A Novel Ring Expansion of 3-Indoleacetamides[1]

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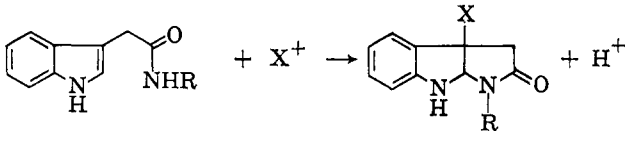
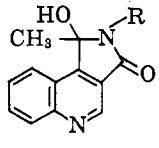
The phosphorus oxychloride-catalyzed condensation of *N*-(3-indoleacetyl)benzylamine with *N*,*N*-dimethylacetamide followed by alkaline hydrolysis gives a compound $C_{19}H_{16}N_2O_2$, in 10% yield. The condensation product is shown to be 1-methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline (1) by n.m.r. spectroscopy and degradative studies. A possible mechanism for this transformation is suggested.

One possible biogenetic pathway for physostigmine involves the reaction of a protonated formaldehyde molecule at the β-position of tryptophan nucleus giving rise to a labile β-hydroxymethylindolinene which undergoes internal cyclization and reduction to the physostigmine ring system.[2] In an effort to bring about this type of transformation in the laboratory we have examined the reactions of some electrophiles with 3-indoleacetamides.

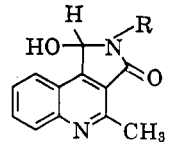


3-Indoleacetamides were chosen rather than tryptamine because it seemed that the decreased basicity of the amide nitrogen would diminish the formation of tetrahydro β-carbolines. We first examined the reactions of formaldehyde with 3-indoleacetamides under a wide variety of acidic conditions. In no instance was it possible to obtain any characterizable compounds from the reaction, and it appears that extensive polymerization takes place even under rather mild conditions. The ultraviolet spectra of the total reaction products showed little indication of the formation of indolines.

The fact that indole gives excellent yields of indole-3-aldehyde by formylation with dimethylformamide and phosphorus oxychloride[3] suggested that the Vilsmeier reaction might be useful for effecting the desired transformation. We were not able to isolate any useful products from the condensation of *N*-(3-indoleacetyl)-benzylamine with dimethylformamide or *N*,*N*-dimethylbenzamide using phosphorus oxychloride as catalyst. However, the condensation of *N*-(3-indoleacetyl)benzylamine with *N*,*N*-dimethylacetamide and phosphorus oxychloride, followed by the usual alkaline hydrolysis, yielded a beautifully crystalline basic compound, $C_{19}H_{16}N_2O_2$, in 10% yield. The cyclohexyl analog, *N*-(3-indoleacetyl)cyclohexylamine, gave a similar compound, $C_{18}H_{20}O_2N_2$, indicating that the benzyl group is not involved in the reaction. The ultraviolet spectra of these condensation products, λ_{max} 238 mμ (ε 60,000), 312 (3210), 325 (1860), are in good agreement with the ultraviolet curves reported for quinoline-3-carboxylic acid derivatives.[4] The infrared spectra (Nujol mull) of the condensation products show a single carbonyl absorption at 1710 cm.$^{-1}$, and no absorption in the 1550-cm.$^{-1}$ region characteristic of a primary or secondary amide. Further studies were carried on only with the condensation product from *N*-(3-indoleacetyl)benzylamine and *N*,*N*-dimethylacetamide. The condensation product gave no carbonyl derivatives even under forcing conditions, and the starting material was recovered unchanged. The material also was recovered after attempted hydrolysis in refluxing 50% aqueous ethanolic potassium hydroxide for five hours. Vigorous permanganate oxidation yielded only benzoic acid showing that the benzyl group does not suffer substitution in the reaction. Chromic acid oxidation afforded the *N*-benzylimide of quinoline-3,4-dicarboxylic acid, identical in all respects with an authentic sample. The oxidation studies and the spectral evidence suggested two possible structures for the condensation product.



