The Formation of the Indolizino[1,2-c]quinolinium System by a Novel Nucleophilic Reaction (1)

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2-Methyl-3-(2-pyridyl)quinoline (1) with a bromomethyl ketone or ethyl bromoacetate yields 6-methyl-12-acylindolizino[1,2-c]quinolinium bromides (5-9). The acyl derivatives can be deacylated in acid yielding 6-methyl indolizino[1,2-c]quinolinium salts (4). Benzoylation of 4 yields the 12-benzoyl derivative (6).

The deacylation product (4) has been synthesized from 2-acetamidophenacyl bromide (10) and 2-pyridylacetone (12).

2-Methyl-3-(2-pyridyl)quinoline (1), a promising intermediate for the synthesis of new heterocyclic systems, is readily prepared by condensation of 2-pyridylacetone with isatin followed by decarboxylation of the intermediate 2-methyl-3-(2-pyridyl)cinchoninic acid (2).
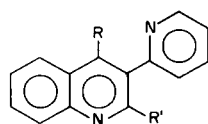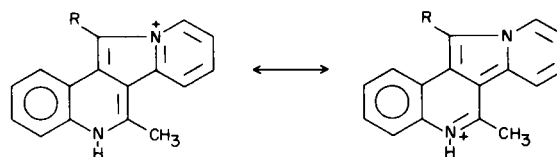

1 R H   R' CH₃
2 R COOH   R' = CH₃
3 R R' = H

Selenium dioxide oxidation of the new base (1) gave a small yield of the dimethylated base (3). The two bases (1 and 3) differed in behavior when warmed in acetone solution with bromoacetone. While the demethylated base (3) gave a colorless salt having the composition and properties expected, the methyl base (1) very rapidly afforded a very insoluble yellow product which exhibited a strong blue fluorescence in alcohol solution. NMR made it clear that the new aromatic system had not been formed by a condensation involving one of the methyl groups, and the IR spectrum showed no significant absorption in the usual ketone carbonyl region (1680-1725 cm⁻¹).

It was soon discovered that not only other bromomethyl ketones but even ethyl bromoacetate reacted with the methyl pyridylquinoline (1) to afford yellow products having a very similar ultraviolet absorption spectrum. It was likewise observed that the products when dissolved in concentrated sulfuric acid or heated with 48% hydrobromic acid underwent deacylation to yield the same compound. In one deacylation experiment the benzoyl group

was recovered as benzoic acid. It was shown that the deacylation product could be rebenzoylated at the same position by heating in benzoyl chloride.

Since the aromatic system behaved like an indolizine derivative, the 6-methyl-indolizino[1,2-c]quinolinium system (4) was suggested to represent the deacylation product and 5-9 to represent the original alkylation-cyclization products.


4 R H
5 R CH₃CO
6 R = C₆H₅CO
7 R = p-BrC₆H₄CO
8 R = p-C₆H₅C₆H₄CO
9 R C₂H₅OCO

Subsequent to the completion of this phase of the problem, the first synthesis of the parent indolizino[1,2-c]quinolinium system (16) was described (2).

The German authors condensed 2-acetamidophenacyl bromide (10) with methyl 2-pyridylacetate (11) to afford an indolizine derivative (13) which, on hydrolysis of the protecting groups, cyclized to afford the 6-hydroxy derivative (15) of the desired system. The hydroxyl group was replaced by chlorine which was subsequently subjected to hydrogenolysis yielding a small quantity of 16.

