[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Pyridine Derivatives. I. Preparation of 3-Chloro-2-pyridone and 6-Chloro-2-pyridone

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The synthesis of the previously unknown 3-chloro-2-pyridone is reported, and a convenient synthesis of 6-chloro-2-pyridone is described.

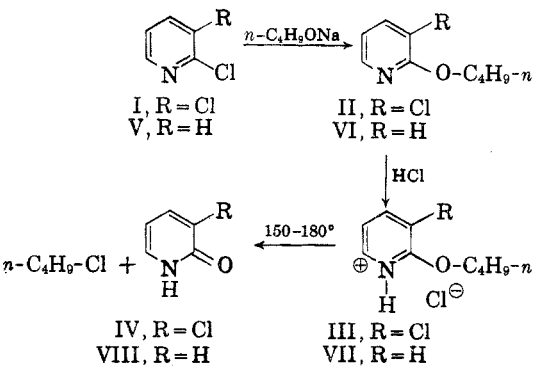
Of the four possible monochloro derivatives of 2-pyridone, only 3-chloro-2-pyridone (IV) has not been described previously. The one recorded observation of the direct chlorination of 2-pyridone mentions 3,5-dichloro-2-pyridone as a product, but 5-chloro-2-pyridone was the only monochlorinated pyridone found in the reaction mixture.[1]

A suitable starting material for an unambiguous synthesis of 3-chloro-2-pyridone is 2,3-dichloropyridine (I), which is readily available from 3-aminopyridine by chlorination to 2-chloro-3-aminopyridine,[2] followed by the replacement of the amino group of the latter by chlorine.[3]

The hydrolysis of the more reactive 2-chlorine atom of 2,3-dichloropyridine to a pyridone function was accomplished conveniently by a two-step process. Treatment of 2,3-dichloropyridine with excess sodium *n*-butoxide in *n*-butyl alcohol for 22 hr. on the steam bath gave, in 64% yield, 3-chloro-2-*n*-butoxypyridine (II). The acid-catalyzed cleavage of 2-alkoxypyridines to 2-pyridones by mineral acids is well known, but the conditions employed may be drastic and inconvenient, *e.g.*, hydrochloric acid under pressure at 160°.[4] A simple and convenient method for the cleavage of mixed aliphatic-aromatic ethers consist in heating the appropriate ether with the thermally stable pyridine hydrochloride.[5]

It was assumed in the case of a 2-alkoxypyridine that the ether and the hydrochloride reagent could be combined in the same molecule; this was found indeed to be possible. When dry hydrogen chloride was passed into an ethereal solution of 3-chloro-2-*n*-butoxypyridine the crystalline hydrochloride (III) of the latter separated in quantitative yield. The dry salt decomposed smoothly at 150–180°, evolving *n*-butyl chloride and leaving a residue which, on crystallization from benzene, afforded pure 3-chloro-2-pyridone (IV), m.p. 180–181°, in 69% yield.

The stepwise hydrolytic procedure described above was found to be equally applicable to the simpler model case of 2-chloropyridine (V). The conversion of 2-chloropyridine to 2-*n*-butoxypyridine (VI) proceeded in 85% yield; pyrolysis of the oily hydrochloride (VII) of the latter at 150°–180° gave *n*-butyl chloride and 2-pyridone (VIII), both essentially in quantitative yield. By contrast, the cleavage of 2-*n*-butoxypyridine by concentrated hydrochloric acid at 98° proceeded very slowly, 75% of the unhydrolyzed ether being recovered after 14 hours of heating.



Of the remaining monochloro-2-pyridones, the one least convenient to prepare has been 6-chloro-2-pyridone (XVI), the only described synthesis of which involves heating the difficultly accessible 6-bromo-2-ethoxypyridine with hydrochloric acid under pressure.[6] A simple new synthesis of 6-chloro-2-pyridone adaptable to large scale preparations, has been developed starting from the commercially available 6-methyl-2-aminopyridine (IX). Diazotization of this amine in cold fuming hydrochloric acid, as described by Seide,[7] gave 2-methyl-6-chloropyridine (X) in 56% yield. Sodium permanganate oxidation of 2-methyl-6-chloropyridine[8] gave, in 61% yield, 6-chloropicolinic acid (XI), esterified by methanolic hydrogen chloride, in 83% yield, to methyl 6-chloropicolinate (XII), m.p. 95–96°. Reaction of this methyl ester with hydrazine produced, in 92% yield, 6-chloropicolinic hydrazide (XIII), m.p. 154–155°. Diazotization of

(1) M. Dohrn and R. Dirksen, U. S. Patent 1,706,775; *Chem. Abstr.*, 23, 2189 (1929).

