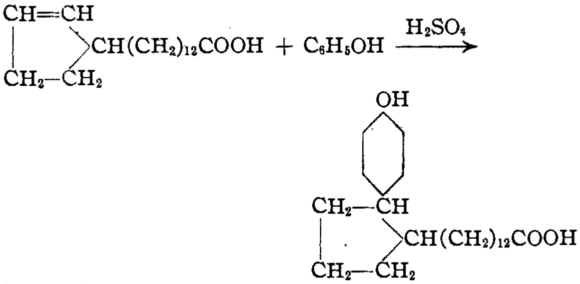
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

The Synthesis of Hydroxyphenyl- and the Hydroxymethylphenyldihydrochaulmoogric Acids[1]

BY JOSEPH B. NIEDERL AND BRADLEY WHITMAN

The synthesis of substances more effective for the treatment of leprosy than chaulmoogric and hydnocarpic acids and their salts and esters has been attempted by several investigators. Hinegardner and Johnson[2] have prepared chaulmoogryl resorcinol and some of its derivatives; Dean, Wrenshall and Fujimoto[3] synthesized ethyl dihydroiodochaulmoograte; Perkins and Cruz[4] made a series of alkyl substituted cyclopentenylacetic acids; Roger Adams and co-workers[5] have made an extended study of the relationship between the structure and molecular weight of acids and their bactericidal activity toward *B. lepræ*. This paper deals with the synthesis of phenolic dihydrochaulmoogric acids, the presence of the phenolic group in which it was hoped would greatly enhance their bactericidal activity.

Niederl and co-workers[6] have shown that phenols can be condensed with unsaturated compounds[7] in the presence of sulfuric acid giving in the majority of cases a substituted phenol. This reaction was utilized in the preparation of the compounds reported in this paper. Briefly the reaction may be formulated as follows



It has not been determined which position the phenyl group occupies in the cyclopentane ring but it is assumed to be the α by analogy to the addition of hydrobromic acid to chaulmoogric acid,[8] in which it has been shown that the bromine attaches itself primarily to the α-carbon.

To determine whether the compounds obtained were substituted phenols or the isomeric ethers, the following quantitative method was used rather than the usual color reactions. The sodium salts were prepared by adding to a weighed sample of the free acid an alcoholic solution of sodium ethoxide containing four molar equivalents of sodium, precipitating the resulting salts with anhydrous ether and destroying excess sodium ethoxide by adding a drop of water. If the condensation product were an ether, it would form a monosodium salt while if it were the isomeric phenol a disodium salt would result. The sodium analyses on these compounds, while not giving theoretical results, leave no doubt that they are substituted phenols. Chaulmoogric acid under the same experimental conditions gave practically theoretical results.

Two of the compounds prepared were tested for optical activity and were found to be inactive, but unreacted chaulmoogric acid recovered from one of the experiments was found to be optically active. It would appear then that racemization takes place during condensation. The theoretical significance of this is to be the subject of future work.

The sodium salts of the four new phenolic dihydrochaulmoogric acids were tested for bactericidal activity in water solution against *staphylococcus aureus*.[9] It was found that all of them were bactericidal in a 1–100 dilution. Their phenol coefficients lie between 1 and 10, while under the same conditions sodium chaulmoograte has a phenol coefficient considerably less than one, if it has any antiseptic properties whatsoever. In a 1% alcoholic solution at a 1–1000 dilution (hydroxy-*m*-tolyl)-dihydrochaulmoogric acid had a phenol coefficient of approximately 15.

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[1] Submitted by Bradley Whitman as part of a thesis for the degree of Doctor of Philosophy at New York University. Presented at the Chicago Meeting of the American Chemical Society, September, 1933.

[2] Hinegardner and Johnson, THIS JOURNAL, **51**, 1503 (1926).

[3] Dean, Wrenshall, Fujimoto, U. S. Public Health Service Bull. No. 168, 28 (1927).

[4] Perkins and Cruz, THIS JOURNAL, **49**, 517 (1927).

[5] Roger Adams and co-workers, *ibid.*, **48**, 1080, 1089, 2385, 2393, 2444 (1926); **49**, 2934, 2940 (1927); **50**, 1475, 1503, 1740, 1983, 2297 (1928); **51**, 1261 (1929); **52**, 1259, 1281, 1289, 2540 (1930).

[6] Niederl and co-workers, THIS JOURNAL, **50**, 2230 (1928); **51**, 2426 (1929); **53**, 272, 806, 1928, 3390 (1931); **54**, 1063 (1932); **55**, 284, 2571, 3025, 4151, 4549 (1933); *Monatsh.*, **51**, 1028 (1929); **60**, 150 (1932); *Z. angew. Chem.*, **44**, 467 (1931); **46**, 396 (1933).

