[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, SETON HALL UNIVERSITY]

Syntheses and Decarboxylation of the Isomeric Nitropyridinecarboxylic Acids

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The ten isomeric nitropyridinecarboxylic acids have been prepared by the oxidation of the corresponding nitropicolines and their decarboxylation temperatures determined. Several of the nitropicolines have not been previously prepared and others have been prepared by new routes.

As a preliminary investigation in connection with a more detailed study of the mechanism of decarboxylation, we wished to prepare and determine the temperatures of decarboxylation of the isomeric nitropyridinecarboxylic acids. In the pyridine series there are ten isomeric compounds possible when two different groups are attached to the pyridine ring. It seemed most likely that these acids could be prepared most readily by oxidation of the corresponding nitropicolines.

The first problem then became the preparation of the ten isomeric nitropicolines. For preparative purposes these fall into three classes depending upon whether the nitro group is in the 2-, 3- or 4-position in the pyridine ring. The first type with the nitro groups in the 2-position consists of four isomers with methyl groups in the 3-, 4-, 5- and 6-positions, respectively. These have been prepared by Wiley and Hartmann[1] by oxidation of the corresponding commercially available aminopicolines with persulfuric acid.

The second class consists of four isomers containing the nitro group in the 3-position and the methyl in either 2-, 4-, 5- or 6-positions. Of these the 2,3- and 6,3-(5,2) have been prepared by Baumgarten and Su[2] by nitration of 2-amino-6-methylpyridine, separation of the isomers and removal of the amino group by converting it to hydroxy, then to chloro and finally to hydrazino which is oxidized to replace it with hydrogen. The 6,3-(5,2) isomer had been previously prepared by Gruber and Schlögl[3] using a somewhat more simple procedure of converting 5-nitro-2-chloropyridine to the 2-malonic ester with ethyl sodiomalonate and subsequently decarboxylating to the nitropicoline. The 4,3-isomer has been prepared from 4-hydroxypyridine by nitration, conversion of hydroxy to chloro then to malonate with subsequent decarboxylation. We have prepared this 4,3-isomer by nitrating 2-amino-4-methylpyridine, converting the 2-amino-3-nitro-4-methylpyridine to the 2-hydroxy and this in turn to 2-chloro-3-nitro-4-methylpyridine. Applying the dechlorination procedure of Smith,[4] we have been able to convert this to 3-nitro-4-methylpyridine. This leaves the 5,3-isomer which we have prepared from 2-amino-5-methylpyridine by the method of Baumgarten and Su.[2] Application of the dechlorination procedure[4] to the 2-chloro-3-nitro-5-methylpyridine gave a 47% yield of 3-nitro-5-methylpyridine in one step as opposed to two steps and a 50% yield in the procedure of Baumgarten and Su.[2]

(1) R. H. Wiley and J. L. Hartmann, THIS JOURNAL, **73**, 494 (1951).
(2) H. E. Baumgarten and H. C. Su, *ibid.*, **74**, 3828 (1952).
(3) W. Gruber and K. Schlögl, *Monatsh.*, **18**, 473 (1950).
(4) W. T. Smith, THIS JOURNAL, **71**, 2855 (1949).

In the last type of nitropicoline, we have the nitro groups in the 4-position and now there are only two isomers, one in which the methyl group is in the 3- and the other in which it is in the 2-position. These had not been previously prepared. We were able to synthesize them from the corresponding α- and β-picolines by a route which involved formation of the picoline-1-oxide, nitration to the 4-nitropicoline-1-oxide, reduction to the 4-aminopicoline[5] and oxidation with persulfuric acid.

All of the nitropyridinecarboxylic acids were prepared by the oxidation of the above nitropicolines using aqueous potassium permanganate. None of these was previously known. We have determined the decomposition temperatures of these acids by a technique used by Norris and Young[6] and also by Gilman and co-workers[7] on a number of furoic acids. The data are summarized in Table I.

Experimental

2-Chloro-3-nitro-5-methylpyridine.—2-Hydroxy-3-nitro-5-methylpyridine[8] (20 g.) was treated with 50 ml. of phosphorus oxychloride and 10 g. of phosphorus pentachloride and heated at 115° for 2 hours. The reaction mixture was poured onto a cracked ice-water slurry and stirred until the product crystallized. Chloroform extraction followed by evaporation of the solvent gave the chloro compound which was crystallized from petroleum ether (60–75°). There was obtained 16 g. (71%) of 2-chloro-3-nitro-5-methylpyridine, m.p. 40–41°. *Anal.* Calcd. for $C_6H_5N_2O_2Cl$: C, 41.74; H, 2.90. Found: C, 41.95; H, 3.30.

