The solution of diazonium salt was then added dropwise to a boiling solution of 80 ml. sulfuric acid in 340 ml. water, the phenol being continuously removed by steam distillation after the method of Lambooy,[6] in all, about 3.5 to 4 l. of distillate being collected. After addition of ammonium sulfate the distillate was extracted four times with benzene, the benzene dried over anhydrous sodium carbonate and evaporated *in vacuo* to yield the 3-phenoxymesitol as a colorless oil (4.5 g; 98%) which could not be induced to crystallize.

The phenol was characterized through its α-naphthylurethane which, for analysis, was chromatographed on acid washed alumina (benzene and *n*-heptane) and recrystallized from the same solvents, colorless needles melting at 173° *in vacuo*.

Anal. Calcd. for $C_{26}H_{23}O_3N$: C, 78.7; H, 5.84; N, 3.53. Found: C, 78.89; H, 5.96; N, 3.53.

Oxidation of V. To 3.31 g. of V (0.0145 mole) dissolved in 200 ml. of 5% potassium hydroxide solution there was added over a period of 30 min. and with rapid stirring, 5.1 g. (0.0155 mole) of potassium ferricyanide dissolved in 25 ml. 5% KOH solution. During the addition the solution acquired a bright violet color and then became milky in appearance. After an additional 2.5 hr. stirring the solution became clear and colorless. At this time the reaction mixture was neutralized with acetic acid, the precipitated oil extracted with benzene and the benzene solution washed with a little water and dried over Na_2CO_3. The yellow, viscous oil obtained by removal of solvent *in vacuo* was taken up three times in 25-ml. aliquots of boiling *n*-heptane, each time the solution was allowed to cool and the supernatant decanted. The combined supernatants were allowed to pass through (slight suction) a 6″ × 0.5″ acid washed alumina column previously wetted with *n*-heptane. Evaporation of the column effluent yielded 1.7 g. (52%) of starting material (α-naphthyl urethane and infrared spectra). The oil remaining after extraction with *n*-heptane was dissolved in a minimum volume of benzene which was then passed through the column. The column was then washed with additional aliquots of benzene until a yellow band separated from the origin and traversed the length of the column. The benzene effluent when evaporated yielded a pale yellow glass which crystallized when stored at 40° under *n*-heptane (product A). The column was next washed with 25 ml. of a 10% ethanol-benzene mixture and the effluent evaporated to yield a yellow glass which also crystallized under *n*-heptane at 40° (product B).

On repeated recrystallization from benzene by addition of *n*-heptane, product A yielded 0.46 g. (14%) of 4,4′-dihydroxy-3,3′,5,5′-tetramethyl-2,2′-diphenoxybibenzyl (XIII) as buttons of white needles, m.p. 154–155°.

Anal. Calcd. for $(C_{15}H_{15}O_2)_2$: C, 79.4; H, 6.66. Found: 79.23; H, 6.38. A Rast molecular weight determination could not be performed because of the reactivity of the product with camphor. A molecular weight by the isothermal distillation method of Childs:[9] Calcd. 454, found 436.

Recrystallization of product B from benzene and *n*-heptane mixtures yielded 0.33 g. (10%) of flat colorless plates of 2,6-dimethyl-1-hydroxy-3-phenoxybenzyl alcohol, m.p. 131–132°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.7; H, 6.59; mol. wt., 244. Found: C, 73.95; H, 6.68; mol. wt., 288 (Rast).

NEW HAVEN, CONN.

(9) C. E. Childs, *Anal. Chem.*, **26**, 1963 (1951).

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

1-Ketolilolidine and Some of Its Reactions

HENRY RAPOPORT AND JAMES R. TRETTER

Received September 9, 1957

Cyanoethylation of indoline gave 1-indolinepropionitrile which was cyclized directly to 1-ketolilolidine in very poor yield. However, hydrolysis to 1-indolinepropionic acid and heating this acid in polyphosphoric acid gave an excellent yield of cyclic ketone. Condensation with benzaldehyde or furfuraldehyde led to the α-ylidene ketone which was isomerized readily with alkali to the corresponding 4-quinolone.

As a possible entry to the difficulty prepared 7-substituted indoles and indolines, the synthesis of 1-ketolilolidine[1] (IV) was undertaken. Although its conversion to 7-substituted indolines as yet has not been achieved, a convenient preparation of the desired ketone (IV) and an account of some of its reactions are presented at this time.

