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BASE-INDUCED REARRANGEMENTS OF 3-(α-HALOACYL)INDOLES

A CONVENIENT ROUTE TO INDOLE-3-ACETIC ACIDS AND TRYPTOPHOLES

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Abstract—Base-induced reactions of 3-(α-haloacyl)indoles have been investigated. Rearrangement is a general reaction observed under the influence of various bases, e.g. hydroxide, hydride and Grignard reagent. Indole-3-acetic acids (**20–32**) are formed in fair yields when the reaction is performed with sodium hydroxide in 80% aqueous ethanol. The carbon monoxide evolved during the reaction appears to be eliminated from an intermediate cyclopropanone (**33**). Tryptopholes (**53–55**) are prepared in good yields by $LiAlH_4$-reduction of 3-(α-haloacyl)indoles.

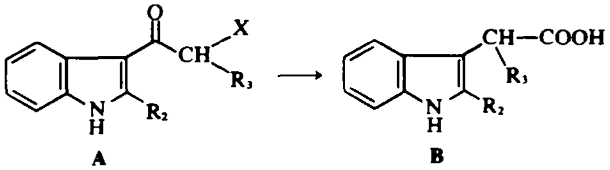
In base-induced reactions of α-haloacylated aromatic compounds, the product pattern depends largely on the conditions used. Thus, powdered sodium hydroxide in ether or boiling xylene caused rearrangement of α-chlorocyclohexyl phenyl ketone to 1-phenylcyclohexane-1-carboxylic acid,[1,2] whereas reaction of the same ketone with alcoholic sodium methoxide gave exclusively the epoxyether, 2-methoxy-2-phenyl-1-oxaspiro(2.5)-octane.[3] Rearrangements of similar systems in aprotic media with powdered sodium hydroxide have been studied by Smissman *et al.*[4,5] These "quasi Favorskii" rearrangements were explained either by a semi-benzilic mechanism[2] or by an ion-pair mechanism.[5] Reaction of phenacyl halides with sodium ethoxide in ethanol resulted in the formation of α- and β-diphenacyl halides[6] (2-benzoyl-3-halomethyl-3-phenyloxiranes), whereas solvolysis gave only substitution products.[7]

Cromwell *et al.*[8] have reported a facile silver ion-catalyzed rearrangement of 4-phenyl-(2-bromoisobutyryl)benzene to the corresponding Favorskii product. A push- and pull-mechanism with aryl migration was proposed.

We have recently found that 3-(α-haloacyl)indoles (**A**), when heated with base under rather mild conditions, are rearranged to indole-3-acetic acids (**B**).[9] This reaction should not be considered as a classical "quasi-Favorskii" rearrangement since assistance from the electron pair on the nitrogen is most likely to be involved.

We now report a more extensive and general study of the base-induced reactions of 3-(α-haloacyl)indoles.* Indole-3-acetic acids, which promote growth in plants,[11] can conveniently be prepared by this method. The appropriate 3-(α-haloacyl)indole (**1–13**) was added to a solution of sodium hydroxide in aqueous ethanol. The rearranged acid (**20–32**) was isolated by extraction. Competitive substitution (RCHXCOAr → RCHOHCOAr + RCHOEtCOAr) and in some cases decarbonylation are the most prevalent side-reactions. The results are given in Table 1.

The rearrangement presumably proceeds *via* a cyclopropanone intermediate.[12]† The high acidity of 3-(α-haloacyl)indoles‡ should facilitate formation of the anion and accordingly the cyclopropanone intermediate§ (**33**) (Scheme 1). The suggested mechanism also accounts for the carbon monoxide elimination (more or less pronounced) observed in all of the base-induced reactions of α-haloacylindoles. Thus, compound **10** with sodium hydroxide in boiling aqueous ethanol gave **35** and benzaldehyde as the main products and the acid **29** in 19% yield. The proposed mechanism is shown in Scheme 1. Decarbonylation of **33** should give the indolidene compound **34**, which is known[15] to be readily hydrolysed under alkaline conditions. Thus, Burr and Gortner[15] obtained benzaldehyde and di(2-methylindol-3-yl)phenylmethane (**35**) on alkaline hydrolysis of **34a**.



