[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

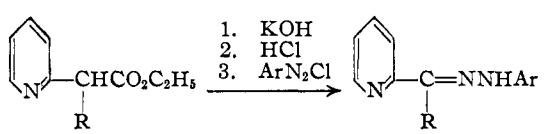
Pyridines. V. The Japp–Klingemann Reaction Applied to 2-Pyridylacetic Acids[1]

BY ROBERT L. FRANK AND ROBERT R. PHILLIPS

The Japp–Klingemann reaction,[2] involving the elimination of carbon dioxide from a carboxylic acid in the presence of a diazonium salt to form an aryl hydrazone, has thus far been applied only to β-keto acids[2,3] and to substituted malonic acids.[4] This investigation has extended its scope to pyridylacetic acids.

Studying synthetic routes for 2-acylpyridines,[5] we tested the Japp–Klingemann method by treating the hydrolysis product of ethyl 2-pyridylacetate (I) with solutions of diazotized *p*-nitroaniline, sulfanilic acid and *p*-aminobenzoic acid. We were gratified to obtain excellent yields of the corresponding aryl hydrazones of 2-formylpyridine (III).

Extension of this reaction for the formation of aryl hydrazones of higher homologs of 2-formylpyridine presented the problem of preparation of substituted 2-pyridylacetic acids or their derivatives. Ethyl 2-pyridylacetate (I) is obtainable in 35–40% yield by carbonation of 2-picolyllithium followed by esterification,[6] but application of this method to the ethylpyridyl homolog (II) gave only traces of impure product.

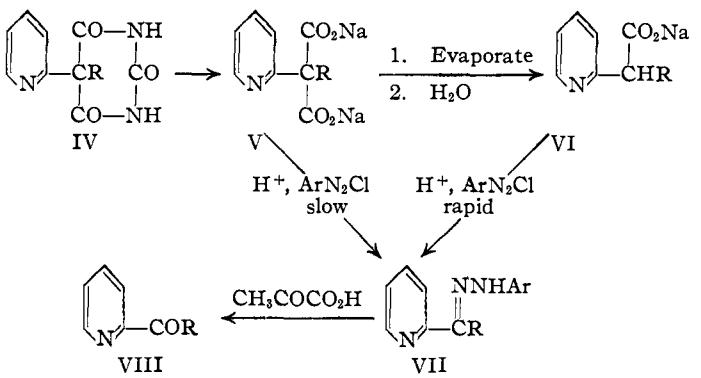


I, R = H
II, R = CH_3

III, R = H

The use of 5-alkyl-5-(2′-pyridyl)-barbituric acids (IV) makes possible the synthesis in high yields of 2-acylpyridines by the steps IV–VIII.

The preparation of 5-alkyl 5-(2′-pyridyl)-barbituric acids (IV) was suggested by a patent of Gebauer.[7] Condensation of 2-bromopyridine with 5-*n*-propylbarbituric acid by heating in dimethylaniline solution gave a 29% yield of 5-*n*-propyl-5-(2′-pyridyl)-barbituric acid (IV, R = *n*-C_3H_7). Similar condensation with 5-*n*-butylbarbituric acid formed the butyl analog (IV, R = *n*-C_4H_9) in 28% yield.



Conversion of 5-*n*-propyl-5-(2′-pyridyl)-barbituric acid to the *p*-carboxyphenylhydrazone VII (Ar = *p*-$HOOCC_6H_4$; R = *n*-C_3H_7) is accomplished in 74–94% yield in either of two ways without isolation of intermediate products. The aqueous hydrolysate (V) of the barbituric acid may be acidified directly and the malonic acid solution treated with the diazonium salt, or the strongly alkaline solution may be evaporated to dryness to bring about decarboxylation[8] to the disubstituted acetic acid salt (VI) before acidification. Of theoretical interest is the fact that while either scheme gives a high yield of hydrazone, the reaction with the malonic acid requires a much longer period of time. This indicates that monodecarboxylation of the pyridylmalonic acid occurs before attack by the diazonium salt can take place, and that for the Japp–Klingemann reaction to occur it is necessary to have a hydrogen atom on the carbon attached to the carboxyl group being replaced.

