The Reduction of Some Alicyclic- and Aryl-substituted 3-Acyl Derivatives of 2-Methylindole

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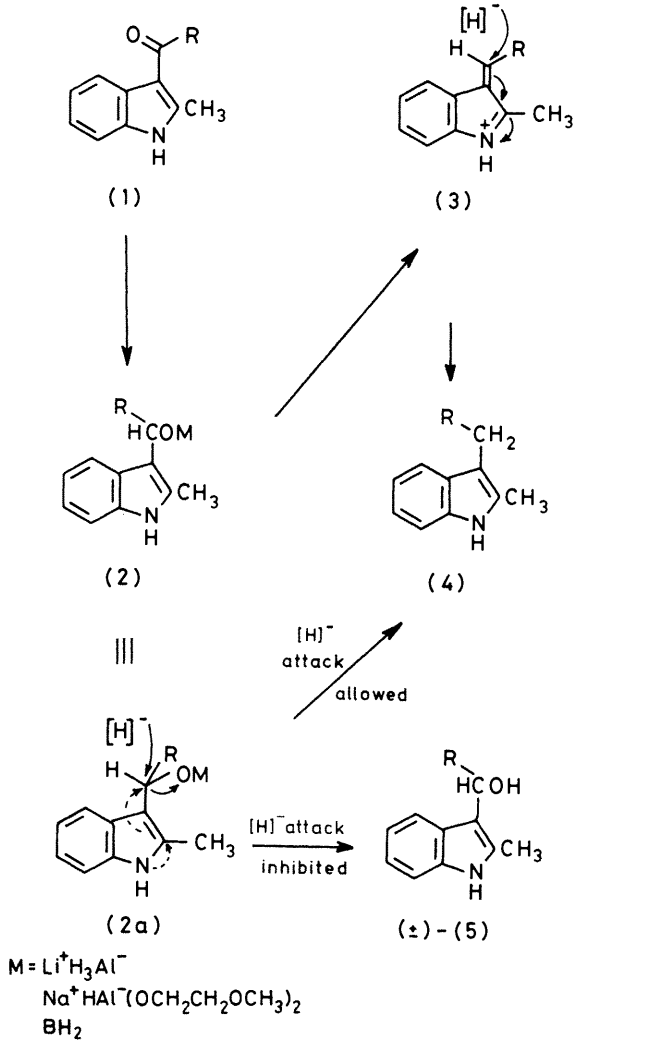
The structures of the products formed from the reduction of some 3-acyl derivatives of 2-methylindole were dependent on the nature of the substituent α to the carbonyl group and the reducing agent being used. When the substituent was aryl the only recoverable product had the hydrogenolysed structure; when the substituent was alicyclic the product had either the intermediate hydroxy or fully hydrogenolysed structure.

In our continuing work on the synthesis of 4-substituted-1,2,3-benzotriazines we required intermediates of structure (5; R = aryl, alicyclic) and we have now investigated their availability from the reduction of the corresponding 3-acyl derivatives (1) of 2-methylindole.

For the category R = aryl the reduction of compounds (1) with diborane † results in complete hydrogenolysis to the 3-alkylindole (4). This conversion was first reported for 3-benzoylindole and 3-benzoyl-1-methylindole [1] and was utilised in our synthesis of 4-arylmethyl-1,2,3-benzotriazines from (1; R = phenyl, *p*-tolyl, *p*-methoxyphenyl, and 1-naphthyl).[2] Further work using this series of compounds showed that reduction of (1) with lithium aluminium hydride † and sodium bis-(2-methoxyethoxy)aluminium hydride (Redal) † also resulted in complete hydrogenolysis to (4). Our attempts to synthesise the required intermediates (5; R = aryl) by reduction of (1) with the sodium, lithium, and zinc borohydride group of reagents ‡ proved to be unsuccessful in that, using (1; R = *p*-tolyl) as the model compound, no reduction was observed using a two—five-fold excess of reagent with reaction times of up to 24 h at room temperature. At higher temperatures some reaction was observed but the unstable product(s) rapidly decomposed to a red oil. Therefore when R = aryl the intermediate (5) is not available from the reduction of the corresponding ketone and other routes are under consideration. For example, a recent report described the synthesis of the *N*-phenylsulphonyl analogue of (5; R = phenyl) from the reaction between 3-lithio-1-(phenylsulphonyl)indole and benzaldehyde.[3] This was not a particularly straightforward procedure, though, and no yields were quoted for the *N*-desulphonated products.

