The Fischer Indolisation of Cyclopropyl Phenyl Ketone and Cyclobutyl Phenyl Ketone Phenylhydrazones†

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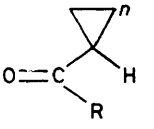
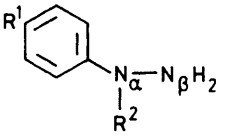
Reaction of cyclopropyl phenyl ketone (**3**) with an equimolar quantity of phenylhydrazine (**6**) in boiling ethanolic hydrogen chloride under reflux affords 2,3,4,5-tetrahydro-2,6-diphenylpyridazine (**23**) and 3-(2-chloroethyl)-2-phenylindole (**22**). 8b-Methoxy-, ethoxy-, and propoxy-1,2,3,3a,4,8b-hexahydro-3a-phenylcyclopent[*b*]indoles (**27**), (**26**), and (**28**), respectively, are isolated from the reaction of cyclobutyl phenyl ketone phenylhydrazone in cooled methanol, ethanol, and propan-1-ol, respectively, saturated with hydrogen chloride.

Of the many aldehydes and ketones which have been employed in the Fischer indole synthesis,[1] those with a ring-strained cycloalkyl moiety (*i.e.* cyclopropyl or cyclobutyl) adjacent to the carbonyl group had not been investigated until a recent report[2] that compound (**1**) reacts with the hydrochlorides of the arylhydrazines (**6**)—(**10**) and that compounds (**2**), (**3**), and (**4**) react with the hydrochlorides of the arylhydrazines (**7**), (**11**), and (**12**), respectively, in boiling alcoholic solutions, to afford the corresponding tryptamines (**13**)—(**20**), respectively. These reactions clearly involve nucleophilic attack by the β-nitrogen of the arylhydrazine moiety upon, with concomitant lysis of, the cyclopropyl ring at some stage during the indolisation process. Indeed, they could be mechanistically analogous to Grandberg's application[3] of the Fischer indolisation to the synthesis of tryptamines in which arylhydrazines react with γ-halogeno aldehydes or γ-halogeno ketones in boiling alcoholic solutions under reflux. An examination of the non-basic products resulting from the Fischer indolisation of a mixture of cyclopropyl phenyl ketone (**3**) with phenylhydrazine (**6**) in boiling ethanolic hydrogen chloride is described along with a study of the products resulting from the Fischer indolisation of a mixture of the homologous cyclobutyl phenyl ketone (**5**) with phenylhydrazine (**6**), with hydrogen chloride in various alcoholic solutions under cooling.

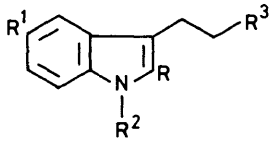
Reaction of an equimolar mixture of cyclopropyl phenyl ketone (**3**) with phenylhydrazine (**6**) in boiling ethanolic hydrogen chloride under reflux, followed by removal of the solvent, left a green solid from which the basic material, including any 2-phenyltryptamine (**21**) which may have been formed in accord with the earlier observations,[2] was removed with 1M-hydrochloric acid. Column chromatography of the residue then afforded, along with unchanged starting ketone, 2,3,4,5-tetrahydro-2,6-diphenylpyridazine (**23**)[4] and 3-(2-chloroethyl)-2-phenylindole (**22**). The latter product is clearly formed under the above reaction conditions *via* nucleophilic attack on, and with synchronous lysis of, the cyclopropyl ring by Cl^- ion, although whether this occurs prior to, during, or subsequent to indolisation [*i.e.* on the 3*H*-indole cation (**24**)] remains to be established. If the first of these possibilities is operative, compound (**23**) could result from the subsequent nucleophilic displacement of Cl^- ion by the α-nitrogen atom of the intermediate hydrazone. Indeed, compound (**23**) has previously[4] been isolated after a mixture of 3-chloropropyl phenyl ketone and phenylhydrazine in methanol had been boiled under reflux. Alternatively, the tetrahydropyridazine (**23**) could result from a direct nucleophilic attack by the α-nitrogen atom on the cyclopropyl moiety in the hydrazone.