Since acrylonitrile has been used to cyanoethylate numerous aromatic amines, the reaction of acrylonitrile and indoline was examined for the preparation of 1-indolinepropionitrile (I). Following the procedure which had been used successfully to cyanoethylate tetrahydroquinoline,[2] indoline and acrylonitrile were heated in acetic acid. Some 1-indolinepropionitrile was obtained, but a by-product of major proportions was 1-acetylindoline. Similar difficulty had been encountered in the cyanoethylation of *o*-toluidine[3] and since it had been overcome by the addition of cuprous chloride, a comparable addition was made in the present case. As a result the formation of 1-acetylindoline was eliminated almost completely and 1-indolinepropionitrile (I) was obtained in excellent yield.

Cyclization to the ketone (IV) was considered first directly from the nitrile (I). Several examples of closely-related ring-closures have been re-

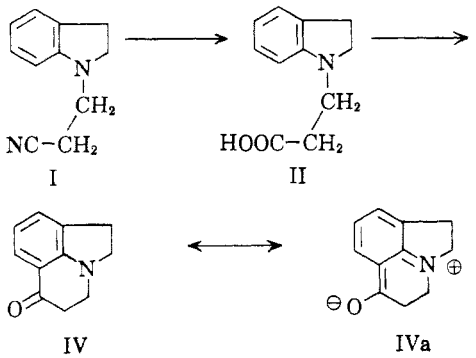
(1) The nomenclature proposed by C. Y. Almond and F. G. Mann, *J. Chem. Soc.*, 1870 (1952), based on liline, liloline, and lilolidine has been used throughout the discussion with the usual delta designation for the position of the double-bond in liloline except when it is 1,2. In the experimental part, alternative names have been given for most compounds, derived from the *Chem. Abstr.* name for lilolidine, 1,4,5,6-tetrahydro-2*H*-pyrrolo[3,2,1-*ij*]quinoline.

(2) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanko, *J. Am. Chem. Soc.*, **66**, 725 (1944).

(3) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1817 (1953).

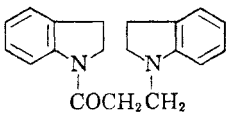
ported, *e.g.*, in which *N*,*N*-bis-2-cyanoethylaniline,[3,4] *p*-chloro-*N*,*N*-bis-2-cyanoethylaniline,[5] *N*-2-cyanoethyl-*N*-methylaniline,[6] 1-(2′-cyanoethyl)-1,2,3,4-tetrahydroquinoline,[7] and 9-(2′-cyanoethyl)carbazole[7] have been converted to the corresponding ketones. Various combinations of aluminum chloride with hydrochloric acid in chlorobenzene and aluminum chloride, sodium chloride, and potassium chloride have been used, although it is interesting to note that attempts to repeat the cyclization of 1-(2′-cyanoethyl)-1,2,3,4-tetrahydroquinoline[8] and 9-(2′-cyanoethyl)carbazole[9] have failed.

Numerous reactions were performed with 1-indolinepropionitrile (I) and aluminum chloride under conditions suggested by the above. Small amounts of 1-ketolilolidine (IV) were obtained, but the yields were quite poor and an appreciable proportion of the starting nitrile was converted to indoline as well as to polymeric material. For this reason, direct ring-closure of the nitrile was abandoned. It was hydrolyzed to the acid (II) and cyclization of the acid then was undertaken.



I II IV IVa

Three methods were investigated for cyclizing the propionic acid. The first, anhydrous hydrogen fluoride, led to no ketone, and the starting acid was recovered quantitatively. Trifluoroacetic anhydride in benzene[10] then was applied and although about a 20% yield of ketone (IV) was obtained, most of the propionic acid (II) was converted to indoline and 1′-indolinepropionyl-1-indoline (III).



III

The structure of 1′-indolinepropionyl-1-indoline was established by its analysis, the presence of a strong band at 1645 cm.$^{-1}$ in its infrared spectrum, and its ultraviolet spectrum which was almost exactly that of indoline plus 1-acetylindoline. Its formation had probably occurred through the mixed anhydride of II and trifluoroacetic acid which had in part eliminated indoline, and the latter then was acylated by the anhydride.