A **B**

The base-induced reaction of **11**[16,17∥] also yielded much carbon monoxide and secondary decarbonylation products (54%) but in this case the intermediate indolidene compound (**34b**) underwent dimerization rather than

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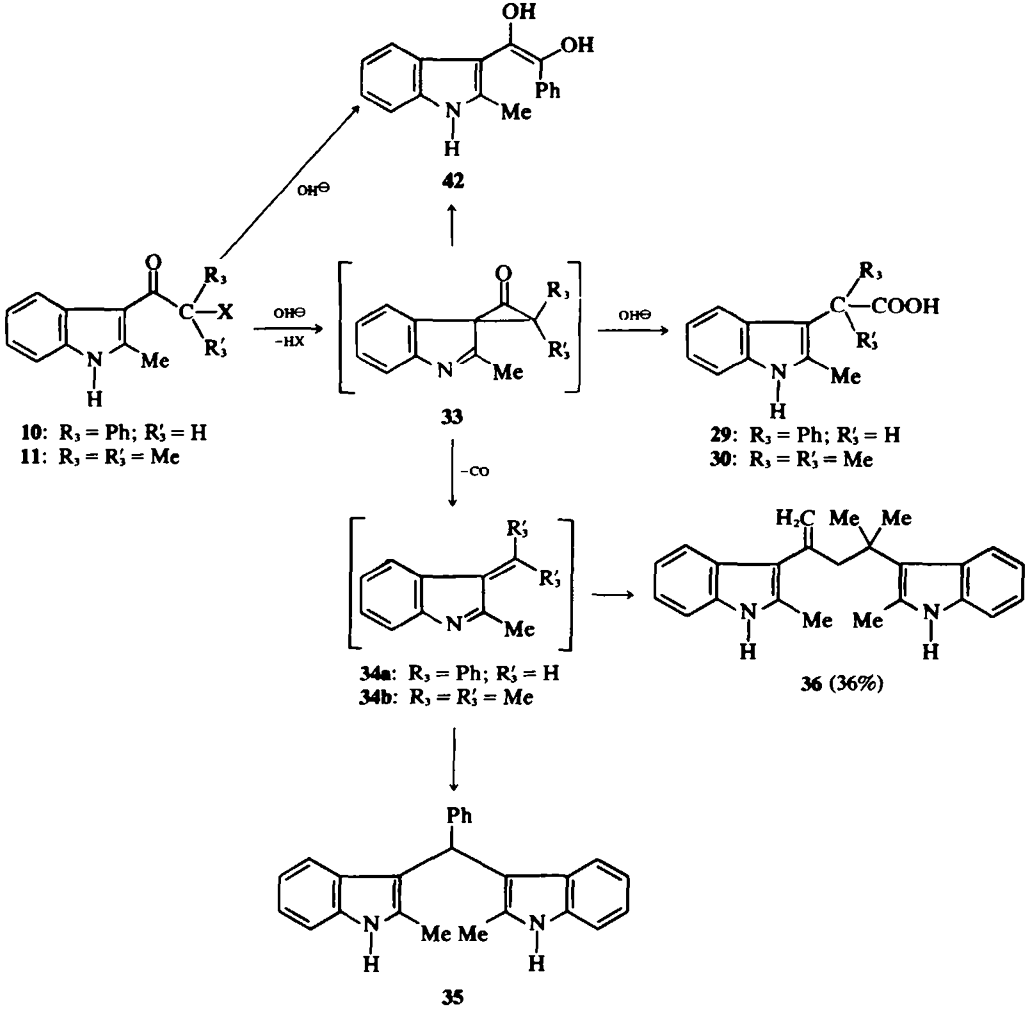
[*] The 3-(α-haloacyl)indoles were readily obtained from indole and pyridine α-haloacyl halide reagent.[10]

[†] A similar cyclopropane intermediate (6-aza4,5-benzspiro(2.4)hepta-4,6-diene) has been isolated in the hydrolysis of tryptophyl tosylate.[13]

[‡] 3-Acetylindole has the pK_a value 12·4, cf ref. 14.

