[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

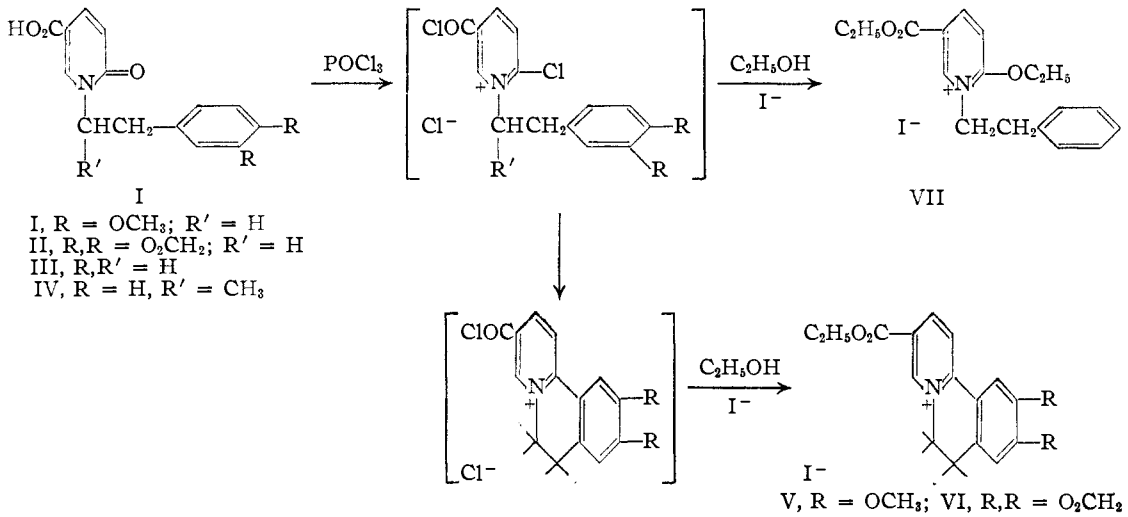
Quinolizinium Compounds by Cyclization of Pyridones from Methyl Coumalate and β-Phenylethylamines

BY RICHARD H. WILEY, NEWTON R. SMITH AND LOUIS H. KNABESCHUH[1]

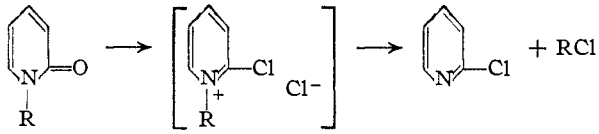
RECEIVED MARCH 9, 1953

7-Carboxyquinolizinium derivatives (V,VI) have been prepared by cyclization of 2-pyridones obtained from methyl coumalate and β-phenylethylamines. 2-Pyridones (I–IV) have been obtained from methyl coumalate and β-phenylethylamine, its 3,4-dimethoxy and 3,4-methylenedioxy derivatives, and α-methyl-β-phenylethylamine. Of these pyridones, those with activating groups in the benzene ring have been converted to previously undescribed quinolizinium salts (V,VI) on treatment with phosphorus oxychloride. The β-phenylethyl derivative has been converted to an alkoxypyridinium salt (VII).

A limited variety of methods are available for synthesis of bi- or polycyclic heterocycles containing a nitrogen atom at a bridgehead. Recently used syntheses are: cyclization of piperidine derivatives as amides[2,3] or halides,[4] diene syntheses with a pyridine and acetylenedicarboxylic ester,[5] Dieckmann ring closures of N-substituted carbalkoxypyridines,[6,7] and cyclizations of N-substituted pyridones.[8,9] These N-bridgehead heterocycles are of interest because they occur in alkaloids such as emetine,[10] sparteine,[11] erythroidine,[12] yohimbine[7] and sempervirine,[13] many of which have significant chemical and biological properties. Development of syntheses for these N-bridgehead heterocycles is, therefore, of importance and we wish to record an adaptation of the pyridone cyclization[9] which considerably broadens its utility and scope. In the studies reported herein, we have shown that 7-carboxyquinolizinium derivatives are available by cyclization of carboxy-2-pyrones (I) which in turn can be obtained from β-phenylethylamines and methyl coumalate. The cyclization procedure was originally developed by Sugasawa.[9] The pyridone synthesis from 2-pyrones, although widely used since first reported,[14] has not previously been used with β-phenylethylamines.



