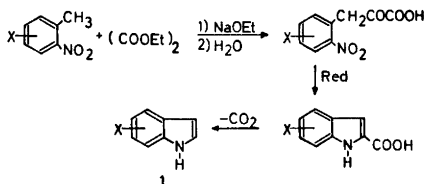


New Syntheses of Substituted Indoles

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A number of syntheses of indoles are recorded.¹ Few of these, however, are suitable for the synthesis of indoles substituted in the benzene ring and unsubstituted in the pyrrole ring (e.g. 1). The Reissert synthesis² is one of the more used methods for the preparation of this type of indole, and has been applied in the case of number of substituted indoles.^{3,4}

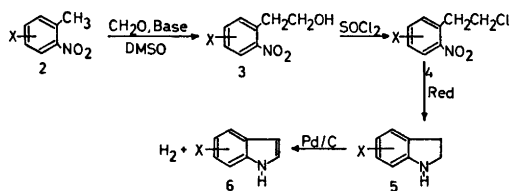


Although the yields are high for the first two steps, the decarboxylation in the last step gives highly varying yields.³ A new synthesis for indoles of the type 1 could therefore be useful.

Some time ago, the addition of substituted and unsubstituted *o*- and *p*-nitrotoluenes to various aldehydes was reported.⁵ The products (3) from the addition of *o*-nitrotoluenes (2) to formaldehyde were considered as potential starting materials for the synthesis of indoles as they contained a chain of two carbon atoms in the *ortho* position to a nitrogen atom. One possible way to the indoles would be *via* the 2,3-dihydroindoles (5). Ferber⁶ obtained dihydroindole itself (5, X=H) by reduction and cyclization of 2-(*o*-nitrophenyl)ethyl chloride (4, X=H) prepared by nitration of 2-phenylethyl chloride.

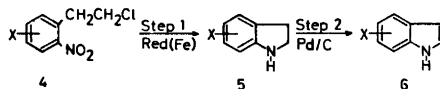
Chlorination with thionyl chloride of 2-(*o*-nitrophenyl)ethanol obtained from *o*-nitrotoluene and formaldehyde gave 2-(*o*-nitrophenyl)ethyl chloride (4, X=H) in 80% yield. Reduction of this compound by iron turnings activated by hydrochloric acid in aqueous suspension gave 2,3-dihydroindole (5, X=H) which was isolated by steam distillation (yield 85%). The dehydrogenation of dihydroindole to indole was performed with palladium on carbon in refluxing toluene (yield 93%). Volumetric experiments showed that 1 mol of hydrogen gas was evolved in the course of this reaction.

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After success in the synthesis of indole itself, the reaction sequence was tried for some substituted indoles. The results are given in Table 1. The conditions are not optimized and the results might be improved by using bromination instead of chlorination of the alcohol 3. In some cases, catalytic hydrogenation may be of advantage instead of the reduction by iron turnings.

Table 1. Synthesis of substituted indoles from *o*-nitrotoluenes.

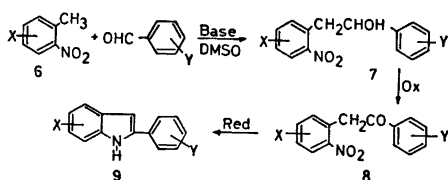


X (pos. in 4)	Yield, Step 1, %	Yield, Step 2 ^a , %
H	85	93
4-Cl	55	52 ^b
6-Cl	71	73 (m.p. 84–86°) ^c
4-NO ₂	59	64 (m.p. 105–107°) ^d

^a Products were identified by comparison of IR, GLC, and m.p. (for crystalline compounds) with authentic samples. Products containing halogens gave satisfactory halogen analyses. ^b GLC showed the product to be 96% pure and to contain 3% indole. ^c M.p. lit.³ 86–87°. ^d The products were 4-aminodihydroindole and 4-aminoindole, m.p. 4-aminoindole lit.⁴ 108°.

This convenient preparation of dihydroindole itself also facilitates the synthesis of indoles substituted in the 5- or 7-positions. Terentév *et al.*⁷ have synthesized such indoles by substitution of dihydroindole followed by dehydrogenation. The limitation of our procedure with respect to the preparation of 5- or 7-substituted indoles lies in the fact that the intermediate nitrotoluenes substituted at position 3 or 5 are not readily available.