[7] Thompson and Edee, THIS JOURNAL, **47**, 2556 (1925), and Ponndorf, German Patent 338,737 (1921), have condensed *p*-cresol with maleic and fumaric acids obtaining 6-methylcoumarin. This reaction appears to be of a different type and does not involve an addition to the double bond.

[8] Shriner and Adams, THIS JOURNAL, **47**, 2730 (1925).

[9] The authors wish to thank Dr. Wm. A. Feirer of Sharp and Dohme, Inc., Philadelphia, for determining the phenol coefficients of these compounds.

TABLE I

CHAULMOOGRIC ACID–PHENOL CONDENSATIONS (METHYL ESTERS)

No.	Chaulmoograte	Boiling point °C.	Boiling point Mm.	M. p., °C.
1	(Hydroxyphenyl)-methyldihydro-	255–261	3	56–57
2	(Hydroxy-*o*-tolyl)-methyldihydro-	245–255	2	40–41
3	(Hydroxy-*m*-tolyl)-methyldihydro-	230–237	2	[a]
4	(Hydroxy-*p*-tolyl)-methyldihydro-	240–250	3	62–63

No.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	$HOC_6H_4C_5H_8(CH_2)_{12}COOCH_3$	77.32	77.38	10.31	10.58
2	$HOC_6H_3(CH_3)C_5H_8(CH_2)_{12}COOCH_3$	77.61	77.41	10.45	10.63
3	$HOC_6H_3(CH_3)C_5H_8(CH_2)_{12}COOCH_3$	77.61	77.65	10.45	10.45
4	$HOC_6H_3(CH_2)C_5H_8(CH_2)_{12}COOCH_3$	77.61	77.36	10.45	10.60

[a] Sp. gr. 0.9946 (28°); n_D 1.5100 (28°).

TABLE II

CHAULMOOGRIC ACID–PHENOL CONDENSATIONS (FREE ACIDS)

No.	Chaulmoogric acids	M. p., °C.	Sodium, %[a] Calcd.	Sodium, %[a] Found
1	(Hydroxyphenyl)-dihydro-	80–81	11.00	10.30
2	(Hydroxy-*o*-tolyl)-dihydro-	56–61	10.65	11.30
3	(Hydroxy-*m*-tolyl)-dihydro-	50–52	10.65	10.95
4	(Hydroxy-*p*-tolyl)-dihydro-	49–50[b]		

No.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Neut. equiv. Calcd.	Neut. equiv. Found
1	$HOC_6H_4C_5H_8(CH_2)_{12}COOH$	77.01	77.09	10.16	10.79	374	364
2	$HOC_6H_3(CH_3)C_5H_8(CH_2)_{12}COOH$	77.32	77.38	10.31	10.29	388	388
3	$HOC_6H_3(CH_3)C_5H_8(CH_2)_{12}COOH$	77.32	77.45	10.31	10.27	388	388
4	$HOC_6H_3(CH_3)C_5H_8(CH_2)_{12}COOH$	77.32	77.49	10.31	10.48	388	381

[a] The values given are for the di-sodium salts: for the mono-sodium salts the theoretical values are: phenol compound Na, 5.81: cresol compounds Na, 5.61.

[b] It was realized that it was unusual for an acid to have a lower melting point than its methyl ester. In an effort to account for this the following work was done: from the above acid the methyl ester was resynthesized and it had the same melting point as the original and a mixed melting point gave no depression: the synthesis was repeated and the same constants were obtained for both the ester and free acid; the isomeric ether was synthesized from bromodihydromethylchaulmoograte and was a liquid. It would not crystallize on cooling to 1° and seeding with a crystal of the ester obtained previously. The following constants were obtained for *p*-cresoxydihydromethylchaulmoograte: sp. gr. 0.959; n_D 1.4919; b. p. 245–265 (4–5 mm.); for *p*-cresoxydihydrochaulmoogric acid the constants were: m. p. 62–64.5; neut. equiv., calcd. 388, found 385.8; analysis of sodium salt, calcd. for mono-sodium salt, Na, 5.61; found, 5.57; analysis calcd. C, 77.32; H, 10.31; found, C, 77.15; H, 10.39.

Experimental

Condensation.—One tenth of a mole (28 g.) of chaulmoogric acid, purified by crystallization from 80% alcohol, and one tenth of a mole plus 10% excess of the phenol or cresol freshly distilled were melted together in a flask, then chilled in an ice-bath and stirred vigorously to obtain fine crystals. (It is advisable to use a heavy-walled suction flask rather than an Erlenmeyer flask as it is less liable to fracture when breaking up the lumps of solidified material.) When the contents of the flask reached 0–5°, a mixture of 5.6 cc. of concd. sulfuric acid and 5.6 cc. of glacial acetic acid chilled to the same temperature was added in four portions with vigorous stirring. The stirring was continued for one hour, by which time the material had become a reddish-brown viscous liquid.

