Preparations and Reactions of 6-Oxo-5,6,7,8-tetrahydroquinoline and 5-Oxo-4,5,6,7-tetrahydroindole

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Previously we reported that 6-methoxyquinoline and 5-methoxyindole could be reduced to dihydro derivatives (*e.g.*, **1** and **9a**) by lithium and methanol in ammonia (2). These dihydro derivatives have vinyl ether functions which, by analogy to earlier investigations (3), seemed suitable for hydrolysis to the corresponding ketones. In this note we describe such hydrolyses, and the various transformations that could be effected with the resulting ketones.

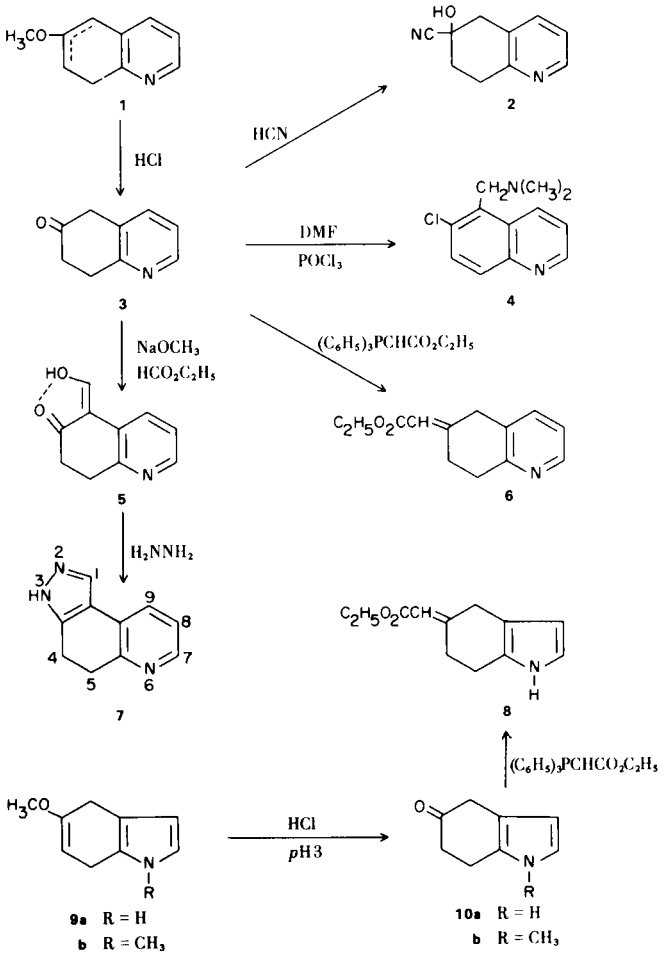
Thus the mixture of isomeric 5,8- and 7,8-dihydro-6-methoxyquinolines (**1**), obtained from reduction of 6-methoxyquinoline, was easily converted into ketone **3** by aqueous hydrochloric acid. This ketone had the order of reactivity expected for a cyclohexanone, since it readily gave a cyanohydrin (**2**) and an oxime. It formed carbethoxymethylene derivative **6** when heated with (carbethoxymethylene) triphenylphosphorane, a Wittig reagent known to react at good rates only with relatively active carbonyl groups (4).

The two methylene groups adjacent to the carbonyl group in **3** are in different environments from each other. Since the 5-methylene group is in conjugation with the pyridine ring, we expected that it would undergo base-catalyzed condensations in preference to the 7-methylene group. Consistent with this expectation was the isolation of only the 5-hydroxymethylene derivative **5** when **3** was treated with ethyl formate and sodium methoxide. Unfortunately the yield of **5** was only 11%.

Condensation of **5** with hydrazine gave 4,5-dihydro-3*H*-pyrazolo[5,4-*h*]quinoline (**7**), a crystalline, heat-sensitive solid. It represents a new ring system.

Vilsmeier-Haack formylation of **3** gave a tarry mixture from which a small amount of 6-chloro-5-(dimethylaminomethyl)quinoline (**4**) was isolated. We previously observed examples of this unusual type of transformation with 4-oxotetrahydroindoles (5).

Hydrolysis of the vinyl ether function in 4,7-dihydro-5-methoxyindole (**9a**) presented difficulty because the pyrrole ring in this compound is unstable toward acid. However, conditions for this hydrolysis (50% aqueous ethanol at apparent *p*H 3) were found and the resulting ketone **10a** was obtained in 76% yield. The 1-methyl homolog **10b** was also prepared from the corresponding vinyl ether **9b**. We were unable to find conditions suitable for the conversion of the tryptamine analog (2) of **9a** to the related ketone.



