holic groups to form a cross-linked structure. The reactions occurring during the deacylation of the original cellulose mixed ester were interpreted by the mechanism usually assumed for Walden inversions.

The anhydrocellulose was partly degraded by hot dilute mineral acid, decomposed in cold, concentrated acid and swelled but did not dissolve in various solvents for cellulose. These observations, together with the similar behavior of the anhydrocellulose acetate toward many organic liquids, were all consistent with the structure proposed for the substance.

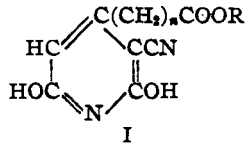
CAMBRIDGE, MASS. RECEIVED NOVEMBER 6, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC., RAHWAY, NEW JERSEY]

3,4-Substituted Pyridines. II. β-(4-Pyridyl)-propionic Acid

BY JOSEPH R. STEVENS AND RALPH H. BEUTEL

In continuing our studies on the synthesis of 3,4-substituted pyridines,[1] a series of compounds having the formula I, where n = 0, 1 and 2, has been made.



I

With the removal of the 2 and 6 hydroxyl groups, compounds with active functional groups in the 3 and 4 positions would result which should serve as good starting points for syntheses of 3,4-substituted pyridines. However, in all members of the series, preliminary results showed that these substances on treatment with phosphorus oxychloride yielded intractable products. With the removal of the cyano group prior to the phosphorus oxychloride treatment, elimination of the hydroxyl groups proceeded smoothly. Utilizing these reactions, β-(2,6-dichloro-4-pyridyl)-propionic acid was prepared which, on catalytic reduction, was converted into β-(4-pyridyl)-propionic acid.

Compounds with formula I were prepared by the general method[2,3] of condensing the appropriate β-keto ester with cyanoacetamide in the presence of piperidine. Diethyl β-ketoadipate, required for the synthesis of ethyl β-(2,6-dihydroxy-3-cyano-4-pyridyl)-propionate, I (n = 2), was prepared by the "acid cleavage" of diethyl α-acetyl-β-ketoadipate which, in turn, was obtained from sodium acetoacetic ester and β-carbethoxypropionyl chloride. The procedures followed in the preparation of the various derivatives and the data concerning them are given below.

(1) Stevens, Beutel and Chamberlin, THIS JOURNAL, **64**, 1093–1095 (1942).

(2) Guareschi, *Mem. Acad. Torino*, [2] **46**, 11 (1895); *Ber.*, **29** ref. 655 (1896).

(3) Thole and Thorpe, *J. Chem. Soc.*, **99**, 422–428 (1911).

Experimental

2,6-Dihydroxy-3-cyano-4-carbethoxypyridine, I (n = 0).—Forty-three grams of ethyl oxaloacetate was added to a solution of 20 g. of cyanoacetamide in 100 cc. of warm methanol together with 20 g. of piperidine. After standing for two days at room temperature the bright orange-red crystals of the piperidine salt were filtered off and crystallized from water; yield 23 g. (36% of the theoretical); m. p. 180–181°.

Anal. Calcd. for $C_{14}H_{19}N_3O_4$: C, 57.31; H, 6.58; N, 14.3. Found: C, 57.50; H, 6.82; N, 14.6.

A solution of 29.3 g. of the piperidine salt in 293 cc. of hot water was acidified with hydrochloric acid. The mixture was cooled in ice and filtered. The white crystals were washed with water and dried under vacuum; yield 20 g. (96% of the theoretical). For analysis, some of the compound was crystallized several times from dilute methanol; it has no definite melting point but softens at 120° and finally becomes liquid at 150°.

Anal. Calcd. for $C_9H_8N_2O_4$: N, 13.5. Found: N, 13.5.

Ethyl (2,6-Dihydroxy-3-cyano-4-pyridyl)-acetate, I (n = 1).—Robinson[4] has attempted this condensation but was unable to obtain the desired compound. To a solution of 4.2 g. of cyanoacetamide in 50 cc. of methanol was added 10.1 g. of ethyl acetonedicarboxylate and 4.4 g. of piperidine. The solution was refluxed for six hours and allowed to stand overnight. The solvent was removed under vacuum; the residue was dissolved in 25 cc. of 2.5 *N* hydrochloric acid and the solution was cooled in ice until crystallization was complete. The crystals were filtered, washed with water, and dried; yield 3.5 g. (31.5% of the theoretical). Recrystallization twice from isopropanol and once from water gave a product, m. p. 239°.