The preferred synthetic procedure is to employ the evaporation step (V to VI) in order to avoid the excessively long reaction period with the diazonium salt. Diazotized *p*-aminobenzoic acid appears to be the best choice of diazonium salts.

Hydrolysis of the aryl hydrazones is accomplished readily by interchange with pyruvic acid[9]; the *p*-carboxyphenylhydrazone of 2-*n*-butyrylpyridine (VII, R = *n*-C_3H_7), yielded the ketone (VIII, R = *n*-C_3H_7) in 81% yield.

Direct coupling of diazonium salts with 2-

(1) For the previous communication on pyridine chemistry, see Frank and Seven, THIS JOURNAL, **71**, 2629 (1949).

(2) Japp and Klingemann, *Ber.*, **20**, 2942, 3284, 3398 (1887); *Ann.*, **247**, 190 (1888).

(3) For leading references see Linstead and Wang, *J. Chem. Soc.*, 807 (1937).

(4) Sempronj, *Gazz. chim. ital.*, **68**, 263 (1938); *C. A.*, **32**, 9077 (1938).

(5) 2-Acylpyridines, except for the special case of 2-formylpyridine, have been prepared in the past by dry distillation of mixtures of the calcium salts of picolinic acid and aliphatic acids (Engler and co-workers) *Ber.*, **24**, 2527, 2530, 2536 (1891); Hess, *ibid.*, **52**, 987 (1919)), by condensation of ethyl picolinate with aliphatic esters, followed by hydrolysis and decarboxylation (Pinner, ref. 19) and by treatment of 2-cyanopyridine with Grignard reagents (Kolloff and Hunter, THIS JOURNAL, **63**, 490 (1941); Craig, *ibid.*, **56**, 1144 (1930)).

(6) R. B. Woodward and E. C. Kornfeld, private communication. This preparation has been submitted for publication in "Organic Syntheses."

(7) Gebauer (Chemische Fabrik von Heyden A. G.), German Patent 626,411 (June 6, 1936); *C. A.*, **30**, 5594 (1936).

(8) Gebauer (Chemische Fabrik von Heyden A. G.), German Patent 638,596 (Nov. 19, 1936); *C. A.*, **31**, 3067 (1937); German Patent 644,193 (April 26, 1937); *C. A.*, **31**, 6257 (1937).

(9) Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

alkylpyridines has also been considered, since reactive methylene groups are known to undergo such coupling.[10] In the case of 2-picoline, coupling failed with diazotized sulfanilic acid and *p*-aminobenzoic acid, and yielded 7% of the *p*-nitrophenylhydrazone of 2-formylpyridine with diazotized *p*-nitroaniline. Similar trials failed with 2-ethylpyridine. A further experiment involved the methiodide of 2-picoline, known to have increased reactivity at the 2-methyl group.[11] The product from diazotized *p*-nitroaniline was *p*-iodonitrobenzene in 93% yield.

Experimental

Ethyl 2-Pyridylacetate (I).—The method of Woodward and Kornfeld[6] using 2-picolyllithium from 93.1 g. (1.00 mole) of 2-picoline gave 41.4 g. (25%) of light yellow ester, b. p. 122–125° (12 mm.); $n^{20}D$ 1.5063. Its picrate, recrystallized four times from absolute ethanol to form yellow needles, melted at 138–139°.

Anal.[12] Calcd. for $C_{15}H_{14}N_4O_9$: N, 14.21. Found: N, 14.37.

2-Ethylpyridine.—A solution of 52.5 g. (0.50 mole) of 2-vinylpyridine (Reilly Tar and Chemical Corporation) in 90 ml. of absolute ethanol, purified by refluxing over Raney nickel, was hydrogenated for one hour (until the theoretical amount of hydrogen was absorbed) over 0.2 g. of platinum oxide catalyst at 25° and three atmospheres of hydrogen pressure. Fractional distillation in a 10-cm. helix-packed column gave 46.2 g. (86%) of 2-ethylpyridine, b. p. 146° (12 mm.); $n^{20}D$ 1.4966.

