

with ethanol gave no other compounds, although dark-colored bands could be seen on the column.

The white solid was identified as N-benzylformamide, mp 59.5–60.5° (lit.<sup>32</sup> mp 60–61°). Its nmr spectrum was identical with that reported previously.<sup>33</sup>

**Reaction of 1-Benzyl-3-bromopyridinium Chloride with Hydrogen Peroxide and Sodium Bicarbonate.**—Treatment of 1-benzyl-3-bromopyridinium chloride (14.2 g, 50.0 mmol) with 30% hydrogen peroxide (15.2 ml, 148 mmol) and sodium bicarbonate (4.20 g, 50.0 mmol) in water (50 ml) yielded a yellow solution, pH 9.0. After 6 days at 0–5°, an oil had begun to form. The solution had a pH of 8.0 and effervescence was noted. The evolved gas was passed through a trap filled with saturated barium hydroxide solution. A white precipitate was formed immediately, indicating that the gas contained carbon dioxide. A control test with air was performed.

After 30 days the solution had a pH of 8.0 and was decanted from the yellow-orange oil that had formed. The oil was rinsed with water, taken up in 15 ml of chloroform (solution turned dark in color), and poured onto a 31 × 2 cm column of dry Florisil (100–200 mesh). Elution of the column with 2:1 hexane-ether gave a small amount of yellow oil which darkened on standing, a colorless fraction which was evaporated to give a white solid (2%), and a second yellow oil in very low yield. The white solid was identified as N-benzyl-2,2-dibromoacetamide. It was recrystallized several times from ethanol-water: mp

(32) F. F. Blicke and C.-J. Lu, *J. Amer. Chem. Soc.*, **74**, 3933 (1952).

(33) C. Franconi, *Z. Elektrochem.*, **65**, 645 (1961).

136.5–138° (uncor) and mmp (with an authentic sample<sup>34</sup>) 138–139° (uncor); ir (KBr disk) 3410 (w, broad), 3260 (m), 1648 (s)  $\text{cm}^{-1}$ ; nmr (60 MHz, chloroform-*d*)  $\delta$  7.33 ( $\text{C}_6\text{H}_5$ , s, 5.09), 6.92 (NH, broad, 0.91), 5.86 ( $\text{CHBr}_2$ , s, 1.03), 4.46 ( $\text{CH}_2$ , d, 1.98,  $J_{\text{CH-NH}} = 6.0$  Hz); mass spectrum (70 eV, indirect inlet, 25°) *m/e* (relative intensity) 227 (47.1), 225 (47.6), 146 (32.8), 104 (20.0), 103 (13.3), 91 (100.0).

*Anal.* Calcd for  $\text{C}_9\text{H}_9\text{NOBr}_2$ : C, 35.31; H, 2.95; N, 4.56; Br, 52.06; mol wt, 307. Found: C, 35.06, 35.25; H, 2.83, 2.99; N, 4.41, 4.66; Br, 52.06; 51.86; mol wt, 313 (chloroform).

**Registry No.**—Hydrogen peroxide, 7722-84-1; 1-methyl-3-carbamoylpyridinium chloride, 1005-24-9; 1-benzyl-3-carbamoylpyridinium chloride, 5096-13-9; N-[(5-hydroxy-2-oxo-3-pyrrolidinyl)methyl]-N-methylformamide, 24744-90-9; N-benzyl-N-[(5-hydroxy-2-oxo-3-pyrrolidinylidene)methyl]formamide, 24744-91-0; N-benzyl-N-[(5-hydroxy-2-oxo-3-pyrrolidinyl)methyl]formamide, 24744-92-1; N-benzyl-2,2-dibromoacetamide, 24744-94-3; **2a**, 24744-81-8; **2b**, 24744-82-9; **3**, 24744-83-0; **4**, 24744-84-1; **4a**, 24744-85-2; **5**, 24744-86-3; **6**, 24799-54-0; **7**, 24744-87-4; **8**, 24744-88-5; **9**, 24744-89-6; **13**, 24744-93-2.

(34) The authentic sample was prepared by treatment of dibromoacetyl chloride with benzylamine.