The best method for converting acid (II) to ketone (IV) was by the use of polyphosphoric acid which resulted in an 87% yield. 1-Ketolilolidine is bright yellow and in its color and ultraviolet absorption (Fig. 1) is very similar to the 1,2,3,4-

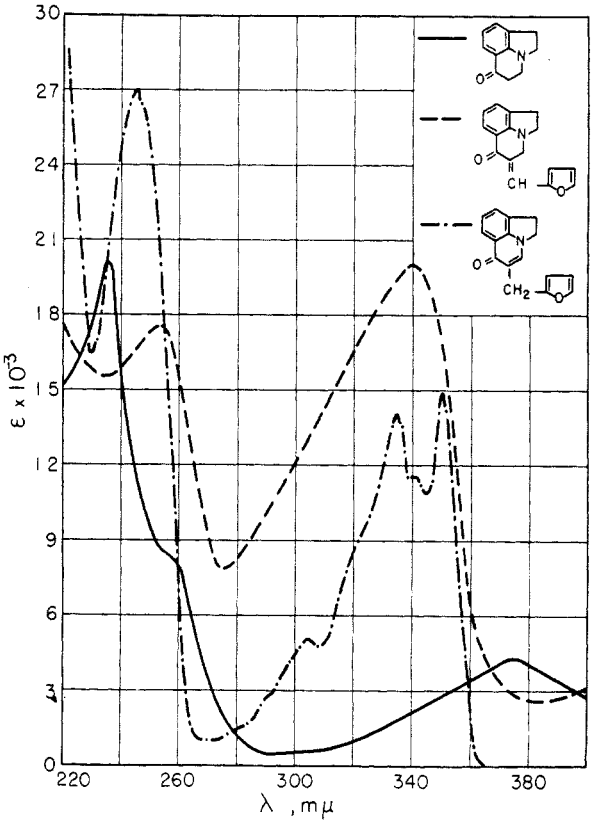


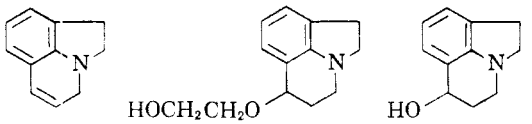
FIG. 1. ULTRAVIOLET SPECTRA IN ETHANOL: ——— 1-Ketolilolidine; – – – – 1-Keto-2-furfurylidenelilolidine; — · — · — 1-Keto-2-furfuryl-Δ^2-liloline.

tetrahydro-4-oxoquinolines. The color of these compounds has been ascribed[6] to the contribution of the *o*-quinonimine form, and similarly the resonance form IVa undoubtedly is responsible for many properties of 1-ketolilolidine. In addition to the color, this should lead to a strong base-weakening effect as is the case. Spectral and distribution studies indicated the ketone (IV) had a pK_a' of 1 or less.

To prepare liloline (V), the method of Bamford and Stevens[11] was applied. This consists in heating the ketone *p*-toluenesulfonylhydrazone in ethylene

(4) R. C. Cookson and F. G. Mann, *J. Chem. Soc.*, 67 (1949).
(5) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 651 (1954).
(6) J. A. C. Allison, J. T. Braunholtz, and F. G. Mann, *J. Chem. Soc.*, 403 (1954).
(7) French Patent **806,715** (1936).
(8) F. G. Mann and B. B. Smith, *J. Chem. Soc.*, 1898 (1951).
(9) P. A. S. Smith and T. Yu, *J. Am. Chem. Soc.*, **74**, 1096 (1952).
(10) R. J. Ferrier and J. M. Tedder, *J. Chem. Soc.*, 1435 (1947).
(11) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

glycol with sodium glycolate. However, instead of the olefin (V), the product was the ethylene glycol ether (VI).[12] An alternative approach to liloline was through the alcohol (VII). Reduction of 1-ketolilolidine with sodium borohydride gave 1-hydroxylilolidine in quantitative yield, but it could be converted neither to the chloride nor tosylate for subsequent elimination.



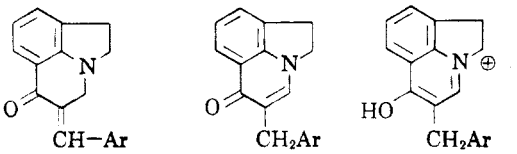
V VI VII

Condensation of 1-ketolilolidine with aromatic aldehydes offered a particularly promising path to 1,7-disubstituted indolines since such α-ylidene ketones have been successfully oxidized to the ring-opened dibasic acids.[13] The first stage of this method proceeded readily in the condensation of furfural and 1-ketolilolidine to the red 1-keto-2-furfurylidenelilolidine (VIII). When the latter compound was subjected to the action of alkaline hydrogen peroxide,[14] a rapid reaction took place as indicated by the fading of the red color and the appearance of a yellow substance. This yellow material was not an oxidation product but was isomeric with the red starting material (VIII), suggesting that an alkali-catalyzed isomerization rather than an oxidation had occurred.

