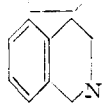
TABLE IV (*continued*)

No.	Am_1	Am_2	m	n	Isomer	B.p. lowering, % I.v. dose 1.0 mg./kg.	B.p. lowering, % I.d dose 10.0 mg./kg.	Duration[b], min. I.v.	Duration[b], min. I.d.[a]
					$Am_1(CH_2)_mC(OH)(C{\equiv}CH)(CH_2)_nAm_2 \cdot 2CH_3Br$				
34		$(CH_3)_2N$	2	3		0		0	
35		$(CH_3)_2N$	2	2		−28	−34	165	120

[a] Intraduodenal. [b] The "duration" of action figures cannot be taken as absolute values. In some instances the b.p. had come back to normal, in other cases the experiment had to be discontinued, with the b.p. still at its lowest point, because additional anesthesia would have had to be administered. Usually, with the longer-acting (>60 minutes) hypotensives b.p. was still reduced substantially at the end of the experiment. [c] I.v. dose = 0.30 mg./kg [d] Bis-maleate.

hexyne added dropwise with stirring. The temperature was held at 60° for 3 hours and the solution then poured onto crushed ice. After the addition of sufficient solid potassium hydroxide to produce two distinct layers, the alkaline mixture was extracted repeatedly with ether. The combined ether extracts were dried with potassium carbonate and the product collected by distillation, b.p. 95–100° (0.30 mm.), yield 15 g. (63%).

The hydrochloride salt was prepared in acetone with ethereal hydrochloric acid, m.p. 168–169°. The hydrochloride salt obtained from the hydration of the 1,6-bis-diethylamino-3-hexyne melted also at 168–169°; a mixed melting of the two hydrochlorides showed no depression, indicating that the hydration of either 1,6-diethylamino-2-hexyne or 1,6-diethylamino-3-hexyne yields the same ketone: 1,6-diethylamino-3-hexanone.

Bis-aminoalcohols. (5) **1,6-Bis-diethylamino-3-hexanol.**—To 38 g. (1.0 mole) of sodium borohydride in 100 cc. of methanol was added dropwise 47 g. (0.20 mole) of the ketone described above. The mixture was heated on the steam-bath for one hour, poured on ice and acidified with dilute aqueous hydrochloric acid. The solution was concentrated, the residue dissolved in water and the solution treated with solid KOH until two layers appeared. The alkaline mixture was extracted with ether and the combined ether extracts dried with potassium carbonate. The product was collected by distillation, b.p. 102–104° (0.30 mm.), yield 32 g. (70%).

The dimethobromide salt was prepared in isopropyl alcohol, m.p. 226–228°. The sodium borohydride reduction of the ketone obtained from the hydration of the 3-hexyne derivative yielded the identical dimethobromide, m.p. 226–228°. A mixed m.p. of the two salts showed no depression. The two hydrochloride salts melted at 176–177° and 176–178°, respectively. A mixed m.p. showed no depression. This is additional proof for the identity of the 1,6-diethylamino-3-hexanone obtained from the two isomeric 2- and 3-alkynes.

Bis-amino-ethinylalcohols. (6) **1-Pyrrolidino-6-dimethylamino-3-ethinylhexan-3-ol.**—In a 500-cc. 3-necked flask equipped with stirrer, Dry Ice condenser, gas inlet tube and dropping funnel was placed 200 cc. of liquid ammonia, 0.1 g. of ferric nitrate and 3.4 g. (0.15) of sodium. Tank acetylene, scrubbed with sulfuric acid and dried, was admitted until the theoretical amount had been added (color change: milky white solutions turn gray). To the sodium acetylide thus formed was added dropwise 30 g. (0.14 mole) of 1-pyrrolidino-6-dimethylamino-3-hexanone, the solution allowed to reflux for 2.5 hours at room temperature and then hydrolyzed with 100 cc. of ammonium hydroxide. The mixture was extracted with ether, the ether extracts dried with potassium carbonate and the product collected by distillation at 83–86° (0.1 mm.), yield 14 g. (50%). *Anal.* Calcd. for $C_{14}H_{26}N_2O$: N, 11.76. Found: N, 12.00.

MILWAUKEE 1, WISC.

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

The Reaction of 2-Aminopyridine with α-Halo Ketones

BY ROGER ADAMS AND J. S. DIX[1]

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Unequivocal syntheses of 2-phenylimidazo[1,2-a]pyridine and 3-phenylimidazo[1,2-a]pyridine and their methyl analogs have been achieved. These results confirm structures previously assigned products of the reaction of 2-aminopyridine with α-halo ketones.

