[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

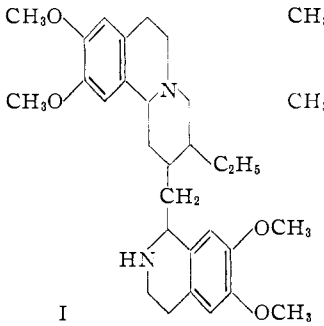
Synthetic Approaches to Ipecac Alkaloids. I. A New Synthesis of 2-Pyridones[1a,b]

BY JEROME A. BERSON AND THEODORE COHEN[1c]

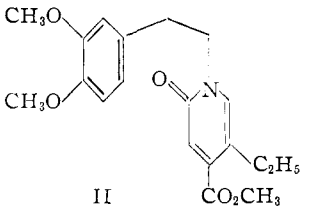
RECEIVED MAY 31, 1955

A new method of converting 2-methylpyridines to 2-pyridones is described. The reaction affords a selective method of introducing pyridone oxygen at a pre-determined site.

Although construction of the gross skeleton of emetine (I), the principal base of ipecac, has been recorded in syntheses of (i) C-noremetine,[2b,d] (ii) a mixture of diastereomers of the structure I which was dehydrogenated to *d,l*-rubremetine,[2c] and (iii) a mixture of diastereomers from which emetine itself was isolated,[2a] none of these studies was concerned with the formidable problem of stereochemistry and sterically controlled synthesis. As a stage in our approach to this latter goal, we have had occasion to investigate routes to the pyridone II. The present article reports our discovery of a novel method for the preparation of 2-pyridones and its significance to the emetine problem.

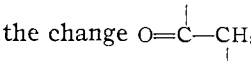
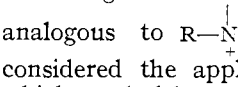


I



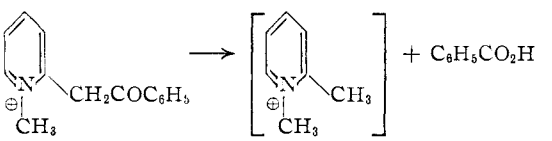
II

The synthetic problem presented by pyridones of the type II originates in the fact that direct introduction of pyridone oxygen (or a suitable progenitor thereof) *para* to a C_3-alkyl group does not appear to be feasible, since nucleophilic reaction occurs preferentially *ortho* to the alkyl group. Thus, the alkaline ferricyanide oxidation of 1,3-dialkylpyridinium salts invariably gives the corresponding 1,3-dialkyl-2-pyridones, rather than 1,5-dialkyl-2-pyridones,[3,4,4a] amination of 3-methylpyridine gives 2-amino-3-methylpyridine[5], and the Katada rearrangement[6] of 3-methylpyridine-1-oxide gives 2-acetoxy-3-methylpyridine.[7] With the weight of experimental precedent so unfavorable, it seemed unlikely to us that II could be prepared from a pyridine precursor by one of these known methods.

In devising a selective method for the introduction of pyridone oxygen, we were guided by the well-known analogy between the behavior of methyl ketones and that of 2-methylpyridines. Thus, the change  is electronically analogous to  . We considered the application of three reactions in which methyl ketones are converted to carboxylic acids: (i) the haloform reaction, (ii) the "acid cleavage" of β-dicarbonyl compounds, (iii) the "acid-cleavage" of N-phenacylpyridinium salts.[8]

Although α-picoline methiodide is reported[9] to give iodoform with hypoiodite, our preliminary attempts to apply the haloform reaction to this substance were unsuccessful. We obtained only unstable products which appeared to be polyiodides. These quickly decomposed in solution or as such with the liberation of iodine.[10] We therefore did not pursue approach i any further.

Reaction ii appeared unpromising. Thus, 1-methyl-2-phenacylpyridinium iodide (III) in alkali gives benzoic acid (and presumably an α-picolinium methosalt) rather than 1-methyl-2-pyridone and acetophenone.[11] Other examples are not abundant,



III

but the same pattern holds in the vinylogous case of cinchene, which gives lepidine (IV) and meroquinene (V) on hydrolysis, rather than 4-quinolone and 3-vinyl-4-acetonylpiperidine.[12]

(1) (a) Taken in part from a dissertation presented by Theodore Cohen in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) Supported in part by a grant, G-3149-CR from the National Institutes of Health, Public Health Service. (c) Fulbright Grantee, Department of Chemistry, University of Glasgow, Glasgow, Scotland.