This was proved to be the case by treating the furfurylidene ketone (VIII) with alkali and obtaining the same isomeric yellow material in excellent yield. In parallel experiments with benzaldehyde, the initial red benzylidene compound (IX) was observed, but it proved too unstable and the alkali used in the condensation was sufficient to cause isomerization to yellow material. It was also demonstrated that acid caused this isomerization to occur, but at a much decreased rate.

Although the possibility existed that the red and yellow isomers were cis-trans isomers about the double bond, this seemed unlikely in view of the accompanying gross changes in ultraviolet absorption (Fig. 1) and infrared absorption. In the infrared, the carbonyl band moved from 1660 cm.$^{-1}$ to 1630 cm.$^{-1}$, indicating even greater conjugation. In the ultraviolet, the peak at 340 mμ was replaced by a clear bifurcation in the 320-360 mμ region, and the absorption at 252 mμ underwent a 7 mμ hypsochromic shift while its extinction coefficient increased from 17,500 to 27,000. This spectrum is very characteristic of 4-quinolones[15] and provides sufficient evidence to assign structures X and XI to the yellow isomers. Actually, this type of condensation and isomerization offers an interesting alternative to the general methods for preparing 4-quinolones.[15]

The quinolone spectrum is only slightly effected by alkali, but in 1*N* hydrochloric acid, the bifurcation disappears and the short wavelength maximum increases tremendously in extinction coefficient to 64,500 and 75,000 for X and XI, respectively. This is probably due to acid stabilization of the highly conjugated form XII.



VIII, Ar = C_4H_3O X, Ar = C_4H_3O XII
IX, Ar = C_6H_5 XI, Ar = C_6H_5

EXPERIMENTAL[16]

1-Indolinepropionitrile (I). Indoline was prepared in 76% yield by hydrogenation of indole using Raney nickel[17] in absolute ethanol at 90 atmospheres and 100° for twelve hours.[18] For the cyanoethylation, 10 g. (.084 mole) of indoline, 3 ml. of acetic acid, 8 g. of acrylonitrile, and 0.8 g. of freshly prepared cuprous chloride were heated under reflux (bath temperature, 125°) for 12 hr. in a nitrogen atmosphere, with an additional 6 g. of acrylonitrile being added after the first seven hours had elapsed. The reaction mixture was then cooled, made alkaline with concentrated ammonium hydroxide, and extracted thoroughly with methylene chloride. Evaporation of the methylene chloride and distillation of the residue gave 2 g. of recovered indoline plus a fraction, b.p. 125–140°/1 mm., consisting of 1-indolinepropionitrile and a small amount of 1-acetylindoline. This fraction was dissolved in benzene, hexane was added almost to turbidity, and the organic phase was washed repeatedly with 3*M* sulfuric acid. Addition of ammonium hydroxide to the cooled aqueous solution then precipitated the nitrile which was crystallized from ethanol; yield, 11.0 g. (95%), m.p. 40–41°. Ultraviolet spectrum in ethanol: λ_{max} 253 mμ (ϵ 10,400), 299 (2400).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.7; H, 7.0; N, 16.3. Found: C, 77.0; H, 7.0; N, 16.0.

1-Indolinepropionic Acid (II). 1-Indolinepropionitrile (18 g., 0.1 mole) and 200 ml. of 3*N* potassium hydroxide were heated under reflux in a nitrogen atmosphere until solution was complete (about 3 hr.). The reaction mixture then was cooled, washed with methylene chloride, and acidified to *p*H

(12) Although the original reference (ref. 11) gives two examples of ethylene glycol mono ether formation in this reaction, these were all with compounds having no α-hydrogens. In the present case and also with two other 6-membered cyclic aromatic ketones each having two α-hydrogens, we have obtained glycol ethers as the sole products.

(13) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **78**, 6354 (1956).

(14) In other experiments with ozone, the entire material was oxidized to non-isolable, highly water soluble products.