It has now been found that replacement of the methyl 2-pyridylacetate (11) used by Niederdellmann and Kröhnke (2) by 2-pyridylacetone (12) affords 1-acetyl-
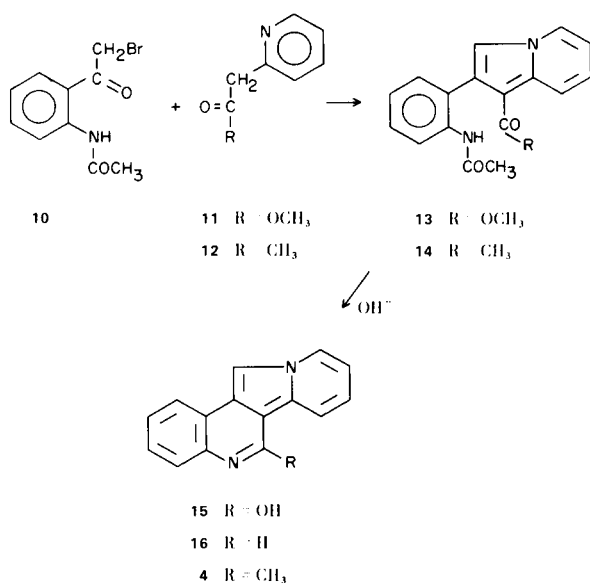
2-(2-acetamidophenyl)indolizine (14) which, on hydrolysis and cyclization, affords our deacylation product (4), identified as the salt.

The rapidity with which the probable intermediate quaternary salt (17) must cyclize under the extremely mild conditions (refluxing acetone) is remarkable. Most likely the basic quinoline nitrogen atom removes one of the very acidic hydrogen atoms from the methylene group forming an enolate anion (17) which attacks the quinolinium ring nucleophilically. It is less clear how the dehydrogenation step can occur so rapidly under such mild conditions, but this might be due in part to disproportionation since in no case have yields exceeded 60%.

17
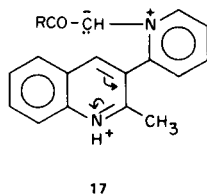
The failure to observe a normal ketone carbonyl IR absorption for addition compounds (5-8) may be due to the vinylogous amide character of the carbonyl which may shift absorption into the lower frequency region where it can be confused with absorptions due to the double bond.

EXPERIMENTAL

The analyses were carried out by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany or Galbraith Laboratories, Knoxville, Tennessee. The melting points were determined in capillaries with a Laboratory Devices Melt-Temp block and are uncorrected. Ultraviolet absorption spectra were measured in 95% ethanol using 1 cm matched silica cells in a Cary Model 14

Spectrometer. NMR data was obtained with the Varian A-60 Spectrometer using tetramethylsilane as the standard.

2-Methyl-3-(2-pyridyl)cinchoninic Acid (2) (3).

To a solution containing 163.7 g. of potassium hydroxide, 289 ml. of water, 263 ml. of ethanol and 43.7 g. of 2-pyridylacetone (4), 52.6 g. of isatin was added with shaking and the resulting mixture stirred at 80-85° for 5.5 hours. The mixture was poured on ice and adjusted to a pH of approximately 5.6 (pH meter). After the suspension had stood overnight in the refrigerator, the solid was collected and recrystallized from ethanol, affording 43.7 g. (51%) of 2 as colorless crystals which blackened but did not melt below 360°.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.86; H, 4.54; N, 10.64.

The picrate of 2 crystallized from ethanol as fine bright yellow needles which decompo sed but did not melt below 300°.

Anal. Calcd. for $C_{22}H_{15}N_5O_9$: C, 53.55; H, 3.06; N, 14.20. Found: C, 53.08; H, 2.98; N, 13.94.

2-Methyl-3-(2-pyridyl)quinoline (1) Salts.

To 9 g. of 2 in boiling ethanol was added an ethanolic solution containing 2.25 g. of potassium hydroxide. The resulting solution was filtered and then evaporated to dryness on a steam bath. The resulting tan salt was pulverized in a mortar with 8.5 g. of calcium oxide. The resulting powder was heated at 270-300° for 4 hours. A viscous oil, 6.0 g. (78%), was obtained and used directly in further experiments without purification; NMR (carbon tetrachloride), τ 7.30 (S, 3, CH_3) and 1.3-3.2 (m, 9, aromatic H).

The picrate crystallized from ethanol as fine yellow needles, dec. 227-229°.

