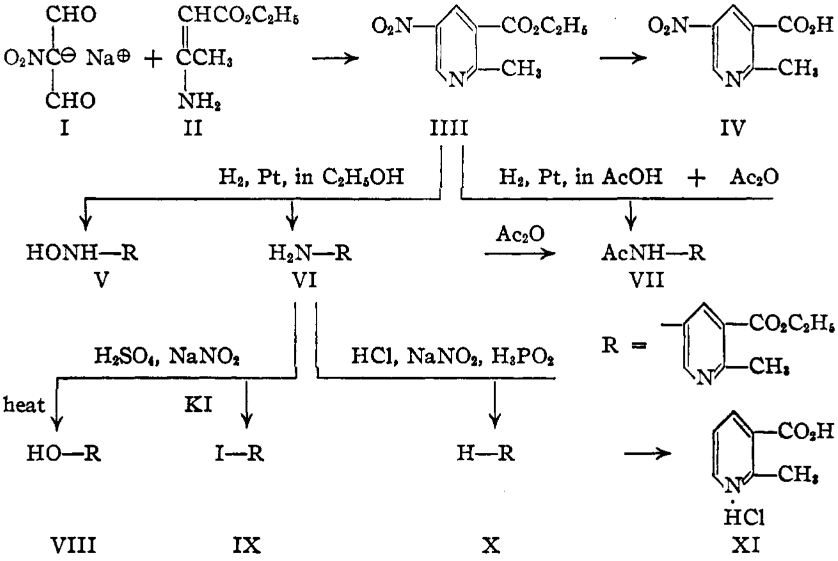
NOTES

Some 5-Substituted Derivatives of Ethyl 2-Methylnicotinate[1]

By Paul E. Fanta

Received October 6, 1952

The reaction of sodium nitromalonaldehyde (I) with ethyl β-aminocrotonate (II) was studied as part of a program of synthesis of new heterocyclic compounds of possible pharmacological interest. The only product isolated from the reaction mixture was ethyl 2-methyl-5-nitronicotinate (III). This is the first reported use of sodium nitromalonaldedehyde for the synthesis of a nitropyridine.[2] The nitro ester was readily hydrolyzed to the carboxylic acid (IV), which unexpectedly was not decarboxylated by heating at its melting point. Catalytic hydrogenation of the nitro ester with platinum catalyst in neutral alcohol gave a large amount of ethyl 5-hydroxamino-2-methylnicotinate (V, 45% yield) in addition to the expected ethyl 5-amino-2-methylnicotinate (VI, 46% yield). Ethyl 5-acetylamino-2-methylnicotinate (VII) was obtained when the catalytic reduction was conducted in a mixture of acetic acid and acetic anhydride.



The amino group of VI reacted in the expected manner upon diazotization. Heating the diazonium sulfate gave the hydroxy derivative (VIII), while reaction with potassium iodide yielded the iodo compound (IX). The diazonium chloride was reduced by treatment with hypophosphorus acid to the previously reported ethyl 2-methylnicotinate (X).[3] The latter compound is an oil which was identified by means of its picrate and the hydrochloride of the corresponding acid (XI).

Table I

Wave Lengths of Principal Infrared Bands in the Region 2.50 to 7.40 μ

All determinations on 0.7 to 0.8% solutions in chloroform

Compound	—OH	—NH	Ester	Aromatic ring	—NO_2	—NHOH	—NO_2
	Probable assignment[4]						
Nitrobenzene	....	....	..	6.23	6.53	..	7.39
N-Phenylhydroxylamine	2.80 (weak)	3.03 (weak)	..	6.23	..	6.67	..
Nitro compound III	....	....	5.80	6.24, 6.32	6.53	..	7.36
Hydroxamino compound V	2.80 (weak)	3.03 (weak)	5.84	6.25, 6.35	..	6.82	..

The hydroxamine V instantaneously reduced Tollens reagent and cold Fehling solution. It was further characterized by comparison of the infrared absorption spectrum with the spectra of several model compounds. From the data summarized in Table I it is evident that the spectra of V and III have the same relationship to each other as N-phenylhydroxylamine has to nitrobenzene.

Experimental[5]

Ethyl 2-Methyl-5-nitronicotinate (III).—Ethyl β-aminocrotonate was prepared by saturating a solution of 26.0 g. (0.20 mole) of ethyl acetoacetate in 200 ml. of absolute ether with ammonia gas at −10°. The granular, white precipitate was quickly collected on a cold buchner funnel and added to a solution of 15.7 g. (0.10 mole) of sodium nitromalonaldehyde[6] in 100 ml. of water. The mixture was heated to 50° with stirring, then cooled to −5°. The precipitated product was collected on a filter and purified by two recrystallizations, using 150 ml. of 50% alcohol each time. The yield of pure product was 7.46 g. (35%, based

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[1] This work was supported by a grant from the Office of Ordnance Research.

