Fischer Indole Synthesis of 3-Acyl- and 3-Alkoxy-carbonylindoles

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N-Benzyl-*N*-phenylhydrazine derivatives of 1,3-diketones and 1,3-ketoesters undergo normal Fischer cyclisations to indoles, but no method could be found for the subsequent removal of the *N*-protecting group. No method could be found for the indolisation of *N*-aroyl-*N*-phenylhydrazine derivatives of dimedone with retention of the *N*-protecting group, though heating in tetralin did effect the electrocyclic step of the Fischer sequence and the formation of a carbon–carbon bond.

THE Fischer indole synthesis [1] is the most widely used method for the preparation of indoles from non-indolic precursors. In essence, a phenylhydrazone (1) is rearranged to the indole (3), often in acidic solution, with loss of the second nitrogen. Although there has been much speculation over the details of the sequence, it almost certainly involves initial tautomerism to an ene-hydrazine (2) and an electrocyclic process for bonding C-3 to C-3a while breaking the nitrogen–nitrogen bond.

Despite the wide applicability of the process to the phenylhydrazones of ketones and aldehydes, a problem arises, in the form of a competing process, in attempts to

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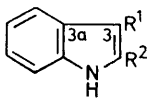
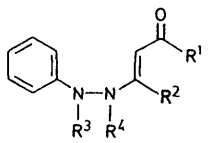


(3)

utilise phenylhydrazine derivatives (4; $R^3 = H$) † of acyclic 1,3-dicarbonyl-compounds (5). The reaction which, usually successfully, competes with an indole-forming process [which from (4; $R^3 = R^4 = H$] would give (6; $R^3 = H$)] is a cyclisation, involving bonding of N′ to the second carbonyl group, giving rise to a pyrazole (7) or pyrazol-3-one (8) and indeed such cyclisations represent the most efficient route [2] for the synthesis of pyrazoles and pyrazol-3-ones.

In the hope that the scope of the Fischer synthesis could be even further enlarged, to include acyclic 1,3-dicarbonyl-compounds, we embarked on a study aimed at evolving a way of avoiding the unwanted (in this context) pyrazole/pyrazolone formation. We were encouraged by the knowledge that the 1,3-dicarbonyl phenylhydrazine derivatives (4; $R^3 = R^4 = H$) exist in the ene-hydrazine form, and that analogous though simpler ene-hydrazines, even with an amidic N,[3a] undergo [3] Fischer cyclisation particularly easily, the first tautomerism [to (2)] of the ' normal ' sequence having already been achieved.

In looking for a way of avoiding the unwanted



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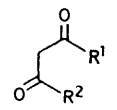
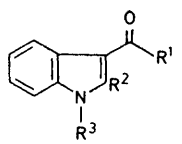


(5)

	R^1	R^2	R^3	R^4
a	OEt	Me	H	H
b	OEt	CH_2CO_2Et	H	H
c	OMe	CO_2Me	H	Ph
d	OMe	H	H	Ph
e	OEt	Me	CH_2Ph	H
f	OEt	Ph	CH_2Ph	H
g	OEt	CH_2CO_2Et	CH_2Ph	H
h	Me	Me	CH_2Ph	H
i	Me	Me	COPh	H
j	Me	Me	4—$MeOC_6H_4CO$	H

	R^1	R^2
a	OEt	Me
b	OEt	Ph
c	OEt	CH_2CO_2Et
d	Me	Me



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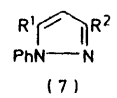
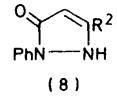


(7)

	R^1	R^2	R^3
a	OEt	Me	H
b	OEt	CH_2CO_2Et	H
c	OMe	CO_2Me	H
d	OMe	H	H
e	OEt	Me	CH_2Ph
f	OEt	Ph	CH_2Ph
g	OCH_2CH_2OH	$CH_2CO_2CH_2CH_2OH$	CH_2Ph
h	Me	Me	CH_2Ph



(8)

pyrazole-forming process we turned first to the literature. For example, many years ago it was demonstrated [4] that, albeit in poor yields, indoles could be obtained by the reaction of phenyl- and tolyl-hydrazine derivatives of ethyl acetoacetate using concentrated sulphuric acid as catalyst and solvent; presumably pyrazole formation is discouraged by protonation of N′ in the very strongly acid medium. We have now evolved conditions (addi-

† No stereochemistry implied.

tion of the hydrazone, either alone or in acetic acid solution, gradually to the concentrated acid at −10 °C with vigorous stirring) which considerably improve the yield [60% of (6a) from (4a)] and have shown additionally that indolisation [to (6b)] also occurred with the phenylhydrazine derivative (4b) of diethyl acetonedicarboxylate, but that with ethyl benzoylacetate (5b), pyrazolone formation was so fast as to make even isolation of the phenylhydrazine derivative impossible. It was already clear that such an approach to the problem was very unlikely to achieve a general solution.