1. R = benzyl



2. R = benzyl

Plausible mechanisms can be written for the formation of either of the compounds and both contain the quinoline-3-carboxylic acid chromophore. While compound **2** might not be expected to give the *N*-benzylimide of quinoline-3,4-dicarboxylic acid upon chromic acid oxidation, we find that chromic acid oxidation of the *N*-benzylimide of 2-methylquinoline-3,4-dicarboxylic acid removes the methyl group to give the *N*-benzylimide of quinoline-3,4-dicarboxylic acid under the same conditions used for the chromic acid oxidation of the condensation product. This is in contrast to the results of Engelhard[5] who recovered only starting material from the chromic acid oxidation of 2-methylquinoline-3,4-dicarboxylic acid, although he reports the evolution of carbon dioxide during the reaction. The failure to obtain carbonyl derivatives is reasonable owing to the severe steric hindrance at the masked carbonyl group. Both the infrared and ultraviolet spectra are consistent with the alkanol amide structure.

A dehydration experiment and proton magnetic resonance spectra of the condensation product and its dehydration product were decisive in favor of structure **1**. The proton magnetic resonance spectrum of the condensation product in concentrated hydrochloric acid shows a singlet at τ 7.70 ascribed to a methyl group, and a singlet at τ 4.83 attributed to the methylene of the benzyl group. In the same solvent the methyl group of quinaldine is at τ 6.68 and the proton magnetic resonance spectrum in 85% phosphoric acid of the *N*-benzyl-

(1) Supported in part by research grant B3232 from the National Institutes of Health and a Faculty Research grant from the Graduate School of the University of Oregon.

(2) B. Witkop and R. K. Hill, *J. Am. Chem. Soc.*, **77**, 6592 (1955).

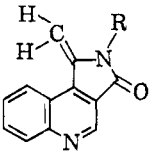
(3) P. N. James and H. R. Snyder, *Org. Syn.*, **39**, 30 (1959).

(4) E. A. Fehnel, J. A. Deyrup, and M. B. Davidson, *J. Org. Chem.*, **23**, 1996 (1958).

(5) C. Engelhard, *J. prakt. Chem.*, [2] **57**, 481 (1898).

imide of 2-methylquinoline-3,4-dicarboxylic acid shows a singlet at τ 6.25 ascribed to the methyl group and a singlet at τ 4.85 assigned to the methylene of the benzyl group. This evidence indicates that the condensation product does not contain a methyl group of the quinaldine type. The proton magnetic resonance spectrum of the condensation product in dimethyl sulfoxide solution shows a singlet at τ 0.70 attributed to the proton adjacent to the nitrogen of the quinoline ring.

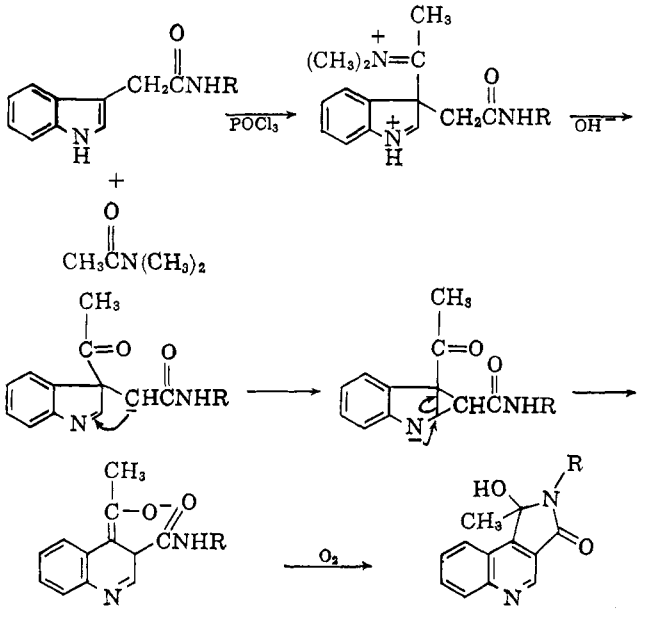
Hot acetic anhydride converted the condensation product to an anhydro compound, $C_{19}H_{14}N_2O$. The ultraviolet spectrum (λ_{max} 250, 296, 306, 338, 349 mμ) indicates that the new double bond has changed the chromophore. Based upon structure **1** for the condensation product, the anhydro compound is considered to be the following.



3. R = benzyl

The proton magnetic resonance spectrum in deuteriochloroform provides strong support for the proposed structure. The peak ascribed to the methyl group is absent while a singlet at τ 4.71 is ascribed to the methylene protons of the benzyl group. Two doublets with J = 3.2 c.p.s. at τ 4.49 and 3.97 are attributed to the two nonequivalent protons of the *exo* methylene group. The proton adjacent to the nitrogen of the quinoline ring is seen as a singlet τ 0.55.