2-Aminopyridine is reported to react with an alkyl halide in two ways dependent upon whether the free base or a metallic salt of the aminopyridine is used. 2-Aminopyridine generally leads preponderantly to substitution on the ring nitrogen while sodium 2-aminopyridine leads only to amino group substitution.[2,3] The reaction of 2-aminopyridine with α-halo ketones generally has been assumed to follow a similar course and to proceed with substitution on the ring nitrogen. In the case of phenacyl bromide, the primary reaction product loses water with formation of a compound of structure III, 2-phenylimidazo[1,2-a]pyridine[4] (R = C_6H_5). However, the 2-substituted imidazo[1,2-a]pyridine structures previously assigned to this and analogous products were made questionable by the disclosure that the reaction of phenacyl bromide with either 2-aminopyridine or its lithium salt[5] resulted in the same compound. With the lithium salt the amino nitrogen would be expected to react, and thus upon cyclization 3-phenylimidazo[1,2-a]pyridine (VIII, R = C_6H_5) would be formed. The main product resulting from either procedure was

(1) University of Illinois Fellow, 1954–1955; Standard Oil of California Fellow, 1955–1957.

(2) T. M. Sharp, *J. Chem. Soc.*, 1855 (1939).

(3) I. A. Kaye, I. C. Kogon and C. L. Parris, THIS JOURNAL, **74**, 403 (1952).

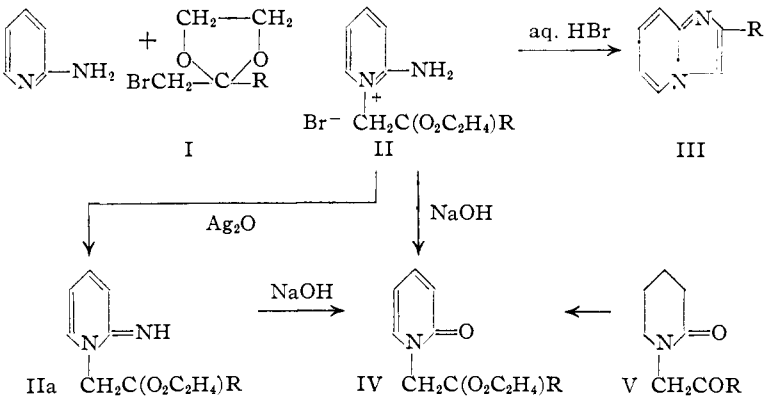
(4) A. E. Chichibabin, *Ber.*, **59**, 2048 (1926).

(5) C. Djerassi and G. Pettit, THIS JOURNAL, **76**, 4470 (1954).

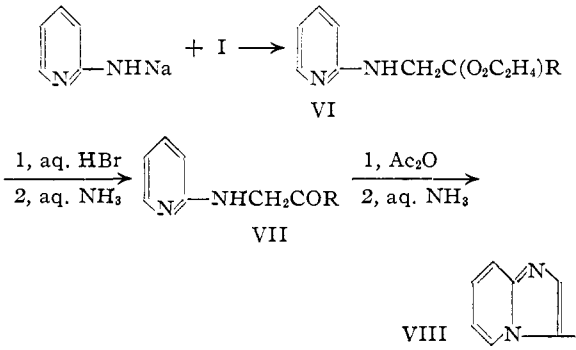
proved by Kröhnke to be the 2-phenyl isomer by an unequivocal synthesis, the ammonolysis of 1-phenacyl-2-chloropyridinium bromide.[6] The same isomer and its methyl analog were also prepared by acid hydrolysis of 1-phenacyl-2-acetamidopyridinium bromide and 1-acetonyl-2-acetamidopyridinium bromide, respectively.[7] Work in this Laboratory has confirmed the structures of these compounds by an independent route and unequivocal syntheses of the 3-substituted isomers have been achieved.

The ethylene glycol ketals of phenacyl and acetonyl bromide (I) reacted with 2-aminopyridine to give products represented by II. These products upon treatment with dilute hydrobromic acid were hydrolyzed and concomitantly cyclized to 2-substituted imidazo[1,2-a]pyridines (III) (isolated as hydrobromide). The low reactivity of the halogen atom of the ketals of structure I necessitated stringent reaction conditions with 2-aminopyridine and the yields were low.