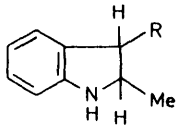
RESULTS AND DISCUSSION

Dimethyl indole-2,3-dicarboxylate (6c) was prepared [5] by heating the adduct (4c) of hydrazobenzene and dimethyl acetylenedicarboxylate; (4c) is effectively the *NN'*-diphenylhydrazine derivative of diethyl oxaloacetate. Only limited success was achieved in attempts [6] to extend this process. We have now prepared the hydrazobenzene adduct (4d) of methyl propiolate (effectively the *NN'*-diphenylhydrazine derivative of ethyl formylacetate), but attempted formation of an adduct with methyl hept-2-ynoate, even under more forcing conditions, failed. Adduct (4d) was transformed into indole (6d) following the suggested [5] refluxing xylene conditions. Incidentally and interestingly, a comparison showed that (6d) was formed at about the same rate by heating in xylene or dimethylformamide, solvents of comparable boiling point but markedly different dielectric constants; the latter gave the best preparative yield. It was simple to discern that (4d) had *trans*-geometry from the 13-Hz coupling constant between the olefinic hydrogen atoms. It seems reasonable to assume that the dimethyl acetylenedicarboxylate adduct (4c) also had ester and hydrazine *trans*; such a geometry explains the disfavouring of pyrazolone formation to allow indole cyclisation to proceed. This approach, however cannot be viewed as generalisable, depending as it does on the availability and reactivity of an appropriate carbonyl-conjugated alkyne.

It was known [7] that *N*-methyl-*N*-phenylhydrazine derivatives (4; R^3 = Me, R^4 = H) of 1,3-dicarbonyl compounds, where the N-substituent prevents pyrazole formation, undergo Fischer cyclisations with no complications. As a potentially generalisable solution to the problem, we next investigated the use of *N*-blocked phenylhydrazines. Clearly a blocking group was needed which could be subsequently removed. The benzyl group, reputedly easily removable from indolic nitrogen, *e.g.* by treatment [8] with sodium in ammonia, seemed a good choice.

N-Benzyl-*N*-phenylhydrazine was prepared from *N*-benzylaniline by nitrosation and lithium aluminium hydride reduction in refluxing ether. As anticipated, unexceptional Fischer reactions, using a variety of conditions (the best, apart from some transesterification complications, being refluxing ethylene glycol), were achieved starting from a representative group of 1,3-dicarbonyl compounds (5a—d) and giving, *via* (4e—h), the indolic products (6e—h). It remained to devise a means for the removal of the protecting group, so a study of one of these *N*-benzylindoles (6e), as a model, was undertaken.

Treatment of (6e) with hydrogen and palladium–charcoal (commercial or prepared after Brown [9]) in neutral or acidic media, failed completely to remove the benzyl group. Refluxing ethyl chloroformate [10] had no effect on the compound. Warm concentrated sulphuric acid, a medium which has been used [11] to debenzylate *N*-benzylamides, resulted only in water-soluble products. Treatment [8] with sodium–liquid ammonia gave 2-methylindoline (9a) and 3-hydroxymethyl-2-methylindoline (9b) and only a trace of the desired



(9)

a ; R = H
b ; R = CH_2OH

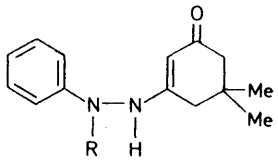
indole (6a). It was concluded that the benzyl blocking group is not a suitable one for the present purpose and we turned accordingly to an examination of the use of a potentially more easily removable group.

It was known [12] that *N*-aroyl-*N*-phenylhydrazones of ketones undergo Fischer cyclisation easily to yield *N*-aroylindoles although in some cases [12b,13] major or minor products have been obtained in which the heterocyclic ring has failed to form (the penultimate stage in the Fischer sequence), presumably because of the lowered nucleophilicity of the amidic N. Taken with the knowledge that acyl groups on indolic nitrogen are readily hydrolysed with base, an investigation was next undertaken into the potential of an aroyl group as a blocking group. Preliminary investigations soon showed that indolisation of *N*-benzoyl-*N*-phenylhydrazine derivatives (4; R^3 = COPh) of 1,3-dicarbonyl compounds is very much more difficult to achieve than in the comparable simpler cases. Accordingly a search was made for a method of indolising, using *N*-aroyl derivatives (10b—d) of dimedone as substrates. This choice was made to allow the quest for an efficient method for promoting the indole-forming process to be made in the absence of the pyrazole-forming complication, and in the knowledge both that *N*-aroyl-*N*-phenylhydrazine derivatives of cyclohexanone indolise [12] readily and that the phenylhydrazine derivative (10a) of dimedone gives an indole (11a) under a variety of conditions.