For the category R = alicyclic we had expected, by analogy with previous results of reductions when R = alkyl,[4] that reduction with Group A reagents would result in hydrogenolysis and reduction with Group B reagents would result in termination at the hydroxy stage. However, as can be seen from the Table, this was not what we observed and the results suggested that steric effects were playing a significant role in determining the outcome of these reductions particularly when Group A reagents were being used.



Scheme 1.

Discussion

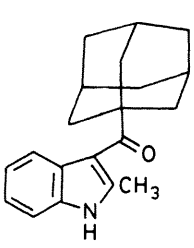
Reduction with Group A Reagents.—The most probable mechanistic explanation for the results is shown in Scheme 1 where displacement of MO^- from (2) is required for hydrogenolysis. When R = aryl, spontaneous displacement of MO^- may occur, yielding the stabilised intermediate (3), followed by $[H]^-$ attack § to give (4). Alternatively, displacement of MO^- by $[H]^-$ may take place with only anchimeric assistance from the enamine as in structure (2a). When R = alicyclic the mechanism involving (3) cannot apply otherwise

† Group A reagent.
‡ Group B reagents.

§ $[H]^-$ is used to represent both $[AlH_4]^-$ and $[(CH_3OCH_2CH_2O)_2AlH_2]^-$ but we prefer $(H_2BO^- \overset{\curvearrowright}{H_2B}\text{–}H^{\curvearrowright})$ instead of BH_4^-. However, see C. F. Lane, *Chem. Rev.*, 1976, **76**, 779 where BH_4^- is used in hydrogenolysis mechanisms for diborane.

Table. [a]

Substrate



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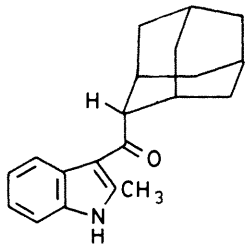

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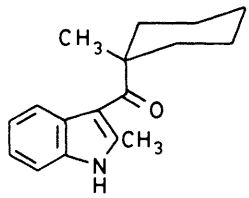

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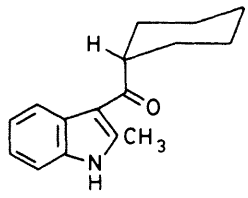
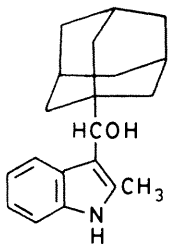


(9)

Reducing agent	C=O reduced to	Yield (%)	C=O reduced to	Yield (%)	C=O reduced to	Yield (%)	C=O reduced to	Yield (%)
$NaBH_4$	HCOH	89	—		HCOH	87	—	
$LiBH_4$	HCOH	82	—		HCOH	84	—	
REDAL	HCOH	84	CH_2	83	HCOH	88	CH_2	89
$LiAlH_4$	HCOH	89	CH_2	85	HCOH	90	CH_2	88
B_2H_6	HCOH	86	CH_2	86	HCOH	89	CH_2	91

Product



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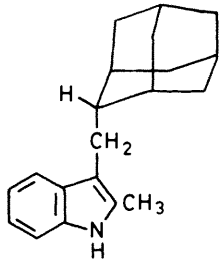

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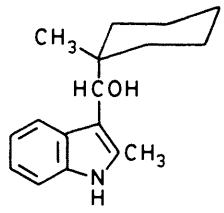