[2] For examples of pyridine syntheses utilizing ethyl β-aminocrotonate and other β-dicarbonyl compounds see H. S. Mosher in R. C. Elderfield's "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 468.

[3] E. Ochiai and Y. Ito, *Ber.*, **74B**, 1111 (1941); P. Baumgarten and A. Dornow, *ibid.*, **72B**, 563 (1939).

[4] With the exception of the —NHOH band, for which no assignment was given, these data agree with the range of values published by H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, facing p. 20.

[5] All melting points are corrected. Analyses are by Micro-Tech Laboratories, Skokie, Illinois.

[6] P. E. Fanta, *Org. Syntheses*, **32**, 95 (1952). The furoic acid used in this preparation was obtained from the Quaker Oats Company through the courtesy of Dr. A. P. Dunlop.

on the amount of sodium nitromalonaldehyde used) of very pale yellow needles, m.p. 64–65°.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.76; H, 4.80; N, 13.40.

2-Methyl-5-nitronicotinic Acid (IV).—A solution of 2.00 g. of the ester III in a mixture of 5 ml. of concentrated hydrochloric acid and 5 ml. of water was refluxed for one hour. The solution was diluted with 30 ml. of water and neutralized by the addition of solid sodium bicarbonate. After cooling, 1.47 g. (85%) of crude acid was obtained. Recrystallization from a mixture of 40 ml. of water and 10 ml. of alcohol gave 1.26 g. (73%) of fine, white needles which melted with decomposition at 215–215.5°, when placed in the melting point bath at 211° with the temperature rising 2° per min.

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.43; H, 3.62; N, 15.64.

When a small portion of IV was melted in a test-tube at atmospheric pressure and then sublimed at 60 mm., the fluffy, white sublimate was shown by melting point to be pure starting material.

Catalytic Hydrogenation of III in Alcohol.—A solution of 6.30 g. (0.03 mole) of III in 70 ml. of absolute alcohol was shaken with 0.05 g. of platinum oxide catalyst (American Platinum Works) for five minutes at 32–35° and a hydrogen pressure of 900 lb. After removal of the catalyst by centrifugation, the solvent was distilled on the steam-bath at 60 mm. pressure and the sirupy residue was dissolved in 100 ml. of hot benzene. Cooling gave 2.67 g. (45%) of nearly pure, fine, colorless needles of **ethyl 5-hydroxamino-2-methylnicotinate** (V). The analytical sample, prepared by recrystallization from benzene, melted at 111.5–112.5° and became slightly pink after standing for several weeks.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.11; H, 6.28; N, 14.38.

The benzene solution from the isolation of V was evaporated to a volume of 30 ml. and 60 ml. of 60–70° petroleum ether was added. Cooling to −5° gave 2.50 g. (46%) of crude **ethyl 5-amino-2-methylnicotinate** (VI) which consisted of a yellow powder melting at 60–70°. It was used in subsequent experiments without further purification. A sharply melting, analytically pure sample was not obtained by recrystallization from various solvents. A **picrate** was obtained by mixing an aqueous solution of the amine with saturated aqueous picric acid. After recrystallization from water containing a little alcohol it formed yellow platelets which melted to a dark red liquid at 191–192°.

Anal. Calcd. for $C_{15}H_{15}N_5O_9$: C, 44.01; H, 3.69. Found: C, 44.48; H, 3.82.

An analytically pure sample of VI was obtained by extracting an ether suspension of the pure picrate with strong, aqueous sodium hydroxide solution until the yellow color was discharged. Evaporation of the ether and recrystallization of the residue from benzene–ligroin gave fine, white clusters, m.p. 64–65°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.94; H, 6.74; N, 15.87.

Catalytic Hydrogenation of III in Acetic Acid–Acetic Anhydride.—A solution of 0.50 g. of III in a mixture of 5 ml. of acetic acid and 1 ml. of acetic anhydride was shaken with 0.05 g. of platinum oxide catalyst for five minutes at 30–40° and a hydrogen pressure of 1500 lb. After removal of the catalyst by centrifugation, the solvent was removed on the steam-bath at 60 mm. pressure. The slightly greenish, sirupy residue of crude **ethyl 5-acetylamino-2-methylnicotinate** (VIII) could not be induced to crystallize and was not submitted for analysis. On mixing an aqueous solution of the crude product with a saturated aqueous solution of picric acid, the **picrate** was precipitated. Upon recrystallization from water it was obtained in the form of yellow clusters which sintered at 169–170° and melted to a clear, light red liquid at 170–171°.

