colorless crystals which were collected and washed with ether. This product melted at 187°; after several recrystallizations from alcohol and passage through a column of alumina, it had m.p. 194–195°; λ_{max}^{Nujol} 3.75–3.95, 5.71, 5.89, 6.17 μ.

Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.35; N, 5.54.

Diacetyl derivative of o-toluidine (X). This was prepared by the method of Sudborough[26] and obtained as an oil, b.p. 142–143° (9 mm.) [lit.[26] b.p. 152–153° (20 mm.)]; λ_{max}^{Nujol} 5.78–5.83 μ (poorly resolved doublet).

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Configurations of the Isophorone Oximes

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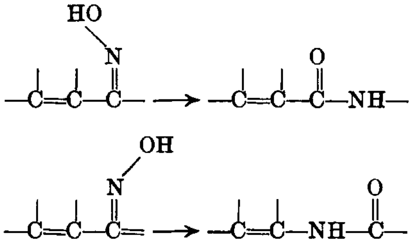
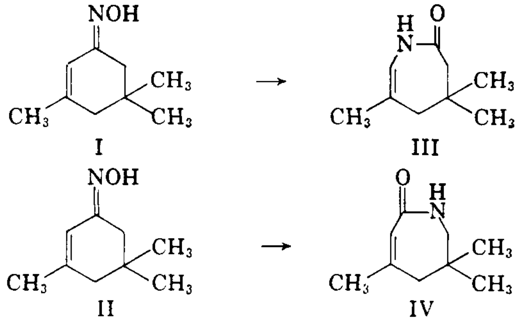
The Beckmann rearrangement has not only been a useful synthetic tool but has proved of great value in determining the configurations of *syn* and *anti* aldoximes and ketoximes.[1] Previous work has been virtually exclusively limited to the study of oximes of saturated carbonyl compounds with a few references to rearrangement of α,β-unsaturated ketoximes.[2–10] The latter type should be especially valuable for configuration determination since only an ultraviolet spectrum might be necessary to distinguish between the products. Thus, *syn*-α,β-unsaturated ketoximes lead to α,β-unsaturated amides or lactams while the *anti*-isomers give acylated enamines or enamine lactams. The two types of products might be expected to have markedly different ultraviolet absorption maxima but which should be reasonably constant from compound to compound. Also, if the unsaturated and saturated lactams and/or oximes can be related (reduction or oxidation), the configurations of the saturated oximes are simultaneously determined.



We attempted to use this method to assign the proper structure to a C-ring steroid lactam.[9] Although the isophorone (3,5,5-trimethyl-2-cyclohexenone) oximes and resulting lactams were excellent models for the steroid case from the standpoint of both ring size and substitution, the evidence which had been presented suggested that the configurations had been incorrectly assigned,[5] a premise shown to be true by the present work.

The existence of the two oximes of isophorone was a subject of controversy in the early chemical literature.[11–15] It was assumed[12,15] that their formation was due to a double bond isomer present in some preparations of isophorone. Apparently the concept[16] of *syn*- and *anti*-oximes was slow to gain acceptance. Finally, Montgomery and Dougherty[5] repeated the separation of the two isomers, demonstrated their interconvertibility, and isolated a Beckmann rearrangement product in low yield from each. We have repeated and confirmed this work and have greatly improved the yield in the Beckmann rearrangement of the *anti*-oxime by using the polyphosphoric acid method of Horning.[4]



That the two oximes were really *syn*- and *anti*-isomers of an α,β-unsaturated ketone was shown by their nearly identical ultraviolet spectra.[5] The additional question arises in a reaction proceeding in low yield as to whether the product truly represents the configuration of the starting material. However, when a good yield is obtained, either the product is related directly to the starting material or isomerization of the starting material is essentially complete before reaction takes place. Since, in the

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[12] J. Bredt and R. Rübel, *Ann.*, 299, 160 (1898).

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[14] L. Wolff, *Ann.*, 322, 351 (1902).