## Pyrido[2',1':2,3]imidazo[5,1-a]isoquinolinium Cation<sup>1</sup>

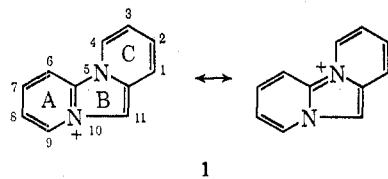
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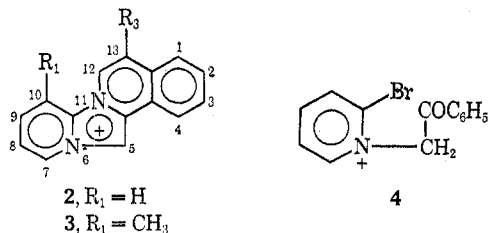
Received October 31, 1969

The first synthesis of the title cation has been effected *via* aromatic cyclodehydration of appropriately substituted 1-methylene-2-phenylimidazo[1,2-a]pyridinium bromides (**9** and **11**). The possibility that cyclization occurred in the pyrido ring (position 8) was excluded by showing that similar products (**3**) were obtained when position 8 was blocked with a methyl group.

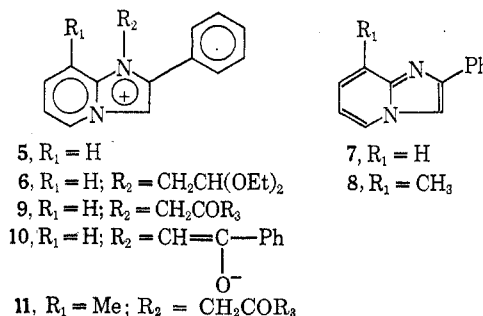
Although the dipyrdo[1,2-*a*:1',2'-*c*]imidazolium cation (**1**)<sup>2,3</sup> and some of its benzologs<sup>2,4,5</sup> have been



known for several years, the benzolog with the ring attached at positions 1 and 2 does not appear to have been reported. The synthesis of this benzolog, the pyrido[2',1':2,3]imidazo[5,1-a]isoquinolinium cation (**2**) has now been accomplished.



It has been shown<sup>6</sup> that, when certain amines are allowed to react with 2-bromo-1-phenacylpyridinium bromide (**4**), the product is a derivative of the 2-phenylimidazo[1,2-a]pyridinium ion (**5**). When the acetal of aminoacetaldehyde was allowed to react with the same quaternary salt (**4**), a product was obtained which was presumed to be impure 1-(2',2'-diethoxyethyl)-2-phenylimidazo[1,2-a]pyridinium bromide (**6**). It would be expected that an acetal such as **6** would be hydrolyzed in hot mineral acid to the corresponding aldehyde (**9**,  $\text{R}_3 = \text{H}$ ). In analogy to the behavior of 2-biphenylacetaldehyde<sup>7</sup> the resulting aldehyde would be expected



(1) This research was supported by Public Health Service Grant No. H-2170 of the National Heart Institute.

(2) B. R. Brown and J. Humphreys, *J. Chem. Soc.*, 2040 (1959).

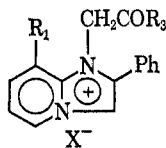
(3) M. Hamana, B. Umezawa, and K. Noda, *Chem. Pharm. Bull.* (Tokyo), **11**, 694 (1963).

(4) B. R. Brown and E. H. Wild, *J. Chem. Soc.*, 1160 (1956).

(5) B. R. Brown and D. White, *ibid.*, 1589 (1957).

(6) C. K. Bradsher, R. D. Brandau, J. E. Boliek, and T. L. Hough, *J. Org. Chem.*, **34**, 2129 (1969).

(7) C. K. Bradsher and W. J. Jackson, *J. Amer. Chem. Soc.*, **76**, 734 (1954).

TABLE I  
 FORMATION OF PYRIDOIMIDAZOLIUM SALTS
9, R<sub>1</sub> = H11, R<sub>1</sub> = CH<sub>3</sub>

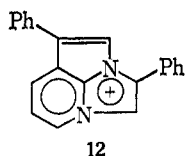
Compd no.	R <sub>3</sub>	Mp of Br, <sup>a</sup> °C	Mp of ClO <sub>4</sub> , <sup>b</sup> °C	Yield <sup>c</sup> of ClO <sub>4</sub> , %	Uv max, mμ (log ε)
11	Ph	186–187 <sup>d</sup>	206–208 <sup>e-g</sup>	54	204.5 (4.71), 224.5 (4.48), 238 (4.50), 252 sh (4.39), 287 (4.32)
9	Me	205–207 <sup>f</sup>	222–223 <sup>d,e,h</sup>	64	204 (4.39), 222 sh (4.19), 284 (3.89)
11	Me	184–185 <sup>f</sup>	175–176 <sup>i-k</sup>	68	205 (4.41), 212 sh (4.36), 225 (4.29), 233 sh (4.26), 276 sh (4.01), 285 (4.06)
9	<i>t</i> -Bu	227–229 <sup>i</sup>	211–212 <sup>e,i,l</sup>	41	206 (4.20), 222 sh (4.00), 287.5 (3.88)

