Fusion at Higher Temperatures.—Fusions for 5 minutes, similar to that just described, were performed at 190° and at 225°. In neither case was it found possible to isolate either dihydroxy-stearic acid, or hydroxy-octyl-sebacic acid.

Fusion of Dihydroxy-stearic Acid with Potassium Hydroxide.—The fusion was made in exactly the same way as described above for the fusion of diketostearic acid. At 160°, it was found possible to recover (pure) 90% of the original dihydroxy acid. No hydroxy-octyl-sebacic acid could be found. At 180°, the results were the same, 93% of the original acid being recovered.

Summary

1. The formation of α-hydroxy-α-octyl-sebacic acid in the alkaline fusion of dihydroxy-stearic acid, as observed by Le Sueur, is probably the first recognized "benzilic acid" rearrangement of a compound of the type $RCH_2COCOCH_2R'$, proceeding through diketostearic acid as an intermediate product.

2. This same product is formed when diketostearic acid is fused with alkali at 160°.

3. In this same fusion (2) dihydroxy-stearic acid is formed, along with pelargonic and azelaic acids, in a modified Cannizzaro reaction.

CHICAGO, ILLINOIS

[CONTRIBUTION NO. 11 FROM THE DEPARTMENT OF CHEMICAL RESEARCH, PARKE, DAVIS AND COMPANY]

ALKYLBENZYL BARBITURIC ACIDS

BY ARTHUR W. DOX AND LESTER YODER

Received January 26, 1922

Notwithstanding the great number of dialkyl and alkyl-aryl barbituric acids that have been prepared and described since Emil Fischer's discovery of the hypnotic properties of veronal (diethyl barbituric acid), little attention has been given the alkylbenzyl derivatives. The fact has been repeatedly demonstrated that the presence of two hydrocarbon radicals on the 5-carbon atom is necessary to confer sleep-producing properties upon barbituric acid. The two radicals may or may not be identical, but one alone is not sufficient to give any marked physiological action.

In view of the recent work of Macht[1] and others on the antispasmodic effect of benzyl derivatives, notably benzyl alcohol and its esters, the possibility suggested itself that a barbituric acid derivative with combined hypnotic and antispasmodic properties might be prepared by substituting a benzyl group for one of the alkyls in the derivatives of the veronal series. The benzyl would then play the role of an alkyl radical in stabilizing the molecule and thus confer hypnotic properties within the limits of the "distribution coefficient," or ratio of solubility in fat to solubility in water, and at the same time contribute its specific antispasmodic "benzyl effect."

[1] Macht, *J. Pharmacol.*, **11**, 176 (1918).

In an homologous series with increasing fat solubility and decreasing water solubility it should be possible to find one derivative with the distribution coefficient required by the Overton-Meyer hypothesis. In this regard we were successful, for the benzylethyl derivative showed marked hypnotic properties. However, the specific effect of the benzyl group was quite at variance with our predictions. Instead of an antispasmodic effect the result was quite the opposite. When the dose administered, approached the toxic dose, a condition of tetanus resulted. The physiological experiments on mice and dogs were performed by other workers in this laboratory and will be discussed in detail elsewhere.

Of the many possible alkylbenzyl barbituric acids, only three have thus far been described. The allylbenzyl derivative was prepared by Johnson and Hill[2] from ethyl allylbenzyl malonate, urea and sodium ethylate. *Iso*propylbenzyl and cyclohexylbenzyl barbituric acids, prepared by condensing the corresponding di-substituted cyano-acetic esters with guanidine and hydrolyzing the resulting di-imino-pyrimidines, are described in a Bayer patent.[3] Arylbenzyl derivatives known are dibenzyl[4] and phenylbenzyl[5] barbituric acid.

To any one familiar with the properties of hypnotics of the veronal series, it will be apparent that three of the above, namely dibenzyl, phenylbenzyl and cyclohexylbenzyl, on account of the size of the substituent groups, would be too insoluble in water to exert any marked hypnotic action when administered by mouth. Regarding the other two, allylbenzyl and *iso*propylbenzyl, no physiological data are available. Of these true alkylbenzyl derivatives one contains an unsaturated alkyl and the other a secondary alkyl radical. Our purpose was to prepare a series of alkylbenzyl barbituric acids, with alkyl radical derived from the primary aliphatic alcohols. No such derivatives have thus far been described.