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.04; H, 4.54; N, 12.6. Found: C, 53.56; H, 4.24; N, 13.0.

Diethyl α-Acetyl-β-ketoadipate.[5]—To 23 g. of sodium ribbon suspended in 795 g. of sodium-dried benzene, 390 g.

(4) Robinson and Watt, *ibid.*, 1537 (1934).

(5) Robinson and Watt, *ibid.*, 1539 (1934).

of ethyl acetoacetate was added as rapidly as possible. When the reaction was complete, 165 g. of freshly prepared β-carbethoxypropionyl chloride was added over a period of forty-five minutes. After standing overnight, acidified ice water was added; the benzene extract was dried, and concentrated to about 700 cc. The concentrate was placed in a separatory funnel and was shaken with 100, 50 and 50 cc. portions of a solution of 200 g. of anhydrous potassium carbonate in 200 cc. of water. Three layers were formed. The brown middle layer was the potassium salt of the desired compound; the bottom layer contained unchanged potassium carbonate solution together with solid potassium bicarbonate, whereas the top layer held the alkali-insoluble fraction (enol ester). The two lower layers were withdrawn and filtered free from potassium bicarbonate (45 g.). These filtered layers were shaken with benzene and, after standing, the lowest layer was discarded. The middle layer was acidified while ice-cold with 300 cc. of 2.5 *N* hydrochloric acid and extracted with ether. The ether extract was dried and concentrated and left 81 g. of residue. The residue was distilled in a molecular still at 65–76° under a pressure of 5×10^{-4} to 5×10^{-3} mm. An initial fraction of 16 g. was taken off; yield 40 g. (18.4% of the theoretical).

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.79; H, 7.02; mol. wt., 258. Found: C, 55.59; H, 6.86; mol. wt. (cryoscopic in benzene), 246, 253.

Robinson prepared the corresponding methyl ester; however, he was unable to convert it to the ester of β-ketoadipic acid.

Diethyl β-Ketoadipate.—A solution of 10 g. of diethyl α-acetyl-β-ketoadipate in 50 cc. of anhydrous ether was cooled to 0° and a stream of ammonia gas was passed through for thirty minutes. The solution turned to a crystalline mush within a few minutes. The ice-bath was removed and the reaction mixture stood at room temperature for thirty minutes during which time ammonia was evolved and a solution was formed again. The solution was concentrated on the steam-bath to one-half its volume, cooled, diluted with ether and shaken in a separatory funnel for ten minutes with 2.5 *N* hydrochloric acid. The ether extract was washed with water, dried, and concentrated. The residue was distilled in a molecular still under a pressure of 10^{-3} mm. at 65–70°; the middle fraction gave a crude product; yield 5 g. (60% of the theoretical). For analysis, the product was redistilled as above, giving 2 g. of pure material.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46; mol. wt., 216. Found: C, 55.35; H, 7.36; mol. wt. (cryoscopic in benzene), 218.

1-Phenyl-3-(β-carbethoxyethyl)-pyrazolone.—A mixture of 1.08 g. of diethyl β-ketoadipate and 0.54 g. of phenylhydrazine was heated on a steam-bath for two hours. A mixture of ether–petroleum ether was added to the warm oil and caused it to crystallize; yield 1.12 g. (86% of the theoretical). For analysis, the product was crystallized from hot water and twice more from dilute isopropanol, giving fine white crystals melting at 107.5°.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.58; H, 6.20; N, 10.8. Found: C, 64.72; H, 6.06; N, 10.9.

Ethyl β-(2,6-Dihydroxy-3-cyano-4-pyridyl)-propionate.—A solution of 4.32 g. of diethyl β-ketoadipate, 2 g. of cyanoacetamide, and 2 g. of piperidine in 20 cc. of ethanol was heated at 85° for sixteen hours. The alcohol was distilled; the residue was taken up in a little water and acidified with hydrochloric acid. After cooling for several hours, the crystals were filtered off, washed with water, and dried; yield 1.72 g. (36.5% of the theoretical). For analysis, a portion was crystallized from ethanol, m. p. 247°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.9. Found: C, 55.95; H, 5.51; N, 12.0.

