A FACILE SYNTHESIS OF 4-OXO-4,5,6,7-TETRAHYDROINDOLES

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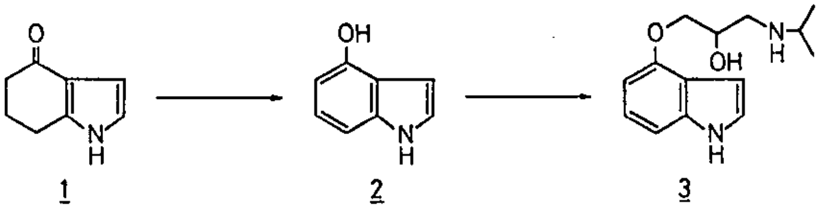
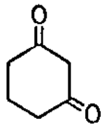
Abstract—— Condensation of 1,3-cyclohexanedione with chloroacetaldehyde followed by dehydration gave 4-oxo-4,5,6,7-tetrahydrobenzofuran in a good yield. The tetrahydrobenzofuran was quantitatively converted into 4-oxo-4,5,6,7-tetrahydroindoles.

The synthon using 4-oxo-4,5,6,7-tetrahydroindole (1) as a key intermediate possesses a potentiality applicable for the synthesis of a variety of 4-substituted indoles.[1] A successful representative is the synthesis of an arrhythmic agent, pindolol (3), which is practically prepared from the tetrahydroindole 1 through 4-hydroxyindole (2).[2]

The indole 1 has been synthesized by condensation of 1,3-cyclohexanedione (4) with aminoacetaldehyde diethyl acetal[3] or with oxoiminoglyoxal[4] with low efficiency. The more practical method known so far is transformation of the endocyclic oxygen atom to the nitrogen in 4-oxo-4,5,6,7-tetrahydrobenzofuran skeleton. To attain the ammonolysis of the furan, activation of the furan ring has been thought to be required. Stetter synthesized a furan carboxylic acid 5 as a precursor of 1 from the dione 4 and expensive bromopyruvic acid ester.[5] On the other hand, Torii electrolyzed 4 together with a large excess of ethyl vinyl ether to yield an ethoxyhexahydrobenzofuran 6, which was transformed into 1 in a moderate total yield.[6]





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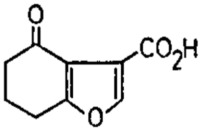

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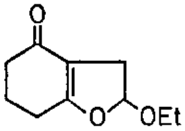

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We report here that 4-oxo-4,5,6,7-tetrahydrobenzofuran (9) is, without any special activation, quantitatively converted into the indole 1, and that the furan 9 is conveniently sysnthesized by the condensation of the dione 4 with inexpensive chloroacetaldehyde (7).[7]

The condensation of 4 with 7 proceeded in the presence of a base in water to yield a hydroxyfuran 8,[8] which was dehydrated into the desired furan 9 thermally or by acid catalysis in a quantitative yield. The furan 9 was preparatively obtained without isolation of 8 in the procedure described above. The reaction of 4 with 7 was significantly affected by the acidity of the aqueous solution regardless of the base used. As shown in the figure, the condensation must be carried out under nearly neutral conditions to attain the optimum yield of 9. The yield of 9 was further improved by devising addition of the reagents to the reaction system as described in the experimental section.

The NMR spectrum of the aldehyde 7 in aqueous solution displayed no peak due to an aldehyde proton. This fact showed that the aldehyde 7 exists as no monomeric but as strongly hydrated or polymeric form. Therefore, the balance between the rate of the desired condensation affording 8 and the dissociation rate forming monomeric 7 might significantly affect the efficiency of the reaction. It is enough possible that the acidity of the reaction system influences the balance described above. In fact, under strong acidic or basic conditions, the reaction of 4 with 7 gave, in addition to 8, a considerable amount of unidentified 2:1 adducts, of which mass spectrum showed the parent peak at m/z 248 (2 x 4 + 7 - HCl - H_2O).

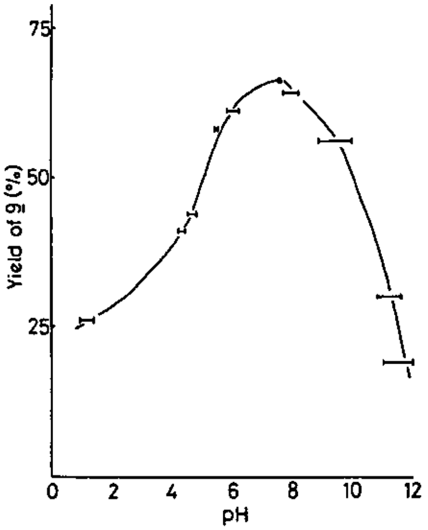
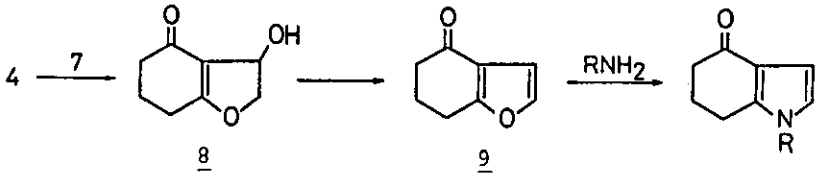