In the preparation of these alkylbenzyl barbituric acids we employed the method introduced by Fischer and Dilthey, and subsequently adopted by many other investigators. Briefly, it consists in heating an ethyl dialkylmalonate with urea and an excess of sodium ethylate in an autoclave. The desired alkyl groups are introduced into the ethyl malonate. Direct substitution in barbituric acid is not feasible except in the case of the very reactive alkyl halides, such as allyl bromide. We found, however, that the benzyl group may be introduced directly into barbituric acid or a mono-alkyl barbituric acid, though the yield is not satisfactory.

In the series of ethyl alkylbenzylmalonates which we prepared the only one previously described is the methyl derivative. This was prepared

[2] Johnson and Hill, *Am. Chem. J.*, **46**, 544 (1911).

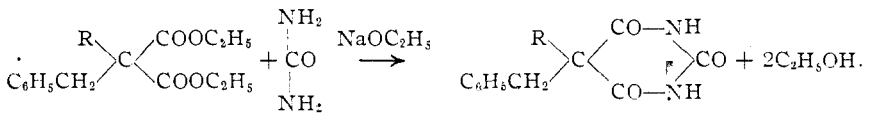
[3] Ger. pat. 293,163, **1916**.

[4] Fischer and Dilthey, *Ann.*, **334**, 337 (1904).

[5] Hoerlein, U. S. pat. 1,025,526, **1912**.

by Conrad and Bischoff[6] by methylating the benzyl derivative and by benzylating the methyl derivative, the product being identical in both cases. Although we employed both methods, we found it advantageous to put the benzyl group in first. The reason for this will be seen from the fact that in the preparation of a mono-substituted malonic ester a di-substituted derivative is invariably formed as a by-product except in the case of secondary alkyl radicals and a corresponding amount of ethyl malonate remains unsubstituted. With the lower alkyl radicals the boiling points of the three substances lie rather closely together, and consequently a purification of the ethyl mono-alkylmalonate requires repeated fractionation. On the other hand, the monobenzylmalonate is easily separated from the dibenzyl derivative and the unsubstituted ethyl malonate. When making the second substitution, however, an excess of alkyl halide may be used to advantage so as to bring the reaction to completion. By benzylating an impure lower mono-alkylmalonate with an excess of benzyl chloride the benzyl alkylmalonate is also easily separated from the other impurities but the yield from the malonic ester used is considerably less.

These di-substituted malonic esters readily condense with urea in the presence of sodium ethylate at 100–105°, yielding the sodium salt of the di-substituted barbituric acid, from which the free acid is obtained by acidifying with hydrochloric acid.



Experimental Part

Preparation of the Esters.—Ethyl ethylbenzylmalonate was prepared by treating ethyl benzylmalonate with ethyl bromide and sodium ethylate in absolute alcohol. The other esters were prepared by treatment of the ethyl alkylmalonates with benzyl chloride in the same manner. We believe the first method is the more satisfactory. After completion of the reaction the alcohol was removed by distillation and the sodium chloride or bromide by shaking the residual oil with water. The product was dried with calcium chloride and purified by distillation *in vacuo*. Since the alkylbenzylmalonic esters were regarded merely as intermediates in the preparation of the corresponding barbituric acids, they were not analyzed or fractionated for the purpose of determining the exact boiling points. The product collected over a 10° range was considered pure enough for our purpose. Identification was made through the barbituric acids which were carefully purified by recrystallization.

[6] Conrad and Bischoff, *Ann.*, **204**, 177 (1880).

Ester	Fraction collected °C.	Pressure Mm.	Yield %
Ethyl methylbenzylmalonate	165–175	15	63
Ethyl ethylbenzylmalonate	160–170	9	72
Ethyl *iso*propylbenzylmalonate	170–180	12	23
Ethyl *n*-butylbenzylmalonate	177–185	10	65
Ethyl *iso*butylbenzylmalonate	177–187	10	47
Ethyl *iso*amylbenzylmalonate	180–190	10	75

Condensation of the Esters with Urea.—A uniform procedure was followed except in the case of the *n*-propyl derivative where the benzyl group was introduced directly into *n*-propyl barbituric acid. A mixture consisting of 10 g. of the ester, three times the molecular equivalent of sodium dissolved in 20 parts of alcohol, and 1.5 moles of urea was heated in an autoclave at 105° for 5 hours. The resulting white mass consisting mainly of the sodium salt of the di-substituted barbituric acid was treated with a slight excess of hydrochloric acid and the alcoholic solution filtered from the sodium chloride. The filtrate was evaporated on the steam-bath until crystals began to form, and then cooled. Addition of water to the mother liquor gave a further yield. One or two recrystallizations from benzene containing a little alcohol gave a pure white product.