(2) O. Schickh, A. Binz, and A. Schultz, *Ber.*, 69, 2593 (1936).

(3) H. J. den Hertog, J. C. M. Schogt, J. de Bruyn, and A. de Klerk, *Rec. trav. chim.*, 69, 673 (1950).

(4) C. R. Kolder and H. J. den Hertog, *Rec. trav. chim.*, 72, 285 (1953).

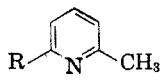
(5) V. Prey, *Ber.*, 74, 1221 (1941).

(6) H. J. den Hertog and J. de Bruyn, *Rec. trav. chim.* 70, 182 (1951).

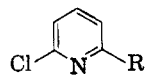
(7) O. A. Seide, *J. Russ. phys. chem. Soc.*, 50, 534 (1918).

(8) Oxidation of this compound using potassium permanganate is mentioned in Swiss Patent 227,124.

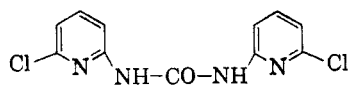
the hydrazide gave 6-chloropicolinic azide (XIV) which, without purification, was decomposed directly in warm 50% aqueous acetic acid to 6-chloro-2-aminopyridine (XV), m.p. 65–67°; the over-all yield of pure amine from the hydrazide was 64%. As a by-product of the azide decomposition there was isolated, in 7% yield, bis(6-chloro-2-pyridyl) urea (XVII), m.p. 250–251°. Finally, the 6-chloro-2-aminopyridine was diazotized in aqueous sulfuric acid, giving 6-chloro-2-pyridone (XVI) in a yield of 70%.



IX: R = NH_2
X: R = Cl



XI, R = COOH
XII, R = $COOCH_3$
XIII, R = $CONH—NH_2$
XIV, R = CON_3
XV, R = NH_2
XVI, R = OH



XVII

EXPERIMENTAL[9]

3-Chloro-2-(n-butoxy)pyridine (II). To a solution of sodium (12.3 g.) in dry *n*-butyl alcohol (180 ml.) was added a solution of 2,3-dichloropyridine[3] (20.0 g.) in the minimum necessary volume of dry *n*-butyl alcohol. The mixture was heated for 22 hr. on the steam bath with occasional shaking, cooled, and made strongly acid by the addition of concentrated hydrochloric acid. The butanol solution was decanted from the sodium chloride precipitate, which was washed first with methanol, then with ether. The combined organic extracts were diluted with water, the mixture was made strongly basic with sodium hydroxide, and the organic layer separated. The aqueous layer was extracted further with several portions of ether. The combined organic extracts were washed with water, dried (sodium sulfate), and distilled. The desired chloroether (16 g., 66%) was collected at 72–75° (2 mm.). On redistillation an analytical sample was obtained, b.p. 75° (2 mm.).

Anal. Calcd. for $C_9H_{12}ClNO$: C, 58.22; H, 6.48; N, 7.55; Cl, 19.15. Found: C, 57.82; H, 6.71; N, 7.39; Cl, 19.06.

3-Chloro-2-pyridone (IV). Dry hydrogen chloride gas was passed into a cooled solution of 3-chloro-2-(*n*-butoxy)-pyridine (15.0 g.) in dry ether (200 ml.) until no further solid separated. The white precipitate of hydrochloride (15.0 g.) was filtered off, washed with ether, followed by 30–60° petroleum ether, and sucked dry. The dried hydrochloride was placed in a round-bottomed flask provided with a water separator, and the flask was heated in a sand bath. The bath temperature was raised from 150 to 180° over a period of 90 min., when *n*-butyl chloride (2.3 ml.) collected in the separator. The flask was cooled and the white crystalline 3-chloro-2-pyridone (5.5 g., 64%), m.p. 180–181°, was rubbed with a little benzene, filtered and dried. After recrystallization from a large volume of benzene glistening flakes, m.p. 180–181°, were obtained.

Anal. Calcd. for C_5H_4NOCl: C, 46.40; H, 3.09; N, 10.80; Cl, 27.42. Found: C, 46.54; H, 3.17; N, 10.47; Cl, 27.44.