(2) For recent literature in this field, *cf. inter alia*, (a) R. P. Evstigneeva, R. S. Livshits, M. S. Zakharkin, M. S. Bainova and N. A. Preobrazhenskii, *Doklady Akad. Nauk S.S.S.R.*, **75**, No. 4, 539 (1950); *C. A.*, **45**, 7577 (1951); N. A. Preobrazhenskii, R. P. Evstigneeva, T. S. Levchenko and K. M. Fedyushkina, *ibid.*, **81**, 421 (1951); *C. A.*, **46**, 8130 (1952); (b) S. Sugasawa and K. Oka, *Pharm. Bull.*, **1**, 230 (1953); *C. A.*, **49**, 4658 (1955); (c) A. R. Battersby and H. T. Openshaw, *Experientia*, **6**, 378 (1950); A. R. Battersby, H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.*, 2463 (1953); (d) M. Pailer, K. Schneglberger and W. Reifschneider, *Monatsh.*, **83**, 513 (1952); M. Pailer and H. Strohmayer, *ibid.*, **82**, 1125 (1951); **83**, 1198 (1952).

(3) H. L. Bradlow and C. A. VanderWerf, *J. Org. Chem.*, **14**, 509 (1949).

(4) S. Sugasawa and Y. Ban, *J. Pharm. Soc. Japan*, **72**, 1336 (1952).

(4a) Since our manuscript was submitted, S. Sugasawa and M. Kirisawa, *Pharm. Bull.*, **3**, 190 (1955), have reported that ferricyanide oxidation of the methosulfates of 3-(α-ethylenedioxyethyl)-pyridine and 3-(α-ethylenedithioethyl)-pyridine gave the corresponding 5-substituted-2-pyridones.

(5) O. Seide, *Ber.*, **57**, 1802 (1924).

(6) M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947).

(7) V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954).

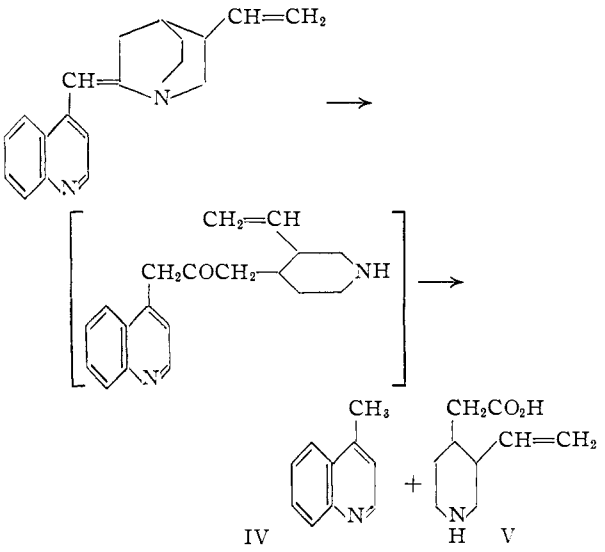
(8) (a) E. Bamberger, *Ber.*, **20**, 3338 (1887); (b) S. H. Babcock, F. I. Nakamura and R. C. Fuson, THIS JOURNAL, **54**, 4407 (1932); (c) S. H. Babcock and R. C. Fuson, *ibid.*, **55**, 2949 (1933); (d) L. C. King, *ibid.*, **66**, 894, 1612 (1944); (e) L. C. King, M. McWhirter and D. M. Barton, *ibid.*, **67**, 2089 (1945).

(9) J. A. Gautier, *Bull. soc. chim.*, [5] **10**, 160 (1943).

(10) This agrees qualitatively with the observations of P. Murrill, THIS JOURNAL, **21**, 828 (1899).

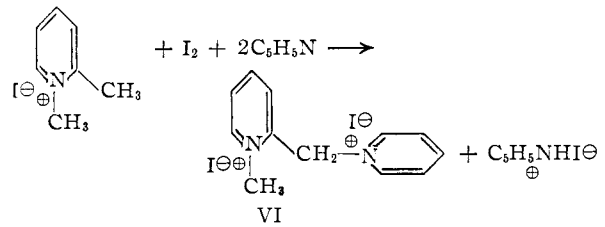
(11) F. Kröhnke, *Ber.*, **68**, 1177 (1935).

