

taken against the camphor-benzene solution,<sup>12</sup> and also those of *dextro* and *levo* camphor-sulfonic acids against the camphor-benzene solution.

TABLE II  
DROP NUMBER AGAINST A SOLUTION OF CAMPHOR IN BENZENE

Conc. of acid <i>d</i> -Tartaric <i>l</i> -Tartaric Racemic			Conc. of acid <i>d</i> -Camphor- <i>l</i> -Camphor-			
in water			in water sulfonic acid sulfonic acid			
%	17%			%	26%	
..	720	724	728	..	613	619
3	796	791	810	3.7	795	777
6	846	852	891	7	915	916
9	920	925	983	10.5	1056	1059
10.4	...	...	1015	14.7	1257	1253
12	994	990	..	..	..	..

### Conclusion

The results show that there is no measurable difference in interfacial tension, against the several liquids, between the *dextro* and the *levo* substances chosen, indicating that there is no selective absorption of such enantiomorphs, which are remarkable for their similarity of physical properties.

The divergence of the curve for either of the active tartaric acids from that for the racemic acid (see Figs. 1, 2 and 3) appears to admit of only one explanation, the existence in solution of the racemic acid molecule. As the dilution increases, the curves indicate an increasing "dissociation" of the racemic acid into the *d* and *l* forms.

I am indebted to Professor H. G. Denham, now of the University of Cape Town, South Africa, for his initial suggestion and for his advice during the progress of this work.

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

## C<sub>18</sub> FATTY ACIDS. IV. A REARRANGEMENT OF THE BENZILIC ACID TYPE IN THE ALIPHATIC SERIES

BY BEN H. NICOLET AND ALFRED E. JURIST<sup>1</sup>

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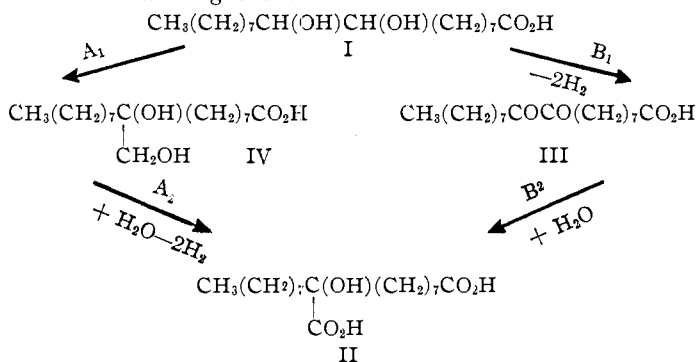
Some time ago Le Sueur<sup>2</sup> described the fusion of 9,10-dihydroxystearic acid (I) with potassium hydroxide. The principal reaction was shown to be the formation of  $\alpha$ -hydroxy- $\alpha$ -octyl-sebacic acid (II), resembling benzilic acid in structure, and the evolution of hydrogen, though the considerable amount of material not accounted for indicated that side reactions were also taking place.

<sup>12</sup> The author is indebted to Professor Read, University of Sydney, for the supply of camphor-sulfonic acids.

<sup>1</sup> The material here presented was used by Alfred E. Jurist in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

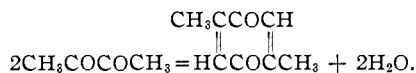
<sup>2</sup> Le Sueur, *J. Chem. Soc.*, **79**, 1313 (1901).

Apparently, these results might have been reached in either of two ways, as shown in the following chart.



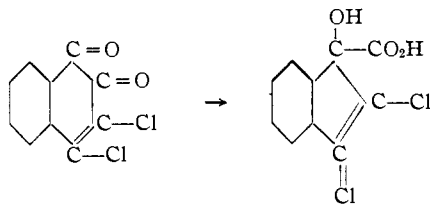
The reaction scheme designated as  $A_1$  and  $A_2$  has little to commend it. The reaction  $A_2$  is perfectly normal, but  $A_1$  has, to the writer's knowledge, no strong resemblance to any known type of rearrangement. No product corresponding to the glycol (IV) has been isolated from the products formed, either by us or by Le Sueur, and the assumption of such a course of reaction is accordingly purely hypothetical. Formally, Reactions  $B_1$  and  $B_2$  appear more likely to represent the reaction correctly. The oxidation represented by  $B_1$  is perfectly normal, and  $B_2$  represents a typical benzoic acid rearrangement.

Von Pechmann<sup>3</sup> attempted in vain to obtain a rearrangement of this type by fusion of "diacetyl" or of "acetylpropionyl" with alcoholic potash. Instead, quinones were formed.



From this result, von Pechmann draws the rather sweeping conclusion that aliphatic  $\alpha$ -diketones which do *not* give this reaction, will undergo the benzoic acid rearrangement. Considering that no cases of the latter type were investigated by him, the conclusion seems unduly far-reaching.

There remains, on the other hand, very little doubt that this rearrangement occurs much more generally than has usually been recognized, as shown, for example, by the following reaction described by Zincke.<sup>4</sup>



<sup>3</sup> Von Pechmann, *Ber.*, **21**, 1411 (1888).