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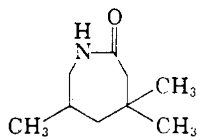
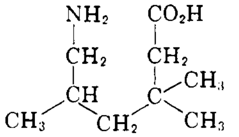
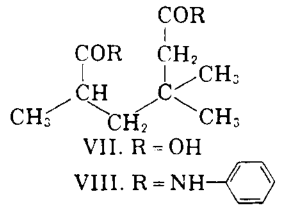
present case, oxime I gave a good yield of lactam III, either the two are related or oxime I isomerized to oxime II and then rearranged to lactam III. However, if the latter situation applied, then rearrangement of oxime II *under the same conditions* would also give a good yield of lactam III. In fact, though, oxime II led to a poor yield of lactam IV and the material isolated from the mother liquors of this reaction was shown by infrared spectra to be a mixture of lactams III and IV. Thus, we may surely conclude that a proof of the structures of lactams III and IV demonstrates the configuration of oximes I and II respectively.

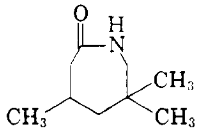
In a parallel series of experiments, each lactam was successively hydrogenated to a trimethyloxohexamethylenimine, hydrolyzed to an aminotrimethyl-hexanoic acid and oxidized[17] to a trimethylhexanedioic acid. These changes are shown by formulas III → V → VI → VII and IV → IX → X → XI. The final products are known compounds of unambiguous structure[18,19] so that identification of the acid eventually obtained from oxime I with 2,4,4-trimethyl-hexanedioic acid and that from oxime II with 2,2,4-trimethylhexanedioic acid established the configurations of the oximes. In addition, the results show that a seven-membered enamine lactam has an ultraviolet absorption maximum about 20 mμ higher than the corresponding α,β-unsaturated lactam so that the spectra constitute a firm basis for distinguishing between two α,β-unsaturated six-membered ketoximes. Even when only one oxime can be obtained, absorption by the resulting lactam in the 240 mμ region would be excellent evidence for an *anti*-oxime, while absorption in the 220 mμ region would enable the conclusion that a *syn*-oxime was the starting material.

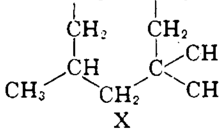

V

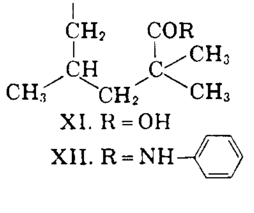

VI


VII. R = OH

VIII. R = NH—


IX


X


XI. R = OH

XII. R = NH—

The saturated lactams V and IX have been previously reported.[20] They were prepared by Beckmann rearrangement of dihydroisophorone (3,3,5-trimethylcyclohexanone) oxime and subsequent fractional crystallization. The melting points recorded were α: m.p. 111–112°, β: m.p. 82–84°. When our pure lactams prepared from III and IV showed m.p. 110–111° and m.p. 109–110° (m.p. 114–115°, polymorph) respectively, we repeated the work of Wallach[20] and isolated his α-lactam, m.p. 108–109° (m.p. 112–114°, polymorph). Not only the formation of a polymorph on melting but the infrared spectrum showed this to be identical with lactam IX. The so-called β-form may be presumed to be a mixture of V and IX (mixed m.p. 80–86°).

Lactam mixtures from both isophorone[8] and dihydroisophorone[21] have been claimed in patents but no attempt was made to separate the isomers. The lactams were converted to amino acids,[8,21] again giving mixtures.

EXPERIMENTAL[22]

Isophorone oxime. Redistilled isophorone (13.8 g., 0.1 mole) and 8.7 g. (0.125 mole) of hydroxylamine hydrochloride were dissolved in 20 ml. of pyridine and 100 ml. of 95% ethanol. The solution was heated under reflux for 1.5 hr., concentrated to a small volume and diluted with 100 ml. of water. The resultant oil crystallized on standing. The yield of isophorone oxime, m.p. 74–79°, was 15.1 g. (98%).

A systematic fractional crystallization from aqueous methanol gave approximately equal quantities of the less soluble *anti*-oxime I, m.p. 102–104° (lit.[5], m.p. 101.8–102.4°) and the more soluble *syn*-oxime II, m.p. 77–78.5° (lit.[5], m.p. 78.2–78.5°).