(12) (a) W. Koenigs, *ibid.*, **23**, 2669 (1890); **27**, 900 (1894); (b) *cf.* R. B. Turner and R. B. Woodward in "The Alkaloids," Vol. III, edited by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, N. Y., 1953, p. 14.



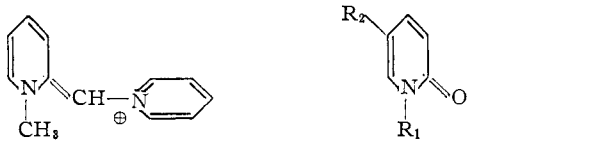
IV V

However, reaction iii was successful. When equimolar amounts of N-methyl-α-picolinium iodide and iodine were heated on the steam-bath in pyridine solution, a beautifully crystalline, water-soluble diiodide, $C_{12}H_{14}N_2I_2$, precipitated in 73% yield. We formulate this substance as N-[ω-



VI

(α-picolyl)]pyridinium iodide methiodide (VI). When an aqueous solution of VI was treated with dilute sodium hydroxide at room temperature, a blood-red color appeared and then rapidly faded. We attribute the color to the transient presence of the anhydrobase VII. The addition of alkali was continued until the color no longer was developed. By extraction of the reaction mixture with chloroform, 1-methyl-2-pyridone (VIIIa) was isolated in 71% yield, spectrophotometrically virtually pure. It was identified by its ultraviolet absorption spectrum and characterized as the picrate by direct comparison with an authentic sample.



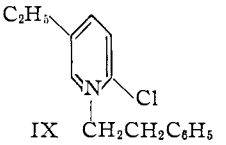
VII

VIIIa, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = CH_2CH_2C_6H_5$; $R_2 = H$
c, $R_1 = CH_2CH_2C_6H_5$; $R_2 = C_2H_5$
d, $R_1 = CH_2CH_2C_6H_5$; $R_2 = COOH$

We have extended the reaction to test the possibility that Hofmann elimination might occur as an undesirable competing process in alkaline solution with pyridinium salts of the type $\equiv\overset{+}{N}—CH_2CH_2—R$. However, the hydrolytic conditions necessary for pyridone formation are so mild that no such difficulty was experienced. Thus, the salt obtained from 1-(2-phenylethyl)-2-methylpyridinium bromide, iodine and pyridine was smoothly hydrolyzed to 1-(2-phenylethyl)-2-pyridone (VIIIb). In this case, the double salt was not isolated but merely extracted from the reaction mixture with water and the aqueous solution treated directly with alkali. In the hydrolysis, a transient red color was again observed. The over-all yield for the sequence bromide → double salt → pyridone was 45%.

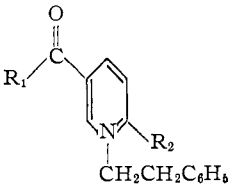
To demonstrate the utility of the method for our original purpose, *i.e.*, introducing pyridone oxygen *para* to a C_3-alkyl substituent, we applied the reaction to 1-(2-phenylethyl)-2-methyl-5-ethylpyridinium bromide. The desired pyridone (VIIIc) was obtained (without isolating the double salt) in 44% over-all yield from the bromide.

The pyridone VIIIc failed to undergo Bischler–Napieralski cyclization to a quinolizinium salt with phosphorus oxychloride in benzene, but was merely converted to the corresponding 2-chloropyridinium salt (IX).



IX

Although cyclization of pyridones onto an activated (dimethoxy- or methylenedioxy-substituted) benzene nucleus appears to occur smoothly with phosphorus oxychloride,[13] the reagent is not always effective when applied to 1-(2-phenylethyl)-2-pyridones with an unsubstituted phenyl ring. Thus, although 1-(2-phenylethyl)-2-pyridone (VIIIb) gives the corresponding quinolizinium salt,[14] 1-(2-phenylethyl)-5-carboxy-2-pyridone (VIIId) does not.[15] In the latter case, the proximate product is presumably the chloro compound Xa[15] which gives the corresponding ethoxy ester Xb when the reaction mixture is treated with alcohol.[15]



Xa, R_1, R_2 = Cl
b, R_1, R_2 = OC_2H_5
c, R_1 = OC_2H_5; R_2 = Cl

Our quaternary chloride IX appears to be much less reactive than Xa. It can be recovered, at least in part, from boiling alcoholic silver chloride and recrystallized from alcoholic solution. This difference in reactivity is doubtless due to the fact that while the nuclear chlorine in Xc is, as Wiley and co-workers have pointed out,[15] subject to activation by the electron-withdrawing carbethoxy group, the chlorine in IX is, if anything, slightly deactivated by the weakly electron-releasing 5-ethyl group.