<sup>4</sup> Zincke, *ibid.*, **19**, 2500 (1886); **20**, 1265, 2053, 2890 (1887).

Furthermore, Nef<sup>5</sup> in his extensive work on saccharinic acids explained their formation on the basis of this rearrangement, and his pupil Evans<sup>6</sup> considered a similar rearrangement obvious in the case of diketosuccinic acid. Finally, Lachman<sup>7</sup> has, since the completion of the present investigation, discussed the very similar case of dihydroxy-tartaric acid from this point of view.

It is then evident that aliphatic compounds may, and sometimes do, undergo the benzilic acid rearrangement. An analysis of the work quoted above shows, however, that in none of the cases mentioned has the compound undergoing rearrangement had the structure  $RCH_2COCOCH_2R'$ ; in other words, the absence of two hydrogens attached to each of the carbons adjoining each of the keto groups, has prevented interference by the reaction described by von Pechmann.

The present work was undertaken to show whether diketostearic acid (III) could be considered as an intermediate product in Le Sueur's reaction.

This acid (III) has been prepared by Overbeck<sup>8</sup> by the oxidation of stearolic acid with nitric acid. A somewhat more convenient method involving the oxidation of dihydroxy-stearic acid with chromic acid, was developed. The diketo acid so obtained was fused with caustic potash at 160°, 190° and 225°. Only at the lowest temperature could dihydroxy-stearic acid (I) and hydroxy-octyl-sebacic acid (II) be isolated, so that the reactions at higher temperatures were not further studied. Azelaic and pelargonic acids were also obtained.

As hydrogen is not evolved in the action of potassium hydroxide on diketostearic acid (cf. also Reaction B<sub>2</sub>), the formation of dihydroxy-stearic acid can be readily explained only on the ground of an intermolecular oxidation and reduction, which would be quite similar to the well known Cannizzaro Reaction<sup>9</sup> of aromatic aldehydes. By analogy, one might expect the formation, for each mol. of dihydroxy acid, of 2 mols. of pelargonic acid and 2 mols of azelaic acid. It is worthy of note that no diketostearic acid is recoverable after the fusion, and that a *reduction product*, the dihydroxy acid, is formed on heating it with potassium hydroxide, a reaction usually associated with oxidation.

From the considerations advanced above, each gram of the dihydroxy acid formed should involve the formation of 1.19 g. of azelaic acid and 1.0 g. of pelargonic acid. These acids were isolated in quantities of 0.36 g. and 0.54 g., respectively, which, considering the properties of the acids

<sup>5</sup> Nef, *Ann.*, **357**, 306, 308 (1907) and elsewhere.

<sup>6</sup> Evans, *Am. Chem. J.*, **35**, 116 (1906).

<sup>7</sup> Lachman, *THIS JOURNAL*, **43**, 2092 (1921).

<sup>8</sup> Overbeck, *Ann.*, **140**, 63 (1866).

<sup>9</sup> Cannizzaro, *ibid.*, **88**, 129 (1853).

in question and the methods available for their isolation, are considered to be in satisfactory relation with the requirements mentioned above.

In addition, the fusion at  $160^{\circ}$  yielded  $\alpha$ -hydroxy- $\alpha$ -octyl-sebacic acid (II), which was sufficiently identified with Le Sueur's product. This is interpreted to mean that the diketo acid has undergone a rearrangement of the benzilic acid type, as indicated by Reaction B<sub>2</sub>. Simultaneously, intermolecular oxidation and reduction yielded dihydroxy-stearic acid, pelargonic acid, and azelaic acid. As much of the original material was unaccounted for, and products were obtained which could not be distilled even under very greatly reduced pressure, the formation of a complex quinone according to von Pechmann is not excluded.

The fact that dihydroxy-stearic acid is obtained in this reaction makes it at least conceivable that the presence of the acid (II) might be explained by the intermediate formation of the dihydroxy acid. This is doubted for the following reasons: (1) dihydroxy-stearic acid, heated with potassium hydroxide at temperatures of  $160^{\circ}$  or  $190^{\circ}$ , was recovered almost quantitatively unaltered; (2) the concentration of the dihydroxy acid formed in these reactions is relatively small.

Consequently it is considered that diketostearic acid is an intermediate product in Le Sueur's reaction. The relatively small yield (11.86%) of acid (II) here recorded, may be explained on the following grounds: (1) the relatively large concentration of dihydroxy-stearic acid under the conditions used by Le Sueur would tend to prevent the formation of pelargonic and azelaic acids; (2) the hydrogen evolved under Le Sueur's conditions (but not in the case here described) would tend likewise to prevent this loss; (3) condensation of the diketo acid to form quinone derivatives, according to von Pechmann (suspected, but not actually demonstrated) is a reaction bimolecular with respect to the diketo acid, and its rate is accordingly proportional to the square of the latter's concentration. It therefore makes an enormous difference whether this acid is the starting material, or merely an intermediate product in the reaction.