In order to assess the effect, if any, of substituents on the aroyl ring, *N*-benzoyl-, *N*-*p*-methoxybenzoyl-, and *N*-*p*-nitrobenzoyl-*N*-phenylhydrazine derivatives (10b—d) of dimedone were prepared and subjected to a range of the conditions which have typically been used for Fischer cyclisations, including those which converted

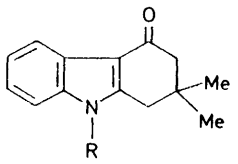
(10a) into (11a), and the *N*-aroyl-*N*-phenylhydrazine derivatives of cyclohexanone into the corresponding *N*-aroyltetrahydrocarbazoles.

All three ene-hydrazines (10b—d) were unchanged on treatment with anhydrous zinc chloride in acetic acid at reflux, ethanolic hydrogen chloride at reflux, formic



(10)

a ; R = H
b ; R = PhCO
c ; R = 4—$MeOC_6H_4CO$
d ; R = 4—$O_2NC_6H_4CO$



(11)

a ; R = H
b ; R = PhCO
c ; R = 4—$MeOC_6H_4CO$

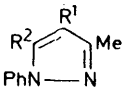
acid [14] at reflux, dichloroacetic acid in acetonitrile,[3] polyphosphate ester [15] in chloroform at reflux, and pyridine hydrochloride [16] in pyridine at reflux.

While both hot 3.5M sulphuric acid and boron trifluoride in refluxing acetic acid brought about indolisation of (10b) and (10c), but not of (10d), the isolation of deprotected indole (11a) in each case cast doubt on the exact sequence of events. For example, both of these conditions caused indolisation of (10a), thus hydrolysis could have preceded indole formation. On the other hand, indole formation could have occurred before loss of the aroyl group, for it was also shown that the *N*-aroylindoles (11b) and (11c), separately prepared, were converted into (11a) by subjection to the reaction conditions.

In any event, attempts to apply either of these sets of conditions to the ' real ' situation where pyrazole formation could compete, were disappointing. With sulphuric acid (4i) [17] gave no indolic product, only hydrolysis of the starting material occurring. With boron trifluoride in acetic acid, the trivial product, *N'*-acetyl-*N*-benzoyl-*N*-phenylhydrazine, was obtained.

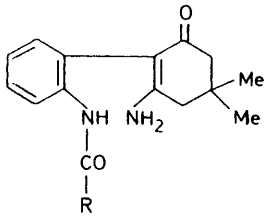
Refluxing di- and tri-ethylene glycol are the so-called ' non-catalytic ' conditions [18] for Fischer cyclisation. Refluxing ethylene glycol was sufficient to convert (10b) and (10c) cleanly into the deprotected indole (11a). Indeed, this represents the most efficient way to make this keto-indole. The *p*-nitro-analogue (10d) gave a complex mixture, containing no indole, which was not further investigated. Again it is difficult to be sure whether de-aroylation preceded or followed Fischer cyclisation: the phenylhydrazine derivative (10a) was efficiently indolised in refluxing glycol and the *N*-aroylindoles (11b) and (11c) were converted into (11a) in hot glycol. The suitability of refluxing glycol as a general procedure for the solution of the problem under discussion is in any case impaired by problems of ester exchange which would appear in dealing with derivatives of 1,3-keto-esters. Nonetheless the acetylacetone derivative (4i) was refluxed in glycol; only the pyrazole (12a) [17] was obtained.

Undoubtedly the most intriguing result, from a mechanistic viewpoint, emerged from heating the aroylenehydrazines (10b) and (10c) in tetralin at reflux.[19] The nitro-analogue (10d) gave a product mixture too complex to warrant further study; however, with (10b) and (10c) in each case there was obtained a separable mixture of *N*-hydrogen-indole (11a), *N*-aroyl-indole [(11b) or (11c)], and a third component, isomeric, in each case, with its starting material. Structural studies were



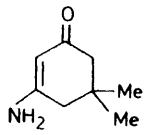
(12)

a ; R^1 = COMe, R^2 = Ph
b ; R^1 = COPh, R^2 = Me



(13)

a ; R = Ph
b ; R = 4—$MeOC_6H_4$



(14)

conducted on the isomeric product from (10b). It was, for example, stable to aqueous potassium hydroxide at 95 °C but though equally resistant to 2M hydrochloric acid at room temperature, cleanly and rapidly converted at 95 °C into the indole (11a). The new material still contained an intact benzoyl group, for the base peak in its mass spectrum, as in that of its precursor, was at *m/e* 105. In the aliphatic region of the n.m.r. spectrum there were still signals for two methyl and two methylene groups; however, the olefinic proton resonance was no longer present. Two signals at τ 1.10 and 5.06, disappearing after D_2O addition, represented NH and NH_2 signals. These, together with i.r. carbonyl absorption at 1 660 and 1 680 cm^{-1}, all suggested structure (13a) and a ^{13}C n.m.r. spectral analysis was able to confirm this.