β-(2,6-Dihydroxy-4-pyridyl)-propionic Acid.—A mixture of 0.62 g. of ethyl-β-(2,6-dihydroxy-3-cyano-4-pyridyl)-propionate and 3 cc. of concentrated hydrochloric acid was heated at 150° for seven hours. The solution was distilled to dryness under a vacuum and then the residue was broken up into a little water, filtered, and dried; yield 0.29 g. (61% of the theoretical). Recrystallization twice from water gave a product melting at 268–269°.

Anal. Calcd. for $C_8H_9NO_4$: C, 52.44; H, 4.95. Found: C, 52.38; H, 5.00.

β-(2,6-Dichloro-4-pyridyl)-propionic Acid.—A mixture of 0.29 g. of β-(2,6-dihydroxy-4-pyridyl)-propionic acid and 3 cc. of phosphorus oxychloride was heated at 175° for seven hours. The solution was poured onto ice and, after standing for several hours, was extracted with chloroform. The extract was decolorized with charcoal and concentrated. The oily residue, which crystallized on cooling, was triturated with a small amount of petroleum ether and filtered. The product (0.22 g.) sublimed at 115° and 10^{-3} mm.; yield 0.20 g. (57% of the theoretical); m. p. 127°.

Anal. Calcd. for $C_8H_7Cl_2NO_2$: C, 43.65; H, 3.21. Found: C, 43.97; H, 3.24.

β-(4-Pyridyl)-propionic Acid Hydrochloride.—A solution of 0.05 g. of palladium chloride in 1 cc. of 2.5 *N* hydrochloric acid was mixed with 10 cc. of methanol and 0.5 g. of acid-washed charcoal and then reduced. To the reaction mixture was added 0.20 g. of β-(2,6-dichloro-4-pyridyl)-propionic acid and the mixture was reduced for two hours with hydrogen at 30 lb. pressure. After filtering off the catalyst, the filtrate was distilled to dryness under a vacuum. The crystalline residue was dissolved in a little absolute alcohol and the hydrochloride was precipitated with ether; yield 0.13 g. (77% of the theoretical). The hydrochloride was crystallized from isopropanol and several times by dissolving in methanol and precipitating with ether, giving crystals melting at 208°.

Anal. Calcd. for $C_8H_{10}ClNO_2$: C, 51.22; H, 5.37; N, 7.47. Found: C, 51.34; H, 5.78; N, 7.54.

Diethyl α-(β-Ethoxyethyl)-β-ketoadipate.—To a solution of 2.3 g. of sodium in 50 cc. of absolute alcohol was added 21.6 g. of diethyl β-ketoadipate. The solution was heated to boiling and 16.8 g. of β-ethoxyethyl bromide was added over a period of one hour. The solution was refluxed for five hours and allowed to stand overnight. Acidified water was added and the mixture was extracted with ether. After concentrating the extract, the concentrate was distilled in a molecular still at 5×10^{-4} mm. and 90°. The distillate was cut into three equal fractions, and the last fraction was analyzed; yield approx. 6 g. (20% of the theoretical).

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.31, H, 8.39; mol.

wt., 288. Found: C, 58.14; H, 8.27; mol. wt. (cryoscopic in benzene), 287.

It was hoped that this compound would condense with cyanoacetamide to give I (n = 2) with a β-ethoxyethyl group substituted in the 5 position, but this could not be accomplished under the experimental conditions used.

Acknowledgment.—The authors are grateful for the interest taken by Dr. Randolph T. Major in this investigation and for his helpful suggestions. The microanalyses were made by Messrs. Douglass Hayman, Wilhelm Reiss, Howard Clark and Richard Boos. The molecular weight determinations were made by Dr. John Conn.

Summary

1. Diethyl β-ketoadiapate has been synthesized and identified.

2. β-(4-Pyridyl)-propionic acid has been synthesized from this ester.

