

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.

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C₁₈ FATTY ACIDS. V. MOLECULAR REARRANGEMENTS IN SOME DERIVATIVES OF UNSATURATED HIGHER FATTY ACIDS

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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 work⁷ 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 fulfillment 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 Jeautorenaud, *ibid.*, **22**, 1270 (1889).

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

The Lossen rearrangement yielding the corresponding ureas was obtained in every case tried. Certain of the compounds thus formed may be of use in identifying substances which are otherwise oils or very low-melting solids. The Lengfeld-Stieglitz rearrangement, giving urethanes,⁸ was also successful in all cases. In these reactions the double bond apparently had no effect whatever on the course of the reaction and was not affected by it, although the physical properties of some of the substances concerned made the reactions take place somewhat more slowly than usual.

It was therefore all the more unexpected that the preparation of isocyanates from oleo- and elaidohydroxamic acids by warming them with an excess of acetic anhydride led, whichever acid had served as starting point, to a mixture of *cis*- and *trans*-heptadecylenyl isocyanates. This was definitely proved by the isolation, in each case, of both the possible urethanes and monophenyl ureas. The actual separation of the two isocyanates did not prove feasible. It is of interest to note, in this connection, that acetic anhydride is not recorded as a reagent capable of converting oleic into elaidic acid, or *vice versa*. Furthermore, the urethanes when treated with acetic anhydride under the same conditions showed no tendency to rearrange to form geometrical isomers.

The possibility that this rearrangement at the double bond may have taken place under the influence of a shock to the molecule as a whole, involved in the rearrangement taking place to form the isocyanate radical is, however, rendered rather remote by the fact that a corresponding change does not take place during the Lossen and Lengfeld-Stieglitz rearrangements mentioned above, in each of which the accepted explanation involves the assumption of isocyanates as intermediate products. The present observation remains, therefore, an unexplained fact which will require consideration in any future discussion of the mechanism of rearrangements of the types under consideration here.

Experimental Part

Oleo-hydroxamic Acid.—This acid has been described by Morelli⁹ who prepared it from triolein. For its preparation, 15 g. of hydroxylamine hydrochloride in 100 cc. of hot alcohol was treated with a solution of 9.2 g. of sodium in 100 cc. of alcohol, and the mixture added to a solution of 62 g. of ethyl oleate in 200 cc. of alcohol. After heating under a reflux condenser for 2 hours most of the alcohol was removed by distillation and a considerable excess of 15% hydrochloric acid added. After filtration the product was recrystallized from alcohol (acetone is also good). Various modifications of the process gave no better results.

Elaido-hydroxamic Acid.—Prepared from ethyl elaidate by a method similar to that already described, this acid formed white flakes, m. p. 86°. It is less soluble in alcohol than is the oleo derivative.

⁸ Lengfeld and Stieglitz, *Am. Chem. J.*, **15**, 215, 504 (1893); **18**, 751 (1896). Stieglitz, **29**, 49 (1903).

⁹ Morelli, *Zentr.*, 1908, II, 1019.

Analysis. Calc. for $C_{18}H_{35}O_2N$: N, 4.71. Found: 4.70.

Ricinoleo-hydroxamic Acid.—Ethyl ricinoleate was prepared from the fatty acids of castor oil without special purification. From this the hydroxamic acid was made in the usual way. It crystallizes from ether in white flakes, m. p. 65°.

Analyses. Calc. for $C_{18}H_{35}O_3N$: N, 4.47. Found: 4.41, 4.38, 4.41.

Linolo-hydroxamic Acid.—Ethyl linolate, prepared from linolic acid regenerated from the tetrabromide, was used for this preparation. The product obtained melted at 8–10°, and darkened and resinified on standing, doubtless due to oxidation. No additional derivatives were prepared.

Analyses. Calc. for $C_{18}H_{35}O_2N$: N, 4.74. Found: 4.69, 4.68, 4.71.

Oleo-acetylhydroxamic Acid.—In the acetylation, 10 parts of dry acetone was used as solvent, and only a very slight excess of anhydride. The solution should not be too concentrated. After heating under a reflux condenser for 0.5 hour, the solvent was evaporated. Recrystallized from alcohol, the product melted at 63°.

Analyses. Calc. for $C_{20}H_{37}O_3N$: N, 4.19. Found: 4.17, 4.15, 4.14.

Elaido-acetylhydroxamic Acid.—Prepared as above, this acid forms silvery flakes from alcohol, m. p. 84°.

Analyses. Calc. for $C_{20}H_{37}O_3N$: N, 4.19. Found: 4.12.