The model compound (14) [20] showed ^{13}C n.m.r. signals at δ 197.6, 163.5, and 99.5 for carbonyl carbon and alkene carbons, respectively, the signal at δ 99.5 being coupled to a hydrogen, thus differentiating the two double-bond carbon signals. In the ^{13}C spectrum of (10b) the corresponding three atoms resonated at comparable fields, δ 197.9, 162.5, and 98.1, with the δ 98.1 signal being coupled to a proton. In the spectrum of the isomer (13a), two key differences could be observed. Firstly, though signals for carbonyl and one alkene carbon were very similar to those in the starting material, δ 194.8 and 162.9, there was now no alkene carbon coupled to a pro-

ton: the signal, now somewhat shifted by its attachment to the aromatic ring, at δ 107.9, was a singlet. Secondly, one more quaternary aromatic carbon had appeared, at δ 127.8. These data and the acid transformation into (11a) lead unambiguously to structure (13a). The isomer from (10c) was spectroscopically analogous in all respects to (13a) and thus has structure (13b).

In these compounds the electrocyclic carbon–carbon bonding and nitrogen–nitrogen bond-breaking steps of the Fischer sequence have occurred. The sequence is presumably arrested at this stage by the neutrality of both nitrogen atoms, coupled with the absence of a strong proton source. There have been several previous reports [12b,13,21] of the isolation of compounds representing arrest at this step of the normal Fischer sequence.

On attempted application of the tetralin conditions to the ' real ' situation, in the hope of obtaining a product analogous with (13), (4i) was transformed cleanly, though disappointingly, into an isomeric pyrazole (12b).[18,23] The rearrangement which leads to this product is of some interest and will be the subject of a future publication. Very recently another example of this type of process has been described,[23] and a mechanistic interpretation given.

In a patent it is claimed [23] that *N*-(4-chlorobenzoyl)-*N*-(4-methoxyphenyl)hydrazine hydrochloride and pentane-2,4-dione react in acetic acid at 70 °C to give the corresponding *N*-aroylindole. In our hands, however, the reaction of *N*-(4-methoxybenzoyl)-*N*-phenylhydrazine hydrochloride and pentane-2,4-dione, under these conditions, led only to the derivative (4j).[17] This result makes the claim [23] very doubtful.

The original quest with which this work was undertaken remains unanswered; no generally useful *N*-protecting group for Fischer reactions using 1,3-dicarbonyl compounds has been found. However, interesting incidental comments on the Fischer sequence have emerged. We conclude that Fischer indole synthesis utilising phenylhydrazine derivatives in which both nitrogen atoms are neutral, is considerably more difficult, if not impossible, to achieve in most cases, and that the electrocyclic step can be effected *only* when competition from another process is not possible.

EXPERIMENTAL

General.—M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. Wet organic solutions were dried with anhydrous $MgSO_4$, Na_2SO_4, or K_2CO_3 and evaporated under reduced pressure. For i.r. and n.m.r. spectra only those absorptions/resonances which were clearly distinguished and/or of particular structural significance are detailed; for mass spectra only ions of abundance greater than 10% are detailed, except where less abundant ions have importance for structure establishment.