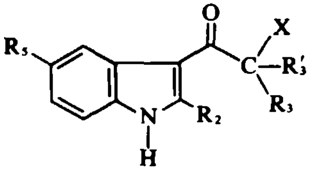
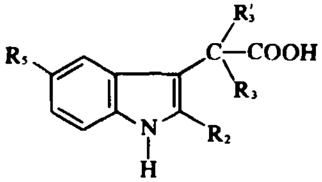
[§] Attempted capture of the intermediate cyclopropanone **33** by furan or cyclopentadiene has so far been unsuccessful.

[∥] This compound could not be prepared by the general route,[10] which resulted in the formation of 2-methyl-3-isobutyrylindole. The reason for this debromination is not clear (see Ref. 16) but presumably proceeds via a pyridinium salt. Dehalogenation via pyridinium salts has recently been observed.[17] The desired compound **11** could, however, be prepared by bromination of 2-methyl-3-isobutyrylindole with trimethylphenylammonium tribromide.



Scheme 1.

Table 1. Reaction of 3-(α-haloacyl)indoles with NaOH in 80% aqueous EtOH

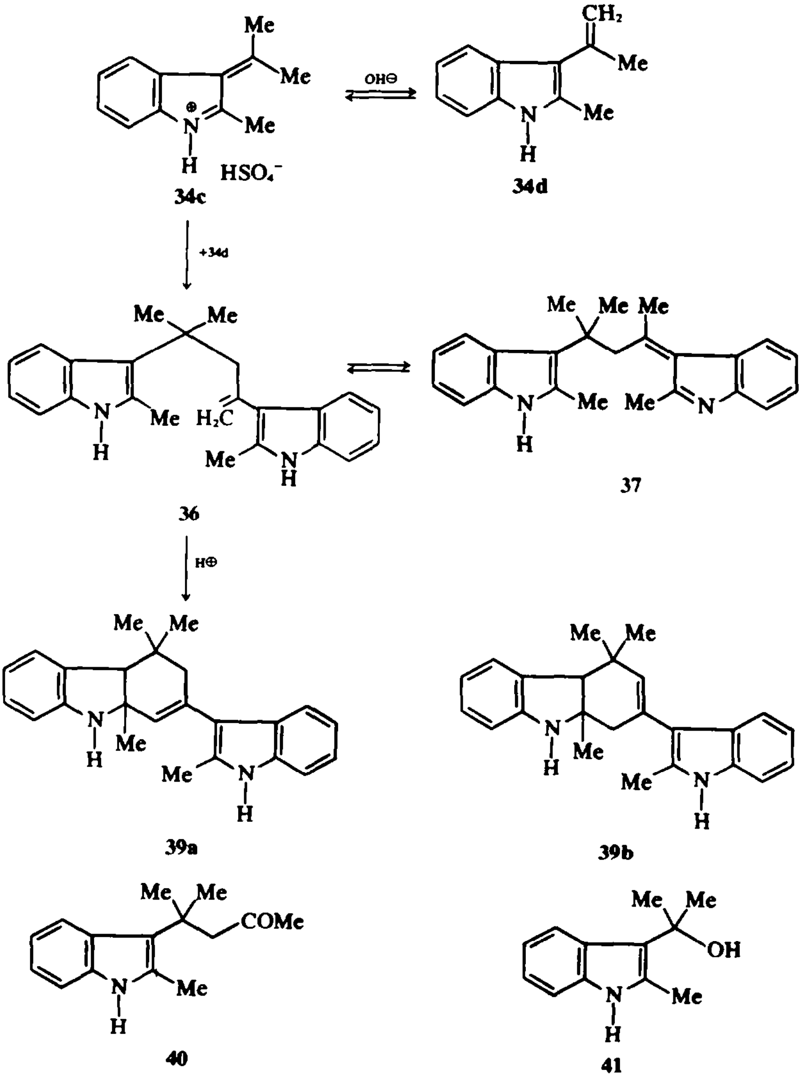
Starting material					Product		
							
Halide	X	R_2	R_3	R_3'	R_5	Acid	Yield,[a] (%)
1a	Cl	H	CH_3	H	H	**20**	11
1b	Br	H	CH_3	H	H	**20**	15
1c	I	H	CH_3	H	H	**20**	11
2	Br	H	C_2H_5	H	H	**21**	12
3	Cl	H	C_6H_5	H	H	**22**	18
4	Br	H	CH_3	CH_3	H	**23**	19[b]
5a	Cl	H	H	H	H	**24**	0·5[d]
6	Br	H	CH_3	H	OCH_3	**25**	11
7	Cl	H	C_6H_5	H	OCH_3	**26**	10
8	Br	CH_3	CH_3	H	H	**27**	25[e]
9	Br	CH_3	C_2H_5	H	H	**28**	18
10	Cl	CH_3	C_6H_5	H	H	**29**	64[c]
11	Br	CH_3	CH_3	CH_3	H	**30**	47[b]
12	Cl	CH_3	H	H	H	**31**	0·5
13	Cl	C_2H_5	C_6H_5	H	H	**32**	59[c]

[a] 0·3 M NaOH at reflux; [b] 2·4 M NaOH at 25°C; [c] 4·8 M NaOH at 25°C; [d] Isolated as the methyl ester; [e] 2·4 M NaOH at 40°C.

hydrolysis. Actually, the expected hydrolysis product, di(2-methylindol-3-yl)dimethylmethane could not be detected. The structure of the dimer **36** follows from its MS and NMR data (Experimental). Compound **36** could be more conveniently prepared by treating the readily[18] prepared sulfate **34c** with water followed by alkalinization.* Hydrolysis of this same sulfate in refluxing alkaline 80% ethanol gave **36** and 2-methylindole together with the cyclized dimeric compound **39**. Treatment of pure **36** with acid also gave **39** (Scheme 2) in agreement with Noland's mechanism† for the acid catalyzed condensation of 2-methylindole with acetone. As the dimer **36** is formed under alkaline conditions hydrolysis to the ketone **40**, via the equilibrium **36** ⇄ **37**, should be expected.[21] However, this ketone could only be detected under forcing conditions (heating with strong alkali). Steric hindrance probably accounts for this behaviour.