From the preceding discussion we conclude that the structure of the compound obtained from the phosphorus oxychloride-catalyzed condensation of *N*-(3-indoleacetyl)benzylamine with dimethylacetamide is 1-methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline (**1**) and the corresponding product from *N*-(3-indoleacetyl)cyclohexylamine is 1-methyl-1-hydroxy-2-cyclohexyl-3-oxopyrollo[3,4-*c*]quinoline. We propose that these condensation products are formed by the following reaction scheme.



From the structure of the product of the reaction, it appears that electrophilic attack occurs at the β-position of the indole ring to give the desired indolinene intermediate. It was anticipated that the indolinene intermediate would undergo internal cyclization to the physostigmine ring system as observed with similar indolinenes.[2,6] It may be that formation of the physostigmine ring system is reversible in this instance while the cyclopropane intermediate rearranges irreversibly to the dihydroquinoline which suffers air oxidation to the stable quinoline system.

Interestingly, Pleninger and Müller[7] find that the boron trifluoride-catalyzed reaction of 3-indoleacetamide and acetic anhydride yields an indolopyridone. While we were not able to isolate any compounds of this type, the low yields of identified material make it impossible to decide about the other reactions which may be taking place.

Experimental[8]

The Phosphorus Oxychloride-Catalyzed Condensation of *N*-(3-indoleacetyl)benzylamine with *N*,*N*-Dimethylacetamide.—To 6.0 ml. of *N*,*N*-dimethylacetamide at 5° was added slowly 1.7 g. of phosphorus oxychloride with stirring. After completion, a solution of 2.60 g. of *N*(-3-indoleacetyl)benzylamine[9], m.p. 154–155°, and 6.0 ml. of *N*,*N*-dimethylacetamide was added with continued cooling. The resulting mixture was heated at 90–95° for 2 hr., cooled, and diluted with water. The aqueous mixture was extracted three times with ether, and the ether extracts were discarded. The aqueous phase was made basic with 30% sodium hydroxide and heated on the steam bath for 10 min., then cooled, and extracted with chloroform. The chloroform extracts were extracted five times with 10% hydrochloric acid. The hydrochloric acid extracts were made basic and extracted with chloroform. Evaporation of the chloroform afforded 0.50 g. of material which solidified upon standing at room temperature. After two crystallizations from ethyl acetate there was obtained 0.30 g. (10%) of 1-methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline (1), m.p. 219–220°; ultraviolet absorption: λ_{max}^{EtOH} 238 mμ (ϵ 60,000), 312 (3210), 325 (1860).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20; mol. wt., 304. Found: C, 74.83; H, 5.44; N, 9.20; mol. wt., 320.

***N*-(3-Indoleacetyl)cyclohexylamine** was prepared in 80% yield from 3-indoleacetic acid, m.p. 164–65°, and cyclohexylamine by the procedure of Katritzky.[9] The analytical sample melted at 155–156° after several crystallizations from 50% aqueous ethanol.

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.25; H, 7.62; N, 11.09.

The Phosphorus Oxychloride-Catalyzed Condensation of *N*-(3-Indoleacetyl)cyclohexylamine with *N*,*N*-Dimethylacetamide.—A 5.1-g. sample of *N*-3(indoleacetyl)cyclohexylamine was condensed with *N*,*N*-dimethylacetamide and worked up as previously described to yield 500 mg. (8%) of 1-methyl-1-hydroxy-2-cyclohexyl-3-oxopyrollo[3,4-*c*]quinoline, m.p. 129–130°, after several crystallizations from ethyl acetate; ultraviolet absorption: λ_{max}^{EtOH} 233 mμ (ϵ 60,000), 310 (3000), 322 (1780).

Anal. Calcd. for $C_{18}H_{21}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.60; H, 7.13; N, 9.18.