RAHWAY, N. J. RECEIVED DECEMBER 15, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

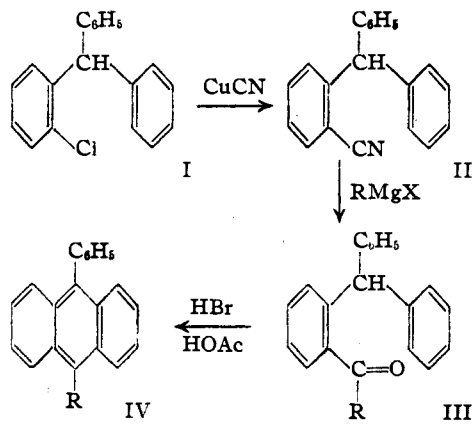
Aromatic Cyclodehydration. X.[1] 9-Alkyl- and 9-Aryl-10-phenylanthracenes

BY CHARLES K. BRADSHER[2] AND E. STUDLEY SMITH[3]

In earlier communications,[4] there has been described the cyclization of *o*-benzylphenones to give *meso* substituted hydrocarbons.

The present work was undertaken to discover whether this mode of cyclization might be extended to *o*-benzhydrylphenones. If this could be accomplished, a new method would be afforded for the synthesis of 9-alkyl- or 9-aryl-10-phenylanthracenes.

First *o*-chlorotriphenylmethane[5] (I) was converted to the nitrile[6] (II) by the action of cuprous cyanide. The nitrile (II) with phenylmagnesium



bromide, on hydrolysis of the imine, gave *o*-benzhydrylbenzophenone[7] (III, R = C_6H_5). This ketone (III) when refluxed for ten days with hydrobromic and acetic acids gave 9,10-diphenylanthracene in 81% yield. If refluxing was interrupted at the end of four days, the hydrocarbon was obtained in a yield of only 45% as compared with the 75% yield of 9-phenylanthracene obtained from *o*-benzylbenzophenone under the same conditions.

In the other two cases investigated (R = CH_3 and C_2H_5), the crude ketimine was added directly to the refluxing mixture of hydrobromic and acetic acids. Apparently both hydrolysis and cyclization occurred under these conditions, for after eleven days, the expected hydrocarbons were obtained. The properties observed for our hydrocarbons are in substantial agreement with those found by previous authors.[8,9,10]

After completion of the above work, it was discovered that *o*-benzhydrylbenzophenone (III, R = C_6H_5) can be cyclized in 95% yield by heating it for only forty-five minutes in acetic anhydride containing a few drops of sulfuric acid. This method of cyclization was found to be ineffective in the case of *o*-benzylbenzophenone.

Experimental

***o*-Chlorotriphenylmethane** (I).—We found it desirable to simplify the method of Tschitschibabin[7] by eliminating the isolation of the intermediate *o*-chlorotriphenylcarbinol and by reducing with red phosphorus and iodine instead of the more expensive hydriodic acid. Thus the crude carbinol obtained from 25 g. of methyl *o*-chlorobenzoate was refluxed with acetic acid (375 cc.), water (62 cc.), red phosphorus (12.5 g.) and iodine (12.5 g.) for twenty-four

(1) For the preceding communications of this series see THIS JOURNAL, **63**, 493 (1941).

(2) National Research Fellow (participating basis) 1941–1942.

(3) Eastman Kodak Scholar (1941–1942).

(4) Bradsher, THIS JOURNAL, **62**, 486, 1077 (1940).

(5) Tschitschibabin, *Ber.*, **44**, 443 (1911).

(6) Drory, *ibid.*, **24**, 2563 (1891).

(7) (a) Seidel and Begner, *ibid.*, **65**, 1566 (1932); (b) Koelsch, *J. Org. Chem.*, **3**, 456 (1938).

(8) (a) Haller and Guyot, *Compt. rend.*, **138**, 1251 (1904); (b) Clar, *Ber.*, **64**, 2194 (1931).

(9) Barnett and Mathews, *ibid.*, **59**, 1429 (1926).

(10) Barnett, Cook and Wiltshire, *J. Chem. Soc.*, 1724 (1927).