The *n*-propyl derivative was prepared by heating under a reflux condenser for 5 hours an alcoholic solution of *n*-propyl-barbituric acid with the calculated amounts of benzyl chloride and ammonium acetate. Ammonium chloride gradually separated from the alcoholic solution and the latter on evaporation gave *n*-propylbenzyl-barbituric acid, which was purified by recrystallization.

Of the following derivatives, *iso*propylbenzyl-barbituric acid has been previously described and a melting point of 230° reported.[7]

Substance Barbituric acid derivative	M. p.	Nitrogen Calc.	Found		Yield
	°C.	%	%	%	%
5,5-methylbenzyl	207	12.07	12.01	11.94	74
5,5-ethylbenzyl	206–7	11.38	11.44	11.30	79
5,5-*n*-propylbenzyl	210	10.77	10.85	10.99	51
5,5-*iso*propylbenzyl	229	10.77	10.64	10.57	56
5,5-*n*-butylbenzyl	195	10.22	10.22	10.22	95
5,5-*iso*butylbenzyl	255	10.22	10.36	10.29	89
5,5-*iso*amylbenzyl	194–6	9.72	9.42	9.49	94

In this series the solubility in water decreases and the solubility in alcohol increases with increasing size of the alkyl group. All are soluble in dil. alkali. All have a bitter taste which is most pronounced in the lower members. The ethyl derivative showed the strongest hypnotic action

[7] Ger. pat. 293,163, **1916.**

but this was accompanied by symptoms of tetanus. It is doubtful therefore whether any of these derivatives will be of therapeutic value.

Summary

From the ethyl esters of alkylbenzylmalonic acids, urea and sodium ethylate, a series of alkylbenzyl-barbituric acids was prepared by the "veronal" synthesis.

In this series, ethylbenzyl-barbituric acid was found to have the strongest physiological action. Contrary to our expectations, the hypnotic effect was accompanied by symptoms of tetanus instead of the anti-spasmodic effect commonly attributed to the benzyl group.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

C_{18} FATTY ACIDS. V. MOLECULAR REARRANGEMENTS IN SOME DERIVATIVES OF UNSATURATED HIGHER FATTY ACIDS

BY BEN H. NICOLET AND JOSEPH J. PELC[1]

Received January 28, 1922

The hydroxamic acids belonging to the aromatic and saturated aliphatic series are well known. Their properties and reactions have been carefully studied by Lossen,[2] Hofmann,[3] Hantzsch,[4] Werner,[5] and others. Their formation from esters and hydroxylamine is recognized as a quite general reaction.[6]

The rearrangement of unsaturated hydroxamic acid derivatives does not appear to have been investigated. A certain amount of work[7] has, however, been done on the rather analogous Hofmann rearrangement, and the general conclusion is that, at least for amides having the double bond in the α,β-position, the reaction usually proceeds normally and without complications.

It is the purpose of the present paper to show that the rearrangements characteristic of hydroxamic acids and their derivatives take place, in general, normally, for the derivatives of oleic, elaidic and ricinoleic acids. Certain abnormal and rather surprising results were, however, also obtained.

[1] The material here presented is used by Joseph J. Pelc in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

[2] Lossen, *Ann.*, **150,** 314 (1869); **161,** 347 (1872); **175,** 271 (1875); **186,** 1 (1877); **252,** 170 (1889); **265,** 176 (1891); **281,** 169 (1894); etc.

[3] Hofmann, *Ber.*, **15,** 412 (1882); **22,** 2854 (1889).

[4] Hantzsch, *ibid.*, **27,** 799, 1256 (1894).

[5] Werner, *ibid.*, **25,** 27 (1892); **26,** 1561 (1893); **29,** 1155 (1896).

[6] Jeanrenaud, *ibid.*, **22,** 1270 (1889).

[7] Jeffreys, *Am. Chem. J.*, **22,** 43 (1899). Weerman, *Rec. trav. chim.*, **26,** 203 (1907). Rinkes, *ibid.*, **39,** 200 (1920).