When *o*-nitrotoluenes are added to arylaldehydes, 2-arylandoles (9) may be synthesized by oxidation of the alcohols 7 followed by reduction of the ketones 8:



o-Nitrotoluene and benzaldehyde gave 1-phenyl-2-(*o*-nitrophenyl)ethanol (7, X = Y = H) which was oxidized by concentrated nitric acid in the presence of chloroform. *o*-Nitrobenzyl phenyl ketone (8, X = Y = H) was obtained in 98 % yield (m.p. 75–77°, IR (KBr): 3100, 2910, 1690, 1620, 1600, 1580, 1520, 1450, 1410, 1360, 1290, 1210, 1005, 995, 790, 730, 700, 690, 675 cm⁻¹).

Catalytic reduction of 8 gave 2-phenylindole in 85 % yield (m.p. 187–188°, lit.⁸ 186°).

Our results thus show two useful routes to substituted indoles; one to indoles substituted in the benzene ring and unsubstituted in the pyrrol ring, and one to indoles with an aryl group in the 2-position.

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1. Julian, P. L., Meyer, E. W. and Printy, H. C. In Elderfield, R. C., Ed., *Heterocyclic Compounds*, Wiley, New York 1952, Vol. 3.
2. Reissert, A. *Ber. Deut. Chem. Ges.* 30 (1897) 1030.
3. Rydon, H. N. and Tweddle, J. C. *J. Chem. Soc.* (1955) 3499.
4. Plieninger, H. *Chem. Ber.* 88 (1955) 370.
5. Bakke, J. *Acta Chem. Scand.* 21 (1967) 1967.
6. Ferber, E. *Ber. Deut. Chem. Ges.* 62 (1929) 183.
7. Terentév, A. P., Preobrazhenskaya, M. N., Bobkov, A. S. and Sorokina, G. M. *Zh. Obshch. Khim.* 29 (1959) 2541.
8. Fischer, E. and Schmitt, T. *Ber. Deut. Chem. Ges.* 21 (1888) 1071.

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The Conformation of a *gem*-Dimethyl-substituted Cycloheptene

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In a previous paper¹ the synthesis of a cycloheptene derivative, 2-carboxy-3,3,6,6-tetramethyl-cycloheptene is described. Variable-temperature NMR-spectra are now obtained of this compound, with a coalescence temperature as high as –40° in 100 MHz NMR.

In Fig. 1 the ¹H NMR-spectra of 2-carboxy-3,3,6,6-tetramethyl-cycloheptene in CDCl₃ at 35°, –41°, and –66° and in CHFCl₂ at –85° are shown.

The absorption for the *gem*-dimethyl protons at lowest field changes gradually into two sharp lines at low temperature, the other methyl signal is broad, but is not resolved at –85°C. The difference in chemical shift between the two methylene protons alpha to the double bond is ca. 50 Hz, their geminal coupling constant 14 Hz. The vicinal coupling, to the olefinic proton, of the methylene proton at lowest field is 7 Hz, the other is uncertain because of overlapping of lines from the other methylenes in the ring.

The triplet of the olefinic proton is not fully resolved at –66°, at –85° the signal is hidden by the signals of the proton in the solvent.

The free energy of activation for the exchange process was calculated² resulting in $\Delta G^\ddagger = 12.2$ kcal/mol.

The infrared spectra were taken of the crystalline solid in KBr and in CS₂ solution. IR-absorption bands at 1730 and 3510 cm⁻¹ showed that the solution contained some monomeric acid together with the hydrogen-bonded dimer. Otherwise, the spectra of the two phases were alike which indicate that the cycloheptene skeleton takes the same conformation in solution as in the crystal, and that there is only one conformer in the solution.

The compound melted at 130° and no solid-solid transition was observed by differential calorimetry. The entropy and enthalpy of fusion were $\Delta S = 23.9$ cal/mol deg. and $\Delta H = 9.7$ kcal/mol.

As a result of independent calculations Favini *et al.*³ found the chair and Allinger *et al.*⁴ the boat to be the lowest energy form of cycloheptene. From NMR-data most investigators find the chair conformation in cycloheptene derivatives.^{5,6} In 20 different benzocycloheptene derivatives, described by Kabuss *et al.*⁷ including one with substituents in 3 and 6 positions analogous to our compound, only one conformer occurred in the low temperature NMR-spectra, presumably that of the chair form. Grunwald and Price⁸ found two conformers by low temperature NMR of 3,3,6,6-