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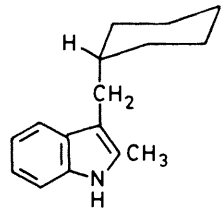


(13)

[a] The results are for reactions carried out under ' normal conditions ' (*i.e.* using only 2—4 times excess of reagents and temperatures 0—25 °C. All reactions went to completion in less than 12 h and the products shown were formed exclusively. For the reactions that terminated at the hydroxy stage no attempt was made to force the reduction further by employing higher temperatures or a greater excess of reagent.

we should have observed complete hydrogenolysis for all four alicyclic derivatives (6)—(9) (Table). However, if the alternative concerted mechanism, structure (2a), is in operation, then when $[H]^-$ attack is prevented by the proximity of the steric bulk of the substituent, *e.g.* for (2a; R = 1-adamantyl and 1-methylcyclohexyl), the reduction terminates at the hydroxy stage; when the steric bulk is less interfering, *e.g.* for (2a; R = 2-adamantyl and cyclohexyl), $[H]^-$ attack is allowed and hydrogenolysis ensues.

However, the possibility existed that direct displacement of MO^- by $[H]^-$ was prevented by all four alicyclic substituents and that an indirect displacement with accompanying 1,2-hydride shift, structure (14), might be taking place for the 2-adamantyl (7) and cyclohexyl (9) derivatives to give the hydrogenolysed products. In order to investigate this possibility we reduced compounds (7) and (9) with lithium aluminium deuteride and obtained the products shown in the Figure. High-resolution mass spectrometry indicated that two deuterium atoms had been incorporated into the products and the ^1H n.m.r. spectra showed complete absence of signals at δ 2.80 and 2.53, respectively, where the CH_2 groups in compounds (11) and (13) resonated. Thus the carbonyl group in both cases had been reduced to a CD_2 group and no 1,2-hydride shift had taken place. This evidence therefore strengthens our proposal that the differences observed in these reductions can be best explained on steric grounds, with regard to the proximity of the steric bulk of the substituents to the carbon centre carrying the displaceable OM group.

Reduction with Group B Reagents.—With the exception of diborane all the other reducing agents may function as bases in solution and under such conditions (1) will equilibrate with its enolate form (1a). When R = aryl the formation of this enolate structure will be favoured; hence with lithium aluminium hydride and Redal the rate of reduction will be slowed [5] but not prevented; with the Group B reagents the stabilised enolate must be resistant to reduction but at higher temperatures it can react with any reduced intermediate (2) to give a compound of structure (17) (Scheme 2). Although we isolated (preparative t.l.c.) a small amount of this product it rapidly degenerated to a red oil.

When R = alicyclic the observed results for the reduction of compounds (6)—(9) are not easy to explain. We cannot use steric reasons since the least sterically hindered ketones (7) and (9) are not even reduced to the hydroxy stage. It is also difficult to see how even assumptive enolate formation could account for these differences and we can only present the results, without plausible explanation, as examples of the

