Experimental

Girard hydrazones were prepared as described previously.[4] Other materials were of reagent grade unless otherwise specified. Kinetic measurements were made polarographically at 25±0.1° as described previously with a Yokogawa Polarograph, type POL-11.[5] pH values were measured by a Tōadempa, model HM-5A, pH meter with a glass-saturated calomel electrode.

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5) *Idem*: J. Chem. Soc., **1964**, 3951.

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The Fischer Indole Synthesis with Formic Acid. I. A Convenient Synthesis of 4a-Ethyl-9-formyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole.

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Various procedures including thermal cyclizations are available for the Fischer indole synthesis.[1] Formic acid has been sometimes used as an effective catalyst for this reaction as well as acetic acid or propionic acid.[2]

It seems, however, not to be known in the literature that anhydrous (98~100%) formic acid has been used for indolization of 2-alkylcyclohexanone arylhydrazone (for instance, I). In this reaction with the other catalysts, there produces a mixture of indolenine and indole (as are exemplified by Ⅲ and Ⅳ, respectively), the relative quantities of which have been found to be dependent upon the catalyst used.[3,4]

In connection with the synthetic studies on aspidosperma alkaloids,[5] it became necessary for us to effect the smooth Fischer indolization of 2-substituted cyclohexanone arylhydrazone with the more predominant formation of indolenine rather than indole.

Thus, as a preliminary, a solution of the phenylhydrazone (I, 1 mole eq.), freshly prepared from 2-ethylcyclohexanone and without purification,[2a] in 98~100% formic acid (5 mole eq.) was refluxed for 45 min., during which time evolution of carbon dioxide was observed. The resulting mixture was separated into two portions, the neutral and the basic, in the usual manner. The neutral material was purified twice by chromatography on alumina and the elution with *n*-hexane-benzene (3:1) yielded a main fraction of pale red oil (63.7% yield), which was unexpectedly identified, by comparison of ultraviolet and infrared spectra, with the N-formylindoline (Ⅱ), the entitled compound, prepared from

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1*a*) B. Robinson: Chem. Rev., **63**, 373 (1963). *b*) A.H. Kelly, D.H. McLeod, J. Parrick: Can. J. Chem., **43**, 296 (1965).
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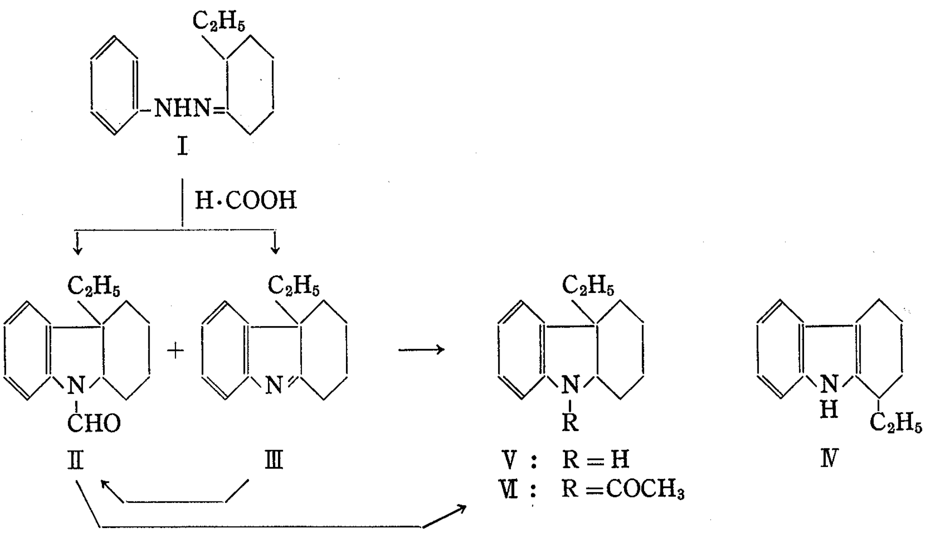

the indolenine (Ⅲ)[4,6] through lithium aluminum hydride reduction followed by formylation with formamide. The product (Ⅱ) was further derived to the corresponding indoline hydrochloride (Ⅴ·HCl, m.p. 193\~195°) and also N-acetylindoline (Ⅵ, m.p. 68.5\~69.5°). The hydrochloride (Ⅴ·HCl) was again identified with the specimen prepared from the indolenine (Ⅲ)[4] as above.

Meanwhile, the basic portion (3.3% yield) in the present synthesis (red brown oil, one spot on thin-layer chromatography over silica gel developed with *n*-hexane-benzene (3:1)) was identified with the indolenine (Ⅲ) prepared by the method of polyphosphate esters[4] through ultraviolet and infrared spectral comparisons and the mixed melting point test of the picrates, m.p. 147\~149° (lit.[6] 148\~150°). Although formation of a trace of the indole (Ⅳ) was deduced on checking an ultraviolet spectrum of the crude product in some repeated experiments, it was neither isolated nor recognized on the above chromatography.

Moreover, when refluxed with formic acid, it was found that the indolenine (Ⅲ) yielded the N-formylindoline (Ⅱ) with the simultaneous evolution of carbon dioxide. Thus, the present procedure for the predominant formation of the N-formylindoline (Ⅱ) in the Fischer synthesis has been successfully applied to the synthesis of aspidosperma alkaloids.[5] The mechanism of this reaction and the stereochemistry at B-C ring juncture of the present product (Ⅱ) are now being investigated.