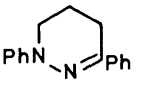
(1) R = H, *n* = 1
(2) R = Me, *n* = 1
(3) R = Ph, *n* = 1
(4) R = $PhCH_2$, *n* = 1
(5) R = Ph, *n* = 2



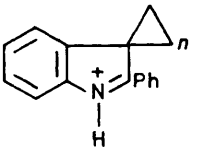
(6) $R^1 = R^2 = H$
(7) $R^1 = H, R^2 = Me$
(8) $R^1 = Br, R^2 = Me$
(9) $R^1 = R^2 = Me$
(10) $R^1 = PhCH_2O, R^2 = Me$
(11) $R^1 = H, R^2 = Ph$
(12) $R^1 = H, R^2 = PhCH_2$



(13) $R = R^1 = R^2 = H, R^3 = NH_2$
(14) $R = R^1 = H, R^2 = Me, R^3 = NH_2$
(15) $R = H, R^1 = Br, R^2 = Me, R^3 = NH_2$
(16) $R = H, R^1 = R^2 = Me, R^3 = NH_2$
(17) $R = H, R^1 = PhCH_2O, R^2 = Me, R^3 = NH_2$
(18) $R = R^2 = Me, R^1 = H, R^3 = NH_2$
(19) $R = R^2 = Ph, R^1 = H, R^3 = NH_2$
(20) $R = R^2 = PhCH_2, R^1 = H, R^3 = NH_2$
(21) $R = Ph, R^1 = R^2 = H, R^3 = NH_2$
(22) $R = Ph, R^1 = R^2 = H, R^3 = Cl$



(23)

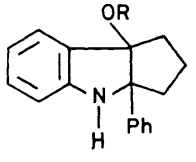


(24) *n* = 1
(25) *n* = 2

† Preliminary communications, *Chem. Ind.* (*London*), 1985, 660; 1986, 108.

Cyclobutyl phenyl ketone (**5**) was converted into its phenylhydrazone, a chilled solution of which in commercial absolute ethanol was saturated with dry hydrogen chloride for 4 h. Evaporation of the solvent followed by column chromatography of the residue yielded a trace of unchanged starting ketone along with the major reaction product which was shown to have structure (**26**).

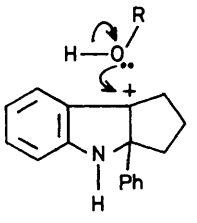
Of particular structural significance is the typical indoline u.v. absorption of this product in ethanol which is changed to characteristic benzenoid absorption in ethanolic hydrochloric acid, thereby eliminating possible structures for the product in which the ethoxy group is at the 2-position of the indoline nucleus, since in acidic media these would afford 3*H*-indolium cations with the attendant u.v. absorptions. Product (**26**) is possibly formed *via* the initially expected 3*H*-indolium salt (**25**), a [1,2]-group migration then affording the carbonium ion (**29**) which then electrophilically attacks the ethanolic function as shown. Alternatively, the migration and nucleophilic attack by the ethanolic oxygen could be a concerted process. In order to investigate the involvement of the alcoholic solvent in the reaction, it was repeated with the commercial absolute ethanol



(26) R = Et

(27) R = Me

(28) R = Pr



(29)

replaced by methanol or propan-1-ol. From these reactions were isolated, by column chromatography, moderate yields of compounds (**27**) and (**28**), respectively.

[1,2]-Group migrations between the 3- and the 2-positions of 2,3,3-trisubstituted 3*H*-indoles leading to their rearrangement are well established when the two 3-substituents are alkyl or aryl groups or tetra- or penta-methylene spiro systems.[5] However, such arrangements only occur using 'strong' acid catalysts [*e.g.* polyphosphoric acid, boron trifluoride, anhydrous aluminium, iron(III) or zinc chlorides] and then only at elevated temperatures (*e.g.* 150 °C).[5,6] In the present instance, the [1,2]-migration in (**25**) and the subsequent reaction of (**29**) with an alcoholic moiety under relatively mild conditions is probably associated with the concomitant relief of the steric strain caused by the ring expansion of the cyclobutyl moiety.

In an attempt to sterically hinder the alcoholic moiety's approach to, and thereby reaction with, the intermediate carbonium ion (**29**) and thus possibly modify the ultimate reaction product(s), the indolisation was repeated using 2-methylpropan-2-ol as the solvent–reactant and with the further modification that, since this alcohol has a m.p. of 25 °C, the reaction was carried out at 35 °C. T.l.c. examination of the product resulting from this reaction showed it to be a complex mixture from which all attempts to isolate a crystalline homogeneous fraction by column chromatography were unsuccessful.

