-phenylbutyric acid[9] and absolute ethanol using the method of Hershberg and Fieser.[10] A standard work-up and distillation produced 94.5 g. (84.5%) of ethyl γ-phenylbutyrate, b.p. 80° (0.5 mm.), n_D^{20} 1.4919.

Sulfonation of ethyl γ-phenylbutyrate. To 45 g. (0.234 mole) of ethyl γ-phenylbutyrate, 236 g. of 99% sulfuric acid was slowly added with stirring. With constant agitation the mixture was heated to and maintained at 60–65° for 4 hr. The mixture was cooled to 33° and 100 ml. of water was added slowly, maintaining the temperature at below 50°. The mixture was then poured into 300 g. of ice and stirred for 1 hr. The resulting turbid mixture was extracted 4 times with 50 ml. portions of benzene, and the extracts were combined.

Identification of α-tetralone (I). The benzene extract was washed 3 times with 25 ml. portions of water and then concentrated to 14 g. by evaporation on a steam bath. The benzene concentrate was refluxed with 100 ml. of 10% sodium hydroxide for 16 hr. Acidification of the aqueous phase gave no precipitation indicating the absence of γ-phenylbutyric acid. The oil phase was dried over anhydrous sodium sulfate and distilled under diminished pressure to yield 5.3 g. (15%) of a colorless oil, b.p. 125–129° (11 mm). I was identified as its semicarbazone, m.p. 216.5–217.5°. A mixed melting point with an authentic sample of the semicarbazone of I, m.p. 217°, showed no depression.

Identification of the acetaldehyde-sodium bisulfite adduct. The mother aqueous acid solution was carefully neutralized with a 50% sodium hydroxide solution, and then evaporated to dryness yielding 353 g. of salt. The salt mixture was stirred with 2.4 l. of boiling 70% alcohol and filtered while hot. On cooling the filtrate gave 5.3 g. of a white crystalline salt which was identified as its *p*-chlorobenzylthiuronium derivative,[11] m.p. 218–219° (dec.). A mixture with the *p*-chlorobenzylthiuronium derivative of an authentic sample of acetaldehyde-sodium bisulfite adduct, m.p. 220–221° (dec.) melted at 218–219° (dec.).

Anal. Calcd. for $C_{18}H_{24}Cl_2N_4O_4S_3$:[12] C, 40.98; H, 4.59; N, 10.62; S, 18.23. Found: C, 40.20; H, 4.65; N, 10.45; S, 17.74.

(8) All melting points and boiling points are uncorrected. Elementary analyses were made by Mr. C. W. Nash and his staff, Rohm and Haas Co.
(9) Christian, *J. Am. Chem. Soc.*, **74**, 1591 (1952).
(10) Hershberg and Fieser, *Org. Syntheses*, **Coll. Vol. II**, 196 (1950).
(11) Campaigne and Suter, *J. Am. Chem. Soc.*, **64**, 3040 (1942).
(12) The requirement of two moles of p-chlorobenzylthiuronium chloride for each mole of the acetaldehyde-sodium bisulfite adduct is interesting, but not unanticipated. This means that the hydroxyl group alpha to the sulfonic acid group in the adduct is weakly acidic. The dissociation constant for a similar group in benzaldehyde-sodium bisulfite adduct is 7×10^{-10} (Bayer, Ger. Pat. **464,010** (July 26, 1928).