4,5-Dihydro-4,4,6-trimethyl-2(3H)-azepinone (III). *anti*-Oxime (15.00 g.) in 150 ml. of polyphosphoric acid was heated at 131–135° for 10 min. The solution was poured into 1 l. of water and continuously extracted overnight with ether. The ether was dried over potassium carbonate and distilled and the residue washed well with water giving 10.74 g. (72%) of enamine lactam III, m.p. 89–91°. Crystallization from aqueous methanol yielded small needles, m.p. 92–93° (lit.[5], m.p. 90.1–90.7°); $\lambda_{max}^{CH_3OH}$ 237 mμ, ε 7,200.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.75; H, 9.97; N, 9.14.

6,7-Dihydro-4,6,6-trimethyl-2(5H)-azepinone (IV). *syn*-Oxime (2.06 g.) in 40 ml. of polyphosphoric acid was heated at 132–135° for 10 min. and the reaction mixture worked up

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(20) O. Wallach, *Ann.*, **346**, 249 (1906).

(21) A. V. Snider and R. C. Morris, U. S. Patent **2,462,-008** (Feb. 15, 1949).

(22) We would like to thank R. T. Dillon, H. W. Sause, and their associates for analyses (samples dried overnight at room temperature under high vacuum) and spectra (ultraviolet in methanol, infrared in chloroform). Melting points are uncorrected.

We are indebted to W. M. Selby and R. L. Johnson for hydrogenations and to E. G. Daskalakis and Miss S. Glanville for cellulose column partition chromatography. The solvent systems used for paper chromatography (ascending) were BAW: *n*-butyl alcohol–acetic acid–water 5:2:3, MPW: methyl ethyl ketone–pyridine–water 60:15:25 and PAW: isopropyl alcohol–concd. ammonium hydroxide–water 7:1:2.

as described above. The residue from ether extraction was crystallized three times from petroleum ether (b.p. 60–80°) yielding 0.44 g. (21%) of the α,β-unsaturated lactam IV as long prisms, m.p. 112–113° (lit.[5], m.p. 108.8–109.1°); $\lambda_{max}^{CH_3OH}$ 218 mμ, ε 11,800.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.77, H, 9.98; N, 9.29.

4,4,6-Trimethyl-2-oxohexamethylenimine (V). Lactam III (14.0 g., 0.091 mole) in 50 ml. of acetic acid was hydrogenated over 5% palladium on carbon at room temperature and atmospheric pressure. Hydrogen uptake stopped at 106% of one molar equivalent (3 hr.). The filtrate after removal of catalyst was concentrated to dryness and the residue slurried with a little cold petroleum ether (b.p. 60–80°) to give the saturated lactam V as irregular prisms, 12.8 g. (90%), m.p. 109–111°. A sample was sublimed for analysis at 90° (0.01 mm.), m.p. 110–111°; $\lambda_{max}^{CH_3OH}$ 202.5 mμ, ε 6,500.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.03. Found: C, 69.53; H, 10.88; N, 9.18.

6-Amino-3,3,5-trimethylhexanoic acid (VI). Lactam V (1.55 g., 0.01 mole) in 30 ml. of 48% hydrobromic acid was heated under reflux for 24 hr. The solution was concentrated to dryness, the residue taken up in water and the amino acid liberated by passage through an Amberlite IR-45 ion exchange column. Concentration of the ninhydrin positive fractions to dryness yielded 1.30 g. (75%) of compound VI, m.p. 180–181°. Crystallization from methanol–ethyl acetate gave glistening plates, m.p. 181.5–183°; R_F .79 (BAW), .55 (MPW).

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.70; H, 11.08; N, 8.18.