The first step in this reaction sequence is visualized as the conversion of the pyridone to the corresponding 2-chloropyridinium salt. Phosphorus halides are known to react with N-substituted pyridones[15] to give 2-chloropyridines, but this reaction has previously been reported to occur only with the concurrent loss of the 1-alkyl group. Our studies indicate that the intermediate in this reaction is presumably the quaternary salt which under the conditions of our experiment does not undergo fission of the N–R bond. With the dimethoxy and methylenedioxy compounds which have activated



(1) This research was supported by grants from the Research Corporation and the National Science Foundation. The authors wish to express their appreciation for this support and to thank the National Aniline Division of Allied Chemical and Dye Corporation for generously supplying the malic acid used in preparing starting materials, and the Smith, Kline and French Company for supplying α-methyl-β-phenylethylamine.

(2) V. Boekelheide, *et al.*, THIS JOURNAL, **73**, 3681 (1951).

(3) N. J. Leonard, *et al.*, *ibid.*, **74**, 1700 (1952).

(4) G. Walther, *Ber.*, **84**, 304 (1951).

(5) O. Diels, *et al.*, *Ann.*, **505**, 103 (1933); R. H. Wiley and L. H. Knabeschuh, *J. Org. Chem.*, **19**, 836 (1953).

(6) G. Clemo, *et al.*, *J. Chem. Soc.*, 487 (1949); 1318 (1938); 165 (1937); 1429 (1936).

(7) N. J. Leonard and S. H. Pines, THIS JOURNAL, **72**, 4931 (1950).

(8) P. L. Julian and A. Magnani, *ibid.*, **71**, 3207 (1949).

(9) S. Sugasawa, *et al.*, *Ber.*, **74**, 459 (1941); **73**, 782 (1940); **72**, 980, 977 (1939); **71**, 1860 (1938).

(10) R. P. Evstigneeva, *et al.*, *Doklady Akad. Nauk U.S.S.R.*, **75**, No. 4, 539 (1950); *C. A.*, **45**, 7577 (1951).

(11) G. R. Clemo and B. Nath, *J. Chem. Soc.*, 2196 (1952).

(12) V. Boekelheide, *et al.*, THIS JOURNAL, **73**, 2286 (1951); **74**, 1866, 2637 (1952).

(13) R. B. Woodward and W. M. McLamore, *ibid.*, **71**, 379 (1949).

(14) H. von Pechmann, *Ber.*, **17**, 2396 (1884).

(15) E. Fischer, *ibid.*, **32**, 1297 (1899).

benzene rings this quaternary salt cyclizes under the influence of the phosphorus oxychloride and, after treatment with ethanol and iodide, is isolated as a quinolizinium salt (V and VI). When the benzene ring is unsubstituted, cyclization does not take place under similar conditions and the ethoxy ester (VII) is formed during the isolation procedure. No characterizable product has been obtained from attempted cyclization of IV.

In these reactions a reactive 2-chloro group is required either for ring closure or for replacement by ethoxy. That such reactivity exists is indicated by previous studies[16] which have shown that 2-bromopyridinium salts are hydrolyzed by acid at room temperature to the corresponding 2-hydroxy compounds. Moreover, in our compounds this type of reactivity is probably enhanced by the carbethoxy group on the position para to the halogen. If water were used in place of ethanol in the isolation of the uncyclized product, one would expect to replace the chloro group with hydroxy, and re-form the starting material. This has been shown to take place and thus confirms the postulated reactivity.

The methyl coumalate used in this study has been prepared by the reaction of coumalic acid chloride with methanol. We have found other methods for preparing this ester, which have been considered in detail previously[17] to be unreliable. Apparently the lactone ring is opened under some esterification conditions with the formation of products other than the coumalate.

The 3,4-methylenedioxyphenylethylamine was prepared by the lithium aluminum hydride reduction of 3,4-methylenedioxy-β-nitrostyrene following the practice established by several others[18] who have used this reaction and found it to be one of the most convenient routes to β-phenylethylamines. During one experiment toward the end of the reduction when nearly all of the nitrostyrene had been transferred from the Soxhlet extractor to the reaction flask a violent explosion took place completely shattering the reaction vessel. It is accordingly recommended that suitable precautions be observed in the use of this reaction.