(15) E. A. Steck, G. W. Ewing, and F. C. Nachod, *J. Am. Chem. Soc.*, **71**, 238 (1949).

(16) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley.

(17) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(18) F. E. King, J. A. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945). In some hydrogenations, as much as 5% of perhydrogenated material was formed, but this was easily removed by extraction with methylene chloride at pH 6. Under these conditions, indoline goes into the organic phase while the strongly basic perhydrogenated material stays in the water.

3–4, precipitating the acid. Crystallization from hexane gave 14.1 g. of 1-indoline propionic acid, and extraction of the aqueous acid solution with methylene chloride, evaporation of the methylene chloride, and crystallization of the residue gave an additional 4.1 g.; total yield, 18.2 g. (91%), m.p. 75–76°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.8; equiv. wt., 191. Found: C, 69.2; H, 6.8; equiv. wt., 192.

Cyclization of 1-indolinepropionic Acid (II) *to 1-ketolilolidine* (IV) (*6-oxo-1,4,5,6-tetrahydro-2H-pyrrolo [3,2,1-ij] quinoline*). *A. Using polyphosphoric acid.* 1-Indolinepropionic acid (100 g., 0.52 mole) and 3000 g. of polyphosphoric acid were heated at 100° with stirring in a nitrogen atmosphere for 24 hr. after which 12 l. of water was added and the pH was adjusted to 3.5 with concentrated sodium hydroxide. Continuous extraction with ether was carried on for 3 days and the ether extract then was washed with 2*N* potassium hydroxide to remove uncyclized acid. Acidification of this extract to pH 3.5, extraction with ether, and evaporation of the ether gave 30 g. of recovered 1-indolinepropionic acid. Evaporation of the ether that had been washed with alkali left a viscous residue which was distilled at reduced pressure, b.p. 151°/2.4 mm. This material solidified to yellow crystals and could be recrystallized from heptane, m.p. 55–56°; 55 g., 61% conversion, 87% yield based on recovered acid. Ultraviolet spectrum in ethanol: λ_{max} 236 mμ (ε 20,000), 376 (4,200), shoulder at 256 mμ (ε 8,200).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.3; H, 6.4; N, 8.1. Found: C, 76.4; H, 6.2; N, 8.2.

The dark red *p-nitrophenylhydrazone* was prepared in the usual way and was crystallized from ethanol, m.p. 245° (dec.).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.2; H, 5.2; N, 18.2. Found: C, 66.2; H, 5.1; N, 18.2.

On standing in ethanol for 24 hr., a solution of 1-ketolilolidine and *p*-toluenesulfonylhydrazine precipitated the yellow *p-toluenesulfonylhydrazone* which was recrystallized from aqueous acetone, m.p. 217° (dec.).

Anal. Calcd. for $C_{18}H_{19}N_3O_2S$: C, 63.3; H, 5.6; S, 9.4. Found: C, 63.1; H, 5.9; S, 9.6.

B. Using trifluoroacetic anhydride. After 20 ml. of benzene was distilled from a solution of 5 g. (.026 mole) of 1-indolinepropionic acid in 70 ml. of benzene, a solution of 4 ml. of trifluoroacetic anhydride in 4 ml. of benzene was added over 5 min. and the solution was heated under reflux for another 10 min. Excess, dilute potassium hydroxide then was added to the cooled solution, the aqueous phase was extracted with two additional portions of benzene, and acid was added to pH 4. Extraction of the aqueous acid solution with ether led to the recovery of 0.8 g. of 1-indolinepropionic acid. The combined benzene extracts were washed with water and evaporated leaving a residue which was distilled at reduced pressure. From the fraction boiling at 70–110°/0.3 mm., 0.95 g. of 1-ketolilolidine (IV) was isolated. The distillation residue was dissolved in ethanol, treated with decolorizing carbon, and crystallized from benzene to give 2 g. of *1'-indolinepropionyl-1-indoline* (III), m.p. 125–126°. Ultraviolet spectrum in ethanol: λ_{max} 255 mμ (ε 23,200), 282 (7600), 292 (7000).

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.1; H, 6.9; N, 9.6. Found: C, 78.3; H, 6.8; N, 9.6.