<sup>a</sup> The bromides, which tend to be hydrated, were used directly in the cyclization. <sup>b</sup> Mp of the analytical sample. Suitable analytical data were submitted, Ed. <sup>c</sup> This is the quaternization reaction when the salt is isolated as the perchlorate. <sup>d</sup> Needles. <sup>e</sup> From ethanol. <sup>f</sup> Powder. <sup>g</sup> Nmr (CF<sub>3</sub>COOH) δ 6.20 (s, 2 CH<sub>2</sub>), 2.73 (s, 3, CH<sub>3</sub>). <sup>h</sup> Nmr (CF<sub>3</sub>COOH) δ 5.45 (s, 2, CH<sub>2</sub>), 2.37 (s, 3, CH<sub>3</sub>). <sup>i</sup> Prisms. <sup>j</sup> From methanol. <sup>k</sup> Nmr (CF<sub>3</sub>COOH) δ 5.61 (s, 2, CH<sub>2</sub>), 2.73 (s, 3, ArCH<sub>3</sub>), 2.37 (s, 3, CH<sub>2</sub>CO). <sup>l</sup> Nmr (CF<sub>3</sub>COOH) δ 5.57 [s, 2, CH<sub>2</sub>), 1.15 (s, 9, (CH<sub>3</sub>)<sub>3</sub>].

to undergo aromatic cyclodehydration<sup>8</sup> to afford the pyrido[2',1':2,3]imidazo[5,1-*a*]isoquinolinium cation (2). In any case the product obtained by refluxing the acetal (6) in 48% hydrobromic acid was a pale yellow salt with no nonaromatic protons (below δ 7.18 in the nmr spectrum), and with a complex ultraviolet absorption spectrum characteristic of condensed polycyclic aromatic systems.

If this were the correct interpretation of our observations, it would follow that quaternization of 2-phenylimidazo[1,2-*a*]pyridine (7) at position 1 with an  $\alpha$ -halomethyl ketone could provide intermediates (9) for the synthesis of homologs of the pyridoimidazoisoquinolinium cation (2) substituted at position 13. The 1-phenacyl-2-phenylimidazo[1,2-*a*]pyridinium ion (9, R<sub>3</sub> = C<sub>6</sub>H<sub>5</sub>) and the betaine (10) derived from it had been prepared by Tschitschibabin.<sup>9</sup> The betaine (10) in cold concentrated sulfuric acid gave a cyclization product (2, R<sub>3</sub> = C<sub>6</sub>H<sub>5</sub>) which from its ultraviolet absorption spectrum was easily recognizable as a derivative of 2.

Whereas cyclization into the phenyl group rather than into the electron-deficient pyridine ring seemed attractive from a mechanistic viewpoint, it was necessary to exclude the possibility that the cyclization product was 12.



Since 2-phenyl-8-methylimidazo[1,2-*a*]pyridine (8) was known,<sup>10</sup> it was easy to test whether cyclization would be blocked by a methyl group at position 8. The quaternization product (11, R<sub>3</sub> = C<sub>6</sub>H<sub>5</sub>; see also Table I) was cyclized to yield a cation which from the ultraviolet absorption spectrum (Table II) was very closely related in structure to the cyclization products obtained earlier (2, R<sub>3</sub> = H and 2, R<sub>3</sub> = Ph) and hence was not 12.

By use of bromoacetone or 1-bromo-3,3-dimethyl-2-butanone as quaternizing agents, followed by cyclization of the resulting 2-phenylimidazo[1,2-*a*]pyridinium salts (Table I) the expected alkyl derivatives were obtained (Table II). The three alkyl derivatives of 2, but not the 10-methyl-13-phenyl derivative (3, R<sub>3</sub> = Ph), crystallized with an additional 0.5 mol of perchloric acid/mol of salt. Other examples of this type of hydrogen bonding have been reported.<sup>11</sup> It is interesting that neither the parent compound nor the aryl derivatives exhibit this residual basicity which may depend upon the electron-release provided by the alkyl groups.