A picrate melted at 111° rather than at 187–189° as reported by Bergstrom and McAllister.[13] Analysis showed our picrate to have the proper composition and, since this preparation was carried out, we have noted two other reports calling attention to the discrepancy.[14,15]

Anal. Calcd. for $C_{13}H_{12}N_4O_7$: C, 46.41; H, 3.60; N, 16.67. Found: C, 46.61; H, 3.68; N, 16.51.

Ethyl 2-(2′-Pyridyl)-propionate (II).—The procedure was the same as that for ethyl 2-pyridylacetate,[6] using 13.9 g. (2.0 gram-atoms) of lithium, 160.0 g. (1.00 mole) of bromobenzene, 800 ml. of anhydrous ether and 107 g. (1.00 mole) of 2-ethylpyridine. The final product, b. p. 80–90° (5 mm.), weighed 19.0 g. A small sample, redistilled, boiled at 74° (4 mm.), $n^{20}D$ 1.5580, but was still not at all pure, as indicated by an analysis. A picrate, m. p. 104–105°, formed yellow needles after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{16}N_4O_9$: C, 47.06; H, 3.95. Found: C, 46.92; H, 3.83.

Further characterization of the ester was obtained by hydrolysis of a 1.0-g. portion of the distillate in 10 ml. of 5% aqueous sodium hydroxide, followed by acidification and treatment with *p*-carboxybenzenediazonium chloride, as described under the Japp–Klingemann reactions below. The solution deposited a yellow precipitate on standing overnight in a refrigerator. A portion of this, dissolved in ethanol, yielded a picrate which decomposed at 231–233° after recrystallization as yellow needles from ethanol. Its analysis checked for that of 2-acetylpyridine *p*-carboxyphenylhydrazone picrate.

Anal. Calcd. for $C_{20}H_{16}N_6O_9$: C, 49.59; H, 3.33. Found: C, 49.93; H, 3.35.

5-*n*-Propyl-5-(2′-pyridyl)-barbituric Acid.—A mixture of 8.4 g. (0.049 mole) of 5-*n*-propylbarbituric acid (prepared by the general method of Dickey and Gray)[16] and 8.0 g. (0.05 mole) of 2-bromopyridine[17] in 30 g. of dimethylaniline was heated in an oil-bath at 170° for six hours. The contents were cooled to room temperature, diluted with 100 ml. of ether, and extracted with five 100-ml. portions of 10% aqueous sodium carbonate. The extracts were acidified individually with glacial acetic acid; only the first two deposited significant amounts of cream-colored precipitate, combined weight 3.5 g. (29%), m. p. 235–240° (in spite of this m. p. and its range, the material was essentially pure, as evidenced by the fact that it gave 94% of pure product when subjected to the Japp–Klingemann reaction). Crystallization of a sample from water with the use of Norit gave white feathery clusters, m. p. 249–250°.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.28; H, 5.30. Found: C, 58.29; H, 5.27.

Heating of the reaction mixture longer than six hours did not improve the yield. Other experiments with ethanolic sodium ethoxide and with xylene showed these to be unsatisfactory as media for the reaction.

5-*n*-Butyl-5-(2′-pyridyl)-barbituric Acid.—The procedure used above for the propyl analog was employed with 6.2 g. (0.034 mole) of 5-*n*-butylbarbituric acid,[16] 6.0 g. (0.038 mole) of 2-bromopyridine[17] and 20.6 g. (0.170 mole) of dimethylaniline. The light green precipitated product, m. p. 245–250°, weighed 2.5 g. (29%). A sample was crystallized from water to give colorless needles, m. p. 264–265°.

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79. Found: C, 59.61; H, 5.77.

In making a number of runs, it has been found advantageous to use the dimethylaniline residue, after removal of the ether, from the previous experiment. In this manner the average yield in a series can be raised to 43%.

Japp–Klingemann Reactions. A. With Hydrolyzed Ethyl 2-Pyridylacetate.—Ethyl 2-pyridylacetate was hydrolyzed by shaking 1.06 g. (0.0063 mole) at room temperature for three hours with a solution of 0.4 g. (0.007 mole) of potassium hydroxide in 15 ml. of water. Solution was virtually complete. An additional 10 ml. of water was added, the solution filtered, the filtrate cooled in an ice–salt-bath, acidified with hydrochloric acid, and the cooled diazonium salt solution, formed as described below, immediately added to it. This was followed by a cold solution of 2.0 g. (0.024 mole) of sodium acetate in 4 ml. of water and the mixture allowed to stand overnight in a refrigerator. Colored precipitates gradually formed.