Although ketones **10a** and **10b** appeared to be attractive intermediates for the preparation of new indole derivatives, they proved so unstable that little could be done with them. The only useful transformation we found was the formation of carbethoxymethylene derivative **8** from **10a**

and the appropriate Wittig reagent. It is interesting that the relatively acidic hydrogen ($pK_a \approx 17$) of **10a** did not prevent this reaction. There is a significant difference in stability between 5-oxo-4,5,6,7-tetrahydroindoles such as **10a** and the corresponding 4-oxo-4,5,6,7-tetrahydroindoles in which the carbonyl group is conjugated with the pyrrole ring. The latter-type compounds not only undergo successfully certain base-catalyzed reactions (6), but they are stable to strong acids and may be substituted by a variety of electrophiles (5).

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are corrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer. Infrared spectra were determined neat or in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were determined in the indicated solvents with tetramethylsilane as internal standard on a Varian A-60 spectrometer. Solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure on a rotary evaporator.

6-Hydroxy-5,6,7,8-tetrahydroquinoline-6-carbonitrile (**2**).

A solution of 2.94 g. of 6-oxo-5,6,7,8-tetrahydroquinoline (**3**) in 20 ml. of 1*N* hydrochloric acid was treated dropwise with a solution of 980 mg. of sodium cyanide in 5 ml. of water. After 1 hour the resulting oily mixture was cooled at 5°, whereupon the product slowly solidified. It was washed with water, dried in air, and recrystallized from ethyl acetate containing a small proportion of ethanol. This procedure gave 1.84 g. (53%) of **2** as white prisms, m.p. 156-157.5°; λ max 268 (ε, 4200), 275 nm (3100); ν 3.3 (OH), 4.5 μ (C≡N) w.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.41; H, 5.57; N, 15.82.

6-Oxo-5,6,7,8-tetrahydroquinoline (**3**).

A mixture of 11.6 g. of the isomers 5,8-dihydro-6-methoxyquinoline and 7,8-dihydro-6-methoxyquinoline (**1**) (2) was dissolved in 1 l. of 0.33 *N* hydrochloric acid. After 5 hours, the solution was basified with 5*N* sodium hydroxide and extracted two times with dichloromethane. The combined extracts were dried and concentrated, and the residual oil was distilled through a short column packed with glass helices. This distillation gave **3** as colorless liquid, b.p. 138° at 8 mm, (yield 2.63 g., 25%); λ max 268 (ε, 4300), 275 nm (3100); ν 5.80 μ (C=O); nmr (perdeuteriomethanol) δ 8.33 (dd, J = 6 Hz, J = 6 Hz, 2-hydrogen), 7.68 (dd, J = 6 Hz, J = 2 Hz, 4-hydrogen), 7.35 (dd, J = 6 Hz, J = 6 Hz, 3-hydrogen), 3.3-2.5 (m, 6, aliphatic hydrogens). Upon addition of sodium methoxide four of the aliphatic protons underwent exchange for deuterium.

Anal. Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.30; H, 6.53; N, 9.23.

6-Oxo-5,6,7,8-tetrahydroquinoline Oxime.

To a solution of 6.0 g. of hydroxylamine hydrochloride in 36 ml. of water was added 24 ml. of 10% sodium hydroxide and 2.4 g. of **3**. The mixture was heated on a steam bath for 30 minutes and then cooled overnight at 50°, during which time the oxime crystallized. After drying in air this oxime (2.53 g., 95%) was recrystallized from aqueous ethanol and from ethyl acetate. It then had m.p. 143-154° (probably a mixture of *syn* and *anti* forms); λ max 268 (ε, 4900), 271 nm (4200) sh; ν 3.15-3.6 μ (NH).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.52; H, 6.66; N, 17.43.

6-Chloro-5-(dimethylaminomethyl)quinoline Dihydrochloride (**4**).