2-Hydrazino-3-nitro-5-methylpyridine.—The above chloro compound (15.7 g.) was dissolved in 75 ml. of absolute ethyl alcohol and treated slowly with 8 ml. of hydrazine hydrate (85%) while stirring. The solution became quite warm and deposited crystals of the hydrazino compound. After cooling the product was filtered, washed and dried. There was obtained 15.5 g. (100%) of 2-hydrazino-3-nitro-5-methylpyridine, m.p. 160–166°. After recrystallization from alcohol the compound melted at 167–168°. *Anal.* Calcd. for $C_6H_8N_4O_2$: C, 42.26; H, 4.76. Found: C, 42.13; H, 4.85.

3-Nitro-5-methylpyridine.—2-Hydrazino-3-nitro-5-methylpyridine (12.6 g.) was dissolved in 400 ml. of water and 200 ml. of acetic acid, heated to boiling and treated dropwise with 300 ml. of a 10% solution of copper sulfate. After the addition the solution was boiled 15 minutes, cooled and made basic with sodium hydroxide. The product is obtained by benzene extraction and evaporation of the solvent. There was obtained 5.5 g. of 3-nitro-5-methylpyridine (53%) melting at 84–87°. After recrystallization from petroleum ether the product melted at 90–91°. *Anal.* Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.35. Found: C, 52.02; H, 4.51.

2-Chloro-3-nitro-4-methylpyridine.—2-Hydroxy-3-nitro-4-methylpyridine[8] (4 g.) was treated with phosphorus oxychloride and phosphorus pentachloride in the manner de-

(5) R. Faessinger and E. V. Brown, Abstracts of the Buffalo Meeting, A. C. S., Spring, 1952.
(6) J. F. Norris and R. C. Young, THIS JOURNAL, **52**, 5066 (1930).
(7) H. Gilman and co-workers, *Iowa State College J. Sci.*, **7**, 429 (1933).
(8) G. R. Lappin and F. B. Slezak, THIS JOURNAL, **72**, 2806 (1950).

TABLE I

NITROPYRIDINECARBOXYLIC ACIDS

Group position NO_2	Group position COOH	M.p., °C. (All recryst. from water)	Dec. temp., °C.	Yield, %	Formula	Analyses, % Calculated Carbon	Calculated Hydrogen	Found Carbon	Found Hydrogen
3	2	105	105	45	$C_6H_4N_2O_4$	42.85	2.38	43.21	2.43
4	2	152	152	51	$C_6H_4N_2O_4$	42.85	2.38	43.12	2.72
5	2	210	212	30	$C_6H_4N_2O_4$	42.85	2.38	42.92	2.49
6	2	168	169	45	$C_6H_4N_2O_4 \cdot H_2O$	38.71	3.22	39.00	3.15
2	3	156	157	42	$C_6H_4N_2O_4$	42.85	2.38	43.07	2.43
4	3	120	120	45	$C_6H_4N_2O_4 \cdot H_2O$	38.71	3.22	39.01	3.02
5	3	172	250	40	$C_6H_4N_2O_4$	42.85	2.38	43.05	2.35
6	3	183	184	52	$C_6H_4N_2O_4$	42.85	2.38	42.85	2.54
2	4	175	177	37	$C_6H_4N_2O_4$	42.85	2.38	42.90	2.61
3	4	222	219	35	$C_6H_4N_2O_4$	42.85	2.38	42.74	2.42

scribed above for the preparation of 2-chloro-3-nitro-5-methylpyridine. There was obtained 3.5 g. (80%) of 2-chloro-3-nitro-4-methylpyridine melting at 45–47°. Recrystallization from petroleum ether gave a product melting at 46–47°. *Anal.* Calcd. for $C_6H_5N_2O_2Cl$: C, 41.71; H, 2.90. Found: C, 41.87; H, 3.25.