### Experimental Part

The necessary dihydroxy-stearic acid was prepared essentially according to Saytzeff,<sup>10</sup> except that it was found more convenient to dissolve all of the manganese dioxide formed by treatment with sulfite and an excess of sulfuric acid, thus avoiding a somewhat difficult filtration. The yield of material was 40%, m. p.  $131.5^{\circ}$ .

**Preparation of 9,10-Diketostearic Acid.**—Twenty g. of dihydroxy-stearic acid was dissolved in 1200 cc. of glacial acetic acid. This solution was kept at  $20^{\circ}$ , and stirred while a solution of 12 g. of chromic anhydride in 400 cc. of acetic acid, containing 2 cc. of conc. sulfuric acid was added gradually. Within 20 minutes the solution became blue-green; the reaction was then stopped by pouring the mixture into 1.5 liters of water. The precipitated diketostearic acid was removed by filtration, washed, dried in a vacuum and recrystallized from alcohol and from ether (dihydroxy-stearic acid is very insoluble

<sup>10</sup> Saytzeff. *J. prakt. Chem.*, [2] 33, 304 (1886).

in ether). The yield of material was 25% m. p. 86°. The product was analyzed by titration.

Calc. for  $C_{15}H_{32}O_4$ : Equiv. wt., 312.0. Found: 310.6, 311.7.

Several other methods were tried in the hope of improving the yield. Dilution of the acetic acid with acetone, and oxidation with barium peroxide, manganese dioxide, or permanganate in acid solution, all gave less satisfactory results. Oxidation, under the conditions described above, of esters of dihydroxy-stearic acid, gave good, but not better, results.

**Methyl 9,10-Diketostearate.**—This was prepared from methyl dihydroxy-stearate, by a method similar to that used for the acid. The ester was obtained in 25% yield, m. p. 55°.

*Analyses.* Calc. for  $C_{19}H_{34}O_4$ : C, 69.94; H, 10.43; O, 19.63. Found: C, 69.86, 69.90; H, 10.63, 10.67; O, 19.51, 19.41.

**Ethyl 9,10-Diketostearate.**—Similarly, this was obtained in 15% yield as yellow needles, m. p. 50°.

*Analyses.* Calc. for  $C_{20}H_{36}O_4$ : C, 70.59; H, 10.59; O, 18.82. Found: C, 70.40, 70.54; H, 10.90, 10.63; O, 18.70, 18.73.

**Fusion of Diketostearic Acid with Potassium Hydroxide at 160°.**—Thirteen g. of 9,10-diketostearic acid was fused for 5 minutes at 160° with 65 g. of potassium hydroxide, moistened with sufficient water. The fused mass was then poured into water and acidified with dil. sulfuric acid. After standing overnight the mixture was filtered and the filtrate extracted thrice with ether. After removing the ether and recrystallizing the solid from hot water, the extracted material weighed 0.4 g. and melted at 106°. The equivalent weight was determined by titrating with alcoholic potash.

Calc. for azelaic acid,  $C_9H_{16}O_4$ : Equiv. wt., 94.0. Found: 93.95, 94.05.

The solid obtained above was extracted with chloroform. On standing overnight, the extract deposited crystals which, purified from hot alcohol, melted at 131.5° and weighed 0.9 g. Analysis proved that this was dihydroxy-stearic acid, though special precautions had been taken to see that the original diketo acid had been separated completely from this substance.

*Analyses.* Calc. for  $C_{15}H_{30}O_2$ : C, 68.35; H, 11.39; O, 20.25. Found: C, 68.06, 68.17; H, 11.65, 11.52; O, 20.29, 20.31.

The remaining chloroform solution was distilled with steam until no more oil came over. The distillate was made alkaline, concentrated to a small volume, acidified, and extracted with ether. The oil thus recovered weighed 0.6 g., and had the odor of pelargonic acid.

Calc. for pelargonic acid,  $C_9H_{18}O_2$ : Equiv. wt., 158. Found: 157.9.

The residue from this steam distillation was filtered hot and the filtrate made alkaline, concentrated to a small volume, acidified, and extracted with ether. This extract yielded only 0.4 g. of an oil which was not further identified.

The semi-solid oily material remaining on the filter in the operation described above, was dissolved in ether. After removing the ether the residue was spread on a porous plate and placed in a steam oven. There remained 1.6 g. of a somewhat grayish solid, which, after further purification, melted at 110°, either alone, or after mixing with hydroxy-octyl-sebacic acid obtained by Le Sueur's method. Its identity was further proved by analysis.

*Analyses.* Calc. for  $C_{19}H_{34}O_5$ : C, 65.45; H, 10.30; O, 24.24. Found: C, 65.20; H, 10.59; O, 24.21.

Calc. for  $C_{18}H_{34}O_3$ : Equiv. wt., 330.0. Found: 328.2.

**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  $\alpha$ -hydroxy- $\alpha$ -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.

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

### ALKYLBENZYL BARBITURIC ACIDS

BY ARTHUR W. DOX AND LESTER YODER

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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<sup>1</sup> 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."

<sup>1</sup> Macht, *J. Pharmacol.*, **11**, 176 (1918).