Anal. Calcd. for $C_{21}H_{15}N_5O_7$: C, 56.12; H, 3.36; N, 15.59. Found: C, 56.49; H, 3.23; N, 15.77.

The diperchlorate crystallized from methanol-ethyl acetate and appeared to be hydrated, m.p. 257-259°.

Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O_8 \cdot 0.5 H_2O$: C, 41.88; H, 3.51; N, 6.51. Found: C, 41.88; H, 3.60; N, 6.65.

The dimethiodide prepared by heating the base (1) with an excess of methyl iodide, crystallized from methanol-ethyl acetate as yellow needles, dec. 224.5-225°, nmr (trifluoroacetic acid) τ 7.04 (S, 3, 2-CH_3); 5.72, 5.42 each (S, 3, CH_3N), plus aromatic H.

Anal. Calcd. for $C_{17}H_{18}I_2N_2$: C, 40.50; H, 3.60; N, 5.56. Found: C, 40.48; H, 3.74; N, 5.46.

3-(2-Pyridyl)quinoline (3).

To a hot solution of 3.5 g. of selenium dioxide in a mixture of 31 ml. of pure dioxane and 1.3 ml. of distilled water, was added 4 g. of 1 over a period of 15 minutes. At the end of a two hour reflux, the precipitated selenium was removed by filtration, the solvents evaporated and the residue extracted with aqueous ammonia and ether. The ethereal extract gave 1.8 g. of crude product which was twice sublimed and recrystallized from ethyl acetate-petroleum ether to yield 200 mg. (5%) of ivory needles, m.p. 100-100.5°; ir, no bands 1640-1800 cm^{-1}, nmr, all signals $< 3\tau$.
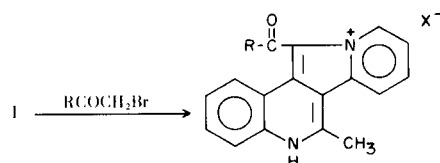
Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.33; H, 5.15; N, 13.72.

Reaction of Bromoacetone with 3-(2-Pyridyl)quinoline (3).

To a suspension of 3 in acetone, an excess of bromoacetone was added and the mixture warmed to effect solution. The solution was allowed to stand for 24 hours at room temperature and the colorless needles which formed were recrystallized from methanol-ethyl acetate, dec. 248-250°.

TABLE I

5H-6-Methyl-12-Acylindolizino[1,2-c]quinolinium Salts

$$I \xrightarrow{RCOCH_2Br}$$

R	X	Yield %	M.p. °C dec. (a)	Formula	Calcd, %			Found, %		
					C	H	N	C	H	N
CH₃	Br	60	286-288	C₁₈H₁₅BrN₂O	60.86	4.26	7.89	60.86	4.43	8.25 (b)
CH₃	ClO₄		258-260	C₁₈H₁₅ClN₂O₅	57.68	4.03	7.48	57.45	3.99	7.51
C₆H₅	Br	32 (c)	310-312	C₂₃H₁₇BrN₂O	66.19	4.11	6.71	66.19	3.95	7.00 (d)
C₆H₅	ClO₄		277-279 (e)	C₂₃H₁₇ClN₂O₅	63.23	3.92	6.41	63.34	4.13	6.44
p-BrC₆H₄	Br	44 (f)	300-301	C₂₃H₁₆Br₂N₂O	55.67	3.25	5.65	55.54	3.09	5.65 (g)
p-BrC₆H₄	ClO₄		>375	C₂₃H₁₆BrClN₂O₅	53.56	3.13	5.43	53.90	3.20	5.57
p-C₆H₅C₆H₄	Br	45	285-287 (e)	C₂₉H₂₁BrN₂O	70.49	4.29	5.68	70.30	4.42	5.76 (h)
p-C₆H₅C₆H₄	ClO₄		272-273 (e)	C₂₉H₂₁ClN₂O₅	67.90	4.13	5.46	67.59	4.28	5.60
C₂H₅O	Br	34	233-235 (i)	C₁₉H₁₇BrN₂O₂	59.23	4.45	7.27	59.20	4.44	7.33
C₂H₅O	ClO₄		255-256.5 (e,i)	C₁₉H₁₇ClN₂O₆	56.37	4.23	6.92	56.58	4.26	7.12 (j)