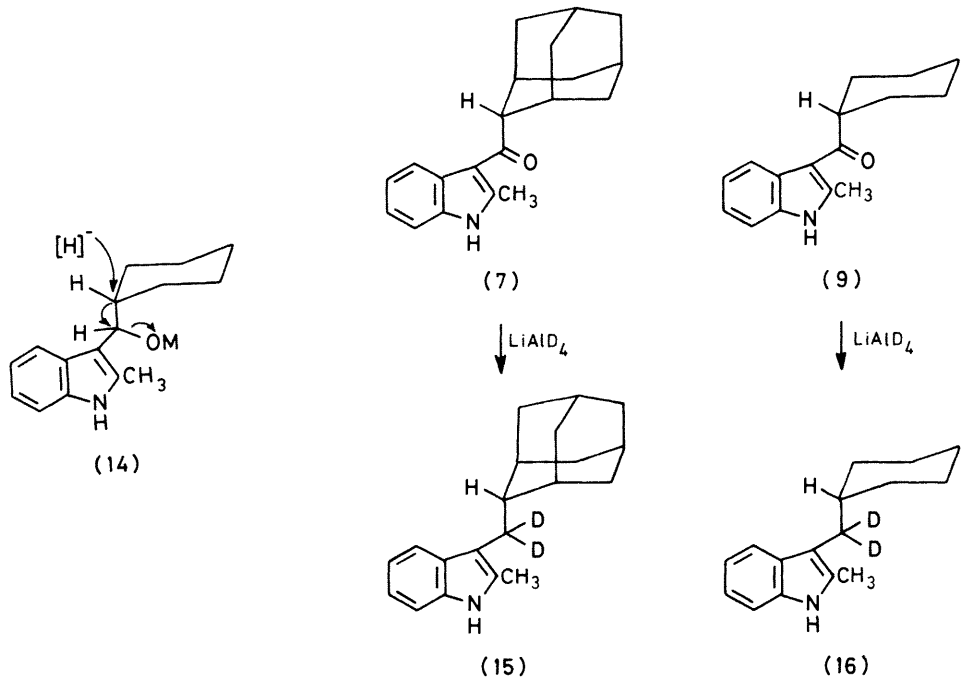
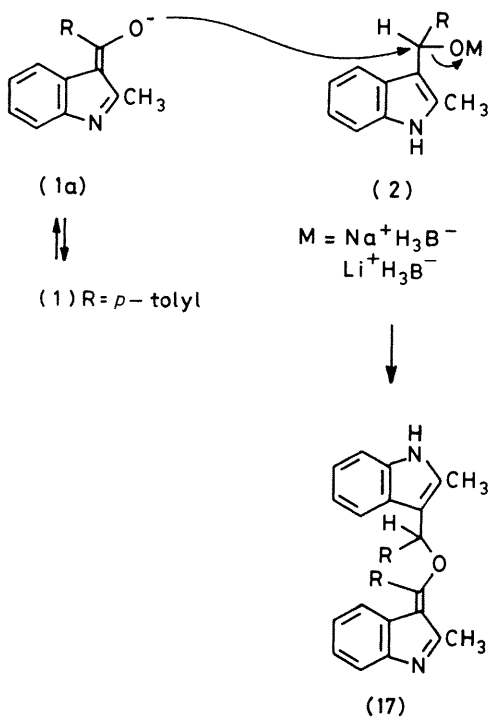


Figure.



Scheme 2.

unpredictability of reduction of this type of substituted 3-acyl-2-methylindole.

In conclusion it has only been possible to obtain the required hydroxy intermediates from the ketones when the substituent α to the carbonyl group was alicyclic and bonded to the carbonyl group *via* a tertiary centre. The successful conversion of these intermediates (5; R = 1-adamantyl and 1-methylcyclohexyl) into benzotriazines will be reported in a later paper.

Experimental

M.p.s were determined on a Reichert Model 4065 micro hot-stage (Kofler) apparatus and are corrected. I.r. spectra were recorded for KBr discs or solutions in $CHCl_3$ on a Perkin-Elmer 157G spectrophotometer. ^1H N.m.r. spectra were taken on a Perkin-Elmer R12B spectrometer for solutions in $CDCl_3$. Mass spectra were measured with an AEI MS9 instrument. Light petroleum refers to the fraction b.p. 60—80 °C.