2-(n-Butoxy)pyridine (VI). To a solution of sodium *n*-butoxide prepared from sodium hydride (7.5 g.) and *n*-butyl alcohol (100 ml.) was added 2-chloropyridine (11.6 g.). The mixture was heated for 10 hours on the steam bath, cooled, and a mixture of water (200 ml.) and concentrated hydrochloric acid (40 ml.) added. The butanol layer was separated and extracted three times with a small volume of dilute hydrochloric acid. The original aqueous acid phase was combined with the acid wash solutions, and residual butanol removed by ether extraction. The aqueous solution was cooled, made strongly basic by addition of aqueous sodium hydroxide, and the separated basic oil extracted by ether. Evaporation of the dried ether extracts left an oil, most of which distilled at 55–65° (3–4 mm.). Redistillation gave pure 2-(*n*-butoxy)pyridine (13.2 g., 85%), b.p. 65–66° (4 mm.).

Anal. Calcd. for $C_9H_{13}NO$: C, 71.52; H, 8.63; N, 9.28. Found: C, 71.59; H, 8.57; N, 9.50.

Ether cleavage of 2-(n-butoxy)pyridine (VI). Dry hydrogen chloride was passed through an ethereal solution of the butyl ether VI (8.0 g.) when the hydrochloride separated as a thick oil: the oil did not crystallize on rubbing or after adding methanol. The methanolic solution of the hydrochloride was evaporated and the residue heated gradually to 220°; during the heating *n*-butyl chloride (5.0 ml.) distilled over. Distillation of the residue at 132–133° (2 mm.) gave 2-pyridone (5.0 g., 99%) as a viscous mass, solidifying to crystals, m.p. 65–70°. The identity of the crude pyridone was confirmed by its infrared spectrum.

6-Chloropicolinic acid (XI). To a gently refluxing and rapidly stirred suspension of 2-methyl-6-chloropyridine[7] (69 g.) in water (700 ml.) was added, during 1 hr., a solution of sodium permanganate (215 g.) in water (300 ml.). Heating and stirring were continued for an additional 3 hr., and the mixture was then steam distilled. From the distillate unchanged 2-methyl-6-chloropyridine (23.0 g.) was recovered. The oxidation mixture was filtered from manganese dioxide and the colorless filtrate concentrated to 300 ml., cooled, and acidified with concentrated hydrochloric acid. The fine white precipitate of acid XI was filtered, washed carefully with ice water, air dried and finally oven dried at 95°: yield 35.0 g. (61%, based on unrecovered starting material), m.p. 192–194° (reported[10] 190°).

Methyl 6-chloropicolinate (XII). A suspension of finely powdered 6-chloropicolinic acid (31.0 g.) in 12% methanolic hydrogen chloride (200 ml.) was refluxed for six hours. The clear solution was concentrated on the steam bath (aspirator pressure), diluted with cold water, and the precipitated ester extracted into a large volume of ether. After washing with water and aqueous sodium bicarbonate, the dried extract was evaporated slowly and the residual mass of needles (28.0 g., 83%; m.p. 95–96°) washed with 30–60° petroleum ether and dried. Recrystallization from absolute ethanol afforded the analytical sample as long white needles, m.p. 96–97°.

Anal. Calcd. for $C_7H_6NO_2Cl$: C, 48.90; H, 3.50; N, 8.17; Cl, 20.70. Found: C, 49.13; H, 3.71; N, 8.02; Cl, 20.89.

6-Chloropicolinic hydrazide (XIII). A solution of the methyl ester XII (28.0 g.) in a mixture of absolute ethanol (150 ml.) and anhydrous hydrazine (11 ml.) was refluxed for 2.5 hr. The clear solution was evaporated under vacuum and the solid residue crystallized from aqueous ethanol to give a microcrystalline white powder (26.0 g., 92%, m.p. 154–155°). The melting point was not appreciably changed (155–156°) after recrystallization from ethanol.

Anal. Calcd. for $C_6H_6N_3ClO$: C, 42.00; H, 3.51; N, 24.50; Cl, 20.71. Found: C, 42.10, H, 3.60; N, 24.28; Cl, 20.87.

Curtius degradation of 6-chloropicolinic hydrazide. A solution of the hydrazide XIII (37.0 g.) in *N* hydrochloric acid (250 ml.) was cooled to −5° and a solution of sodium nitrite (20.0 g.) in water (100 ml.) was added dropwise with good stirring, taking care that the temperature of the acid solution remained below 0° by cooling. The white precipitate of *6-chloropicolinic azide* (XIV) was filtered, washed with ice-water and sucked almost dry: a sample melted at 102–103° with gas evolution. The crude azide was

(9) Analyses carried out by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

dissolved in 50% aqueous acetic acid (400 ml.) and the solution heated on the steam bath. After 1 hr. gas evolution had ceased. The solution was cooled and the precipitate of crude *bis(6-chloro-2-pyridyl)urea* (XVII; 4.5 g., 7.6%, m.p. 230–240°) was removed by filtration. Recrystallization of a sample of XVII from benzene-ethanol gave voluminous white needles, m.p. 250–251°.