(a) The recorded temperature is more accurately described as that at which final decomposition occurs, darkening being observed several degrees lower. (b) Br calcd. 22.49. Found, 22.27; λ max mμ (log ε 4.52), 252 sh (4.51), 268 (4.37), 277 sh (4.35), 294 (4.35), 358 (4.15), 379 (4.12), 399 (4.15). (c) Orange needles from methanol-ethyl acetate. (d) Br calcd. 19.15; Found, 19.27; λ max 255 mμ (log ε 4.63), 307 (4.04), 360 (4.20), 408 (4.14). (e) Yellow needles. (f) Dark orange needles. (g) nmr (trifluoroacetic acid) τ 6.52 (s, 3, CH₃), <2.85 (complex, 13, aromatic H). (h) nmr (trifluoroacetic acid) τ 6.55 (s, 3, CH₃), <2.90 (complex, 18, aromatic H). (i) From methanol-ethyl acetate. (j) nmr (trifluoroacetic acid) τ 8.40 (t, 3, CH₃CH₂), 6.50 (s, 3, CH₃-6), 5.18 (q, 2, CH₃CH₂).

Anal. Calcd. for C₁₇H₁₅BrN₂O: C, 59.48; H, 4.41; N, 8.16. Found: C, 59.09; H, 4.41; N, 8.16.

The failure to obtain an indolozinoquinolinium salt in this reaction suggests that the product may be 1-acetonyl-3-(2-pyridyl)-quinolinium bromide.

5H-6-Methyl-12-acylindolizino[1,2-c]quinolinium Bromides.

A reagent grade acetone solution containing 2-methyl-3-(2-pyridyl)quinoline and approximately three equivalents of the bromomethyl compound was refluxed for 2-3 hours. Yellow solid began to precipitate in the first ten or fifteen minutes of heating. After the mixture had stood at room temperature overnight, the product was collected and recrystallized from methanol.

The perchlorate salts were formed by addition of perchloric acid to a hot methanol solution of the bromide. The perchlorates were recrystallized from methanol as a yellow powder. Data for the salts is summarized in Table I.

5H-6-Methylindolizino[1,2-c]quinolinium Salts.

A. By Deacylation of the 12-Acyl Derivatives Using Hydrobromic Acid.

The 12-acyl derivative (5,6,9) was dissolved in hot 48% hydrobromic acid and the solution heated on the steam bath for 4 hours. Then the mixture was poured on crushed ice and the yellow precipitate collected. The bromide crystallized as a hydrate from methanol as bright yellow needles, dec. beginning 300° m.p. > 375°; nmr τ 6.26 (S, 3, CH₃), all other < 2.95; λ max 211 mμ (log ε 4.35), 230 sh (4.33), 248 (4.50), 264 sh (4.35), 273 (4.30), 283 (4.13), 302 (3.70), 314 (3.71), 367 sh (3.88), 392 sh (4.08), 405 (4.12), 423 (4.07). In solution the new salt showed a bluish green fluorescence. All preparations were shown to be identical by ir.

Anal. Calcd. for C₁₆H₁₃BrN₂·2H₂O: C, 55.02; H, 4.91; N, 8.02. Found: C, 55.25; H, 4.67; N, 8.10.

B. By Deacylation of the 12-Acyl Derivatives Using Concentrated Sulfuric Acid and Perchloric Acid.

One gram of the acyl salt (5-7) was dissolved in 25 ml. of cold concentrated sulfuric acid and the mixture allowed to stand for 1.5 hours. Then the solution was poured into approximately 500 ml. of cold anhydrous ether. After the mixture had stood in the refrigerator for 2 hours, the yellow precipitate was collected, dissolved in water and 70% perchloric acid added. The perchlorate crystallized from methanol as bright yellow needles which were not only hydrated but contained additional perchloric acid as well (5). All of the preparations of the perchlorate were shown to be identical by means of ir.