The structure of compounds shown in II (R = C_6H_5 or CH_3) was proved by treatment of the compounds with silver oxide to form pyridonimines (IIa). Heating compound IIa (R = C_6H_5) with aqueous sodium hydroxide yielded ammonia and the corresponding pyridone IV (R = C_6H_5); compound IV (R = CH_3) was formed directly from compound II (R = CH_3) by the action of aqueous sodium hydroxide. Further proof of structure was furnished by the synthesis from ethylene glycol and 1-phenacyl-2-pyridone (V) of a ketal that proved to be identical with IV (R = C_6H_5).



When sodium 2-aminopyridine and the ethylene glycol ketals of phenacyl and acetonyl bromide reacted, the products shown by formula VI (R = CH_3 or C_6H_5), isomeric with compound IV, were formed. These were hydrolyzed readily with hydrobromic acid to the corresponding ketones (VII) which were cyclized to 3-substituted imidazo[1,2-a]pyridines (VIII) by means of acetic anhydride. Low yields were obtained from reactions of the α-halo ketals with the sodium salt of 2-aminopyridine.



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Experimental

All melting points are corrected.

1-(2-Phenyl-1,3-dioxolan-2-ylmethyl)-2-aminopyridinium Bromide.—A mixture of 9.7 g. of 2-(bromomethyl)-2-phenyl-1,3-dioxolane,[8] 5.6 g. of 2-aminopyridine and 1 ml. of absolute ethanol was heated in a sealed tube at 160° for 6 days. The resultant oil was dissolved in hot methanol, the solution cooled, and a product precipitated with ether. Recrystallization from absolute ethanol yielded 1.45 g. (11% based on the ketal) of product as white needles, m.p. 255–256°.

Anal. Calcd. for $C_{15}H_{17}BrN_2O_2$: C, 53.42; H, 5.08; N, 8.31. Found: C, 53.49; H, 5.11; N, 8.59.

1-(2-Methyl-1,3-dioxolan-2-ylmethyl)-2-aminopyridinium Bromide.—A solution of 2.36 g. of 2-aminopyridine and 5.00 g. of 2-(bromomethyl)-2-methyl-1,3-dioxolane[8] was heated under reflux at 200° for 6 hours. Cooling caused a solid to precipitate which upon washing with absolute ethanol and then with ether weighed 0.78 g. (11%). Recrystallization from absolute ethanol gave white prisms, m.p. 218–219°.

Anal. Calcd. for $C_{10}H_{15}BrN_2O_2$: C, 43.65; H, 5.49; N, 10.18. Found: C, 43.43; H, 5.55; N, 10.06.

1-(2-Phenyl-1,3-dioxolan-2-ylmethyl)-2-pyridonimine.—To a solution of 0.37 g. of 1-(2-phenyl-1,3-dioxolan-2-ylmethyl)-2-aminopyridinium bromide in 6 ml. of water was added in portions 0.35 g. of silver oxide. The mixture was warmed gently, centrifuged, and the aqueous layer decanted. The solid was extracted several times with water. The aqueous solutions were combined and the solvent removed with an air stream. The residual solid was sublimed at 90° (0.2 mm.) to yield 0.17 g. (66%) of product as pale yellow needles, m.p. 114–115°. The compound darkens in presence of air.

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.63; H, 6.26; N, 10.87.

1-(2-Methyl-1,3-dioxolan-2-ylmethyl)-2-pyridonimine.—The same procedure employed in the preparation of 1-(2-phenyl-1,3-dioxolan-2-ylmethyl)-2-pyridonimine was used. From 0.275 g. of 1-(2-methyl-1,3-dioxolan-2-ylmethyl)-2-aminopyridinium bromide was obtained by distillation in a Kugelrohr, 0.015 g. (8%) of product, b.p. 45° (0.1 mm.). The light yellow oil was unstable, turning brown almost immediately upon contact with air.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26. Found: C, 61.47; H, 7.48.

1-(2-Phenyl-1,3-dioxolan-2-ylmethyl)-2-pyridone.—The ketal was prepared by heating a benzene solution of 4.26 g. of 1-phenacyl-2-pyridone[9] and 4.4 g. of ethylene glycol. After removal of solvent, the pure product was sublimed at 92°

(6) F. Kröhnke, B. Kickhöffen and C. Thoma, *Ber.*, **88**, 1117 (1955).

(7) K. Schilling, F. Kröhnke and B. Kickhöffen, *ibid.*, **88**, 1093 (1955).

(8) M. Kühn, *J. prakt. Chem.*, **156**, 103 (1940).

(9) F. Kröhnke and W. Heffe, *Ber.*, **70**, 864 (1937).