Decomposition of 1-ketolilolidine p-toluenesulfonylhydrazone. To 0.3 g. of sodium dissolved in 10 ml. of ethylene glycol was added 1.5 g. of 1-ketolilolidine *p*-toluenesulfonylhydrazone prepared above and the solution was heated to 150° in a nitrogen atmosphere. After 24 hr., the solution was poured into 40 ml. of water and the oil which separated was extracted into benzene. Evaporation of the benzene and distillation (100°/0.1 mm.) of the residue onto a cold finger gave 0.7 g. of *ethylene glycol mono (1-lilolidinyl) ether* (VI) as an oil. Ultraviolet spectrum in ethanol: λ_{max} 252 mμ (ε 7100), 307 (2700).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.4; H, 8.0; N, 6.3.

1-Hydroxylilolidine (VII) (*6-oxy-1,4,5,6-tetrahydro-2H-pyrrolo[3,2,1-ij]quinoline*). A solution of 1 g. of 1-ketolilolidine in 200 ml. of methanol to which 4 g. of sodium borohydride in 25 ml. of water had been added was allowed to stand at room temperature for 24 hr. The methanol was then removed *in vacuo*, the aqueous residue was extracted with benzene, and the benzene was evaporated. Distillation (125°/0.1 mm.) of the residue onto a cold finger gave 0.95 g. of 1-hydroxylilolidine, m.p. 54–54.5°. Ultraviolet spectrum in ethanol: λ_{max} 251 mμ (ε 7400), 304 (2700).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.4; N, 8.0. Found: C, 75.5; H, 7.5; N, 8.1.

1-Keto-2-furfurylidenelilolidine (VIII) (*5-furfurylidene-6-oxo-1,4,5,6-tetrahydro-2H-pyrrolo[3,2,1-ij]quinoline*). A sodium hydroxide solution (10 ml. of 5*N*) was added to a cold solution of 1 g. of 1-ketolilolidine and 1 g. of furfural in 10 ml. of methanol, and the nitrogen filled flask was shaken for 6 hr. The mixture was filtered and the precipitated furfurylidene compound was washed well with cold water and crystallized from ethanol to give 0.9 g. (62% yield) of long, red needles, m.p. 148–149°. Ultraviolet spectrum in ethanol: λ_{max} 252 mμ (ε 17,500), 340 (20,000).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.2; H, 5.2; N, 5.6. Found: C, 76.1; H, 5.5; N, 5.8.

1-Keto-2-furfuryl-Δ²-liloline (X) (*5-furfuryl-6-oxo-1,6-dihydro-2H-pyrrolo [3,2,1-ij] quinoline*). 1-Keto-2-furfurylidenelilolidine (1 g.) was dissolved in 25 ml. of methanol and 5 ml. of 1*N* aqueous potassium hydroxide was added. After this solution was stirred overnight under nitrogen, removal of the methanol at reduced pressure and cooling gave pale yellow crystals of 1-keto-2-furfuryl-Δ²-liloline in quantitative yield, m.p. 177–178° after recrystallization from aqueous methanol. Ultraviolet spectra: in ethanol, λ_{max} 245 mμ (ε 27,000), 335 (14,200), 350 (14,800); in 1*N* ethanolic hydrochloric acid, λ_{max} 238 mμ (ε 64,500), 324 (7000).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 76.5; H, 5.2; N, 5.6. Found: C, 76.1; H, 5.1; N, 5.7.

1-Keto-2-benzyl-Δ²-liloline (X) (*5-benzyl-6-oxo-1,6-dihydro-2H-pyrrolo[3,2,1-ij]quinoline*). To a cold solution of 0.75 g. of 1-ketolilolidine and 0.92 g. of benzaldehyde in 10 ml. of methanol was added 5 ml. of 5*N* aqueous sodium hydroxide. The flask was flushed with nitrogen, stoppered, and shaken. Within a few minutes, the solution became red and shortly after this a red precipitate appeared. This gradually disappeared and was replaced by a yellow-orange precipitate. After 24 hrs. of shaking, the mixture was filtered and the precipitate was recrystallized from aqueous ethanol to give 0.8 g. of 1-keto-2-benzyl-Δ²-liloline, m.p. 171–172°. Ultraviolet spectra: in ethanol, λ_{max} 248 mμ (ε 32,000), 336 (14,600), 352 (15,400); in 1*N* ethanolic hydrochloric acid, λ_{max} 243 mμ (ε 75,000), 328 (8,000).

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.8; H, 5.8; N, 5.4. Found: C, 83.1; H, 6.0; N, 5.5.

BERKELEY, CALIF.