λ -Acetyl-ricinoleo-acetylhydroxamic Acid.—Two mols of acetic anhydride are required in this case, as the hydroxyl of the ricinoleyl radical is also acetylated. The product, which was not completely purified, was an oil at ordinary temperatures. On cooling, it solidified, and melted at 6–8°.

Analyses. Calc. for $C_{22}H_{39}O_5N$: N, 3.52. Found: 3.48, 3.46, 3.50.

Oleo-diacetylhydroxamic Acid.—Attempts to introduce both acetyl groups in a single operation, usually resulted in mixtures containing various amounts of isocyanates (see later). Better results were obtained by dissolving the mono-acetyl derivative in acetone, and warming gently with one mol of anhydride. The product forms shining plates from alcohol, m. p. 64–5°. As expected, it does not rearrange in alkaline solution.

Analyses. Calc. for $C_{22}H_{39}O_4N$: N, 3.67. Found: 3.64, 3.62, 3.64.

Elaido-diacetylhydroxamic Acid.—This acid, m. p. 82°, is very similar in preparation and properties to the one just described.

Analyses. Calc. for $C_{22}H_{39}O_4N$: N, 3.67. Found: 3.62, 3.60, 3.62.

Lossen Rearrangement; Formation of Ureas.—This rearrangement takes place perfectly normally on warming the mono-acetyl hydroxamic acids described above with aqueous alkali, according to the equation $2RCONHOCOCH_3 + K_2CO_3 = RNHCONHR + 2KOCOCH_3 + 2CO_2$. However, on account of the very slight solubility of the acids themselves, a considerable excess of normal carbonate solution (35–70 cc. per g. of acid) is necessary for complete solution. After warming for 0.5 hour on a water-bath the solution becomes cloudy, and the addition of a few drops of hydrochloric acid (sometimes not necessary) causes the urea to separate.

Di-trans-heptadecylenyl Urea.¹⁰—The product obtained as described above from oleo-acetylhydroxamic acid, was a solid from which impurities could be removed by extracting with warm alcohol, in which the urea itself was very insoluble. The product, crystallized from chloroform, formed needles, m. p. 59°.

¹⁰ Michael, *J. prakt. Chem.*, [2] **52**, 349 (1895), is inclined to classify oleic and elaidic acids as maleinoid and fumaroid forms respectively; see also, *ibid.*, **38**, 1 (1888) and **46**, 209 (1892). Without any intention of entering this controversy, the term "trans" is used in this paper to refer to derivatives of the oleic acid type, and "cis" for derivative directly related to elaidic acid, merely as a matter of reference.

Analyses. Calc. for $C_{35}H_{68}ON_2$: N, 5.36. Found: 5.29, 5.25, 5.26.

Di-*cis*-heptadecylenyl Urea.—This substance was prepared from elaido-acetylhydroxamic acid in the same way as described for the *trans* compound. It melted at 92–93°.

Analyses. Calc. for $C_{35}H_{68}ON_2$: N, 5.36. Found: 5.28, 5.24, 5.26.

Dihydroxy-heptadecylenyl Urea.—Acetyl-ricinoleo-acetylhydroxamic acid treated as described above, yields an oily liquid. Analysis shows that the λ -acetyl group is not completely removed in this reaction. On warming the product with 10% caustic alkali at 80–90° the hydrolysis of the remaining acetyl group is completed, and the product, recrystallized twice from alcohol, melted at 57.5°.

Analysis. Calc. for $C_{35}H_{68}O_3N_2$: N, 4.96. Found: 4.92.

Preparation of Urethanes.—The proper acetylhydroxamic acid, carefully dried, is treated with one equivalent of sodium dissolved in absolute alcohol, and warmed for 20 minutes at a suitable temperature. The alcohol is then removed, for the most part, by distillation, and the urethane dissolved in hot 70° ligroin, filtered from sodium acetate, and crystallized.

***Trans*-heptadecylenyl Urethane.**—Oleo-acetylhydroxamic acid was warmed with sodium ethylate at 40° as described; the product from ligroin melted at 42–43°.

Analyses. Calc. for $C_{20}H_{39}O_2N$: N, 4.30. Found: 4.23, 4.17, 4.20, 4.18, 4.22.

The corresponding methyl ester, methyl *trans*-heptadecylenyl carbamate, melted at 40–41°.

***Cis*-heptadecylenyl Urethane.**—The elaido-acetylhydroxamic acid was heated at 70° as described, and the alcohol distilled. When the ligroin is cooled in a freezing mixture, the yield is almost quantitative. The urethane melted at 87–88°.