Experimental

M.p.s. were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Pye Unicam SP3-100 spectrophotometer, u.v. spectra were measured in 96% EtOH, unless otherwise specified, on a Unicam SP 1750 spectrophotometer, and ^1H and ^{13}C n.m.r. spectra were recorded in $CDCl_3$ on a Bruker WP 80 pulsed F.T. spectrometer with $SiMe_4$ as the internal standard. Mass spectra were recorded using a Kratos MS-25 instrument connected to a DS-55 data system. Column chromatography was carried out with neutral Brockmann alumina (BDH) and thin layer chromatography was effected using Polygram Alox N/UV_{254} plates (0.2 mm) supplied by Camlab, Cambridge. All organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure on a Buchi evaporator. Ether refers to diethyl ether and light petroleum to the fraction b.p. 30—40 °C.

Fischer Indolisation of Cyclopropyl Phenyl Ketone Phenylhydrazone.—Cyclopropyl phenyl ketone (**3**) (1.46 g, 0.01 mol) and phenylhydrazine (**6**) (1.08 g, 0.01 mol) were dissolved in ethanol (70 ml) and the solution was boiled under reflux while dry hydrogen chloride was passed through it over a period of 4 h. Evaporation of the solvent then gave a green solid which was dissolved in chloroform (40 ml) and the resulting solution was washed with 1M-hydrochloric acid (2 × 20 ml) and water (50 ml), dried, and evaporated to leave a brown oil (1.62 g). Column chromatography of this oil using ether as the eluant afforded a yellow oil which soon completely crystallised when allowed to stand at room temperature and which showed three spots on t.l.c. [light petroleum–ether (3:1)] (R_F 0.61, 0.53, and 0.21). These were eluted in order of decreasing R_F value from a second column. Initial elution with light petroleum–ether (9:1) yielded white crystals (613 mg, 26%) which after recrystallisation from ether–light petroleum afforded 2,3,4,5-tetrahydro-2,6-diphenylpyridazine (**23**) as white plates, m.p. 128—129 °C [lit.,[4] 127—128 °C (from methanol)]; $\nu_{max.}$ (liquid paraffin) no absorption > 1 610 cm^{-1} other than CH stretching; δ_H 1.98—2.36 (2 H, m), 2.50—2.78 (2 H, t, *J* 5.5 Hz), 3.53—3.78 (2 H, t, *J* 5.5 Hz), and 6.76—7.90 (10 H, m); irradiation of either of the 2 H triplets caused collapse of the 2 H multiplet into a triplet (*J* 5.5 Hz) centred at δ_H 2.16 [Found: M^+ (100%) 236.1315. Calc. for $C_{16}H_{16}N_2$: *M*, 236.1313]. Further elution of the column with the same solvent eventually eluted cyclopropyl phenyl ketone (57 mg, 4%), and subsequent elution with ether gave the third component as a yellow oil which soon completely crystallised at room temperature. Two recrystallisations from ether–light petroleum gave 3-(2-*chloroethyl*)-2-*phenylindole* (**22**) (436 mg, 17%) as light-tan needles, m.p. 98—101 °C (Found: C, 75.1; H, 5.6; N, 5.35. $C_{16}H_{14}ClN$ requires C, 75.1; H, 5.5, N, 5.5%); $\nu_{max.}$(liquid paraffin) 3 360 ± 10 cm^{-1} (NH) [*cf.* 3-methyl-2-phenylindole, $\nu_{max.}$(liquid paraffin) 3 400 ± 10 cm^{-1}]; $\lambda_{max.}$ 304, 225, $\lambda_{infl.}$ 235, $\lambda_{min.}$267 nm (log ε 4.17, 4.31, 4.27, and 3.53, respectively) [*cf.* 3-methyl-2-phenylindole, $\lambda_{max.}$ 307, 227, $\lambda_{infl.}$235, $\lambda_{min.}$271 nm (log ε 4.32, 4.50, 4.46, and 3.82, respectively)]; δ_H 3.21—3.51 (2 H, m, CH_2), 3.61—3.92 (2 H, m, CH_2, apparent AA′BB′ system), 7.00—7.73 (9 H, m), and 8.07 (1 H, br s, NH).