Experimental

The Fischer Indolization of 2-Ethylcyclohexanone——A solution of 1 g. of 2-ethylcyclohexanone and 0.9 g. of phenylhydrazine in 20 ml. of EtOH was refluxed for 15 min. The ethanol was evaporated, to which residue dry benzene was added, and the benzene was evaporated *in vacuo* to leave 1.78 g. of the crude phenylhydrazone (I), that was dissolved in 1.84 g. of the freshly distilled 98\~100% formic acid, when a mild exothermic reaction occurred. The whole solution was gently refluxed for 45 min., during which time evolution of carbon dioxide was observed. On cooling, ethyl acetate was added, the whole mixture was made alkaline with satd. $NaHCO_3$ and extracted. The acetate layer was separated and the extract was washed with 10% HCl, water and dried over Na_2SO_4. The solvent was evaporated to afford 1.805 g. of a red brown oil, which was chromatographed on alumina. Elution with *n*-hexane-benzene (3:1) gave 1.392 g. (75.9%) of a pale red brown oil, which indicated two spots on thin-layer chromatography (TLC), over silica gel developed with benzene-ethyl acetate (4:1) indicating that the substance was contaminated with a trace of impure material.

Thus, rechromatography was carried out and a fraction eluted by *n*-hexane-benzene (3:1) afforded 1.168 g. (63.7%) of the N-formylindoline (Ⅱ) as a pale red brown oil, indicating one spot on TLC over silica gel

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[6] B. Witkop, J.B. Patrick: J. Am. Chem. Soc., **73**, 1558 (1951).

depeloped with benzene-ethyl acetate (4:1). IR ν_{max}^{film} cm^{-1} : 1670 (C=O), 1595 (arom.). UV λ_{max}^{EtOH} mμ : 254, 284, 289.

The HCl layer, after separation of the acetate layer, was made alkaline with $NaHCO_3$, the separated oil was extracted with ethyl acetate, washed with water, and dried over Na_2SO_4. The solvent was removed to leave 52 mg. (3.3%) of a red brown oil, whose IR, UV, Rf values on TLC over silica gel developed with *n*-hexane-benzene (3:1) and picrate (m.p. and mixed m.p. 147~149°) were identical with those of an authentic sample.[4,6]

Characterization of 4a-Ethyl-9-formyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole (II). 4a-Ethyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole Hydrochloride (V·HCl)——a) The foregoing N-formylindoline (II, 600 mg.) was refluxed with 15% HCl (25 ml.) for 2 hr. Worked up in the usual manner, there was obtained the base (V, 470 mg.) in 90% yield as an oil which was dissolved in 10% HCl, and water was evaporated to dryness. The remaining hydrochloride (V·HCl) was recrystallized from alcohol-ether to afford colorless needles, m.p. 193~195°. *Anal.* Calcd. for $C_{14}H_{20}NCl$: C, 70.72; H, 8.47; N, 5.93. Found: C, 70.95; H, 8.66; N, 6.03.

b) The indolenine (0.2 g.) which was prepared from 2-ethylcyclohexanone with polyphosphate esters,[4] was dissolved in tetrahydrofuran, to which was added a solution of lithium aluminum hydride (0.08 g.) in the same solvent. The whole mixture was stirred at room temperature for 2 hr. Tetrahydrofuran containing water enough to decompose the excess of lithium aluminum hydride, was added, the precipitate was filtered off, and the filtrate was dried over Na_2SO_4. Removal of the solvent gave 174 mg. of the indoline (V) which was derived to the hydrochloride (V·HCl), m.p. 193~195°. This hydrochloride was identified with the specimen prepared by the a) method from the product (II) in the present Fischer indole synthesis.

4a-Ethyl-9-acetyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole (VI) [from the Corresponding Indoline (V) prepared by the a) Method]——A mixture of the above free base of indoline (V, 240 mg.), acetic anhydride (2 ml.) and several drops of acetic acid was refluxed for 1 hr. On cooling, water was added to decompose acetic anhydride, the mixture was extracted with $CHCl_3$, the $CHCl_3$ layer was separated, washed with water, and dried over Na_2SO_4. The solvent was removed to leave the crude N-acetylindoline (VI), which was recrystallized from *n*-hexane to afford 141 mg. (50%) of colorless needles, m.p. 68.5~69.5°. *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 79.38; H, 8.70; N, 5.76. Found: C, 78.93; H, 8.65; N, 6.26.

4a-Ethyl-9-formyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole (II) [from the Corresponding Indoline (V) prepared by the b) Method——A mixture of the indoline (V, 500 mg.) and formamide (222 mg.) was heated at 150~160° for 7 hr., during which time evolution of ammonia was observed on wet pH test papers.

On cooling, water was added to separate an oil, which was extracted with benzene. The benzene extract was washed with water to remove the unreacted formamide and dried over Na_2SO_4. The solvent was evaporated to leave an oil, indicating two spots on TLC over silica gel developed with benzene-ethyl acetate (4:1), which was purified on chromatography on alumina in the same way as the above procedure for purification of II, to yield 216 mg. (47%) of the N-formylindoline (II) as a pale red brown oil. This was identical with the neutral product of the Fischer indole synthesis of 2-ethylcyclohexanone with formic acid by comparison of their UV and IR spectral data, and the behavior on TLC over silica gel developed with benzene-ethyl acetate (4:1).

4a-Ethyl-9-formyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole (II) by Reduction of the Indolenine (III) with Formic Acid——A solution of the indolenine (III, 160 mg.) in 98~100% formic acid (184 mg.) was refluxed for 30 min., during which time evolution of carbon dioxide was observed.

On cooling, ethyl acetate was added, which was poured onto ice-water and made alkaline with potassium carbonate. The whole mixture was extracted with ethyl acetate, the acetate extract was washed with 10% HCl, water, and dried over Na_2SO_4.

Removal of the solvent gave 136 mg. (64%) of the N-formyl indoline (II), which was purified by chromatography on alumina. The product (a pale red brown oil) was identified with the specimen (II) prepared by the present Fischer synthesis with formic acid.

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