The thermal decarbonylation of cyclopropanones has been studied by other workers.[12c,22] Dehydrochlorination-decarbonylation of 2,2-dichloro-cyclohexane-1,3-diones leading to cyclopentenones was reported by Schamp and Verzele[22c] and later it was shown that several 2 - chloro - 1,3 - dicarbonyl compounds underwent dehydrochlorination-decarbonylation[23] when refluxed with sodium carbonate in xylene. Decarbonylation via a cyclopropanone intermediate was suggested.[23] Potential surface calculations on the decarbonylation of cyclopropanone seem to support a non-linear non-least-motion reaction path.[24]

Since the elimination of carbon monoxide from the cyclopropanone intermediate **33** (Scheme 1) is a thermal reaction‡ it should be possible to promote the formation of indole-3-acetic acids (**29** and **30**) at the expense of decarbonylation by using lower temperature and higher base-concentration. Indeed, action of 2·4 or 4·8 M NaOH at 25° on **10** and **11** gave a considerably higher yield of rearranged acid (Table 2), while the formation of decarbonylation products was reduced. On the other hand some of the α-haloacylindoles evolved little carbon



Scheme 2.

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*Joule and Smith have made a similar experiment. These workers isolated **41** by treating the sulfate **34c** with water under "controlled conditions".[19]

†Noland proposed **36** as an intermediate (but did not isolate it) in the acid-catalyzed condensation of acetone and 2-methylindole to **39**.[20a]

‡Calculation of the heat of decarbonylation of cyclopropanone gives $\Delta H_0 = -12{\cdot}5$ Kcal/mol.[25]

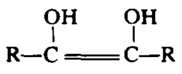
Table 2. The influence of hydroxide concentration on the formation of rearranged acid

Starting material	Yield of rearranged acid, (%)[a] 0·3 M[b]	2·4 M[c]	4·8 M,[c] NaOH
8	20		25[d]
10	19	45	64
11	9	47	
13	23	52	59

[a] Reaction in 80% aqueous EtOH; [b] Reaction performed at reflux; [c] At 25°; [d] At 40°.

monoxide and the yields of the rearranged acid when treated with strong alkali were not improved significantly (see Table 2).

