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.

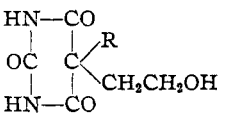
NEW YORK CITY RECEIVED MAY 28, 1934

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, HOFFMANN-LA ROCHE, INC.]

Synthesis of 5-β-Hydroxypropylbarbituric Acids

BY JOSÉ W. LOUBRIEL

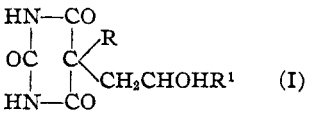
Barbituric acids of the structure



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.

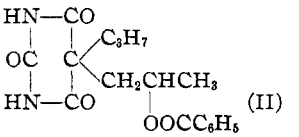
The resistance of the ring in 5,5-ethylisopropylbarbituric acid to the action of sulfuric acid in the cold, prompted the author to study the effect of this reagent on 5,5-alkyl allyl substituted barbituric acids in order to introduce a hydroxyl group in the side chain.

(1) Johnson and Shepard, THIS JOURNAL, **35**, 1003 (1913).
(2) Cretcher, Koch and Pittenger, *ibid.*, **47**, 3083 (1925).

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

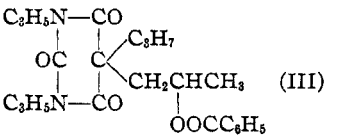
The addition of sulfuric acid to the allyl group takes place very rapidly and smoothly. It has been assumed that the addition of sulfuric acid follows Markownikoff's rule. This method would appear to be applicable to any 5,5-allylalkylbarbituric acid.

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

neutral to congo paper. The product was recrystallized from alcohol. It is soluble in ethyl and in methyl alcohols, but it is insoluble in water, ether, chloroform, acetone or ethyl acetate; m. p. 221–222° (uncorr.); yield 95%.

Anal. Calcd. for $C_{10}H_{16}O_4N_2$: C, 52.61; H, 7.07; N, 12.29. Found: C, 52.45; H, 7.10; N, 12.25.

Preparation of 5-Isobutyl-5-(β-hydroxypropyl)-barbituric Acid.—Repeated above procedure using 14 g. of 5,5-allylisobutylbarbituric acid, 50 cc. of sulfuric acid and 250 g. of ice. The product is soluble in ethyl and in methyl alcohols, but it is insoluble in water, ether, chloroform, acetone or ethyl acetate; m. p. 216–217°; yield 95%.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: C, 54.53; H, 7.49; N, 11.58. Found: C, 54.11; H, 7.46; N, 11.62.

Cold concentrated sulfuric acid has no action on 5,5-ethylisopropylbarbituric acid.

Preparation of (II).—Twenty-three grams of (I) in 50 cc. of pyridine and 15 cc. of benzoyl chloride was refluxed for three hours. The product recrystallized from ethyl acetate had m. p. 169–171°. The compound is soluble in ether, alcohol, chloroform or ethyl acetate; yield 70%.

Anal. Calcd. for $C_{17}H_{20}O_5N_2$: N, 8.44. Found: N, 8.43.

Two grams of the product was refluxed with 50 cc. of alcoholic potash ($N/2$) for five hours. The solution was evaporated to about 20 cc. and made acid to congo paper with hydrochloric acid. The crystals which were formed on standing were recrystallized twice from water; m. p. 120–121°; mixed m. p. with benzoic acid 120–121°.

Di-allylation of (II).—11.1 grams of (II) was treated with 8.1 g. of allyl bromide in the presence of finely divided copper and 10% sodium hydroxide according to the method described in British Patent 391,741. The product obtained was a very heavy oil which was purified by vacuum distillation, b. p. (25 mm.) 260°.

Anal. Calcd. for $C_{23}H_{28}O_5N_2$: N, 6.80. Found: N, 6.74. 0.2859 gram absorbed bromine equivalent to 27.66 cc. of 0.1000 N bromate solution; required for $C_{23}H_{28}O_5N_2$: 27.58 cc.

Summary

Two 5-alkyl-5-β-hydroxypropylbarbituric acids have been prepared from the corresponding 5-alkyl-5-allylbarbituric acids by addition of sulfuric acid at the double bond of the allyl group and subsequent hydrolysis.

NUTLEY, N. J. RECEIVED JUNE 2, 1934

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Analysis of Gamma-Methylfructoside Mixtures by Means of Invertase. III. Behavior of Crystalline Gamma-Methylfructoside in Methyl Alcohol Containing Hydrogen Chloride[1]

BY C. B. PURVES

It has been known for some years that the optical rotation of a methyl alcoholic solution of fructose and hydrogen chloride attained a dextrorotatory maximum when most of the ketose had been changed to non-reducing fructose derivatives of a gamma nature.[2] More recent work[3] indicated that the condensation product included (a) a derivative hydrolyzed by invertase and with a specific rotation, calculated for a methylfructoside, of $[\alpha]_D^{20}$ $-52 \pm 2°$ in water; (b) another non-reducing sirup stable to the enzyme and not more dextrorotatory than $[\alpha]_D^{20}$ $+28°$ and (c) a crystalline gamma-methylfructoside also stable to invertase and with a specific rotation of $[\alpha]_D^{20}$ $+93.0°$ in water and of $[\alpha]_D^{20}$ $+91.6°$ in methyl alcohol. Provided that the reaction was arrested near the point of maximum dextrorotation, no change in the conditions of the condensation seriously affected the relative amounts of the constituents (a), (b) and (c) in the product. In order to discover whether the latter observation indicated the presence in the acid alcohol of an equilibrium among the above three derivatives, a study was made of the behavior of the pure crystalline glycoside (c) when dissolved in the same reagent.

Figure 1, curve A, summarizes the optical data observed, at 20°, when the solvent was 0.0263 normal with respect to hydrogen chloride. The rotation diminished with time in a logarithmic way to a final specific rotation of 22° after which the subsequent decrease was very slow. The unimolecular velocity constant of the primary change, given in minutes and decimal logarithms by $10^4K = 1770$, was no less than 5900 times as large as that determined for the hydrolysis of sucrose with aqueous acid and the same conditions. When the final rotation had been reached (point 1 on the optical curve), the acid methyl alcoholic solution was neutralized and 50% of

(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) Menzies, *J. Chem. Soc.*, **121**, 2238 (1922).

(3) Purves and Hudson, (a) THIS JOURNAL, **56**, 702 (1934); (b) **56**, 708 (1934).