Ethyl 2-Methylindole-3-carboxylate (6a) *and Ethyl 3-Ethoxycarbonylindol-2-ylacetate* (6b).—The crude phenylhydrazine derivative (4a) or (4b), prepared in each case from the reaction of phenylhydrazine (18 g) and ethyl acetoacetate (15 g) or diethyl 2-oxopropane-1,3-dicarboxylate (21 g) in ether (100 ml) with two drops of acetic acid at 0 °C for 1 h, followed by evaporation of solvent at room temperature, was added dropwise to concentrated sulphuric acid (70 ml) cooled rapidly to −5 °C with vigorous stirring during 5 min. After 0.5 h at that temperature the mixture was poured onto ice and for indole (6a) the precipitate (15.7 g) was filtered off, m.p. 133—135 °C (lit.,[4] 135 °C), for *indole* (6b), extraction with ether and crystallisation from benzene gave the product (6b) (14.2 g), m.p. 91—92 °C; $\lambda_{max.}$ 229 and 285 nm (log ε 4.26 and 4.04); $\nu_{max.}$ (Nujol) 3 295m, 1 735s, and 1 665s cm^{-1}; τ ($CDCl_3$) 9.12 (1 H, brs, NH), 5.73 (2 H, s, CH_2CO_2-Et), 5.64 and 5.85 (2 × 2 H, 2 × q, 2 × CH_2Me), and 8.66 and 8.75 (2 × 3 H, 2 × t, 2 × $MeCH_2$); *m/e* 275 (55%, M^+), 229(80), 201(100), 183 (43), 174(59), 156(22), and 129(20) (Found: C, 65.6; H, 6.1; N, 4.8. $C_{15}H_{17}NO_4$ requires C, 65.4; H, 6.2, N, 5.1%).

Methyl 3-(NN'-*Diphenylhydrazino*)*acrylate* (4d).—Methyl propiolate (1 g) and hydrazobenzene (1.8 g) were refluxed together in methanol (5 ml) for 2 h. The mixture was filtered hot, and then cooled to give the *ester* (4d) (1.0 g), together with a further quantity (0.41 g) from the filtrate. The ester had m.p. 145—146 °C (from methanol); $\lambda_{max.}$ 240 and 307 nm (log ε 4.10 and 4.39), $\nu_{max.}$ (Nujol) 3 240 m, 1 670s, and 1 610s, cm^{-1}; τ ($CDCl_3$) 1.80 (1 H, d, *J* 13 Hz, HC:C·CO_2Me), 4.75 (1 H, d, *J* 13 Hz, C : $CHCO_2$Me), and 6.35 (3 H, s, CO_2CH_3); *m/e* 268 (58%, M^+) and 93(100) (Found: C, 71.3; H, 5.8; N, 10.7. $C_{16}H_{16}N_2O_2$ requires C, 71.6; H, 6.0; N, 10.4%).

Methyl Indole-3-carboxylate.—The adduct (4c) (0.5 g) was heated in dry dimethylformamide for 3.5 h. Dilution with water, extraction with ether, drying, and evaporation gave the ester (320 mg), which crystallised from benzene to a m.p. of 144—149 °C (lit.,[5] 147—148 °C).

Ethyl 1-Benzyl-2-methylindole-3-carboxylate (6e).—*N*-Benzyl-*N*-phenylhydrazine (1.35 g) was reacted with ethyl acetoacetate (0.9 g) in the presence of 2 drops of acetic acid at 95 °C for 0.5 h. The resulting material was dissolved in benzene, dried, and evaporated to give the crude *hydrazine derivative* (4e), which was used without purification for the next stage, which involved heating in refluxing ethanol (20 ml) with concentrated sulphuric acid (0.75 ml) as catalyst, for 3 h. The reaction mixture was kept at 0 °C overnight, when filtration gave the *indole* (6e) (0.37 g), m.p. 95—98 °C; $\lambda_{max.}$ 288 nm (log ε 4.20), $\lambda_{sh.}$ 230 and 252 nm (log ε 4.39 and 4.00); $\nu_{max.}$ (Nujol) 1 680s cm^{-1}; τ ($CDCl_3$) 4.70 (2 H, s, PhCH_2N), 5.55 (2 H, q, *J* 7 Hz, CH_2Me), 7.31 (3 H, s, Ar–Me), and 8.55 (3 H, t, *J* 7 Hz, $MeCH_2$); *m/e* 293 (100%, M^+), 248(17), and 91(74) (Found: C, 77.6; H, 6.4; N, 5.2. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.53; N, 4.8%).

Ethyl 1-Benzyl-2-phenylindole-3-carboxylate (6f).—The hydrazine derivative (4f) (2.2 g) was prepared as described above for ethyl acetoacetate only using ethyl benzoylacetate, and was then refluxed in ethylene glycol (12 ml) for 2.5 h. The cooled mixture was diluted with water (200 ml), acidified with hydrochloric acid, and extracted with ether. The dried ether extract gave an oil (3.8 g) which was crystallised from ethanol to give the indole (6f) (2.1 g), m.p. 108—113 °C; $\lambda_{max.}$ 236 and 292 nm (log ε 4.37 and 4.16); $\nu_{max.}$ (Nujol) 1 960s cm^{-1}; τ ($CDCl_3$) 4.80 (2 H, s, PhCH_2N), 5.81 (2 H, q, *J* 7.5 Hz, CH_2Me), and 8.82 (3 H, t, *J* 7.5 Hz, $MeCH_2$); *m/e* 355 (93%, M^+), 310(22), 283(30), and 91(100) (Found: C, 81.5; H, 5.9; N, 3.6. $C_{24}H_{21}NO_2$ requires C, 81.8; H, 6.0; N, 3.94%).