The distribution between the substitution products appeared to depend on the bulkiness of R_3 and R_3'. Increasing substitution (R_3 and R_3' gave (see Ref. 28*c*) a higher relative yield of the hydroxy compound. Interestingly, only the enolic form **42** of the hydroxy substituted product from **10** could be isolated. Symmetric aromatic enediols[26,27] have been described by other workers. Fuson and Corse[26] showed that the enediol **43** was obtained by the action of $Mg + MgI_2$ on mesitoyl chloride. The heterocyclic enediol **44** is probably stabilized by internal H-bonding to the N atom.[27]



$$\mathrm{R{-}\overset{OH}{\overset{|}{C}}{=}\overset{OH}{\overset{|}{C}}{-}R}$$

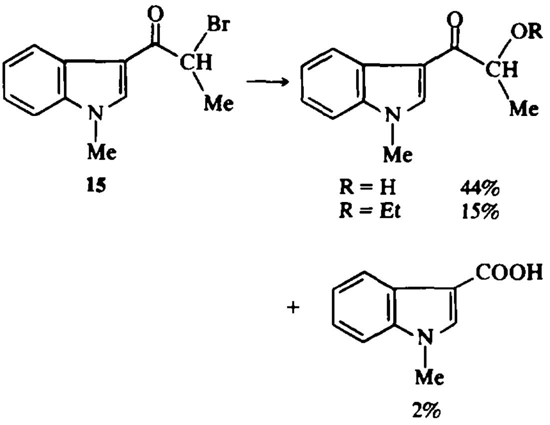
43: R = mesityl
44: R = 2-pyridyl or 2-quinolyl

Substituents at the α-carbon favored rearrangement. Thus, in a series of some 2-methylated 3-haloacylindoles the compound **12** ($R_3 = R_3' = H$) yielded 0·5% of the rearranged acid* whilst the compounds **8** ($R_3 = Me$, $R_3' = H$), **10** ($R_3 = Ph$, $R_3' = H$) and **11** ($R_3 = R_3' = Me$) gave 25, 64 and 47%, respectively of the corresponding acid (Table 1). Similar substituent effects have been observed for the normal Favorskii rearrangement.[28]

The reaction of α-haloacylindoles leading to rearranged acids can be divided into 4 steps. I, Formation of the anion; II, Displacement of the halogen atom leading to a cyclopropanone; III, Opening of the cyclopropanone; IV, Abstraction of a proton from the solvent (Scheme 3).

Since the steps I, III and IV are supposed to be rapid, step II was assumed to be rate-determining. Therefore, the base-induced reactions of the halides **Ia** (X = Cl), **Ib** (X = Br) and **Ic** (X = I) were compared. As expected the rate of acid formation increased in the series Cl < Br < I, but since the same was also true for the competitive substitution of halogen the yield of acid was almost unchanged (11, 15, 11%, respectively, see Table 1). Even weak bases, e.g. sodium carbonate, induced rearrangement which is in accordance with the facile anion formation (step 1).