Diazotized solutions of 0.0063-molar quantities of *p*-nitroaniline, sulfanilic acid and *p*-aminobenzoic acid were prepared at 0° from equivalent amounts of sodium nitrite and excess hydrochloric acid.

The colored precipitate formed from *p*-nitrobennzene diazonium chloride was yellow 2-formylpyridine *p*-nitrophenylhydrazone, 1.25 g. (82% based on the pyridylacetic ester), m. p. 231–234° (lit.,[18] 235°). It showed a purple color with ethanolic sodium hydroxide and a cherry red color with sulfuric acid, as described by Harries and Lenart.[18]

The dark red precipitate from diazotized sulfanilic acid weighed 0.74 g. (crude yield 42%) when dry and melted at 306–308°. Attempts at recrystallization from ethanol, water and nitromethane failed, but the material could be reprecipitated as a yellow powder from aqueous sodium carbonate by means of glacial acetic acid to achieve partial purification.

Anal. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.97; H, 4.00. Found: C, 50.45; H, 4.24.

The third precipitate, from diazotized *p*-aminobenzoic

(10) Parkes and Aldis, *J. Chem. Soc.*, 1841 (1938); Chelintsev, *J. Gen. Chem.* (*U. S. S. R.*), **14**, 941 (1944); *C. A.*, **39**, 4611 (1945).

(11) Koelsch, THIS JOURNAL, **66**, 2126 (1944).

(12) Microanalyses were carried out by Miss Emily Davis, Mrs. Jane Wood and the Clark Microanalytical Laboratory.

(13) Bergstrom and McAllister, THIS JOURNAL, **52**, 2845 (1930).

(14) Proštenik and Balling, *Arkiv Kemi.*, **18**, 10 (1946); *C. A.*, **42**, 3399 (1948).

(15) Gregg and Craig, THIS JOURNAL, **70**, 3138 (1948).

(16) Dickey and Gray, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. II, 1943, p. 60.

(17) Allen and Thirtle, *ibid.*, Vol. 26, 1946, p. 16.

(18) Harries and Lenart, *Ann.*, **410**, 103 (1915).

acid, was 1.50 g. (99%) of impure brick-red 2-formylpyridine *p*-carboxyphenylhydrazone, m. p. 221–227°, which decomposed at 234–236° after reprecipitation as a tan powder from aqueous sodium carbonate by means of glacial acetic acid. It could not be recrystallized.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60. Found: C, 63.81; H, 4.80.

A picrate, prepared as a red powder from 95% ethanol, melted without recrystallization at 250°.

Anal. Calcd. for $C_{19}H_{14}N_6O_9$: C, 48.52; H, 3.00. Found: C, 48.74; H, 3.10.

With Hydrolyzed 5-*n*-Propyl-5-(2′-pyridyl)-barbituric Acid.—Hydrolysis of 1.5 g. (0.0061 mole) of 5-*n*-propyl-5-(2′-pyridyl)-barbituric acid was accomplished by heating in 8 ml. of 20% aqueous sodium hydroxide for one hour on a steam cone. The solution was evaporated to dryness on a hot-plate at low heat (160–170°) to avoid spattering. The dry residue was redissolved in 30 ml. of water, the solution cooled in an ice-bath, and acidified with concentrated hydrochloric acid just before the addition of the diazonium salt to follow. When the solution reached acidity, there was an evolution of gas.

A solution of *p*-carboxybenzenediazonium chloride was prepared as described above from 1.1 g. (0.0080 mole) of *p*-aminobenzoic acid. This was added to the acidified hydrolysate from the barbituric acid, followed by a solution of 3.3 g. (0.04 mole) of sodium acetate in 10 ml. of water. The mixture was kept below 5°, and subsequently allowed to stand at 4° for twenty-four hours, when 0.94 g. (54%) of precipitate was collected. An additional 0.69 g. had formed at the end of ninety-six hours; total yield 1.63 g. (94%), m. p. 243° (dec.). The yellow powder could not be crystallized, but was purified for analysis by reprecipitation from sodium carbonate solution by means of glacial acetic acid, followed by washing with cold water, m. p. 243° (dec.).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05. Found: C, 67.98; H, 5.82.