Permanganate Oxidation of 1-Methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline.—To a stirred solution of 220 mg. of 1 in 9 ml. of pyridine and 1 ml. of water was added 632 mg. of potassium permanganate. The resulting mixture was stirred at room temperature for 2 hr., then heated on the steam bath for 3 hr. The manganese dioxide was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in 5%

(6) R. Robinson and H. Suginome, *J. Chem. Soc.*, 304 (1932); T. Hoshiro and K. Tamura, *Ann.*, **500**, 42 (1932); T. Hoshiro and T. Kobayashi, *ibid.*, **516**, (1935); **520**, 11 (1935); J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.*, 3651 (1954).

(7) H. Plieninger and W. Müller, *Tetrahedron Letters*, No. **11**, 15 (1960).

(8) All melting points are corrected; microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and Berkeley Analytical Laboratories, Berkeley, Calif.

(9) A. R. Katritzky, *J. Chem. Soc.*, 2581 (1955).

sodium hydroxide solution and extracted with ether. The aqueous solution was acidified and extracted with ether. The ether solution was evaporated, and the residue was crystallized from aqueous ethanol to yield 13 mg. (15%) of benzoic identical with an authentic sample in melting point, mixture melting point, and ultraviolet spectrum.

Chromic Acid Oxidation of 1-Methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline.—To a solution of 210 mg. of 1-methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline (1) in 10 ml. of acetic acid was added dropwise a solution of 120 mg. of chromium trioxide in 0.5 ml. of water and 5 ml. of acetic acid. This was heated on steam bath for 2.5 hr. and concentrated to a volume of *ca.* 2 ml. under reduced pressure. The residue was diluted with 20 ml. of water, treated with potassium carbonate, and extracted with chloroform. Evaporation of the chloroform afforded 150 ml. of material which was chromatographed on Woelm neutral alumina, Grade I. Elution with 30 ml. of chloroform gave 81 mg. of the *N*-benzylimide of 2-methylquinoline-3,4-dicarboxylic acid, identical in all respects with an authentic sample. Continued elution with chloroform yielded 48 mg. of 1-methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline, identical with the starting material.

Acetic Anhydride Dehydration of 1-Methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline.—A solution of 130 mg. of 1-methyl-1-hydroxy-2-benzyl-3-oxopyrollo[3,4-*c*]quinoline and 3 ml. of acetic anhydride was heated under reflux for 3 hr. This mixture was diluted with 3 ml. of water, agitated for 30 min., and evaporated under reduced pressure. The residue was triturated with ethyl acetate and collected to afford 90 mg. (69%) of the anhydro compound **3**, m.p. 156–159°. The analytical sample melted at 163–164° after crystallization from ethanol then ether; ultraviolet absorption: λ_{max}^{EtOH} 250 mμ (ε 34,800), 296 (9500), 306 (10,000), 338 (6080), 349 (6340).

Anal. Calcd. for $C_{19}H_{14}ON_2$: C, 79.70, H, 4.83; N, 9.78. Found: C, 79.58; H, 4.98, N, 9.92.

The *N*-Benzylimide of 2-Methylquinoline-3,4-dicarboxylic Acid.—A mixture of 2.0 g. of 2-methylquinoline-3,4-dicarboxylic acid, m.p. 241–243°, prepared by the method of Pfitzinger,[10] 1.0 g. of benzylamine, and 6 ml. of 2,4,6-collidine was heated under reflux for 1 hr. The cooled mixture was diluted with water, and the precipitated imide was collected. After several crystallizations from ethyl acetate, there was obtained 1.20 g. (42%) of the *N*-benzylimide of 2-methylquinoline-3,4-dicarboxylic acid, m.p. 182–183°; ultraviolet absorption: λ_{max}^{EtOH} 255 mμ (ε 69,000), 350 (6080).

Anal. Calcd. for $C_{19}H_{14}O_2N_2$: C, 75.48; H, 4.66; N, 9.26. Found: C, 75.20; H, 4.69; N, 9.50.