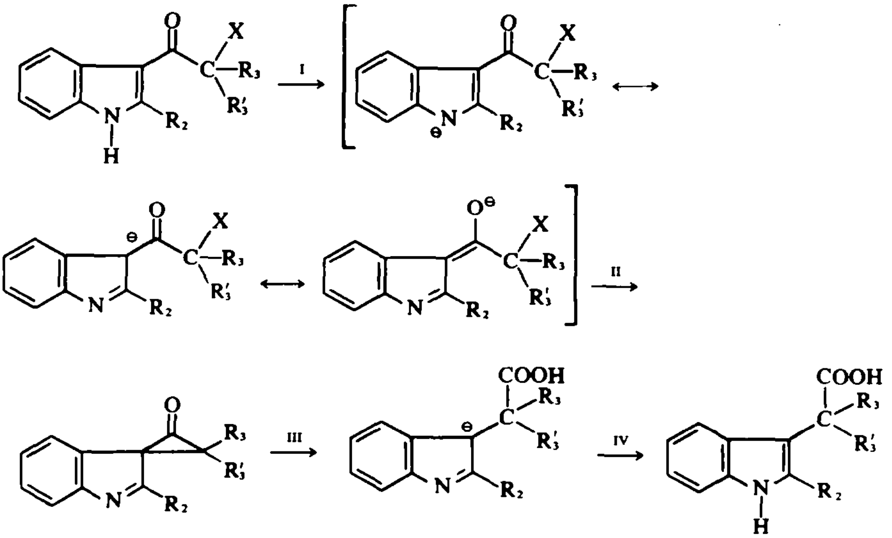
In order to evaluate the importance of the anion formation for the rearrangement, reactions of some N-methylated 3-(α-haloacyl)indoles were studied. When **15** was treated with 0·3 M NaOH in 80% ethanol, substitution products (44% and 15% yield) together with a small amount of 1-methylindole-3-carboxylic acid (2% yield) were isolated. α,N-Dimethylindole-3-acetic acid could not be detected. Attempted rearrangement of **14**



15

R = H 44%
R = Et 15%

2%



Scheme 3.

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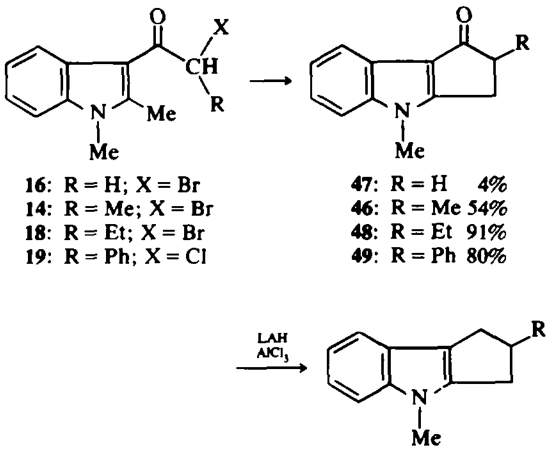
*The 2-methylindole-3-acetic acid formed was always accompanied by a small fraction of 2-methylindole-3-carboxylic acid (Experimental).

gave no rearranged acid either but the cyclized product **46** was isolated in good yield. Base-induced reaction of some other 1,2-dimethyl-substituted haloacylindoles also gave dihydrocyclopentindoles.

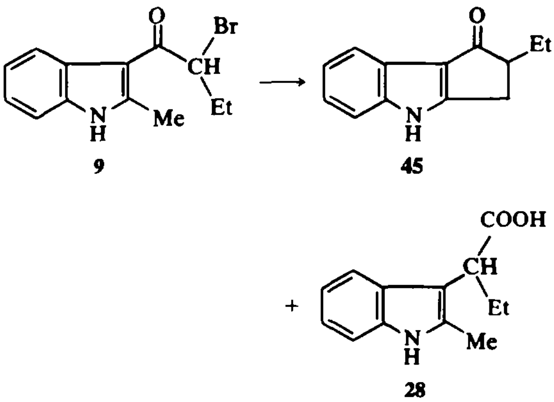
Reduction of the cyclized compound **47** gave N-methyldihydro-5H-cyclopentindole, identical to an authentic sample obtained by Fischer indolization of the N-methylphenylhydrazone of cyclopentanone.[29]



16: R = H; X = Br
14: R = Me; X = Br
18: R = Et; X = Br
19: R = Ph; X = Cl

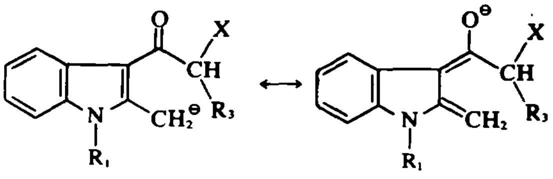
47: R = H 4%
46: R = Me 54%
48: R = Et 91%
49: R = Ph 80%

The base-induced reaction of some sterically hindered 3-haloacyl-2-methylindoles which were unsubstituted on the nitrogen also led to cyclization products. Thus, compound **9** when allowed to react with NaOH in 80% aqueous ethanol gave the cyclized compound **45** together with the rearranged acid **28** as the main products.