2,4,4-Trimethylhexanedioic acid (VII). Amino acid VI (1.56 g., 0.009 mole) was dissolved in 10 ml. of water and 2.25 ml. of 4*N* sodium hydroxide added. The solution was treated with 1.90 g. (0.012 mole) of potassium permanganate in 35 ml. of water and the temperature maintained at 25–30° by external cooling. After the exothermic reaction had subsided, the mixture was allowed to stand at room temperature for 1 hr., heated on the steam bath for 15 min., and the manganese dioxide removed by filtration through Celite. The filter cake was washed thoroughly with boiling water, the combined filtrates acidified to *p*H 1 with 12*N* hydrochloric acid and the solution continuously extracted overnight with ether. Distillation of the ether gave 1.51 g. of an oily solid; R_F .41 (s), .55 (w), .62 (w) (PAW). The product was purified by partition chromatography on a cellulose column using the PAW system. The fractions containing only R_F .41 material were combined, concentrated to dryness, the residue dissolved in water and passed through a Dowex 50 ion exchange column to convert the ammonium salt to the free acid. Concentration of the effluent to dryness gave 0.74 g. (44%) of acid VII, m.p. 66–69°. Two crystallizations from water yielded chunky prisms, m.p. 72–73.5° (lit.[17], m.p. 68.5–69.5).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.59; H, 8.95.

The acid VII was converted to the acid chloride by refluxing in thionyl chloride and the crude acid chloride treated with aniline in benzene to yield the dianilide VIII, granules from benzene, m.p. 164–165° (lit.,[17] m.p. 162.8–163.3°).

4,6,6-Trimethyl-2-oxohexamethylenimine (IX). Lactam IV (6.54 g., 0.0427 mole) was hydrogenated in 80 ml. of acetic acid over pre-reduced platinum catalyst. Hydrogen uptake stopped after 98% of one molar equivalent had been absorted (6 hr.). Work-up as described for lactam V gave 4.91 g. (75%) of the desired product, m.p. 107–110°. The analytical sample was sublimed at 90° (0.01 mm.). The material began to melt at 109°, resolidified at 111° and remelted sharply at 114–115°. On cooling and remelting, the sample had m.p. 109–110° with no resolidification; $\lambda_{max}^{CH_3OH}$ 202.5 mμ, ε 6,700.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.03. Found: C, 69.62; H, 10.97; N, 9.39.

6-Amino-3,5,5-trimethylhexanoic acid (X). The procedure described for compound VI was followed using 1.55 g. (0.01 mole) of lactam IX and yielded 1.25 g. (72%) of the desired amino acid, m.p. 150–152°. Crystallization from methanol–ethyl acetate gave fine needles, m.p. 154–155°; R_F .75 (BAW), .58 (MPW).

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.48; H, 10.94; N, 8.49.

2,2,4-Trimethylhexanedioic acid (XI). The procedure for the oxidation of compound VI was followed using 1.04 g. (0.006 mole) of amino acid X and 1.27 g. (0.008 mole) of potassium permanganate and yielded 1.03 g. of an oily solid; R_F .41 (s), .59 (w), .70 (tr) (PAW). Purification was carried out as under VIII. The crude acid XI, 0.61 g. (54%), had m.p. 97.5–100°. Crystallization from water gave plates, m.p. 100–101.5° (lit.,[17] m.p. 100.1–100.5°).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.61; H, 8.55.

As described above, the acid XI gave the dianilide XII, small prisms from benzene, m.p. 172–173° (lit.,[17] m.p. 169.4–169.8°).

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Improved Preparations of Fluorenone Oxime and 9-Fluorylamine

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In an investigation on the so-called[1] tetrafluorenylhydrazine,[2] a large quantity of 9-fluorylamine was used. This long-known substance has almost always been prepared from fluorene by successive oxidation, oximation, and reduction, following old procedures.[3] An early suggestion by Wislicenus[4] that fluorenone oxime might better be made by direct nitrosation of fluorene has not been acted on.

Wislicenus' reaction has now been studied, using not only ethereal potassium ethoxide as he recommended, but also other solvents and bases. Results are presented in Table I, where each experiment represents use of 15 g. of pure fluorene. A convenient procedure is described using potassium hydroxide in butyl alcohol.

Reduction of fluorenone oxime in acetic acid with zinc dust, added in portions, as heretofore recommended, was vigorous, messy, and difficult to control, and a considerable amount of acetylaminofluorene was formed. These difficulties were easily overcome by using dilute acetic acid and granu-

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[1] It is probable that the compound is really a β-aza analog of α,γ-bisdiphenylene-β-phenylallyl; C. F. Koelsch, *J. Am. Chem. Soc.*, **79**, 4439 (1957).

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