[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

The Chemistry of Nitroacetic Acid and its Esters. I. The Alkylation of Alkylnitroacetates with Gramine

BY D. A. LYTTLE AND D. I. WEISBLAT

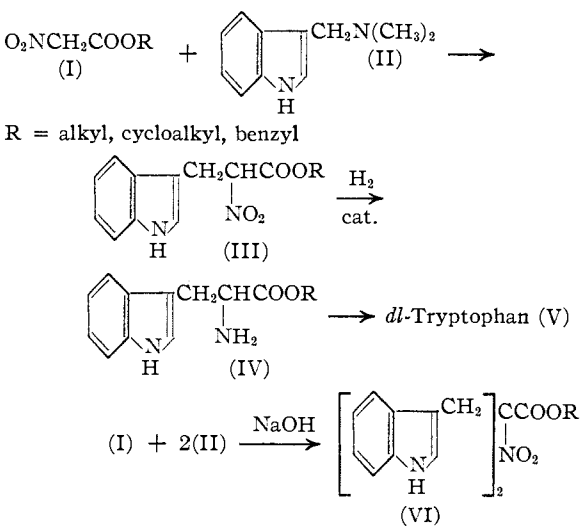
Esters of nitroacetic acid, because of their active methylene group, plus the fact that the nitro group is in the alpha position, seem to be promising intermediates for a number of compounds such as amino acids, nitroparaffins, amines, and their derivatives. In spite of these considerations, the chemistry of alkylnitroacetates has been explored only in a very cursory manner, leaving many interesting questions unanswered, many possibilities unexplored. We have, therefore, begun an investigation of the chemistry of these compounds.

Nitroacetic acid and its esters were the object of research as early as 1872 when Kolbe[1] attempted to prepare nitroacetic acid by the reaction between chloroacetic acid and potassium nitrite. While the compound was undoubtedly formed, it decomposed under the conditions of the experiment to give nitromethane and carbon dioxide. In the twenty-eight years that followed Kolbe's attempt, a number of other investigators[2,3,4] tried unsuccessfully to prepare both the free nitroacetic acid and its ethyl ester. The ethyl ester was finally synthesized quite unintentionally when Bouveault and Wahl,[5] investigating the action of nitric acid on aliphatic compounds related to ethyl acrylate, prepared ethyl α-nitro-β,β-dimethylacrylate which splits into acetone and ethyl nitroacetate when treated with alkali. As proof of its structure, these authors reduced the ethyl nitroacetate to glycine.

The synthesis of free nitroacetic acid was accomplished in 1909 by Steinkopf[6] who obtained the di-sodium salt by treating nitromethane with 50% sodium hydroxide solution. Careful acidification of the di-sodium salt freed the acid, a solid which decomposes at its melting point (87–89°). The same author[7] later reported a simple method of esterifying the free acid which gives the ester in good yield.

Steinkopf's paper also contains what we believe to be the only recorded attempt to C-alkylate esters of nitroacetic acid. Steinkopf treated the silver salt of ethyl nitroacetate with methyl iodide and obtained ethyl α-nitropropionate in yields of 22 to 28%. Ethyl iodide under the same conditions gave yields of 24% on some runs, while on others no ethyl α-nitrobutyrate was obtained. According to Steinkopf, the major product of the methylation reaction is the O-methyl derivative of the aci-form ($C_2H_5OOCCH{=}NOOCH_3$) for which he reports a boiling point of 84° at 25 mm. This explanation of the alkylation reaction was disproved by Arndt and Rose[8] when they prepared the true methylnitronic ester by the action of diazomethane on ethyl nitroacetate. The nitronic ester was too unstable to be distilled at any pressure down to 0.01 mm., and differed from Steinkopf's compound in its other properties. To our knowledge, the structure of the compound which Steinkopf claimed to be nitronic ester has never been determined.

In contrast to the yields of C-alkylation reported by Steinkopf,[7] we have found that esters of nitroacetatic acid (I) are readily alkylated by gramine (II) (3-dimethylaminomethylindole) to give esters of α-nitro-β-(3-indole)-propionic acid (III) in good yield. This product is obtained when the two reactants are heated in xylene in the absence of any catalyst other than the gramine itself. It is interesting to note that when the reaction is carried out in the presence of catalytic amounts of powdered sodium hydroxide[9] a good yield of ester of nitro-bis-(3-methylindole)-acetic acid (VI) is obtained. Catalytic reduction of III proceeds smoothly to give ethyl-*dl*-tryptophan (IV) which is hydrolyzed by a short reflux with 10% sodium hydroxide to give *dl*-tryptophan (V).



Experimental

Ethyl α-Nitro-β-(3-indole)-propionate.—In a 250-cc. flask fitted with stirrer, thermometer, nitrogen inlet and

(1) Kolbe, *J. prakt. Chem.*, **5**, 427 (1872).
(2) Steiner, *Ber.*, **5**, 383 (1872).
(3) Lewkowitsch, *J. prakt. Chem.*, **20**, 163 (1879).
(4) Forcrand, *Bull. soc. chim.*, **31**, 536 (1879).
(5) Bouveault and Wahl, *Compt. rend.*, **131**, 748 (1900).
(6) Steinkopf, *Ber.*, **42**, 3925 (1909).
(7) Steinkopf, *Ann.*, **434**, 21 (1923).
(8) Arndt and Rose, *J. Chem. Soc.*, 1 (1935).
(9) Howe, Zambito, Snyder and Tishler, THIS JOURNAL, **67**, 38 (1945). These authors treated gramine with acetamidomalonic ester in the presence of powdered sodium hydroxide to obtain ethyl α-acetamido-α-carbethoxy-β-(3-indole)-propionate.