(0.1 mm.) to yield 3.88 g. (76%) of white prisms, m.p. 111–115°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.08; H, 5.82; N, 5.48.

The compound was also prepared by heating for 24 hours a solution of 0.20 g. of 1-(2-phenyl-1,3-dioxolan-2-ylmethyl)-2-pyridonimine in 20% aqueous sodium hydroxide. The odor of ammonia could be detected during this period. The product, identified by its infrared spectrum, precipitated in 65% yield upon cooling the solution, m.p. 111–115°.

1-(2-Methyl-1,3-dioxolan-2-ylmethyl)-2-pyridone.—A solution of 0.81 g. of 1-(2-methyl-1,3-dioxolan-2-ylmethyl)-2-aminopyridinium bromide in 20 ml. of 4% aqueous sodium hydroxide was heated under reflux for 24 hours. After removal of the solvent, the residue was taken up in chloroform. Distillation yielded 0.40 g. (70%) of product, b.p. 115° (0.2 mm.), $n^{25}D$ 1.5327.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.13, H, 6.81; N, 7.38.

2-Phenylimidazo[1,2-a]pyridine Hydrobromide.—A solution of 0.101 g. of 1-(2-phenyl-1,3-dioxolan-2-ylmethyl)-2-aminopyridinium bromide in 4 ml. of 24% hydrobromic acid was heated at 60° for 6 hours. Removal of the solvent yielded a solid which was recrystallized from ethanol–ethyl acetate and dried at 56° (0.05 mm.) to yield 0.055 g. (67%) of product as very hygroscopic white needles, m.p. 161–163°. Its infrared spectrum in chloroform was identical with that of the hydrobromide of 2-phenylimidazo[1,2-a]pyridine formed from phenacyl bromide and 2-aminopyridine, m.p. 161–163° [lit.[10] m.p. (preheated bath) 129°, resolidifying and melting at 165°].

Anal. Calcd. for $C_{13}H_{10}N_2 \cdot HBr$: C, 56.74; H, 4.03; N, 10.18. Found: C, 56.59; H, 4.09; N, 9.91.

2-Methylimidazo[1,2-a]pyridine Hydrobromide.—The same procedure followed in the treatment of the phenyl analog was employed. From 0.110 g. of 1-(2-methyl-1,3-dioxolan-2-ylmethyl)-2-aminopyridinium bromide was obtained 0.045 g. (53%) of product, m.p. 196–198° when recrystallized from acetone–chloroform. The infrared spectrum of a chloroform solution of this product was identical with that of the hydrobromide of 2-methylimidazo[1,2-a]pyridine formed from bromoacetone and 2-aminopyridine, m.p. 198–199° (lit.[11] m.p. 197–198°).

Anal. Calcd. for $C_8H_8N_2 \cdot HBr$: C, 45.09; H, 4.26. Found: C, 45.00; H, 4.21.

2-(2-Phenyl-1,3-dioxolan-2-ylmethyl)-aminopyridine.—To a stirred solution of 9.41 g. of 2-aminopyridine in 60 ml. of dry mesitylene was added 3.90 g. of sodium amide and the suspension was heated at reflux temperature for 2 hours. Then 17.15 g. of 2-(bromomethyl)-2-phenyl-1,3-dioxolane in 50 ml. of mesitylene was added over a 20-minute period. Heating was continued for 24 hours and the reaction mixture filtered hot. Removal of solvent from the filtrate left a brown oil which was washed with water and then chromatographed on an alumina column, using as eluent first pure petroleum ether (b.p. 30–60°), then petroleum ether with an increasing percentage of chloroform. A total of 7.41 g. of unreacted ketal was first eluted, then 2.44 g. of crude reaction product. Sublimation of this material at 85° (0.1 mm.) followed by recrystallization from methanol yielded 0.69 g. (5%) of white prisms, m.p. 111–112°. A mixture of this compound (stable) and the isomeric 1-derivative (unstable) melted at 90 (slush)–108°. The infrared spectra (Nujol) of the compounds differed markedly and were in agreement with the assigned structures.

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.06; H, 6.15, N, 11.23.

2-(2-Methyl-1,3-dioxolan-2-ylmethyl)-aminopyridine.—The same procedure followed in the preparation of 2-(2-phenyl-1,3-dioxolan-2-ylmethyl)-aminopyridine was followed, except that xylene instead of mesitylene was used as solvent. The oil left after removal of solvent was washed with water, and upon standing it crystallized and was sublimed at 50° (0.05 mm.). From 18.10 g. of 2-aminopyridine, 7.80 g. of sodium amide and 27.15 g. of 2-(bromomethyl)-2-methyl-1,3-dioxolane there was obtained upon recrystallization from petroleum ether (b.p. 30–60°), 0.82 g. (2%) of pure product, m.p. 66–67°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.43. Found: C, 61.83; H, 7.09; N, 14.60.