3-Nitro-4-methylpyridine.—2-Chloro-3-nitro-4-methylpyridine (3.25 g.) was mixed with 7 g. of benzoic acid[4] and heated to 150°. Copper powder (5 g.) was then added slowly with stirring over a period of five minutes. After stirring a short while the melt was allowed to cool and was then extracted with a mixture of chloroform and 20% sodium carbonate solution. The mixture was filtered, separated and extracted twice more with chloroform. The extracts were combined and evaporated to give 1.8 g. (70%) of 3-nitro-4-methylpyridine.

6(2)-Methyl-3(5)-nitropyridine.—2-Chloro-3-nitro-6-methylpyridine[2] (4 g.) was subjected to the same treatment[4] with benzoic acid and copper powder as described above to give 2.5 g. (80%) of 6(2)-methyl-3(5)-nitropyridine[2,3] which after recrystallization from petroleum ether melted at 107–108°.

4-Nitro-2-methylpyridine.—4-Amino-2-methylpyridine[5] (20 g.) was dissolved in 100 ml. of concentrated sulfuric acid and dropped into a mixture of 350 ml. of fuming sulfuric acid (15%) and 175 ml. of 30% hydrogen peroxide keeping the temperature at 10–20°. After the final addition, the reaction mixture was stirred one hour at 20° and then allowed to come to room temperature and stand two days. At the end of this time it was poured onto cracked ice, neutralized with sodium hydroxide and extracted with benzene. Evaporation of the solvent left 14 g. (55%) of product which after recrystallization melted at 32–34°. *Anal.* Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.35. Found: C, 57.80; H, 4.19.

4-Nitro-3-methylpyridine.—4-Amino-3-methylpyridine (23.5 g.) was oxidized in the manner just described for the 2-methyl isomer. There was obtained 24.5 g. (82%) of crude product which after recrystallization from petroleum ether melted at 28–29°. *Anal.* Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.35. Found: C, 52.27; H, 4.50.

Preparation of the Nitropyridinecarboxylic Acids.—All of the acids were prepared in the same manner, *i.e.*, 1.4 g. of the nitropicoline and 100 ml. of water were heated to 90° and treated with 3 g. of potassium permanganate over a period of one-half hour while stirring. The reaction mixture was cooled to 50° and filtered. The manganese dioxide was washed first with water and then with benzene to remove unchanged starting material and then the filtrate was extracted three times with benzene. The aqueous layer was evaporated to small volume and treated with somewhat more than the calculated amount of sulfuric acid with cooling. The crude acid was filtered and recrystallized from hot water. Ether extraction of the acid mother liquid afforded a small second crop. The yields are calculated after subtracting the amount of recovered starting material and the data are shown in Table I.

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Condensation Reactions of Picoline 1-Oxides

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2- and 4-picoline 1-oxides and 6-benzyloxy-2-methylpyridine 1-oxide condense with ethyl oxalate to give the corresponding ethyl pyridylpyruvate 1-oxides. The pyruvates upon treatment with hydroxylamine form α-oximino derivatives which by means of alkali are converted to the corresponding acetonitriles. Peroxide in acetic acid converts the pyruvates from the 2- and 4-picoline 1-oxides to the corresponding picolinic acid 1-oxides. Peracetic acid reacts with 6-benzyloxy-2-methylpyridine 1-oxide to give a mixture of 2-picolinic acid 1-oxide and 6-benzyloxy-2-pyridylacetic acid 1-oxide. The ester of this latter compound and the 6-benzyloxy-2-methylpyridine 1-oxide upon hydrogenation or hydrolysis give the corresponding 1-hydroxy-2-pyridones.

Many reactions of 2- and 4-picoline have been known and attributed to the inherent electron-attracting nature of the ring nitrogen atom which imparts a positive character to the α-carbon atom. But neither 2-picoline[2] nor 4-picoline condenses with ethyl oxalate. Since the nitrogen oxide group should enhance the polarization, 2- and 4-picoline 1-oxides should be more reactive than the 2- and 4-picolines. This is in fact so and these oxides undergo condensation with ethyl oxalate in the presence of potassium ethoxide to give the corresponding potassium salts of the pyruvates from which ethyl 2-pyridylpyruvate 1-oxide (I) and ethyl 4-pyridylpyruvate 1-oxide are obtained upon acidification.

With hydroxylamine, the corresponding ethyl 2-(and 4)-pyridyl-(α-oximino)-propionate 1-oxides

(1) Rotary Foundation Fellow for advanced study, 1952–1953.

(2) R. Adams and A. W. Schrecker, THIS JOURNAL, **71**, 1190 (1949).