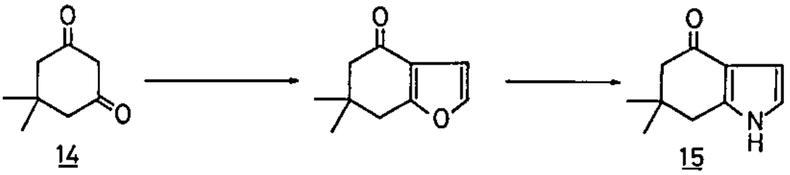
Figure The pH dependence of condensation of 4 with 7



1; R=H	96%
10; R=CH_3	92%
11; R=C_2H_5	86%
12; R=$CH_2CH{=}CH_2$	93%
13; R=$C_6H_5CH_2$	96%

Next, we examined the transformation of the furan 9 into the indole 1. When the furan 9 was heated with ammonia in aqueous ethanol at 150°C, the indole 1 was produced in a 96% yield. In this ammonolysis, aqueous ethanol gave better results than absolute ethanol or methanol as the solvent used. As shown in the scheme, similar reaction of 9 with primary amines, methylamine, ethylamine, allylamine, and benzylamine, afforded the corresponding 1-substituted indoles, 10, 11, 12, and 13, respectively.[9]

Substituted 1,3-dione such as dimedone 14 also gave the corresponding indole 15 by the use of the reaction sequence presented here. Typical procedures to prepare the 4-oxo-4,5,6,7-tetrahydroindoles are described in the following experimental section.



EXPERIMENTAL

Condensation of 1,3-cyclohexanedione (4) with chloroacetaldehyde (7) Chloroacetaldehyde (7) (40% aqueous solution, 2 mL) was added into an aqueous solution of 1,3-cyclohexanedione (4) (1.12 g), of which acidity was controlled by addition of 2N-NaOH. After stirring the reaction mixture for 2 h at room temperature, ethyl acetate (10 mL) and conc. H_2SO_4 (0.5-1 mL) were added. The organic layer was analyzed by GLC(internal standard:p-dimethoxybenzene, column: SE30, 1.2 m, temperature: 130°C). The results were shown in the figure.

4-Oxo-4,5,6,7-tetrahydrobenzofuran (9) The aldehyde 7 (40% solution, 20 mL) and $NaHCO_3$ (10.0 g) was added into water (80 mL) at 0-5°C. To this mixture, an aqueous solution of 1,3-cyclohexanedione (4) (11.2 g/90 mL) was added drop by drop (0.4 mL/min) with stirring. After the addition, the reaction mixture was further stirred overnight at room temperature. Through the reaction, the acidity of the solution was within pH 6-9. To the mixture ethyl acetate (ca. 100 mL) was added, and the resulting solution was acidified (pH 1) and was stirred for 1h. The organic layer was separated, washed with aqueous K_2CO_3 solution, dried over $MgSO_4$, and concentrated. The residue was distilled to give 4-oxo-4,5,6,7-tetrahydrobenzofuran (9) (10.3g, 76% yield) as a colorless oil (bp 66°C/1 torr)(Lit.[7] bp 115-118°C/16 torr).

4-Oxo-4,5,6,7-tetrahydroindole (1) A solution of the furan (9) (1.0 g) and aqueous ammonia (29%, 7 mL) in ethanol (3 mL) was heated in a sealed tube at 150°C (bath temperature) for 12 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel (Wako C-200). Elution with acetone-ethyl acetate gave 4-oxo-4,5,6,7-tetrahydroindole (1) (950 mg, 96% yield) as colorless crystals, which was recrystallized from water to yield colorless leaflets, mp 188 - 190°C (lit.[5a] mp 188 - 190°C). NMR (in acetone-d_6): δ 1.90-2.48 (m,4H), 2.82 (t,J=7.0Hz,2H), 6.37 and 6.74 (two t,J=2.5Hz,2H), and 10.3 (m,1H)ppm. IR (KBr): 1620cm^{-1}. Mass (m/z,%): 135(M^+,83), 107 (82), and 79 (100).

1-Benzyl-4-oxo-4,5,6,7-tetrahydroindole (13) A solution of the furan 9 (850 mg) and benzylamine (2.00 g) in 20% aqueous ethanol (5 mL) was heated in a sealed tube at 145-150°C for 12 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$, concentrated, and chromatographed on silica gel. Elution with CH_2Cl_2-ethyl acetate (10:1) afforded 1-benzyl-4-oxo-4,5,6,7-tetrahydroindole (13) (1.21 g, 96% yield) as colorless needles (from toluene) melted at 80-81.3 °C (Lit.[1] mp 80-81.5°C). NMR (in $CDCl_3$): δ 1.84-2.36 (m,4H), 2.55 (t,J=6.5Hz,2H), 4.98 (s,2H), 6.35 and 6.46 (two d, J=3Hz,2H), and 6.88-7.34(m,5H)ppm. IR (KBr): 1640cm^{-1}. Mass (m/z,%): 225 (M^+,53), 197 (43), 91 (100), and 65 (20).

REFERENCES AND NOTES

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8. Colorless granules (from ether) melted at 119-120°C (Lit.[7] mp 120-121°C). NMR (in $CDCl_3$): δ 1.95-2.20 (m,2H), 2.33-2.60 (m,4H), 3.62 (broad s, 1H), 4.51 (q_{AB} of d, J_{AB}=11Hz,J=9 and 4Hz,2H), and 5.37 (d of d, J=9 and 4Hz,1H)ppm.
9. 10: mp 85-86°C. 11: oil. 12: mp 77.0-77.3°C.

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