### Experimental Section

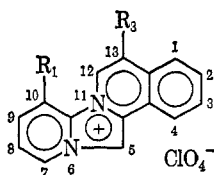
All elemental analyses were by Janssen Pharmaceutica, Beerse, Belgium. The ultraviolet absorption spectra were determined in 95% ethanol solution using a Beckman DB-G spectrophotometer. The nmr data were obtained using tetramethylsilane as an internal standard when trifluoroacetic acid was used as a solvent and as an external standard when deuterium oxide was the solvent.

**Pyrido[2',1':2,3]imidazo[5,1-*a*]isoquinolinium Perchlorate (2).**—To a solution of 3.7 g of 2-bromo-1-phenacylpyridinium bromide (4)<sup>12</sup> in 40 ml of absolute ethanol, 2.66 g of aminoacetaldehyde diethyl acetal was added, and, after the initial vigorous reaction, the mixture was refluxed for 1.5 hr. Removal of the solvent under reduced pressure left an oil which solidified on trituration with ethyl acetate, yield 3.0 g, mp 136–137°. Part of the crude solid (0.5 g) was refluxed for 16 hr in 10 ml of 48% hydrobromic acid although spectroscopic observations indicated that the reaction was essentially complete in 1.5 hr. Most of the hydrobromic acid was removed under reduced pressure, the residue dissolved in water, and 35% perchloric acid added. The precipitate was recrystallized from methanol. Additional data may be found in Table II.

**2-Phenylpyrido[1,2-*a*]isoquino[2,1-*c*]imidazolium Perchlorate (2, R<sub>3</sub> = Ph).**—The betaine (10)<sup>9</sup> of 1-phenacyl-2-phenylimidazo[1,2-*a*]pyridinium hydroxide (1.66 g) was dissolved in 10 ml of cold concentrated sulfuric acid and allowed to stand at room temperature for 6 hr. The solution was cooled in ice and then poured into 300 ml of cold anhydrous ether. The resulting precipitate was crystallized from methanol-ethyl acetate. Additional data may be found in Table II.

**Reaction of Bromomethyl Ketones with 2-Phenylimidazo[1,2-*a*]pyridines (7 and 8).**—Either 2-phenylimidazo[1,2-*a*]pyridine

(8) C. K. Bradsher, *Chem. Rev.*, **38**, 1946.(9) A. E. Tschitschibabin, *Ber.*, **59**, 2045 (1926).(10) F. Mattu and E. Marongin, *Ann. Chim. (Rome)*, **54**, 495 (1964).(11) Cf. H. F. Andrew and C. K. Bradsher, *J. Heterocycl. Chem.*, **3**, 282 (1966) and references cited therein.(12) C. Djerassi and G. R. Pettit, *J. Amer. Chem. Soc.*, **76**, 4470 (1954).

TABLE II  
 PYRIDO[2',1':2,3]IMIDAZO[5,1-a]QUINOLINIUM PERCHLORATES


2 or 3

Substituents		Compd no.	Cyclization		Mp, <sup>a</sup> °C	Yield, %	$\lambda_{\max}$ , m $\mu$ (log $\epsilon$ )
R <sub>1</sub>	R <sub>2</sub>		Time, hr	Temp, °C			
H	H	6	16	126	241-243 <sup>b,c</sup>	38 <sup>d</sup>	208 (4.63), 243 (4.51), 255 (4.46), 263 (4.50), 275 (4.34), 290 (4.06), 302 (4.12), 338 (4.10), 354 (4.09), 370 (3.87)
H	Ph	10	6	20	208-210 <sup>e</sup>	44 <sup>f</sup>	206 (4.41), 243 (4.42), 259 (4.39), 266.5 (4.43), 291.5 (3.96), 303.5 (3.96), 340 (4.03), 358 (4.05), 373 (3.84)
Me	Ph	11 <sup>g</sup>	6	20	245 <sup>b,h</sup>	42	207 (4.30), 246 (4.42), 261 (4.37), 267.5 (4.38), 292.5 (3.76), 304 (3.81), 341 (4.10), 335 (4.12), 370 (4.00)
H	Me	9	4	100	262-264 <sup>i</sup>	38	209.5 (4.34), 238.5 sh (4.44), 244.5 (4.52), 256.5 sh (4.42), 265 (4.49), 274 sh (4.38), 292 (3.97), 303 (3.95), 329 sh (3.97), 340 (4.08), 354 (4.03), 370 (3.95)
Me	Me	11	4	100	288 <sup>b,j</sup>	42	210.5 (4.31), 239 sh (4.06), 246 (4.50), 264 (4.41), 276 sh (4.25), 291.5 (3.91), 304 (3.90), 349 (4.06), 364 (4.02), 383 (3.78)
H	<i>t</i> -Bu	9	8	100	188-189 <sup>k</sup>	22	207.5 (4.43), 239 (4.33), 255 sh (4.17), 265 (4.25), 275 (4.20), 290 (4.06), 301 (4.03), 339 (3.80), 355 (3.69), 373 (3.54)

