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).

[2] S. Goldschmidt, *Ann.*, **456**, 161 (1927); Chu and Weismann, *J. Am. Chem. Soc.*, **76**, 3787 (1954).

[3] J. Schmidt and J. Söll, *Ber.*, **40**, 4257 (1907). J. Schmidt and H. Stützel, *ibid.*, **41**, 1243 (1908); C. K. Ingold and C. L. Wilson, *J. Chem. Soc.*, 1499 (1933); S. Schulman, *J. Org. Chem.*, **14**, 382 (1949).

[4] W. Wislicenus and M. Waldmuller, *Ber.*, **41**, 3334 (1908).

TABLE I

Nitrosation of Fluorene

Solvent	Base	Yield of oxime, %
$(C_2H_5)_2O$, C_6H_6[a]	KOC_2H_5	77,[b] 81[c]
C_2H_5OH	KOH	32
C_4H_9OH	KOH	71
C_4H_9OH	KOH[d]	5
C_4H_9OH	KOH[e]	80, 82, 83
C_4H_9OH	NaOH	11
C_4H_9OH	$NaOC_4H_9$	18
$CH_3CH(OC_3H_7)_2$[f]	KOH	30

[a] Wislicenus conditions. [b] No stirring. [c] Vigorous stirring. [d] 50% aqueous solution. [e] Solvent partially distilled after solution of base to remove water. [f] An excellent solvent for many base-catalyzed reactions. C. Weizmann, E. Bergmann, and M. Sulzbacher, *J. Org. Chem.*, **15**, 918 (1950).

lated zinc, added all at once, as described in the present note.

EXPERIMENTAL

A solution of 100 g. of 85% potassium hydroxide in 500 ml. of butyl alcohol was boiled for 2 hr. under a 20-cm. column with a fractionating head to remove about 30 ml. of water, butyl alcohol being returned. Then 166 g. of technical fluorene was added. This was followed by dropwise addition during 10 min. of 125 ml. (110 g., calcd. 103 g.) of butyl nitrite,[5] and the mixture was boiled for 10 min. It was then diluted with water (two 500-ml. portions) and partially distilled to remove butyl alcohol. The aqueous residue was cooled and extracted with 100 ml. of ligroin,[6] then acidified with acetic acid. There was obtained 143 g. (73%) of fluorenone oxime, m.p. 175–184°, used without purification for reduction. Recrystallization from acetic acid gave tan needles, m.p. 187–188° corresponding to reported values.

A solution of 150 g. of oxime in 450 ml. of warm acetic acid was diluted with 150 ml. of water and heated to about 100°. Then 110 g. of 20 mesh granulated zinc was added, resulting in a smooth reaction which kept the mixture boiling for about 20 min. The mixture was boiled for an additional 20 min., and then decanted from the little remaining zinc into a hot solution of 450 ml. of hydrochloric acid in 1250 ml. of water. Cooling gave gray needles which were pressed on a filter, washed with three 100-ml. portions of ether, and dried. The resulting 9-fluorylamine hydrochloride formed white needles of excellent purity that darkened at 210°, m.p. 220° dec. (reported, 216–217°); yield 128 g. (76%). The yield was raised to 90% by working over the mother liquors, but this was uneconomical.

9-Fluorylamine, m.p. 60–62° was obtained by treatment with base of the salt. It was interesting to discover that although it could be distilled at 20 mm. in quantities of less than 1 g., attempted distillation of larger quantities resulted in much decomposition with formation of dibiphenylene-ethane, -ethylene, and resin.

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[5] (5) Butyl nitrite was prepared by adding a slight excess of iced sulfuric acid in portions to a separatory funnel containing ice and 1 equivalent each of butyl alcohol and concentrated aqueous sodium nitrite, with shaking after each addition. The lower layer was discarded, and the product was washed with a little dilute sodium carbonate and stored over solid potassium carbonate; yield, 94%. Preparation of 2 moles of nearly pure butyl nitrite in this way required only a few minutes, and the product kept well. Samples more than 2 years old gave as good results as fresh ones.

[6] (6) This extraction removed 65 g. of dark oil containing 19 g. of fluorene, 35 g. of crude butylidenefluorene (b.p. 200–240°, m.p. 55°, dibromide m.p. 93–94° dec.) and 8 g. of black resin, probably corresponding to impurities in the technical fluorene used.

Spectral Evidence for the Structures of the Nitrofluorescein Isomers

Felix Borek

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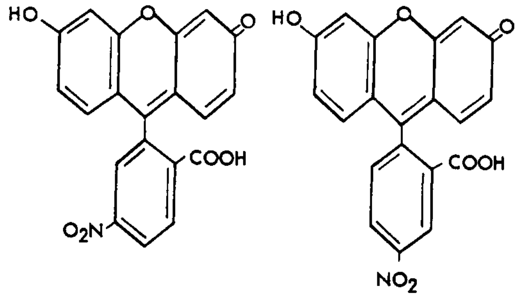
In 1905 Bogert and Wright[1] reported that condensation of 4-nitrophthalic acid with resorcinol yields a nitro derivative of fluorescein. One might expect from this reaction two isomeric products differing in the position of the nitro group (Fig. 1), which would result from the condensation of one or the other carboxyl groups of 4-nitrophthalic acid. The authors, however, have not indicated the existence of such isomers.

In 1942 Coons and co-workers[2] repeated the above reaction with the eventual aim of obtaining a derivative of fluorescein which could be used as a fluorescent label for antibody proteins. They apparently believed the crude product to be 4′-nitrofluorescein (Fig. 1b). In 1950, however, Coons and Kaplan[3] found the product to be a mixture of two isomers and succeeded in separating them by fractional crystallization of the 3,6-diacetates. They called the isomer which was less soluble in benzene-ethanol mixture "nitrofluorescein diacetate I," and the more soluble one "nitrofluorescein diacetate II." Henceforth all other derivatives prepared from these compounds received designations of I or II, respectively. No attempt has been made to determine the position of the nitro group in either isomer, but the separation of the two



(a) (b)

Fig. 1. (a) 5′-nitrofluorescein; (b) 4′-nitrofluorescein

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[1] (1) R. T. Bogert and R. G. Wright, *J. Am. Chem. Soc.*, **27**, 1310 (1905).

[2] (2) A. H. Coons, H. J. Creech, R. N. Jones, and E. Berliner, *J. Immunol.*, **45**, 159 (1942).

[3] (3) A. H. Coons and M. H. Kaplan, *J. Exp. Med.*, **91**, 1 (1950).