The absorption spectrum of the quinolizinium salt V shows three absorption maxima at 270 mμ (log ε 3.76), 305 mμ (log ε 3.98), 390 mμ (log ε 4.23). The pyridinium salt (VII) shows maxima at 265 mμ (log ε 3.98) and 298 mμ (log ε 3.88).

Experimental[19]

N-(β-3,4-Dimethoxyphenylethyl)-5-carboxy-2-pyridone (I).—This compound was prepared from methyl coumalate and 3,4-dimethoxyphenylethylamine. To 1 g. (0.0065 mole) of methyl coumalate[17] dissolved in 10 ml. of methanol were added 10 ml. (*ca.* 10 g., 0.055 mole) of 3,4-dimethoxyphenylethylamine in 10 ml. of methanol with cooling under a tap. After standing overnight, 2 g. of sodium hydroxide in 5 ml. of water were added and the mixture refluxed for 5 minutes. After cooling and acidification, the solution was extracted with ether in a continuous extractor. Evaporation of the ether extracts left a residue which was dissolved in 5% sodium hydroxide with warming. After treatment with Norit and filtering, the pyridone was reprecipitated with acid, filtered, and air-dried to give 1.35 g. (69% of the theoretical amount) of product. Recrystallization from aqueous alcohol gave an analytical sample, m.p. 207.5–209°.

Anal. Calcd. for $C_{17}H_{17}O_3N$: C, 63.37; H, 5.65; neut. equiv., 303.3. Found: C, 63.19; H, 5.77; neut. equiv., 300.1

N-(β-3,4-Methylenedioxyphenylethyl)-5-carboxy-2-pyridone (II).—This compound was prepared from β-3,4-methylenedioxyphenylethylamine and methyl coumalate. The amine was prepared by the lithium aluminum hydride reduction of β-nitro-3,4-methylenedioxystyrene using the procedure previously described for the reduction of β-nitrostyrene.[18] In one instance this reduction exploded violently. Methanol solutions of the amine, 5.0 g. (0.018 mole), and 1.78 g. (0.011 mole) of methyl coumalate were mixed and allowed to stand at room temperature overnight. The crude pyridone, obtained after saponification, was water insoluble and ether extraction was not necessary. The saponified and reprecipitated pyridone was recrystallized from aqueous alcohol to give 1.1 g. (33% of the theoretical amount) of product, m.p. 230–231°.

Anal. Calcd. for $C_{15}H_{13}O_5N$: C, 62.8; H, 4.50; neut. equiv., 287. Found: C, 62.73; H, 4.62; neut. equiv., 276, 282.

N-(β-Phenylethyl)-5-carboxy-2-pyridone (III).—This compound was prepared from β-phenylethylamine and methyl coumalate. Methanol solutions of the amine, 4.8 g. (0.04 mole), and the ester, 1 g. (0.0065 mole), were mixed and treated as in the preceding example. There was obtained 0.7 g., 44% of the theoretical amount, of the pyridone, m.p. 190°.

Anal. Calcd. for $C_{14}H_{13}O_3N$: C, 69.09; H, 5.39; neut. equiv., 243.3. Found: C, 69.15, 69.12; H, 5.49, 5.66; neut. equiv., 242.5.

N-(α-Methyl-β-phenylethyl)-5-carboxy-2-pyridone (IV).—This compound was prepared from α-methyl-β-phenylethylamine and methyl coumalate. Methanol solutions of the amine, 4 g. (0.03 mole), and the ester, 1.0 g. (0.0055 mole), were mixed and treated as in the preceding example. The saponified and reprecipitated pyridone was recrystallized from aqueous alcohol, m.p. 207.5–208.5°, and was isolated in 21.5% yield.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.1; H, 5.83; neut. equiv., 257. Found: C, 70.17; H, 5.86; neut. equiv., 252.