Anal. Calcd. for C₁₆H₁₃ClN₂O₄·1H₂O·½HClO₄: C, 47.92;

H, 3.65; N, 6.99. Found: C, 47.57, 47.71; H, 3.80, 3.48; N, 6.68, 6.86.

The identity of the cations in the bromide and perchlorate salts was demonstrated by interconversion of the bromide to the perchlorate and *vice versa*.

C.   By Synthesis *via* 2-(2-Acetamidophenyl)-1-acetylindolizine (14).

A solution of 0.95 g. of 2-acetamido-ω-bromoacetophenone (10) (2) and 1.0 g. of 2-pyridylacetone (12) (4) in 5 ml. of reagent acetone was allowed to stand at room temperature in a closed flask for 18 days. The 2-pyridylacetone hydrobromide which had precipitated was filtered off and washed with acetone. The combined filtrates were evaporated, 25 ml. of 2 N hydrochloric acid added and the mixture extracted thoroughly with ether. The pale yellow solid remaining on evaporation of the ether was recrystallized from methanol, affording 0.4 g. (44%) of colorless solid, m.p. 151-152°; (probable loss of methanol of crystallization at 87°); UV max 368 mμ sh (log ε 3.99), 352 (4.10), 325 sh (3.68), 232 (4.40); nmr (deuteriochloroform), τ 8.05 (S, 3, CH_3CON). 8.00 (S, 3, CH_3COR), 7.70 (S, 1, OH), 6.55 (S, 3, CH_3OH), 3.30-1.45 (m, 10, aromatic H plus NHCO).

The analysis and the nmr suggested that the product (14) contained one mole of methanol of crystallization.

Anal. Calcd. for $C_{18}H_{16}N_2O_2 \cdot CH_4O$: C, 70.35; H, 6.22; N, 8.64. Found: C, 69.94; H, 5.86; N, 8.96.

A solution containing 100 mg. of the indolizine (14) in 2 ml. of ethanol and 1 ml. of 2 N sodium hydroxide solution was heated for 6 hours on a steam bath. Water was added and the mixture extracted with ether. The ethereal extract was dried (potassium carbonate) and an ether solution of hydrogen bromide was added. The yellow precipitate was crystallized from methanol affording 70 mg (65%) of yellow needles which decomposed but did not melt below 380°. Comparison of ir, uv and nmr spectra with those of the deacylation products (4 Br) showed the preparations to be identical.

Recovery of Benzoic Acid from the Debenzoylation of 6.

One gram of 6 bromide was debenzoylated with sulfuric acid

as described in procedure B, and the ethereal filtrate remaining cautiously washed to remove sulfuric acid. The ether solution was dried and evaporated. The white residue was purified by precipitation from sodium bicarbonate solution and recrystallized from water, affording benzoic acid as colorless needles m.p. 122.5-124° (mixture melting point), yield 0.115 g. (39%).

Reacylation of 6-Methylindolizino[1,2-c]quinolinium (4) Bromide.

If 4 was heated in benzoyl chloride until solution occurred and the resulting mixture allowed to stand in the refrigerator, a yellow precipitate formed. The excess benzoyl chloride was dissolved in ether and the product collected. The yellow product was converted to the perchlorate and recrystallized from methanol-ether affording bright yellow needles decomposing at about 283-284°. Ir spectroscopy demonstrated that this was identical with the perchlorate of the cation (6) formed by reaction of phenacyl bromide with 2-methyl-3-(2-pyridyl)quinoline (1).

REFERENCES

(1) This research was supported by Public Health Service Research Grant No. H-2170 of the National Heart Institute. It was presented at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, July 8, 1969.

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