Analysis. Calc. for $C_{20}H_{39}O_2N$: N, 4.30. Found: 4.25.

The corresponding methyl ester, methyl *cis*-heptadecylenyl carbamate, melted at 85–86°.

In none of these reactions was there any sign of inversion at the double bond.

Heptadecylenyl Isocyanates from Oleo-hydroxamic Acid.—A saturated solution of the hydroxamic acid in acetone was prepared and rather more than two mols of acetic anhydride added. The solution was warmed on the water-bath for 10–15 minutes, the acetone evaporated, and the residue dissolved in ligroin. After crystallizing from this solvent a good yield was obtained of a white crystalline product, rather stable even in air. The following table shows the effect of variations in time of heating 6 g. of sample, and in quantity of anhydride.

No.	Time Min.	Anhydride G.	Melting point ° C.	No.	Time Min.	Anhydride G.	Melting point ° C.
1	5	1	48–60	4	10	1	59–68
2	5	1.5	60–70	5	15	1	66–84
3	5	2	65–80				

The first figure under "melting point" is in each case the point at which melting begins, and the last point that at which fusion is complete. As, however, variable amounts of the *trans*-acetyl derivative are always present, these figures have little significance. No *cis*-acetyl derivative was ever found. Mixture 5, after several recrystallizations, melted at 48–52°. This product gave no test with ferric chloride for hydroxamic acids.

Analysis. Calc. for $C_{18}H_{33}ON$: N, 5.02. Found: 4.93.

Its behavior with alcohol and with aniline leaves no doubt that this product is

essentially a mixture of *cis*- and *trans*-heptadecylenyl isocyanates. It was not found possible to separate these two isocyanates. When, however, a portion of the mixture was gently warmed with absolute alcohol, solution and reaction took place, and it was possible to isolate by fractional crystallization, both *cis*- and *trans*-heptadecylenyl urethanes, melting at 87–88° and 41–42°, respectively. The identities of these substances were confirmed by analyses, and by the fact that the melting points were not lowered when the urethanes obtained by this method were mixed with those obtained by the Lengfeld-Stieglitz rearrangement.

By way of further confirmation, the isocyanate mixture was slightly warmed with an excess of aniline. The product, after a rather tedious process of fractional crystallization from alcohol, yielded two substances, m. p. 72–73° and 83–84°, both of which, after heating at 150° with hydrochloric acid, gave tests for aniline. There is no doubt that these are the two heptadecylenyl ureas; and it is considered highly probable that the higher-melting product is, as usual in this series, the *cis* compound.

Analyses. Calc. for $C_{24}H_{40}ON_2$: N, 7.58. Found, for *cis*-urea: 7.54, 7.47, 7.50, 7.49. Found, for *trans*-urea: 7.51, 7.54, 7.50.

Heptadecylenyl Isocyanates from Elaido-hydroxamic Acid.—The reaction was very similar to that described above. The yield was less good, and heating for about 45 minutes seemed to be necessary. A product was again isolated which had the composition of a mixture of isocyanates (N, calc. 5.02%; found, 4.94, 4.90%) but which melted rather higher than the similar product previously described (72–82°).

On treatment with alcohol this product gave two urethanes which were identical with those already described. The proportion of *cis*-urethane was, however, distinctly greater in this case.

Similarly, with aniline, a product yielding *cis*- and *trans*-heptadecylenyl phenylureas, identical with those described above, was obtained. Because the isocyanate mixture from elaido-hydroxamic acid had a markedly higher melting point, and also gave a much smaller yield of the *trans*-urethane, it is considered that this mixture contained a larger proportion of the *cis*-isocyanate than did the other. This would also imply that an equilibrium was not reached between the two isocyanates. Such a result would not be surprising, however, as under the conditions of the reaction, a number of competing processes are taking place (*e. g.*, the formation of diacetyl derivatives).

Summary

1. Unsaturated fatty acids (oleic, elaidic, linolic, ricinoleic) form hydroxamic acids as do aromatic and saturated aliphatic acids.
2. The Lossen rearrangement, giving ureas, is not affected by, and does not affect, the double bond.
3. The same applies to the Lengfeld-Stieglitz rearrangement, giving urethanes.
4. The supposedly analogous rearrangement to isocyanate, using acetic anhydride, is complicated by the fact that a mixture of *cis*- and *trans*-isocyanates results, whichever pure hydroxamic acid (oleo- or elaido-) is used.