A picrate, crystallized as fine burnt-orange needles from ethanol, melted at 217°.

Anal. Calcd. for $C_{22}H_{20}N_6O_9$: C, 51.55; H, 3.93. Found: C, 51.76; H, 4.17.

The same reaction between the diazonium salt prepared from 2.74 g. (0.020 mole) of *p*-aminobenzoic acid and the hydrolysate from 2.85 g. (0.012 mole) of 5-*n*-propyl-5-(2′-pyridyl)-barbituric acid, with 5.74 g. (0.070 mole) of sodium acetate in 20 ml. of water, carried out without evaporation of the hydrolysate to dryness, gave 1.05 g. (26%) of product, m. p. 242–244° (dec.) in twenty-four hours. This was increased to 74% after seventy-two hours.

2-*n*-Butyrylpyridine.—A 50% aqueous solution containing 6.7 g. (0.076 mole) of pyruvic acid was refluxed for one hour with 6.9 g. (0.024 mole) of 2-*n*-butyrylpyridine *p*-carboxyphenylhydrazone in 80 ml. of glacial acetic acid. The mixture was cooled in ice, and 40% sodium hydroxide added to alkalinity. The solution was then extracted with three 200-ml. portions of ether, and the extracts dried over potassium hydroxide pellets and fractionally distilled to yield 4.58 g. (81%) of 2-*n*-butyrylpyridine, b. p. 215–217°; $n^{20}D$ 1.5078; sp. gr.$^{20}_{20}$ 1.040; *MR* calcd., 42.7; *MR* found, 42.7. A picrate, recrystallized twice from water as yellow prisms, melted at 75° (lit.,[19] 75°).

Coupling Experiments with 2-Picoline, 2-Ethylpyridine and 2-Picoline Methiodide.—To a solution of diazotized *p*-nitroaniline prepared as described in the section above from 13.8 g. (0.10 mole) of *p*-nitroaniline, maintained at 5°, were added 9.3 g. (0.10 mole) of 2-picoline and a cold solution of 29.0 g. (0.35 mole) of sodium acetate in 100 ml. of water. A yellow solid, 1.5 g. (crude yield 7%) of 2-formylpyridine *p*-nitrophenylhydrazone, m. p. 205–212°, formed within forty-five minutes. One recrystallization from nitromethane gave a m. p. of 216–219° which was not depressed in a mixed m. p. with an authentic sample.

Similar experiments with 2-picoline and diazotized sulfanilic acid or *p*-aminobenzoic acid and with 2-ethylpyridine and diazotized *p*-nitroaniline showed no formation of solids on long standing of the reaction mixtures in the cold.

Reaction of cold *p*-nitrobenzenediazonium chloride prepared as described above from 6.9 g. (0.05 mole) of *p*-nitroaniline with 11.75 g. (0.05 mole) of 2-picoline methiodide occurred immediately to form a brown precipitate. A cold solution of 15.0 g. (0.175 mole) of sodium acetate in 50 ml. of water was added and the mixture allowed to stand at 5° for one hour, then filtered. The dried precipitate weighed 11.5 g. (93%), m. p. after recrystallization from nitromethane 168–170°. A mixed m. p. with *p*-iodonitrobenzene, m. p. 171.5°, showed no depression.

Anal. Calcd. for $C_6H_4NO_2I$: C, 28.91; H, 1.60. Found: C, 29.40; H, 1.95.

Acknowledgment.—We wish to thank Smith, Kline and French Laboratories for financial assistance.

Summary

The scope of the Japp–Klingemann reaction has been extended to 2-pyridylacetic acids. Its application to these through the use of 5-(2′-pyridyl)-substituted barbituric acids provides a synthetic route to 2-acylpyridines.

URBANA, ILLINOIS RECEIVED MARCH 18, 1949

(19) Pinner, *Ber.*, **34**, 4234 (1901).