Anal. Calcd. for $C_{17}H_{17}N_5O_{10}$: C, 45.24; H, 3.80; N, 15.52. Found: C, 45.28; H, 3.81; N, 15.47.

The same picrate was obtained when VI was treated successively with hot acetic anhydride, water and saturated aqueous picric acid.

Ethyl 5-Hydroxy-2-methylnicotinate (VIII).—A solution of 0.36 g. (0.002 mole) of VI in a mixture of 10 ml. of water and 1.0 ml. (0.018 mole) of sulfuric acid was diazotized at 0° by the addition of 0.14 g. (0.002 mole) of sodium nitrate. When the clear, yellow solution was rapidly heated to boiling, gas was evolved and the solution darkened. The reaction mixture was cooled, diluted with 10 ml. of water and neutralized to *p*H 6 by the addition of solid sodium carbonate. The desired product was isolated in low yield by ether extraction, followed by two vacuum sublimations and successive crystallizations from aqueous alcohol and benzene–ligroin, when it formed fine, colorless platelets which melted at 163–164.5°.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 60.42; H, 6.22; N, 7.63.

Ethyl 5-Iodo-2-methylnicotinate.—A solution of 0.18 g. (0.001 mole) of VI in a mixture of 5 ml. of water and 0.36 ml. of sulfuric acid was diazotized at 0° by the addition of 0.10 g. of solid sodium nitrite. The yellow solution was added to a solution of 0.33 g. (0.002 mole) of potassium iodide in 5 ml. of water at 0° and the reaction was completed by heating to boiling. A light amber colored solution was obtained which was diluted with 10 ml. of water and neutralized by the addition of solid sodium bicarbonate. A tan precipitate was obtained which was recrystallized from 40 ml. of 50% alcohol, giving 0.16 g. (55%) of dark tan needles which melted at 92–92.5°. A colorless analytical sample was obtained by two vacuum sublimations, m.p. 92.5–93.5°.

Anal. Calcd. for $C_9H_{10}NO_2I$: C, 37.13; H, 3.46; N, 4.81. Found: C, 37.12; H, 3.52; N, 4.91.

Hypophosphorous Acid Deamination[7] of VI.—A solution of 0.90 g. (0.005 mole) of VI in a mixture of 30 ml. of water and 2.0 ml. (0.025 mole) of concentrated hydrochloric acid was diazotized at 0° by the addition of 0.39 g. (0.0055 mole) of sodium nitrite. After two minutes, 9.9 g. (0.075 mole) of cold 50% hypophosphorous acid was added and the mixture was allowed to stand at 0° for 16 hours. The clear solution was brought to *p*H 8 by the addition of solid sodium carbonate and the brown oil which separated was extracted with two 30-ml. portions of ether. Evaporation of the ether and distillation of the residue at 0.5 mm. gave 0.51 g. (62%) of very light yellow, oily ethyl 2-methylnicotinate (X). The picrate crystallized from water in the form of long, fine, yellow needles which melted at 145.5–146.5° (the value previously reported in the literature[3] is 146–147°). The ester was converted to 2-methylnicotinic acid hydrochloride (XI) according to the published directions.[3] After recrystallizations from ethyl acetate it melted with vigorous decomposition at 230.5–231° (the previously reported values[3] are 225 and 226°).

Infrared absorption spectra were determined with the Model 21 Perkin and Elmer double-beam recording infrared spectrophotometer in 0.1-mm. sodium chloride cells.

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[7] N. Kornblum in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 262.

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Polarography of *p*-Chlorobenzophenenone and Xanthone

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Received August 18, 1952

In a recent publication on the polarography of aromatic ketones, several compounds were compared as to their formation of double waves in basic ethanol–water media.[1] It was pointed out that if the aromatic group attached to the carbonyl in a ketone tended to increase the stability of the dimer of a metal ketyl intermediate, double waves were likely to occur. The aromatic groups studied in this work were the 9-fluoryl, benzanthryl, phenyl and α-naphthyl.

It is known that the *p*-chlorophenyl group has less effect in stabilizing a free radical than the

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[1] R. A. Day, Jr., S. R. Milliken and W. D. Shults, This Journal, **74**, 2741 (1952).