3-(1-*Adamantylcarbonyl*)-2-*methylindole* (6).*—To the Grignard reagent prepared by the slow addition of ethyl bromide (0.1 mol) to magnesium turnings (0.1 mol) and a crystal of iodine in anhydrous diethyl ether (125 ml) was added a solution of 2-methylindole (0.1 mol) in diethyl ether (65 ml). The mixture was then refluxed for 2 h, cooled in ice–water, and then a solution of adamantylcarbonyl chloride (0.1 mol) in diethyl ether (65 ml) added dropwise to the vigorously stirred mixture during 30 min. The oily mixture was then stirred or shaken with an equal volume of 10% aqueous ammonium chloride followed by extraction into chloroform. The organic layer was then dried ($MgSO_4$) and evaporated to give a red oil (or solid). Most of the excess of 2-methylindole was then removed by trituration of the red oil with methanol. Subsequent crystallisation of the remaining solid from diethyl ether–light petroleum gave the *product* (6) (60%), m.p. 158—160 °C; $\nu_{max.}$ 3 466 (NH) and 1 660 cm^{-1} (CO); δ 2.26 (3 H, s, CH_3) (Found: C, 82.1; H, 8.0; N, 5.1. $C_{20}H_{23}NO$ requires C, 81.9; H, 7.9; N, 4.8%). The following were prepared by the same method.

3-(2-*Adamantylcarbonyl*)-2-*methylindole* (7) † (52%), m.p. 207—209 °C (from methanol); $\nu_{max.}$ 3 465 (NH) and 1 646 cm^{-1} (CO); δ 3.38 (1 H, m, HCCO) and 2.71 (3 H, s, CH_3) (Found: C, 81.6; H, 8.0; N, 4.8. $C_{20}H_{23}NO$ requires C, 81.9; H, 7.9; N, 4.8%).

2-*Methyl*-3-(1-*methylcyclohexylcarbonyl*)*indole* (8) (57%), m.p. 104—106 °C (from diethyl ether–light petroleum); $\nu_{max.}$ 3 471 (NH) and 1 639 cm^{-1} (CO); δ 2.32 (3 H, s, indole CH_3) and 1.41 (3 H, s, CH_3) (Found: C, 79.9; H, 8.3; N, 5.7. $C_{17}H_{21}NO$ requires C, 80.0; H, 8.3; N, 5.5%).

3-*Cyclohexylcarbonyl*-2-*methylindole* (9) (64%), m.p. 159—160 °C (from chloroform–light petroleum); $\nu_{max.}$ 3 455 (NH) and 1 640 cm^{-1} (CO); δ 3.22 (1 H, m, HCCO) and 2.73 (3 H, s, CH_3) (Found: C, 79.3; H, 7.7; N, 6.0. $C_{16}H_{19}NO$ requires C, 79.6; H, 7.9; N, 5.8%).

Reduction of the Ketones—General procedures. The reducing reagents (2—4 mol. excess) were added to a vigorously stirred solution of the ketone at 0 °C and under nitrogen where necessary. The solvents used were methanol or methanol–diethyl ether for sodium borohydride and zinc borohydride, tetrahydrofuran (THF) or methanol for lithium borohydride, and dry THF (freshly distilled from lithium aluminium hydride) for all the other reducing agents. The reaction mixtures were allowed to warm to room temperature and the reactions were then monitored by t.l.c. Reaction times varied between 1.5 h and overnight but, provided reduction was taking place, reactions were allowed to proceed until t.l.c. showed the absence of starting material. Termination of the reactions consisted of careful destruction of excess of reagents using well established procedures and extraction of the products into diethyl ether or ethyl acetate. The usual work-up then involved washing with water, drying of the organic layer ($MgSO_4$), and evaporation of the solvent to give the products.

3-Benzyl-2-methylindole (4; R = phenyl), 2-methyl-3-(*p*-tolylmethyl)indole (4; R = *p*-tolyl), and 2-methyl-3-(1-naphthylmethyl)indole (4; R = 1-naphthyl) were obtained by reduction of the corresponding ketones with lithium aluminium hydride (*ca.* 80% yield) and Redal (*ca.* 80% yield). These products were identical to those obtained from reduction of the same ketones with diborane.[2]

3-(2-*Adamantylmethyl*)-2-*methylindole* (11). Reduction of 3-(2-adamantylcarbonyl)-2-methylindole (7) with Group A reagents gave the *product* (11) (% yields in the Table), m.p. 130—131 °C (from diethyl ether–light petroleum); $\nu_{max.}$ 3 479 cm^{-1} (NH); δ 2.80 (2 H, d, *J* 7 Hz, CH_2) and 2.28 (3 H, s, CH_3) (Found: C, 85.8; H, 9.2; N, 4.8. $C_{20}H_{25}N$ requires C, 86.0; H, 9.0; N, 5.0%).