2-*Hydroxyethyl* 1-*Benzyl*-2-(2-*hydroxyethoxycarbonylmethyl*)*indole*-3-*carboxylate* (6g).—The hydrazine derivative

(4g) was prepared as described above only using ethyl acetonedicarboxylate (2.1 g) instead of ethyl acetoacetate in reaction with *N*-benzyl-*N*-phenylhydrazine (2 g). The crude hydrazine was heated in refluxing ethylene glycol for 2.5 h; the cooled mixture was poured onto ice and acidified and the product extracted with chloroform and crystallised from ethanol to give the indole (6g) (1.01 g), m.p. 155—161 °C; $\lambda_{max.}$ 232 and 290 nm (log ε 4.35 and 4.20); $\nu_{max.}$ (Nujol) 3 300m, 1 725s, and 1 680s cm^{-1}; τ ([$^2H_5$]pyridine) 4.20 (2 H, br s, 2 × OH), 4.41 (2 H, s, PhCH_2N), 5.35 (2 H, s, CH_2CO_2R), and 5.2—6.2 (8 H, m, 2 × $HOCH_2CH_2OCO$); *m/e* 397 (27%, M^+), 335(29), 291(33), 262(22), 246(35), 244(37), 218(31), and 91(100) (Found: C, 66.2; H. 6.0; N, 3.6. $C_{22}H_{23}NO_6$ requires C, 65.78; H, 5.5; N, 3.65%).

3-*Acetyl*-1-*benzyl*-2-*methylindole* (6h).—The hydrazine derivative (4h), (4.3 g), prepared as described above only using acetylacetone instead of ethyl acetoacetate, was heated in refluxing ethylene glycol for 2.5 h. After dilution with water, extraction with ether, and crystallisation from methanol, the *ketone* (6h) (0.72) was obtained, m.p. 107—109 °C; $\lambda_{max.}$ 245, 268, and 304 nm (log ε 4.10, 3.88, and 4.06); $\nu_{max.}$ (Nujol) 1 625s cm^{-1}; τ ($CDCl_3$) 4.70 (2 H, s, PhCH_2N), and 7.35 and 7.37 (2 × 3 H, 2 × s, Ar*Me* and MeCO); *m/e* 263 (55%, M^+), 248(55), and 91(100) (Found: C, 81.4; H, 6.7; N, 5.2. $C_{18}H_{17}NO$ requires C, 82.1; H, 6.5; N, 5.3%).

2-*Methylindoline* (9a) *and* 3-*Hydroxymethyl*-2-*methylindoline* (9b).—Ethyl 2-methylindole-3-carboxylate (6e) (1 g) in ether (200 ml) was added to a solution of sodium (2 g) in liquid ammonia (400 ml). After 2 h at reflux excess solid ammonium chloride was added, the ammonia allowed to evaporate, and the residue partitioned between ether and water. The organic phase was extracted with dilute hydrochloric acid; the aqueous phase was basified and re-extracted to give an oil (0.485 g). The non-basic material was mainly starting material. Chromatography over silica gave 2-methylindoline (9a) (207 mg), characterised as its carbanilide, m.p. 146—148 °C (lit.,[24] 144.5 °C); and the *alcohol* (9b) (245 mg) as an oil; *m/e* 163 (28%, M^+), 132(100), 130(21), 117(42), and 91(9) (Found: M^+, 163.100 1. $C_{10}H_{13}NO$ requires *M*, 163.099 7).

N-4-*methoxybenzoyl*-N-*phenylhydrazine Hydrochloride*.—This was prepared following the method described [25] for *N*-benzoyl-*N*-phenylhydrazine and was obtained in 65% yield, from acetaldehyde phenylhydrazone, m.p. 119—121 °C (Found: C, 60.5; H, 5.5; N, 10.0. $C_{14}H_{15}ClN_2O_2$ requires C, 60.4; H, 5.4; N, 10.1%).

N-4-*Nitrobenzoyl*-N-*phenylhydrazine Hydrochloride*.—This was prepared following the method described [25] and obtained in 47% yield from acetaldehyde phenylhydrazone, m.p. 138—139 °C (Found: C, 53.3; H, 4.1; N, 14.5. $C_{13}H_{12}ClN_2O_3$ requires C, 53.2; H, 4.1; N, 14.7%).