To 30 ml. of *N,N*-dimethylformamide, cooled in an ice bath, was added dropwise 4.59 g. of phosphorus oxychloride. The resulting solution was cooled and treated with 4.43 g. of **3** in 30 ml. of *N,N*-dimethylformamide. The mixture was then heated to 70° for 2 hours, cooled, poured onto ice, brought to *p*H 10 with 20% sodium hydroxide and extracted two times with dichloromethane. The combined extracts were washed with water, dried, and concentrated to a dark liquid which was purified by adsorption chromatography on magnesia-silica gel with dichloromethane as solvent. Concentration of the eluate gave a liquid which was converted into its crystalline dihydrochloride salt by dry hydrogen chloride gas in ether. Two recrystallizations of this salt from methanol-ethanol gave a low yield of **4** as white plates, m.p. 252-255°; λ max 212 (ε, 57,000), 246 (5000), 299 (3500), 306 (2600), 313 nm (5000); ν 2.8-4.0 ($\overset{+}{N}H$); nmr (deuterium oxide) δ 9.34 (d, J = 5.5 Hz, 2-hydrogen), 9.26 (d, J = 8.7 Hz, 4-hydrogen), 8.40 (d, J = 9 Hz, 8-hydrogen), 8.31 (d, J = 9 Hz, 9-hydrogen), 8.23 (dd, J = 8.7, 5.5 Hz, 3-hydrogen), 5.16 (d, 2, NCH_2-Ar), 3.05 [s, 6, $N(CH_3)_2$].

Anal. Calcd. for $C_{12}H_{13}ClN_2 \cdot 2\,HCl$: C, 49.08; H, 5.15; N, 9.54. Found: C, 48.57; H, 5.23; N, 9.73.

6-Carbethoxymethylene-5,6,7,8-tetrahydroquinoline (**6**).

A mixture of 1.47 g. of **3**, 6.96 g. of (carbethoxymethylene)-triphenylphosphorane, and 50 ml. of toluene was heated at reflux temperature for 24 hours, cooled, and filtered. The filtrate was concentrated and the residue was treated with dichloromethane and 1*N* hydrochloric acid. The acidic layer was washed with dichloromethane, basified (*p*H 11) with sodium hydroxide and extracted with dichloromethane. This extract was dried and concentrated and the residual oil was triturated with ether, whereupon crude product (1.45 g.) crystallized. This product was purified by liquid-liquid partition chromatography on diatomaceous earth with a heptane-methyl cellosolve system and recording spectrophotometer set at 270 nm (7). Concentration of eluate from the major peak afforded **6** as a colorless liquid; λ max 267 (ε, 4100), 280 nm (3500) sh; ν 5.76 μ (COOR).

For analysis **6** was converted into its picrate, which had m.p. 139-142° after recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{15}NO_2 \cdot C_6H_3N_3O_7$: C, 51.12; H, 4.06; N, 12.55. Found: C, 51.49; H, 4.01; N, 12.74.

5-Hydroxymethylene-6-oxo-5,6,7,8-tetrahydroquinoline (**5**).

To a stirred ice-cooled suspension of 6.48 g. of sodium methoxide in 60 ml. of benzene under nitrogen was added a solution of 4.41 g. of **3** and 8.89 g. of ethyl formate in 60 ml. of benzene. The mixture was stirred at room temperature for 17 hours and then treated with 120 ml. of 1*N* sodium hydroxide. The aqueous phase was washed with dichloromethane and brought to *p*H 4.5 with hydrochloric acid, whereupon a yellow by-product separated. The mixture was filtered and the filtrate was extracted with dichloromethane. This extract was dried and concentrated, and the residual solid was crystallized from ethanol. This procedure gave 582 mg. (11%) of **5** as pale yellow solid, m.p. 208-209°; λ max 247 (ε, 8300), 304 nm (12,000); ν 2.8-5.4 (H-bonded OH), 6.15 μ (C=O, chelated); nmr (DMSO-d_6) δ 7.78 (s, ),

7.61 (dd, J = 8 Hz, J = 2 Hz, 2-hydrogen), 7.38 (dd, J = 6 Hz, J = 2 Hz, 4-hydrogen), 6.43 (dd, J = 8 Hz, J = 6 Hz, 3-hydrogen), 2.20 (d, 2, J = 8 Hz, 8-hydrogens), 1.73 (d, 2, J = 8 Hz, 7-hydrogens).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.70; H, 5.31; N, 7.81.

4,5-Dihydro-3*H*-pyrazolo[5,4-*h*]quinoline (**7**).