The *N*-Benzylimide of Quinoline-3,4-dicarboxylic Acid.—To a solution of 584 mg. of the *N*-benzylimide of 2-methylquinoline-3,4-dicarboxylic acid in 17 ml. of acetic acid was added dropwise a solution of 600 mg. of chromium trioxide in 0.5 ml. of water and 10 ml. of acetic acid. The mixture was heated on a steam bath for 3 hr. then concentrated under reduced pressure to *ca.* 4 ml. The residue was diluted with water, treated with potassium carbonate, and extracted with chloroform. The chloroform was evaporated, and the residue was chromatographed on Woelm neutral alumina, Grade I. Elution with 60 ml. of chloroform gave 171 mg. (30%) of starting material, and continued elution with chloroform gave 72 mg. of the impure *N*-benzylimide of quinoline-3,4-dicarboxylic acid. The second fraction was rechromatographed on alumina. Elution with benzene gave 10 mg. of starting material, and elution with 50% benzene–chloroform gave 45 mg. (8%) of the *N*-benzylimide of quinoline-3,4-dicarboxylic acid, m.p. 154–155° after crystallization from 70% ethanol–water; ultraviolet absorption: λ_{max}^{EtOH} 255 mμ (ε 67,000), 350 (5900). The proton magnetic resonance spectrum in dimethyl sulfoxide showed a singlet at τ 0.70, ascribed to the proton adjacent to the nitrogen of the quinoline ring.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: C, 74.99; H, 4.19; N, 9.94. Found: C, 75.19; H, 4.24; N, 9.72.

(10) W. Pfitzinger, *J. prakt. Chem.*, [2] **56**, 283 (1897).

Preparation of *m*-Polyphenyls[1]

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3-Ethoxy-2-cyclohexenone has been used for the synthesis of 3-(3-bromophenyl)-2-cyclohexenone, 1,3-di(3-keto-1-cyclohexenyl)benzene, and 3,3′-di(3-keto-1-cyclohexenyl)biphenyl. These ketones were employed with the appropriate Grignard reagents for the preparation of the following linear *m*-polyphenyls: *m*-quarterphenyl, *m*-sexaphenyl, *m*-octaphenyl, 3,3″-dibromo-*m*-terphenyl, 3,3′′′′-dibromo-*m*-quinquephenyl, and 3,3′′′′′-dibromo-*m*-sexaphenyl. Infrared and ultraviolet spectra data are reported for the preceding polyphenyls.

The use of 3-ethoxy-2-cyclohexenone (I) has been shown by earlier work to be a very valuable reagent for the synthesis of *m*-diarylbenzenes.[4,5] This paper will present the preparation of 3-(3-bromophenyl)-2-cyclohexenone (II), 1,3-di(3-keto-1-cyclohexenyl)benzene (III), and 3,3′-di(3-keto-1-cyclohexenyl)biphenyl (IV) from 3-ethoxy-2-cyclohexenone (I) and subsequent reaction of these diketones to give linear *m*-polyphenyls.

The reaction of 3-ethoxy-2-cyclohexenone (I) and 3-bromophenylmagnesium bromide produced II while reaction of two moles of I with the di-Grignard reagent of 1,3-dibromobenzene afforded III. This latter reaction was accomplished in 90% yield. Earlier, Ruskie[6] had prepared III by the use of *n*-butyllithium as the metalating agent.

The synthesis of IV was achieved by the employment of two moles of I with the di-Grignard reagent of 3,3′-dibromobiphenyl.

3,3″-Dibromo-*m*-terphenyl (V) was produced by the sequence: (1) reaction of II and 3-bromophenylmagnesium bromide, (2) dehydration of the resulting alcohol, and (3) aromatization of the preceding diene. Compound V could not be obtained as a solid in our hands. Interestingly, 3-bromo-*m*-terphenyl,[6] which was prepared earlier in our laboratory, also was found to be a liquid at room temperature.

The diketone (III) was treated with two moles of 3-bromophenylmagnesium bromide to give 3,3′′′′-dibromo-*m*-quinquephenyl (VI). Compound VI was treated with an excess of *n*-butyllithium and, after hydrolysis, *m*-quinquephenyl was obtained. This in itself is not a proof of structure for VI, but it does aid in the proof of structure for the *m*-quinquephenyl skeleton moiety.

(1) This work was supported in part by U. S. Air Force contract AF 33(616)-5063.

(2) Du Pont Teaching Fellow, 1960–1961.

(3) Gillette–Harris Research Fellow, 1961–1962.

(4) G. F. Woods, F. T. Reed, T. E. Arthur, and H. J. Ezekiel, *J. Am. Chem. Soc.*, **73**, 3854 (1951).

(5) G. F. Woods, D. D. Centola, H. E. Ruskie, and C. D. Miller, *ibid.* **82**, 5227 (1960).

(6) Personal communications, H. Ruskie.