3-*Methyl-2-phenylindole.*—A mixture of phenylhydrazine (5.4 g) and ethyl phenyl ketone (6.7 g) in toluene (50 ml) was boiled under reflux with azeotropic removal of water (Dean–Stark head) for 5 h. The solvent was then removed and the residual *hydrazone* was boiled under reflux in monoethylene glycol (50 ml) for 10 h, after which the evolution of ammonia had almost ceased. The reaction mixture was then cooled to room temperature, water (100 ml) was added, and the liberated oil was extracted into ether (2 × 40 ml). The combined ethereal extracts were then washed sequentially with 10% hydrochloric acid (2 × 30 ml) and water (2 × 30 ml), dried, and concentrated to afford 3-methyl-2-phenylindole (6.9 g, 67%) as a light-brown oil which soon completely crystallised. Recrystallisation from light petroleum gave light tan plates, m.p. 90—91 °C [lit.,

91—92 °C (from petroleum, b.p. 60—80 °C),[7] 90—92 °C (after sublimation *in vacuo*)[8]].

Fischer Indolisation of Cyclobutyl Phenyl Ketone Phenylhydrazone.—A mixture of cyclobutyl phenyl ketone (**5**) (3.2 g, 0.02 mol) with phenylhydrazine (**6**) (2.16 g, 0.02 mol) was boiled under reflux in benzene (30 ml) for 5 h with azeotropic removal of water (Dean–Stark head). Evaporation of the benzene then gave the hydrazone as a deep-yellow oil which soon completely crystallised when allowed to stand at 5 °C. This product was dissolved in commercial absolute ethanol (60 ml), and the solution was chilled (ice–water) whilst dry hydrogen chloride was passed gently through it over 4 h. Evaporation of the solvent, partitioning of the residue between water (100 ml) and ether (3 × 35 ml), and evaporation of the combined ethereal layers left a brown semi-solid (5.76 g). Column chromatography of this product, using light petroleum–ether (17:3) as the eluant, and fraction analysis by t.l.c. [light petroleum–ether (9:1)] initially afforded a trace (39 mg) of the starting ketone (R_F 0.95) followed by white crystals (R_F 0.52) of 8b-*ethoxy*-1,2,3,3a,4,8b-*hexahydro*-3a-*phenylcyclopent*[b]*indole* (**26**) which after recrystallisation from ether–light petroleum gave white needles (1.28 g, 23%), m.p. 111—112 °C (Found: C, 82.2; H, 8.0; N 5.0. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.5; N 5.0%); $\nu_{max.}$($CHCl_3$) 3 400 ± 10 cm^{-1} (NH); $\lambda_{max.}$ 312, 249, $\lambda_{min.}$275, 228 nm (log ε 3.46, 3.97, 2.40, and 3.33, respectively); δ_H 0.43 (3 H, t, *J* 7 Hz, (*Me*CH_2), 1.42—1.63 (1 H, m), 1.80—1.94 (1 H, m), 2.01—2.14 (1 H, m), 2.25—2.59 (4 H, m), and 2.80—2.95 (1 H, m) (4 × CH_2), 4.01—4.23 (1 H, br s, NH), and 6.70—6.87 (2 H, m), 7.14—7.47 (5 H, m), and 7.65—7.78 (2 H, m) (9 × Ar H); δ_C (off resonance multiplicities and assignments are shown in parentheses) 14.67 (q, *Me*C), 22.71, 42.94, and 48.20 (all t, *C*H_2C), 60.27 (t, CH_2O), 74.33 and 96.83 (both s, aliphatic quaternary C), 108.48, 118.10, 124.91, 126.19, 126.99, 127.29, and 129.31 (all d, different aromatic CH), and 128.23, 143.79, and 150.67 (all s, aromatic quaternary C) [Found: M^+ (31%) 279.1640. Calc. for $C_{19}H_{21}NO$: *M*, 279.1623]; *m*/*z* 251 (19), 250 (100, M^+ − Et), 233 (7, M^+ − EtOH), 232 (15), 222 (7), 208 (12), and 206 (15).