Anal. Calcd. for $C_{11}H_8N_4Cl_2O$: C, 46.62; H, 2.83; N, 19.80; Cl, 25.10. Found: C, 46.72; H, 2.81; N, 19.90; Cl, 25.09.

The acetic acid filtrate from the crude urea was cooled (ice bath) and neutralized to *p*H 7 by the gradual addition of 20% aqueous sodium hydroxide. The precipitate (21.2 g.) was filtered, air dried, and sublimed at 75–90° (2 mm.) to give colorless granular crystals of 6-chloro-2-aminopyridine (XV; 18.0 g., 64%; m.p. 65–67°). The melting point was not altered by resublimation.

Anal. Calcd. for $C_5H_5N_2Cl$: C, 46.67; H, 3.91; N, 21.80; Cl, 27.62. Found: C, 47.16; H, 3.99; N, 21.67; Cl, 27.72.

6-Chloro-2-pyridone (XVI). To a stirred and cooled (0–5°) solution of 6-chloro-2-aminopyridine (10.0 g.) in 6*N* sulfuric acid (70.0 ml.) was added, in small portions, solid sodium nitrite (10.0 g.). After careful neutralization of the resulting cold suspension to *p*H 5 with aqueous sodium hydroxide the crude pyridone (9.0 g.) was filtered, washed with a very small amount of ice water and air dried. Recrystallization from benzene (charcoal treatment) afforded the pure pyridone XVI (6.9 g., 70%) as fine white needles, m.p. 125–126° (reported[6] 128.5–129°).

Anal. Calcd. for C_5H_4NOCl: C, 46.40; H, 3.09; N, 10.80; Cl, 27.42. Found: C, 46.43; H, 3.17; N, 10.95; Cl, 27.39.

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COLUMBUS 10, OHIO

[CONTRIBUTION NO. 1368 FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Preparation of Some α-(2-Thienyl)-β-arylethylamines[1]

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A series of seven α-(2-thienyl)-β-arylethylamine hydrochlorides has been prepared from the corresponding ketones by Leuckart reaction. The necessary ketones were made from the arylacetyl chlorides by a Friedel-Crafts reaction with thiophene or from the arylacetonitriles by reaction with 2-thienylmagnesium iodide or 2-thienyllithium.

Reports of the analgesic potentialities of α,β-diphenylethylamines[2–6] suggested the substitution of the 2-thienyl group for either or both phenyl groups in these compounds. The substitution of 2-thienyl for phenyl in physiologically active compounds may result in little or no change in properties[7,8] but occasionally activity is markedly enhanced.[9,10]

The route selected for the preparation of the 2-thienyl isosteres of α,β-diphenylethylamines was *via* the arylacetyl chlorides, employing a Friedel-Crafts reaction to produce the ketones, followed by conversion to the amines with a Leuckart reagent. The necessary arylacetic acids were to be prepared from the hydrocarbons by chloromethylation, cyanation, and hydrolysis. In practice, it was found possible to use this route with phenylacetyl chloride and *p*-methoxyphenylacetyl chloride to give the ketones (I and II, Table I). Stannic chloride and iodine were effective catalysts for the reaction with thiophene. The investigation was also extended to include the 1-naphthyl-substituted ketone (III, Table I). With 2-thienylacetyl chloride,[11] on the other hand, no ketone could be obtained with either stannic chloride or iodine. Hydrogen chloride was freely evolved but only tarry products were obtained. An alternative preparation of the ketone by the use of 2-thienylacetonitrile and 2-thienylmagnesium iodide[12] or 2-thienyllithium[13] also failed, only polymeric materials being obtained. This failure was attributed to the involvement of the α hydrogen atoms of the nitrile. Bisalkylation at the α positions permitted successful reaction to give the ketone (IV, Table I). The corresponding phenyl ketone (V, Table I) was also prepared as well as the diethyl analog (VI, Table I).

Application of a Leuckart reaction was uniformly successful to convert the ketones to the primary amines (VII–XI, Table II). The yield of the amine (XII, Table II) from the diethyl ketone (VI, Table

(1) From the doctoral dissertation of Robert A. Brooks; Yale University; present address: Jackson Laboratory, E. I. du Pont de Nemours and Co., Inc., Wilmington 99, Del.

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(10) F. F. Blicke and M. U. Tsao, *J. Am. Chem. Soc.*, **66**, 1645 (1944).

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(13) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **71**, 1870 (1949).