<sup>a</sup> Suitable analytical data were submitted, Ed. <sup>b</sup> With decomposition. <sup>c</sup> From methanol, light yellow needles. <sup>d</sup> Overall yield from 2-bromo-1-phenacylpyridinium bromide (5). <sup>e</sup> From MeOH-EtOAc, powder. <sup>f</sup> This is the yield of the bisulfate (mp 276° dec) which was converted to the perchlorate to afford an analytical sample. <sup>g</sup> The salt used for cyclization was the bromide. <sup>h</sup> From methanol, cream-colored powder, nmr (CF<sub>3</sub>COOH)  $\delta$  3.22 (s, 3, CH<sub>3</sub>). <sup>i</sup> From MeOH, cream-colored powder, nmr (D<sub>2</sub>O)  $\delta$  2.08 (s, 3, CH<sub>3</sub>). <sup>j</sup> From MeOH, light yellow needles, nmr (D<sub>2</sub>O)  $\delta$  2.70 (s, 3, CH<sub>3</sub>), 2.17 (s, 3, CH<sub>3</sub>). <sup>k</sup> From MeOH yellow prisms, nmr (CF<sub>3</sub>COOH)  $\delta$  1.95 [s, 9, (CH<sub>3</sub>)<sub>3</sub>].

(7)<sup>9</sup> or the 8-methyl derivative (8)<sup>10</sup> was mixed with a molar equivalent of the bromomethyl ketone and the mixture heated on a steam bath for 8 hr (18 hr in the case of 1-bromo-3,3-dimethylbutanone<sup>13</sup>). The molten mass had usually become a thick green gum during the heating period. The gum was extracted with hot water; the extract was filtered, cooled, and extracted with several portions of ether. Finally the aqueous solution was charcoaled, filtered, and concentrated under reduced pressure, yielding the crude colorless salt. The crude bromide salt was once recrystallized from methanol-ethyl acetate or ethanol-ethyl acetate and the product (9 or 11) used for the cyclization experiment.

Since the bromide salts tended to be hygroscopic, a duplicate set of experiments was carried out in which the product was recovered as the perchlorate salt and the yields and analyses in Table I are of the perchlorate salts.

**Cyclization of Quaternary Salts (9 or 11).**—The bromide salts (9 or 11, 0.005–0.0025 mol) were dissolved in 10 ml of concentrated sulfuric acid and after the proper interval at the appropriate temperature (Table II) the solution was worked up as in the preparation of 2-phenylpyrido[1',2':2,3]imidazo[5,1-a]isoquinolinium perchlorate (3, R<sub>3</sub> = C<sub>6</sub>H<sub>5</sub>). Further details may be found in Table II.

**Registry No.**—1, 245-75-0; 2 (R<sup>3</sup> = H), 25110-24-1; 2 (R<sup>3</sup> = Ph), 25110-25-2; 2 (R<sup>3</sup> = Me), 25110-26-3; 2 (R<sup>3</sup> = *t*-Bu), 25110-27-4; 3 (R<sup>3</sup> = Ph), 25110-28-5; 3 (R<sup>3</sup> = Me), 25158-28-5; 9 (R<sup>3</sup> = Me) bromide, 25110-29-6; 9 (R<sup>3</sup> = Me) perchlorate, 25110-30-9; 9 (R<sup>3</sup> = *t*-Bu) bromide, 25158-29-6; 9 (R<sup>3</sup> = *t*-Bu) perchlorate, 25110-31-0; 11 (R<sup>3</sup> = Ph) bromide, 25158-30-9; 11 (R<sup>3</sup> = Ph) perchlorate, 25110-32-1; 11 (R<sup>3</sup> = Me) bromide, 25110-33-2; 11 (R<sup>3</sup> = Me) perchlorate, 25110-34-3.

(13) M. Jackman, K. Klenk, B. Fishburn, B. F. Tullar, and S. Archer, *J. Amer. Chem. Soc.*, **70**, 2886 (1948).