(13) *Cf. inter alia* S. Sugasawa and co-workers, *Ber.*, **71**, 1860 (1938), and many subsequent papers.

(14) S. Sugasawa, S. Akahoshi and M. Suzuki, *J. Pharm. Soc. Japan*, **72**, 1273 (1952); *C. A.*, **47**, 10539 (1953).

(15) R. H. Wiley, N. R. Smith and L. H. Knabeschuh, THIS JOURNAL, **75**, 4482 (1953).

The application of the new pyridone synthesis to the preparation of II, and an investigation of the reactions of double salts of the type VI with various bases are now in progress.

Experimental[16]

Reaction of 1,2-Dimethylpyridinium Iodide with Iodine and Pyridine to give VI.—A solution of 3.79 g. (0.0161 mole) of 1,2-dimethylpyridinium iodide and 4.10 g. (0.0161 mole) of iodine in 60 cc. of pyridine was heated on the steam-bath with intermittent stirring for 3 hours and 15 minutes. The precipitated solid, 5.46 g. of a yellow-brown powder, was filtered off and the deep red mother liquor heated on the steam-bath an additional 5 hours. The second crop of material, 0.58 g., was combined with the first crop and the whole taken up in a little dilute ethanol. The solution was treated with Norite, filtered and the salt VI was caused to precipitate by the addition of ethyl acetate. After one recrystallization from dilute ethanol, the yield was 5.17 g. (73%) of pale-yellow staves, sintering above 115° and melting with decomposition at 184°. For analysis, the salt was recrystallized from a mixture of methyl and isopropyl alcohols containing a little water. It was essential that the hot solution be allowed to cool slowly in order to prevent the salt from separating as an oil. The analytical sample, slender, pale-yellow staves, melted at 188–189° with preblackening and decomposition.

Anal. Calcd. for $C_{12}H_{14}N_2I_2$: C, 32.75; H, 3.20; N, 6.37; I, 57.68. Found: C, 32.86, 32.68; H, 3.18, 3.08; N, 6.19; I, 57.70.

The salt VI is extremely soluble in cold water, sparingly soluble in ethyl alcohol and insoluble in ethyl acetate, ether or benzene. Its aqueous solution gives an immediate yellow precipitate with silver nitrate.

Hydrolysis of VI to 1-Methyl-2-pyridone.—When a solution of 1.08 g. of VI in 5 cc. of water was treated with 0.6 *N* sodium hydroxide, a deep blood-red solution resulted. The color faded in a few seconds and more alkali was added (a total of 20 cc.) until no further color was developed. The resulting pale yellow solution was immediately extracted with ten 4-cc. portions of chloroform. The extract was dried over sodium carbonate and evaporated to give 0.19 g. (71% yield) of a pale yellow oil, $\lambda\lambda_{max.}$ 228.5, 300–303 mμ (in ethanol), log ε 3.66, 3.57. 1-Methyl-2-pyridone (VIIIa) is reported[17] to show $\lambda\lambda_{max.}$ 227, 300 mμ, log ε 3.64, 3.70 The oil gave a picrate, m.p. 140.5–142.2°, alone or mixed with an authentic sample of the picrate of VIIIa (from VIIIa prepared by ferricyanide oxidation of 1-methylpyridinium methosulfate[18]), reported[19] m.p. 145°.