4,5-Dimethoxy-7-carbethoxy-3,4-dihydro[1′,2′,1,2]benzoquinolizinium Iodide (V).—This compound was prepared by cyclization of N-(β-3,4-dimethoxyphenylethyl)-5-carboxy-2-pyridone (I). One gram (0.0033 mole) of the pyridone was mixed in 10 ml. of dry xylene with 7 ml. of phosphorus oxychloride and heated in an oil-bath for two hours during which time the temperature was raised from 100 to 135°. The volatile materials were removed under reduced pressure, on a steam-bath, and the residue taken up in 10 ml. of dry ethanol. The ethanol was removed on a steam-bath. The residue was dissolved in 15 ml. of warm water, treated with Norit and filtered hot. To this solution was added 1–2 g. of solid potassium iodide, and the orange precipitate which formed was collected on a filter. After washing with a little water, the iodide salt was air-dried to give 1.2 g. of solid which was dissolved in ethanol and reprecipitated with ether. Drying *in vacuo* over phosphorus pentoxide gave 0.8 g. (55% of the theoretical amount) of a solid softening around 200° and melting at 223–224° dec.

Anal. Calcd. for $C_{18}H_{20}O_4NI$: C, 48.99; H, 4.57; N, 3.18. Found: C, 48.61; H, 4.69; N, 2.87.

4,5-Methylenedioxy-7-carbethoxy-3,4-dihydro[1′,2′,1,2]-benzoquinolizinium Iodide (VI).—This compound was prepared by the same procedure as for the dimethoxy compound using N-(β-3,4-methylenedioxyphenylethyl)-5-carboxy-2-pyridone (II). Five-tenths of a gram of the pyridone gave 0.44 g. (73.7% of the theoretical amount) of the iodide salt. The compound decomposes at 210–212°.

(16) D. J. Wibaut, P. Haagman and J. Van Dijk, *Rec. trav. chim.*, **59**, 202 (1940).

(17) W. T. Caldwell, F. T. Tyson and L. Lauer, THIS JOURNAL, **66**, 1979 (1944); N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1176 (1947).

(18) M. Erne and F. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950); R. T. Gilsdorf and F. F. Nord, THIS JOURNAL, **72**, 4327 (1950); **74**, 1837 (1952); *J. Org. Chem.*, **15**, 807 (1950); F. Ramirez and A. Burger, THIS JOURNAL, **72**, 2781 (1950); R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948); K. E. Hamlin and A. W. Weston, *ibid.*, **71**, 2210 (1949).

(19) Carbon–hydrogen analyses by Clark Microanalytical Laboratories and Micro Tech Laboratories.

Anal. Calcd. for $C_{17}H_{16}O_4NI$: I, 29.81. Found: I, 29.77.

N-(β-Phenylethyl)-2-ethoxy-5-carbethoxypyridinium Iodide (VII).—One gram (0.0041 mole) of N-(β-phenylethyl)-5-carboxy-2-pyridone (III) was mixed with 7 ml. of phosphorus oxychloride in 10 ml. of dry xylene and heated for two hours at 135°. The reaction mixture was worked up as in the preceding example to give 0.25 g. of the iodide salt, m.p. 109–110° dec. The compound decomposed after standing a few weeks.

Anal. Calcd. for $C_{15}H_{22}O_3NI$: C, 50.60; H, 5.19. Found: C, 50.43; H, 5.32.

Ultraviolet Absorption Data.—Ultraviolet absorption measurements were made with a Beckman DU ultraviolet spectrophotometer using 1.00-cm. silica cells and hydrogen and tungsten discharge lamps as light sources. The compounds were measured in 95% ethanol solution. The authors are indebted to Miss LaVerne Duckwall for these measurements.

LOUISVILLE, KENTUCKY

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

New Methods for Porphyrin Synthesis[1]

BY ALSOPH H. CORWIN AND VIRGINIA L. SYDOW

RECEIVED APRIL 25, 1953

The synthesis of etioporphyrin I from dipyrrylmethane-metal complexes has been studied and new complexes of the porphyrin have been prepared. Most favorable results were obtained with the copper complex. Mildly basic media proved unsatisfactory for porphyrin synthesis unless metallic atoms were present to aid the condensation. By the use of cuprous chloride it has proved possible to prepare the copper complex of 1,3,5,7-tetramethyl-2,4,6,8-tetracarbethoxyporphyrin and it has been found that concentrated sulfuric acid will remove the copper from this complex, yielding the free porphyrin.