3-(N′-*Benzoyl*-N′-*phenylhydrazino*)-5,5-*dimethylcyclohex*-2-*en*-1-*one* (10b).—*N*-Benzoyl-*N*-phenylhydrazine hydrochloride [25] (2.6 g) and dimedone (1.5 g) were heated together in refluxing ethanol (20 ml) for 6 h. The solvent was evaporated and the residue partitioned between aqueous potassium carbonate and ethyl acetate to give the *ene-hydrazine* (10b) (2.6 g), m.p. 171—173 °C (from toluene + a little EtOH); $\lambda_{max.}$ (EtOH) 227 and 285 nm (log ε 4.37 and 4.55); $\nu_{max.}$ (Nujol) 3 200m and 1682s cm^{-1}; τ ($CDCl_3$) 4.3 (1 H, s, C=CH), 7.7 (4 H, br s, 2 × CH_2), and 8.85 (6 H, s, 2 × Me); *m/e* 334 (9%, M^+), 316(10), 229(2), 105(100), and 77(4) (Found: C, 75.3; H, 6.8; N, 8.0. $C_{21}H_{22}N_2O_2$ requires C, 75.4; H, 6.5; N, 8.3%).

3-(N′-4-*Methoxybenzoyl*-N′-*phenylhydrazino*)-5,5-*dimethylcyclohex*-2-*en*-1-*one* (10c).—This was made exactly as described for the preparation of (10b) only using *N*-4-methoxybenzoyl-*N*-phenylhydrazine hydrochloride, yield 83%, m.p. 174—177 °C (from toluene + a little EtOH); $\lambda_{max.}$ (EtOH) 220 and 285 nm (log ε 4.16 and 4.47); $\nu_{max.}$ (Nujol) 3 200m, 1 675s, and 1 665s cm^{-1}; τ ($CDCl_3$) 2.35 (1 H, br s, NH), 4.40 (1 H, s, C=CH), 6.25 (3 H, s, OMe), 8.85 (4 H, br s, 2 × CH_2), and 9.00 (6 H, s, 2 × Me); *m/e* 364 (2%, M^+), 346(2), 227(3), 135(100), and 77(14) (Found: C, 72.7; H, 6.5; N, 7.4. $C_{22}H_{24}N_2O_3$ requires C, 72.5; H, 6.6; N, 7.7%).

3-(N′-4-*Nitrobenzoyl*-N′-*phenylhydrazino*)-5,5-*dimethylcyclohex*-2-*en*-1-*one* (10d).—This was made exactly as described for the preparation of (10b) only using *N*-4-nitrobenzoyl-*N*-phenylhydrazine hydrochloride, yield 39%, m.p. 173—175 °C (from toluene + a little EtOH); $\lambda_{max.}$ (EtOH) 223 and 285 nm (log ε 4.36 and 4.62); $\nu_{max.}$ (Nujol) 3 200m and 1 675s cm^{-1}; τ ($CDCl_3$) 1.71 (1 H, br s, NH), 1.91—2.83 (9 H, Ar-H), 4.56 (1 H. s, C=CH), 7.90 (4 H, br s, 2 × CH_2), and 9.06 (6 H, s, 2 × Me); *m/e* 379 (40%, M^+), 361(12), 360(19), 229(91), 201(14), 150(81), 120(14), 104(45), 92(35), 92(35), 83(100), and 77(64) (Found: C, 66.5; H, 5.7; N, 11.1. $C_{21}H_{21}N_3O_4$ requires C, 66.5; H, 5.5; N, 11.3%).

2,3-*Dihydro*-9-(4-*methoxybenzoyl*)-2,2-*dimethylcarbazol*-4(1H)-*one* (11c).—The indole (11a) (0.12 g) in dry DMF (2 ml) was added to a stirred slurry of sodium hydride (12 mg) in DMF (5 ml) under nitrogen at room temperature. After 1 h stirring, a solution of 4-methoxybenzoyl chloride (81 mg) in DMF (3 ml) was added and the whole stirred at room temperature 14 h. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate to give a foam (0.19 g) which was crystallised from ethanol to give the *aroyl-indole* (11c) (0.16 g), m.p. 109—111 °C; $\lambda_{max.}$ 230, 200, and 320(infl) nm (log ε 4.20, 4.02, and 3.84); $\nu_{max.}$ (Nujol) 1 680s and 1 660s cm^{-1}; τ ($CDCl_3$) 6.1 (3 H, s, OMe), 7.10 (2 H, br s, CH_2), 7.50 (2 H, s, CH_2), and 8.86 (6 H, s, 2 × Me); *m/e* 347 (15%, M^+), 135(100), and 77(12) (Found: C, 76.1; H, 5.9; N, 4.5. $C_{22}H_{21}N_3O$ requires C, 76.1; H, 6.0; N, 4.0%).