Preparation of VIIIb.—1-(2-Phenylethyl)-2-methylpyridinium bromide was prepared by heating 2-methylpyridine and 2-phenylethyl bromide. A mixture of 2.78 g. of this salt, 2.54 g. of iodine and 30 cc. of pyridine was heated on the steam-bath. In a few minutes, a heavy precipitate appeared. After 3 hours, the excess pyridine was evaporated in an air current, the residue was taken up in 30 cc. of water and washed with ether to remove any unreacted iodine. The aqueous solution was treated with 10 cc. of 2 *N* NaOH. A transient red color quickly faded. The reaction mixture was allowed to stand overnight in the ice-box and filtered from a small quantity of insoluble material. The pyridone was salted out by saturating the filtrate with sodium carbonate. The resulting oil was separated, the aqueous layer was washed with chloroform and the combined oil and chloroform extract evaporated to dryness. The dark, tacky residue was leached with four 20-cc. portions of boiling ether, the extract evaporated to a small volume and treated with ligroin, whereupon the pyridone VIIIb separated as 0.82 g. (45% yield) of long, clustered blades, m.p. 104–105°, alone or mixed with an authentic sample,[14] reported[14] m.p. 105–106°.

Preparation of VIIIc.—2-Methyl-5-ethylpyridine (Eastman Kodak Co.) was quaternized by heating with 2-phenylethyl bromide. The crude quaternary bromide (6.18 g.), m.p. 175–177°, was heated with 7.62 g. of iodine and 45 cc. of pyridine for three hours on the steam-bath. The excess pyridine was evaporated in an air current and the semi-solid, dark residue leached with ten 50-cc. portions of cold water. The aqueous solution was filtered from a quantity of gummy material, washed with ether and treated with 42 cc. of 2 *N* sodium hydroxide. A transient red color quickly faded to brown. The mixture was extracted with chloroform, the extract dried with sodium sulfate, evaporated, and the viscous, dark residue distilled through a 6-inch Vigreux column. There was virtually no forerun, the main body of the material distilling as 2.0 g. (44% yield) of a pale-yellow oil at 192–195° at 4 mm. (bath at 260–270°). Upon being cooled and triturated with a glass rod, the distillate solidified. It was recrystallized with difficulty from ether–ligroin to give fine needles, m.p. 52–54°. The pyridone showed characteristic[20] absorption at 6.03 μ. For analysis, a sample was chromatographed on alumina in chloroform solution. Elution was continued until evaporation of the solvent left no residue. The crystalline residue was twice recrystallized from petroleum hexane (b.p. 66–67°) to give slender, transparent rods, m.p. 56–57°. The pyridone is extremely soluble in most solvents.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.06; H, 7.37; N, 5.90.

It was converted to a picrate with picric acid in ether. For analysis, the picrate was recrystallized from benzene–ligroin to give yellow needles, m.p. 105–106°.

Anal. Calcd. for $C_{21}H_{20}O_8N_4$: C, 55.26; H, 4.42; N, 12.28. Found: C, 55.16; H, 4.42; N, 12.37.

Action of Phosphorus Oxychloride on VIIIc.—A mixture of 0.39 g. of VIIIc, 5 cc. of phosphorus oxychloride and 10 cc. of benzene was heated at reflux for two hours. The benzene and excess phosphorus oxychloride were evaporated *in vacuo*, the residue taken up in 6 cc. of cold water, the aqueous solution washed with ether and then saturated with solid potassium iodide. The precipitate, 0.54 g. (84%) of the iodide of IX, melted at 169–171°. This material was heated at reflux with 2.0 g. of silver chloride and 50 cc. of ethanol for 45 minutes, the reaction mixture was cooled, filtered through diatomaceous earth and the filtrate evaporated to give rosettes of colorless needles, melting at 171–172°. Recrystallization from isopropyl alcohol–ethyl acetate gave pure IX chloride as hygroscopic needles, m.p. 171–172°. This substance is very soluble in water.

Anal. Calcd. for $C_{15}H_{17}NCl_2$: C, 63.84; H, 6.07; N, 4.96; Cl, 25.13. Found: C, 64.06, 63.99; H, 6.33, 6.35; N, 4.97; Cl, 25.11.

LOS ANGELES 7, CALIFORNIA

(16) Melting points are corrected. The microanalyses are by Mr. W. J. Schenck.

(17) H. Specker and H. Gawrosch, *Ber.*, **75**, 1338 (1942).

(18) E. A. Prill and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, edited by A. H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 419.

(19) O. Fischer and N. Neundlinger, *Ber.*, **46**, 2544 (1913).

(20) (a) F. Ramirez and A. P. Paul, THIS JOURNAL, **77**, 1035 (1955); (b) J. A. Berson and T. Cohen, *ibid.*, **77**, 1281 (1955).