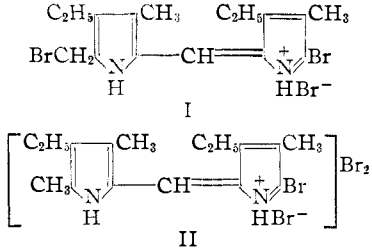
Attempted synthesis of porphyrins containing carbethoxy groups from bromomethenes have led to little or no porphyrin product in the standard acid melts. A recent communication[2] has shown that this is not due to any inherent instability of this type of porphyrin and records relatively good yields of 1,4,5,8-tetramethyl-2,3,6,7-tetracarbethoxyporphyrin. The present paper deals with modifications of porphyrin syntheses designed to obtain both alkyl and carbethoxy substituted porphyrins.

Linstead's[3] synthesis of metal-phthalocyanines in the presence of metal salts and Helberger's[4] synthesis of metal-tetrabenzoporphyrins indicated that the presence of a metal capable of forming square planar bonds might have a beneficial effect upon the synthesis. Since metallic complexes of dipyrrylmethenes are not stable in acids, such a synthesis should be performed in neutral or mildly basic media. Previous attempts at alkaline porphyrin syntheses from methenes have not led to good results[5] although basic porphyrin condensations of other types have been successful.[6]

It was first determined that etioporphyrin II could be recovered from its copper complex in 96–99% yield, thus opening the way to a complete porphyrin synthesis through the metal complex as an intermediate.

The effect of added cupric acetate on the yield of etioporphyrin II was found to be negligible in the formic acid–dipyrrylmethane synthesis. Similarly the condensation of 3,3′-dicarbethoxy-4,4′-dimethyldipyrrylmethane was not improved by cupric acetate. The free porphyrin was first formed and the copper complex appeared only after continued heating.

Attempts to prepare the free base or metallic complexes of 3,4′-dimethyl-4,3′-diethyl-5-bromomethyl-5′-bromodipyrrylmethane hydrobromide (I) were unsuccessful. From 3,5,4′-trimethyl-4,3′-diethyl-5-bromodipyrrylmethene hydrobromide perbromide (II) the free base and copper, cadmium, zinc and ferrous complexes were readily prepared.



I

II

With boiling tributylamine as the solvent and condensing medium, little or no porphyrin could be prepared from the mixture of methenes I and II, from either separately or from the free base of II. On the addition of cupric acetate to these reaction mixtures, the copper complex of etioporphyrin I was obtained in small yields with methene I giving the best yield. Even higher yields were obtained from the metallic complexes of methene II. These diminished in the following order: Cu > Zn > Cd. The ferrous complex gave no porphyrin. We thus conclude that in this case, mildly basic conditions are not satisfactory for porphyrin synthesis unless certain metallic atoms are present to aid the condensation.

After numerous trials it was found that the copper complex of 1,3,5,7-tetramethyl-2,4,6,8-tetracarbethoxyporphyrin (IV) could be prepared from 3,5,4′-trimethyl-4,3′-dicarbethoxy-5′-bromo-

(1) Porphyrin Studies XI. Paper X, A. H. Corwin and E. C. Coolidge, THIS JOURNAL, **74**, 5196 (1952). Taken from the doctoral dissertation of Virginia L. Sydow, The Johns Hopkins University, Baltimore, Md. Presented at the Buffalo Meeting of the American Chemical Society, April, 1952.

(2) J. S. Andrews, A. H. Corwin and A. G. Sharp, *ibid.*, **72**, 491 (1950).

(3) R. P. Linstead, *et al.*, *J. Chem. Soc.*, 1016 (1934).

(4) J. H. Helberger, *Ann.*, **529**, 205 (1937); J. H. Helberger and A. von Rebay, *ibid.*, **531**, 279 (1937); J. H. Helberger, A. von Rebay and D. B. Hever, *ibid.*, **533**, 197 (1938).

(5) H. Fischer, H. Friedrich, W. Lamatsch and K. Morgenroth, *ibid.*, **466**, 164 (1928).

(6) P. Rothemund, THIS JOURNAL, **57**, 2010 (1935); **58**, 625 (1936); S. Aronoff and M. Calvin, *J. Org. Chem.*, **8**, 205 (1943); R. H. Ball, G. D. Dorough and M. Calvin, THIS JOURNAL, **68**, 2278 (1946).