Summary

Acetobacter suboxydans oxidized D-talitol to D-tagatose, m. p. 133–134°, $[\alpha]^{25}\text{D}-5°$, in yields of 75 to 84%.

The isomerization method by which Reichstein and Bosshard prepared tagatose from galactose has been modified to obtain more consistent yields by the use of an ion exchange resin in the purification procedure.

MADISON 6, WISCONSIN RECEIVED MAY 9, 1949

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

An Improved Synthesis of Esters of Nitroacetic Acid[1]

BY H. FEUER, H. B. HASS[2] AND K. S. WARREN[3]

Esters of nitroacetic acid have recently come into prominence as intermediates in the preparation of amino acids.[4] These esters have been prepared by W. Steinkopf[5] who employed two methods. The one which gave a 37% yield of the ethyl ester consisted of suspending dipotassium nitroacetate in absolute ethanol and introducing dry hydrogen chloride.

The second method, which gave a 71% yield based on nitroacetic acid, involved the following three steps

$$2CH_3NO_2 + 2KOH \longrightarrow KO_2N{=}CHCOOK + NH_3 + 2H_2O \quad (1)$$

$$KO_2N{=}CHCOOK + 2HCl \longrightarrow O_2NCH_2COOH + 2KCl \quad (2)$$

$$O_2NCH_2COOH + ROH \xrightarrow{H^+} O_2NCH_2COOR + H_2O \quad (3)$$

The disadvantage of this procedure lies in the second step because it requires the preparation and isolation of nitroacetic acid from the dipotassium salt and this can only be accomplished with a 60–70% yield. Furthermore, nitroacetic acid is very unstable. It decomposes into nitromethane and carbon dioxide, and this further decreases the yield in the esterification step. Steinkopf[5] stated that he was unable to prepare esters directly from the dipotassium salt with concd. sulfuric acid and the desired alcohol. He claimed that the rate of decomposition of the nitroacetic acid liberated from its dipotassium salt was faster than the rate of esterification. This statement seemed, however, contradictory to the fact that he was able to prepare esters by working with the free nitroacetic acid and using an equimolar amount of concd. sulfuric acid at −15 to +3° as indicated in step 3 above.

It seemed therefore advisable to attempt the synthesis of esters of nitroacetic acid directly from the dipotassium salt by acidification with concd. sulfuric acid and by working at low temperatures. As a result, the methyl and ethyl esters have been prepared in a 60% yield.

The results of several experiments are given in the following three tables to illustrate the influence of reaction temperature, reaction time, and amount of sulfuric acid upon the ester formation.

TABLE I

EFFECT OF REACTION TEMPERATURE ON THE YIELD OF METHYL NITROACETATE

In run No. 6 anhydrous sodium sulfate was omitted.

Run	Temp. during first 24 hours, °C.	Temp. during the next 144 hours, °C.	Yield, %
1	0 to +5	23 to 25	12
2	− 2 to 0	23 to 25	28
3	−15 to −10	23 to 25	38
4	−60 to −50	23 to 25	60
5	−60 to −50	1 to 5	60
6	−60 to −50	1 to 5	45

TABLE II

EFFECT OF REACTION TIME ON THE YIELD OF METHYL NITROACETATE

In run No. 9 anhydrous sodium sulfate was omitted. In all ten experiments 90.5 g. (0.5 mole) of dipotassium nitroacetate, 500 ml. (12.38 moles) of methanol, 100 g. (1 mole) of concd. sulfuric acid, and 15 g. (0.1 mole) of anhydrous sodium sulfate (except in 6 and 9), were used.

Run	Time in hr. at −60 to −50°	Yield, %
7	1	25
8	24	40
9	24	29
10	48	45

TABLE III

EFFECT OF THE AMOUNT OF CONCD. SULFURIC ACID ON THE YIELD OF METHYL NITROACETATE

In all these experiments the same conditions and amounts were used as in run No. 4.

Moles concd. H_2SO_4	Yield, %
1	18
1.5	45
2	60
3	60

The data in Table I show that a lower reaction temperature during the first twenty-four hours of

---

[1] Presented before the Division of Organic Chemistry at the St. Louis Meeting of the American Chemical Society, September 8, 1948.

[2] Present address: General Aniline and Film Corp., New York City, N. Y.

[3] Present address: Picatinny Arsenal, Dover, N. J.

[4] Lyttle and Weisblat, THIS JOURNAL, **69**, 2118 (1947).

[5] Steinkopf, *Ann.*, **434**, 21 (1923).

the reaction increases the yields. While a low reaction temperature is important during the first twenty-four hours, a further extension of the reaction at a low temperature does not increase the yields appreciably as indicated in Table II.

Omission of anhydrous sodium sulfate resulted in lower yields. A 2:1 ratio of concd. sulfuric acid to dipotassium nitroacetate is needed to get optimum yields as indicated by the data in Table III.