3-*Amino*-2-[2-(4-*methoxybenzoyl*)*aminophenyl*]-5,5-*dimethylcyclohex*-2-*en*-1-*one* (13b).—The ene-hydrazine (10c) (2.4 g) was heated in refluxing tetralin (60 ml) for 3 h. Most of the solvent was evaporated and the residue partitioned between methanol, light petroleum, and sufficient water to produce two layers. The methanol layer was separated, re-washed with light petroleum, and evaporated to give an oil (1.97 g) which was separated by chromatography over silica, eluting with PhMe–EtOAc (1 : 2) to give 2,3-dihydro-2,2-dimethylcarbazol-4(1*H*-)-one (11a) (0.29 g), identified by comparison with material prepared as described above: 2,3-dihydro-9-(4-methoxybenzoyl)-2,2-dimethylcarbazol-4-(1*H*)-one (11c) (0.73 g), identified by comparison with material prepared as described above, and finally the *amino-enone* (0.34 g), m.p. 189—190 °C (from EtOH); $\lambda_{max.}$ 207 and 255 nm (log ε 4.28 and 4.14), $\lambda_{infl.}$ 295 nm (log ε 3.94); $\nu_{max.}$ (Nujol) 3 310m, 3 180m, and 1 645s cm^{-1}; τ ($CDCl_3$) 1.1 (1 H, br s, NH), 4.85 (2 H, br s, NH_2), 6.20 (3 H, s, OMe), 7.68 (4 H. br s, 2 × CH_2), 8.90 (3 H, s, Me), and 9.05 (3 H, s, Me); *m/e* 364 (3%, M^+), 347(11), 213(16), 135(100), and 77(12) (Found: C, 72.2; H, 6.8; N, 7.6. $C_{22}H_{24}N_2O_3$ requires C, 72.5; H, 6.6; N, 7.7%).

3-*Amino*-2-(2-*benzoylaminophenyl*)-5,5-*dimethylcyclox*-2-*en*-1-*one* (13a).—The ene-hydrazine (10b) (1.25 g) was

heated in refluxing tetralin (30 ml) for 3 h. Most of the solvent was evaporated and the residue partitioned between methanol, light petroleum, and sufficient water to produce two layers. The aqueous methanol layer was washed again with light petroleum and evaporated to give an oil (1.25 g), which was separated by chromatography over silica to give, on elution with PhMe–EtOAc (1 : 1), *N*-benzoylaniline (43 mg), m.p. 157—161 °C (lit., 163 °C): 2,3-dihydro-2,2-dimethylcarbazol-4(1*H*)-one (11a) (0.12 g), identified by comparison with material prepared above: 9-benzoyl-2,3-dihydro-2,2-dimethylcarbazol-4(1*H*)-one (11b) (23 mg), identified by comparison with material prepared as described above: and finally the *amino-enone* (13a) (0.78 g), m.p. 187—188 °C (from EtOH), $\lambda_{max.}$ 228 and 295 nm (log ε 4.20 and 4.28); $\nu_{max.}$ (Nujol) 3 430m, 3 360m, and 1 660 cm^{-1}; τ ($CDCl_3$) 1.10 (1 H, br s, NH), 5.06 (2 H, br s, NH_2), 7.66 (4 H, br s, 2 × CH_2), 8.90 (3 H, s, Me), and 9.10 (3 H, s, Me); δ_C ($CDCl_3$) 194.85 (s, C-1), 165.65 (s, Ph*C*O), 162.87 (s, C-3), 137.26 (s), 134.55 (s), 127.82 (s), 107.91 (s, C-2), 50.7 (t, C-6), 43.16 (t, C-4), 32.18 (s, C-5), and 28.23 (q, Me); *m/e* 334 (3%, M^+), 317(20), 213(22), and 105(100) (Found: C, 75.4; H, 6.5; N, 8.3. $C_{21}H_{22}N_2O_2$ requires C, 75.6; H, 6.5; N, 8.2%).

3-*Amino*-5,5-*dimethylcyclohex*-2-*en*-1-*one* (14).—This was prepared following the literature method;[20] δ_C ($CDCl_3$) 197.55 (s, C-1), 163.45 (s, C-3), 99.50 (d, C-2), 49.96 (t, C-6), 42.79 (t, C-4), 32.91 (s, C-5), and 28.38 (q, Me).

The authors thank Dr. B. Robinson, Department of Pharmacy, University of Manchester, for sight of the manuscript of his forthcoming book on the Fischer indole synthesis. K. M. and F. S. A.-S. thank the S.R.C. and the Department of Education, Bahrain, respectively, for maintenance grants.

[0/738 *Recieved* 19*th May*, 1980]

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