A mixture of 175 mg. of **5**, 50 mg. (1 mmole) of hydrazine hydrate, and 5 ml. of tetrahydrofuran was warmed on a steam bath for 5 minutes, kept at room temperature for 1 hour and concentrated. Trituration of the residue gave a pale yellow solid that showed a single spot on tlc (blue fluorescence) and had no carbonyl group in the ir. Two recrystallizations from dichloromethane-hexane gave 127 mg. (74%) of **7** as a yellow solid m.p. 157-159°; λ max 262 (ε, 11,000), 294 nm (7200); ν 3.3-3.5 μ (NH).

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.09; H, 5.28; N, 24.30.

Treatment of **7** with excess hydrochloric acid in ether-methanol gave an orange hydrochloride, m.p. 275-279° dec. after recrystallization from ether-methanol; nmr (deuterium oxide) δ 8.50 (m, 2,7- and 9-hydrogens), 8.23 (s, 1-hydrogen), 7.96 (dd, J = 9, 5.5 Hz, 8-hydrogen), 3.5-3.0 (m, 4, CH_2CH_2).

5-Carbethoxymethylene-4,5,6,7-tetrahydroindole (**8**).

This compound was prepared by the procedure described for **6**. From 1.35 g. of 5-oxo-4,5,6,7-tetrahydroindole (**10a**) was obtained, upon concentration of the third peak from the liquid-liquid partition chromatographic separation (heptane-methanol system monitored at 240 nm) (**7**), a nearly white solid which had m.p. 65-66.5° (160 mg., 8%) after recrystallization from dichloromethane-hexane; λ max 218 nm (ε, 22,000); ν 3.0 (NH), 5.85 μ (CO_2R); nmr (deuteriochloroform) δ 7.91 (broad, NH), 6.75 (dd, J = 4.5, 2.5 Hz, 2-hydrogen), 5.95 (dd, J = 4.5, 2.5, Hz, 3-hydrogen), 5.85 (s, COC*H*=C), 4.15 (q, 2, J = 8 Hz, CH_2CH_3), 3.33 (s, 2, 4-hydrogens), 3.20 (t, 2, J = 8 Hz, 7-hydrogens), 2.71 (t, 2, J = 9 Hz, $C_{(6)}$ protons, 1.25 (t, s, J = 8 Hz, CH_2CH_3).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.97; H, 7.46; N, 6.83.

5-Oxo-4,5,6,7-tetrahydroindole (**10a**).

A solution of 400 mg. of 4,7-dihydro-5-methoxyindole (**9a**) (2) in 8 ml. of 50% aqueous ethanol was treated with 2% sulfuric acid until an apparent *p*H of 3.0 was obtained. After 30 minutes it was diluted with 20 ml. of water, neutralized with excess sodium bicarbonate and extracted with two 15 ml. portions of ether. The combined extracts were dried and concentrated to a light tan crystalline solid (305 mg., 76%). Two recrystallizations from ether gave **10a** as crystals with m.p. 136-138°; λ max only broad tailing 200-250 nm; ν 3.05 (NH), 5.9 μ (C=O); nmr (deuteriochloroform) δ 8.08 (broad, NH), 6.70 (dd, J = 4.5, 2.5 Hz, 2-hydrogen), 6.00 (dd, J = 4.5, 2.5 Hz, 3-hydrogen), 3.41 (s, 2,4-hydrogens), 3.2-2.5 (m, 4, CH_2CH_2).

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.34; H, 6.88; N, 10.30.

1-Methyl-5-oxo-4,5,6,7-tetrahydroindole (**10b**).

This compound was prepared by the procedure described for **10a**, except that the *p*H was brought to 2.7 and the solution was kept under nitrogen for 3 hours. Concentration of the ether extract gave an oil which was purified by a simple distillation. From 2.64 g. of 4,7-dihydro-5-methoxy-1-methylindole (**9b**) (2) was obtained 1.73 g. (71%) of colorless oil, b.p. 86° @ 4 mm which formed **10b** as a solid, m.p. 37-41° upon storage; λ max broad tailing 200-250 nm; ν 5.83 μ (C=O); nmr (deuteriochloroform) δ 6.53 (d, J = 4.5 Hz, 2-hydrogen), 5.91 (d, J = 4.5 Hz, 3-hydrogen), 3.68 (s, 3, CH_3), 3.40 (s, 2, 4-hydrogens), 3.05-250 (m, 4, CH_2CH_2).

Upon treatment with sodium methoxide in perdeuteriomethanol, the 4- and 6-hydrogens were exchanged, leaving only a two-hydrogen singlet at 2.93 ppm for the 7-hydrogens in the aliphatic region.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.16; H, 7.11; N, 9.26.

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