Continued elution of the column yielded only small amounts of unrecognisable yellow oils and basification with sodium hydroxide of the aqueous phase from the reaction work up followed by sequential ether extraction and column chromatogaphy led only to the isolation of a trace of phenylhydrazine.

The above reaction was repeated using methanol and propan-1-ol in place of ethanol as the solvent. From the former reaction was isolated 1,2,3,3a,4,8b-*hexahydro*-8b-*methoxy*-3a-*phenylcyclopent*[b]*indole* (**27**) as white needles (ether–light petroleum) (1.72 g, 32.5%), m.p. 128—129 °C (R_F 0.49) (Found: C, 81.7; H, 7.0; N, 5.4. $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N 5.3%); $\nu_{max.}$($CHCl_3$) 3 400 ± 10 cm^{-1} (NH); $\lambda_{max.}$ 313, 249, $\lambda_{min.}$297, 228 nm (log ε 3.49, 4.07, 2.88, and 3.68, respectively); δ_H 1.37—1.65 (2 H, m), 1.74—1.91 (1 H, m), 1.91—2.12 (1 H, m), and 2.22—2.53 (2 H, m) (3 × CH_2), 2.38 (3 H, s, MeO), 3.88—4.32 (1 H, br s, NH), and 6.61—6.85 (2 H, m), 7.05—7.43 (5 H, m), and 7.55—7.72 (2 H, m) (9 × ArH); δ_C (off resonance multiplicities and assignments are shown in parentheses) 22.76, 42.75, and 47.59 (all t, *C*H_2C), 52.07 (q, MeO), 74.72, and 97.10 (both s, aliphatic quaternary C), 108.75, 118.36, 125.17, 126.35, 126.91, 127.51, and 129.49 (all d, different aromatic CH), and 127.88, 143.53, and 150.80 (all s, aromatic quaternary C) [Found: M^+ (70%) 265.1462. Calc. for $C_{18}H_{19}NO$: *M*, 265.1467]; *m*/*z* 251 (22), 250 (100, M^+ − Me), 233 (11, M^+ − MeOH) 232 (26), 222 (9), 208 (22), and 206 (36). From the latter reaction was isolated 1,2,3,3a,4,8b-*hexahydro*-3a-*phenyl*-8b-*propoxycyclopent*[b]*indole* (**28**) as white needles (ether–light petroleum) (1.76 g, 30%), m.p. 45—46 °C (R_F 0.65) (Found: C, 81.5; H, 7.9; N, 4.7. $C_{20}H_{23}NO$ requires C, 81.9; H, 7.85; N, 4.8%); $\nu_{max.}$($CHCl_3$) 3 400 ± 10 cm^{-1} (NH); $\lambda_{max.}$ 309, 249, $\lambda_{min.}$ 275, 228 nm (log ε 3.48, 4.02, 2.91, and 3.65, respectively); δ_H 0.41 (3 H, t, *J* 7 Hz, *Me*CH_2), 0.67—0.81 (1 H, m) and 0.90—1.09 (1 H, m) (*C*H_2Me), 1.46—1.63 (1 H, m), 1.80—1.90 (1 H, m), 2.01—2.13 (1 H, m), 2.18—2.28 (1 H, m), 2.28—2.58 (3 H, m), and 2.70—2.80 (1 H, m) (4 × CH_2), 3.93—4.28 (1 H, br s, NH), and 6.70—6.87 (2 H, m) 7.15—7.46 (5 H, m), and 7.66—7.77 (2 H, m) (9 × ArH); δ_C (off resonance multiplicities and assignments are shown in parentheses) 10.07 (q, *Me*C), 22.71 (2 C, very intense peak), 42.71 and 47.98 (all t, *C*H_2C), 60.62 (t, CH_2O), 74.40 and 96.92 (both s, aliphatic quaternary C), 108.64, 118.25, 125.06, 126.25, 127.05, 127.34, and 129.31 (all d, different aromatic CH), and 128.67, 143.87, and 150.70 (all s, aromatic quaternary C) [Found: M^+ (29%), 293.1789. Calc. for $C_{20}H_{23}NO$: *M*, 293.1780]; *m*/*z* 251 (19), 250 (100, M^+ − Pr), 233 (21, M^+ − PrOH), 232 (23), 222 (6), 208 (9), and 206 (16).

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