condenser were placed 8.66 g. (0.05 mole) of gramine,[10] 13.3 g. (0.10 mole) of ethyl nitroacetate,[6,7] and 50 cc. of dry xylene. While passing a slow stream of nitrogen through the vigorously stirred mixture, the temperature was raised to 90–100° and held there for five hours. During this time about one-half of the calculated amount of dimethylamine was collected in an acid trap through which the exit gases were passed. The hot solution was filtered and the xylene removed in vacuum. The residual gum was dissolved in chloroform and the solution was extracted with two 50-cc. portions of 10% hydrochloric acid, then washed with water until neutral. The chloroform solution was dried over anhydrous magnesium sulfate and the chloroform removed by concentration at 20 to 30 mm. Excess ethyl nitroacetate was removed by distillation at a pressure of 1 mm. The oil which remained was dissolved in chloroform and the solution extracted with successive portions of 5% sodium hydroxide until the amount of oil which appeared upon acidification of a test portion of extract was negligible. The combined extracts were carefully acidified with 10% hydrochloric acid, keeping the temperature below 20°, and extracted with chloroform. The oil which remained after drying and concentrating the chloroform solution crystallized readily. The yield of ethyl α-nitro-β-(3-indole)-propionate was 11.8 g. (90%). An analytical sample recrystallized four times from benzene–petroleum ether melted at 62.0 to 62.8° (uncor.).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.69; H, 5.38; N, 10.69. Found: C, 59.65, 59.62; H, 5.46, 5.24; N, 10.83.

***dl*-Tryptophan. A. Catalytic Reduction of III and Hydrolysis.**—In a bomb with a capacity of 40 cc. was placed 2.62 g. (0.01 mole) of ethyl α-nitro-β-(3-indole)-propionate, 15 cc. of absolute ethanol and about 0.5 g. of Raney nickel catalyst. The reduction was carried out at 100° and with an initial hydrogen pressure of 1500 p. s. i. at 25° in an Aminco rocking hydrogenator. The theoretical amount of hydrogen was taken up in two hours. The catalyst was removed by filtration and the filtrate was concentrated in vacuum. The crude *dl*-tryptophan ester, a light yellow oil, was refluxed for two hours with 16 cc. of 10% sodium hydroxide. Treatment of the solution with Darco-G-60 and filtration gave a sparkling filtrate which, after adjusting the *p*H to 5.9 with glacial acetic acid, deposited crystals of *dl*-tryptophan. When crystallization was complete the tryptophan was collected on a filter and then recrystallized from 100 cc. of 33% alcohol to give 1.0 g. of glistening platelets. This represents a yield of 50% based on III. After several recrystallizations from 33% alcohol the product melted at 278.0–280.0° (uncor., dec.). A mixed melting point with an authentic sample of *dl*-tryptophan was 278.0–280.0° (uncor., dec.).

(10) Kuhn and Stein, *Ber.*, **70**, 567 (1937).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N (as NH_2), 6.86. Found: C, 64.50, 64.65; H, 6.06, 5.92; N (as NH_2, Van Slyke), 6.99.

***dl*-Tryptophan. B. Chemical Reduction of III and Hydrolysis.**—In a 250-cc. flask fitted with a stirrer and reflux condenser were placed 2.62 g. of ethyl α-nitro-β-(3-indole)-propionate, 3.5 g. of powdered iron, 7.5 cc. of water, 7.5 cc. alcohol and 10 cc. of concentrated hydrochloric acid. The mixture was stirred vigorously for fifteen minutes and was then heated to boiling during the ensuing fifteen minute period. Refluxing was continued for fifteen minutes to complete the hydrolysis of ethyl tryptophan. The cooled mixture was made alkaline with 10% sodium hydroxide and filtered. The cake was washed thoroughly several times with water and the *p*H of the combined filtrate and washes was adjusted to 5.9 with sulfuric acid. The tryptophan which crystallized overnight was filtered, washed with a little cold water and recrystallized from 33% alcohol, giving 0.2 g. of product melting at 283–284° (uncor., dec.). A mixed melting point with an authentic sample was 282–283.5° (uncor., dec.).

Ethyl Nitro-bis-(3-methylindole)-acetate.—A mixture of 17.32 g. (0.10 mole) of gramine, 13.30 g. (0.10 mole) of ethyl nitroacetate, 85 cc. of dry xylene and 1.2 g. of powdered sodium hydroxide in a 500-cc. flask fitted with a stirrer, nitrogen inlet, condenser and thermometer, was heated to reflux with vigorous stirring. Dimethylamine was evolved and refluxing was continued for eight hours, when the evolution of dimethylamine was negligible. A little solid material was removed by filtration of the hot reaction mixture and washed with hot xylene. The combined filtrate and washes was extracted with two 50-cc. portions of 10% hydrochloric acid and washed well with water. Concentration of the organic layer left a crystalline residue weighing 18.2 g. (91%). An analytical sample recrystallized once from xylene and four times from alcohol melted at 142.0–143.0° (uncor.).

Anal. Calcd. for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; mol. wt., 391. Found: C, 68.17, 67.98; H, 5.57, 5.34; mol. wt. (Rast), 385.

Summary

A new synthesis of *dl*-tryptophan which consists of the alkylation of ethyl nitroacetate by gramine, reduction of the resulting ethyl α-nitro-β-(3-indole)-propionate, and hydrolysis of ethyl *dl*-tryptophan is presented.

An investigation of the chemistry of nitroacetic acid and its esters is being undertaken.

KALAMAZOO, MICHIGAN RECEIVED APRIL 30, 1947