Experimental

Preparation of the Dipotassium Salt of Nitroacetic Acid.—In a three-liter flask provided with stirrer, condenser and dropping funnel was placed 1500 ml. (20.2 moles) of freshly prepared 50% potassium hydroxide. When the temperature had risen to 60° on dissolving of the potassium hydroxide, 300 g. (4.91 moles) of nitromethane was added dropwise with vigorous stirring. During the one and one-half hours required for the addition of the nitromethane, the temperature rose to 102°. Ammonia was liberated during the latter half of the addition and the reflux condenser was removed after the entire amount of nitromethane had been added. The reddish brown mixture was then heated until the first crystals appeared. After cooling, the potassium salt which had separated out was filtered and washed with methanol. This first crop weighed 210 g. representing a yield of 44.5%.

Anal. Calcd. for $C_2HNO_4K_2$: K, 43.03. Found: K, 42.61.

The mother liquor was evaporated further and after cooling a second crop of crystals was obtained which weighed 60 g., representing a yield of 12.7%.

Anal. Found: K, 42.43.

Still further evaporation of the mother liquor gave a third crop of crystals (70 g.) which was found by analysis to be 43% contaminated with potassium carbonate which formed in the reaction.

Anal. Found: K, 48.90.

Preparation of Methyl Nitroacetate.—In a one-liter flask fitted with stirrer, thermometer and dropping funnel were placed 90.5 g. (0.5 mole) of dipotassium nitroacetate, 500 ml. (12.38 moles) of methanol and 15 g. (0.1 mole) of anhydrous sodium sulfate. The flask was placed in a Dewar and cooled down to −50 to −60° by a trichloroethylene-dry ice mixture. One hundred grams (1 mole) of concentrated sulfuric acid (d. 1.84) was added dropwise to the mixture during a period of one and one-half hours. The reaction mixture was kept in the Dewar for twenty-four hours with stirring (temp. −50 to −60°) and then for one hundred and forty-four hours at 23–25° with occasional shaking. The precipitated potassium sulfate was then filtered off and the excess methanol was evaporated under vacuum. The oily residue was diluted with ether and neutralized with a 5% solution of sodium carbonate. The ether layer, which contained the ester, was dried and the ether was evaporated. Vacuum distillation of the residue at 15 mm. yielded 36 g. (60%) of the ester, boiling at 93–94°; $n^{20}\mathrm{D}$ 1.4245; neut. equiv. calcd. for $C_3H_5O_4N$, 119, found 121.

Preparation of Ethyl Nitroacetate. The procedure was the same as for the synthesis of methyl nitroacetate. Forty grams (60%) of ethyl nitroacetate was obtained, boiling at 105–107° at 25 mm., $d^{20}{}_4$ 1.11950, $n^{20}\mathrm{D}$ 1.4252.

Acknowledgments.—The authors wish to express their appreciation to Mr. L. Friedman for his technical assistance and express their thanks to the General Tire and Rubber Company, Akron, Ohio, for financial assistance in this work.

Summary

An improved synthesis of esters of nitroacetic acid has been presented. The methyl and ethyl esters of nitroacetic acid have been prepared in two steps from nitromethane in 60% yield.

LAFAYETTE, INDIANA RECEIVED APRIL 7, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY]

The Chemistry of Nitroacetic Acid and its Esters. II. The Synthesis of Ethyl α-Nitro-β-(3-indole)-propionate from Gramine and Ethyl Nitromalonate[1]

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

We have recently reported a synthesis of *dl*-tryptophan (V) in which the key intermediate, ethyl α-nitro-β-(3-indole)-propionate (IV), was prepared from gramine and ethyl nitroacetate.[2] A new synthesis of this intermediate, starting with ethyl nitromalonate (I), is described in this communication.

The alkylation of ethyl nitromalonate (I) by gramine (II) under reaction conditions similar to those reported for the alkylation of ethyl nitroacetate[2] gives ethyl α-nitro-α-carbethoxy-β-(3-indole)-propionate (III) in excellent yield. The structure of ethyl nitromalonate, in contrast to that of ethyl nitroacetate, excludes dialkylation[2,3] as a possible side reaction and this, together with the activating effect of the second carbethoxy group, probably accounts for the higher yields and purer product obtained in the present alkylation.

Since powdered sodium hydroxide is an effective catalyst for the dialkylation of ethyl nitroacetate by gramine,[2] it was expected that it would greatly accelerate the present alkylation. Contrary to our expectations, however, it was found that not only sodium hydroxide but basic substances in general cause extensive decomposition. For this reason the rapid removal of dimethylamine, which is formed in the reaction, is essential for optimum yield and purity of product.

The conversion of III to IV in a yield of 91.6% was readily accomplished by treating a solution of III in ether with one equivalent of sodium in alcohol.[4]

---

(1) This paper was presented before the Organic Division at the 112th Meeting of the American Chemical Society, New York City, September, 1947.

(2) Lyttle and Weisblat, THIS JOURNAL, **69**, 2118 (1947).

(3) Snyder and Katz, *ibid.*, **69**, 3140 (1947).

(4) Ulpiani, *Gazz. chim. ital.*, **34**, 174 (1904).