3-*Cyclohexylmethyl*-2-*methylindole* (13). Reduction of 3-cyclohexylcarbonyl-2-methylindole (9) with Group A reagents gave the *product* (13) (% yields in the Table), m.p. 106—108 °C (from diethyl ether–light petroleum); $\nu_{max.}$ 3 482 cm^{-1} (NH); δ 2.53 (2 H, d, *J* 7 Hz, CH_2) and 2.20 (3 H, s, CH_3) (Found: C, 84.6; H, 9.6; N, 6.1. $C_{16}H_{21}N$ requires C, 84.5; H, 9.3; N, 6.2%).

(±)-3-[1-*Adamantyl*(*hydroxy*)*methyl*]-2-*methylindole* (10). Reduction of 3-(1-adamantylcarbonyl)-2-methylindole (6) with both Group A and B reagents gave the *product* (% yields in the Table), m.p. 185—186 °C (from diethyl ether–light petroleum); $\nu_{max.}$ 3 611 (OH) and 3 479 cm^{-1} (NH); δ 4.56 (1 H, s, C*H*OH) and 2.37 (3 H, s, CH_3) (Found: C, 81.4; H, 8.6; N, 4.6. $C_{20}H_{25}NO$ requires C, 81.3; H, 8.5; N, 4.7%).

(±)-2-*Methyl*-3-[1-*methylcyclohexyl*(*hydroxy*)*methyl*]*indole* (12). Reduction of 2-methyl-3-(1-methylcyclohexylcarbonyl)indole (8) with both Group A and B reagents gave the *product* (12) (% yields in the Table), m.p. 124—126 °C (from diethyl ether–light petroleum); $\nu_{max.}$ 3 613 (OH) and 3 475 cm^{-1} (NH); δ 4.63 (1 H, s, C*H*OH), 2.31 (3 H, s, indole CH_3), and 1.01 (3 H, s, CH_3) (Found: C, 79.5; H, 9.0; N, 5.3. $C_{17}H_{23}NO$ requires C, 79.3; H, 9.0; N, 5.4%).

3-(2-*Adamantyl*[$^2H_2$]*methyl*)-2-*methylindole* (15). Reduction of 3-(2-adamantylcarbonyl)-2-methylindole (7) (1 mmol) in dry THF (20 ml) with lithium aluminium deuteride (4 mmol) gave, after 5 h at room temperature, followed by the usual work-up, the *product* (15) (80%), m.p. 130—131 °C (from diethyl ether–light petroleum); $\nu_{max.}$ 3 478 cm^{-1} (NH); δ 2.31 (3 H, s, CH_3) (Found: M^+, 281.2114. $C_{20}H_{23}D_2N$ requires *M*, 281.2112).

3-(*Cyclohexyl*[$^2H_2$]*methyl*)-2-*methylindole* (16). Reduction of 3-cyclohexylcarbonyl-2-methylindole (9) (1 mmol) in dry THF (20 ml) with lithium aluminium deuteride (4 mmol) gave, after 5 h at room temperature, followed by the usual work-up, the *product* (16) (85%), m.p. 104—105 °C (from diethyl ether–light petroleum); $\nu_{max.}$ 3 482 cm^{-1} (NH); δ 2.21 (3 H, s, CH_3) (Found: M^+, 229.1799. $C_{16}H_{19}D_2N$ requires *M*, 229.1799).

Acknowledgements

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