2-Phenacylaminopyridine.—A solution of 0.256 g. of 2-(2-phenyl-1,3-dioxolan-2-ylmethyl)-aminopyridine in 4 ml. of 24% hydrobromic acid was heated at 60° for 6 hours. After the solution was cooled, 4 ml. of concd. aqueous ammonia was added slowly. The yellow precipitate which formed was collected and sublimed at 87° (0.2 mm.) to yield 0.149 g. (71%) of pure white needles, m.p. 103–112°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.67; H, 5.74; N, 13.07.

2-Acetonylaminopyridine.—After a solution of 0.537 g. of 2-(2-methyl-1,3-dioxolan-2-ylmethyl)-aminopyridine in 5 ml. of 24% hydrobromic acid was heated at 70° for 3.5 hours, the solution was cooled and added to a cold mixture of 10 ml. of concd. aqueous ammonia and 10 ml. of chloroform. The chloroform layer was removed and the aqueous portion extracted with fresh chloroform. After drying the combined extracts, the solvent was removed and the residual solid sublimed at 55° (0.07 mm.). The fine white needles of product, m.p. 59–60°, weighed 0.353 g. (80%).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.14; H, 6.73; N, 18.50.

3-Phenylimidazo[1,2-a]pyridine Hydrochloride.—A solution of 0.132 g. of 2-phenacylaminopyridine in 5 ml. of acetic anhydride was heated at reflux temperature for 4 hours. The reaction mixture was poured over crushed ice and cold concd. aqueous ammonia was added slowly. The mixture was extracted with chloroform and the combined extracts dried over potassium carbonate. The dry chloroform solution was treated with anhydrous hydrogen chloride. A white precipitate was removed by filtration, and the solvent evaporated from the filtrate. A residual gum was recrystallized from acetone and dried at 56° (0.1 mm.) to give 0.065 g. (45%) of pure 3-phenylimidazo[1,2-a]pyridine hydrochloride, m.p. 181–183°. Its infrared spectrum in chloroform was identical with that of the hydrochloride prepared from 3-phenylimidazo[1,2-a]pyridine formed by the method of Gol'dfarb and Kondakova,[12] m.p. 177–180°.

Anal. Calcd. for $C_{13}H_{10}N_2 \cdot HCl$: C, 67.68; H, 4.81. Found: C, 68.06; H, 4.32.

3-Methylimidazo[1,2-a]pyridine.—2-Acetonylaminopyridine was treated in the same manner as 2-phenacylaminopyridine, except that ether instead of chloroform was used to extract the product. The ethereal extracts were washed with 10% aqueous sodium hydroxide, dried, and the solvent removed. The residual oil was distilled at 62° (0.04 mm.) in a Kugelrohr. From 0.353 g. of 2-acetonylaminopyridine 0.106 g. (34%) of a colorless, extremely hygroscopic product resulted, m.p. 62–66°.

Anal. Calcd. for $C_8H_8N_2$: C, 72.69; H, 6.10. Found: C, 73.09; H, 6.37.

3-Methylimidazo[1,2-a]pyridine Methiodide.—The methiodide formed at room temperature from an ethanolic solution of methyl iodide and 3-methylimidazo[1,2-a]pyridine. A mixture of this product, m.p. 229–232°, with the methiodide of 2-methylimidazo[1,2-a]pyridine, m.p. 194–195° (lit.[13] m.p. 190–192°), caused depression of melting point.

Anal. Calcd. for $C_8H_8N_2 \cdot CH_3I$: C, 39.43; H, 4.05; N, 10.22. Found: C, 39.46; H, 4.03; N, 9.89.

URBANA, ILLINOIS

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(12) Ya. L. Gol'dfarb and M. S. Kondakova, *Zhur. Priklad. Khim.*, **15**, 151 (1942); *C. A.*, **37**, 2380 (1943). "Chemical Abstracts" states incorrectly the base used as $KHCO_3$ instead of $NaHCO_3$. The latter base results in a much better yield of product.

(13) T. Takahashi and J. Shibasaki, *J. Pharm. Soc. Japan*, **69**, 496 (1949); *C. A.*, **44**, 4474h (1950).