The flask was stoppered, a calcium chloride tube attached to the side arm and allowed to stand at room temperature for two weeks. From time to time the material was stirred, particular care being taken to break up unreacted lumps of the starting material.

Esterification.—The methyl ester was made, preparatory to the vacuum distillation, by adding 75 cc. of absolute methyl alcohol directly to the condensation mixture and passing dry hydrogen chloride through the solution for two hours. The contents of the flask was poured into a separatory funnel containing much water and the water layer separated. The ester was taken up in ether, washed twice with 10% sodium carbonate and finally with water. The ether layer was dried over anhydrous sodium sulfate.

The ether was removed and the ester distilled at 2–4 mm. pressure. All material coming over under 200° was discarded. The higher boiling fraction was redistilled. Too much reliance should not be placed on boiling points as they seem to vary a great deal with small changes in pressure, a fact already observed[10] in the fractionation of ethyl chaulmoograte.

Hydrolysis.—The purified ester was refluxed for four hours with 2 *N* alcoholic sodium hydroxide. The alcohol was driven off and sufficient water added to give a clear

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(10) Dean and Wrenshall, THIS JOURNAL, **42**, 2633 (1920).

solution. The solution was acidified with hydrochloric acid and the free acid taken up in ether, separated and dried over sodium sulfate. The ether was evaporated and the acid crystallized from petroleum ether.

Summary

1. Phenol and the three cresols have been condensed with chaulmoogric acid and the resulting products have been shown to be the hydroxyphenyl- and hydroxytolyl-dihydrochaulmoogric acids.

2. Studies of the physiological properties of these new phenolic dihydrochaulmoogric acids show that they have antiseptic activity against *staphylococcus aureus*. These studies are being extended to include bacillus tuberculosis and related bacilli.

3. Chaulmoogric acid is now being condensed with polyhydroxy and other substituted phenols and naphthols.

4. These studies are to be extended to include the synthesis of a series of substituted acetic acids containing various phenolic and aliphatic groups.

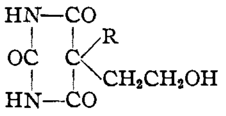
New York City Received May 28, 1934

[Contribution from the Research Laboratories, Hoffmann-La Roche, Inc.]

Synthesis of 5-β-Hydroxypropylbarbituric Acids

By José W. Loubriel

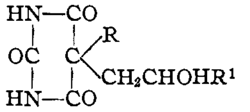
Barbituric acids of the structure



have been prepared by Johnson and Shepard[1] and by Cretcher, Koch and Pittenger.[2]

Johnson and Shepard[1] prepared 5-β-hydroxyethylbarbituric acid by the hydrolysis of 5-β-phthalimido ethyl barbituric acid with hydrochloric acid. Cretcher, Koch and Pittenger[2] prepared a series of such compounds by means of the following scheme: (1) condensation of the sodium salt of mono substituted malonic ester with chloroethyl vinyl ether, (2) condensation of malonic ester thus formed with urea, (3) hydrolysis of product thus obtained.

In order to synthesize barbituric acids of the structure



(I)

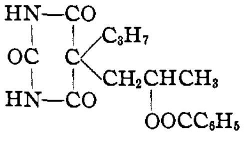
a change in the method of preparation was considered necessary.

The resistance of the ring in 5,5-ethylisopropylbarbituric acid to the action of sulfuric acid in the cold, prompted the author to study the effect of this reagent on 5,5-alkyl allyl substituted barbituric acids in order to introduce a hydroxyl group in the side chain.

The particular allyl compounds studied were 5,5-allylisopropyl and 5,5-allylisobutylbarbituric acids.

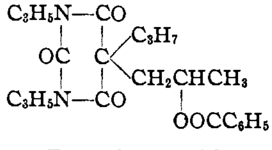
The addition of sulfuric acid to the allyl group takes place very rapidly and smoothly. It has been assumed that the addition of sulfuric acid follows Markownikoff's rule. This method would appear to be applicable to any 5,5-allylalkylbarbituric acid.

The hydroxy compound (I) obtained from 5,5-allylisopropylbarbituric acid was benzoylated to yield the product (II).



(II)

In order to show that the benzoyl group was introduced in the side chain, compound (II) was allylated in the 1,3 positions according to the method described in British Patent 391,741.



(III)

Experimental Part

Preparation of 5-Isopropyl-5-(β-hydroxypropyl)-barbituric Acid (I).—Fifty grams of 5,5-allylisopropylbarbituric acid was added slowly with stirring to 100 cc. of sulfuric acid (sp. gr. 1.84) and allowed to stand at room temperature for eight hours. The solution was poured with constant stirring over 500 g. of ice. The precipitate was then filtered and washed with cold water until the filtrate was

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(1) Johnson and Shepard, This Journal, **35**, 1003 (1913).

(2) Cretcher, Koch and Pittenger, *ibid.*, **47**, 3083 (1925).