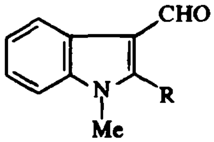


9 **45** **28**

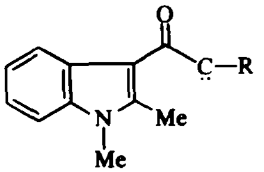
It is conceivable that the cyclization of the 3-haloacyl-2-methylindoles to dihydrocyclopentindoles proceeds via the resonance-stabilized anion **50**. The acidity of the H atoms on the 2-Me group in 3-acylindoles was confirmed by the rapid exchange of hydrogen for deuterium. Thus, it was demonstrated that the model compound **51a** rapidly underwent complete exchange in a solution of 0·3 M NaOD in 80% C_2H_5OD-D_2O to give **51b**, which is in accordance with an anionic mechanism. Another possible reaction pathway might involve initial carbene formation (**52**), followed by intra-molecular insertion into a C–H bond of the 2-Me group.[30] The absence of cyclization products on reaction of **17** with NaOH appears to be at variance with a reaction path-way involving only anionic intermediates but may favor a carbene mechanism (with or without anionic intermediates).



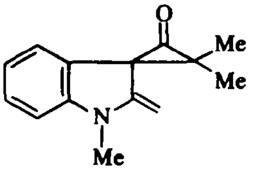
50



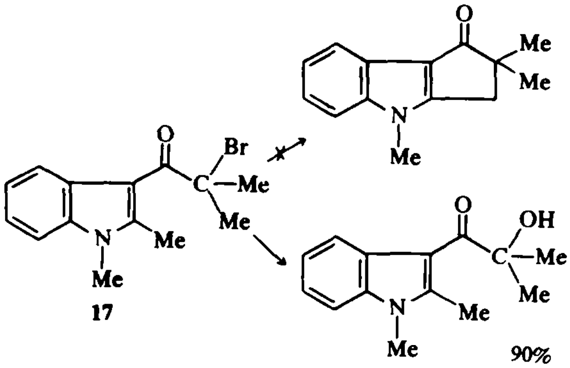
51a: R = Me
51b: R = CD_3



52



53



17

54 90%

An alternative reaction pathway might involve, via the anion of **17**, formation of the cyclopropanone **53**, which subsequently is attacked by OH^- giving the anion of the isolated product **54**.

When treated with Grignard reagents, 3-(α-haloacyl)indoles rearranged into 3-(2-hydroxyalkyl) indoles (tryptopholes). Thus, 3-(chloroacetyl)indole when treated with MeMgBr gave α,α-dimethyltryptophole.[9] Similarly, phenacyl halides have been shown to give rearranged phenethyl alcohols when treated with Grignard reagents.[31]

Reaction of 3-haloacylindoles with LAH in ether[9] gave 3-(2-hydroxyalkyl)indoles (tryptopholes) in variable yields. Results from some reductions with LAH are given in Table 3. The tryptopholes were accompanied by 3-alkylindole and/or 3-alkenylindole. Reduction of α-haloacyl-substituted aromatic compounds with LAH has been studied by Schwarz and Flor,[32] who showed that reduction of α-bromoalkyl-4′-hydroxy-3′,5′-di-t-butylphenyl ketones to β-phenetyl alcohols proceeds with aryl ring migration.[32] Several mechanisms for these rearrangements were discussed,[32c] but a mechanism involving cyclopropanol formation with displacement of halogen via a halohydrin was favored.

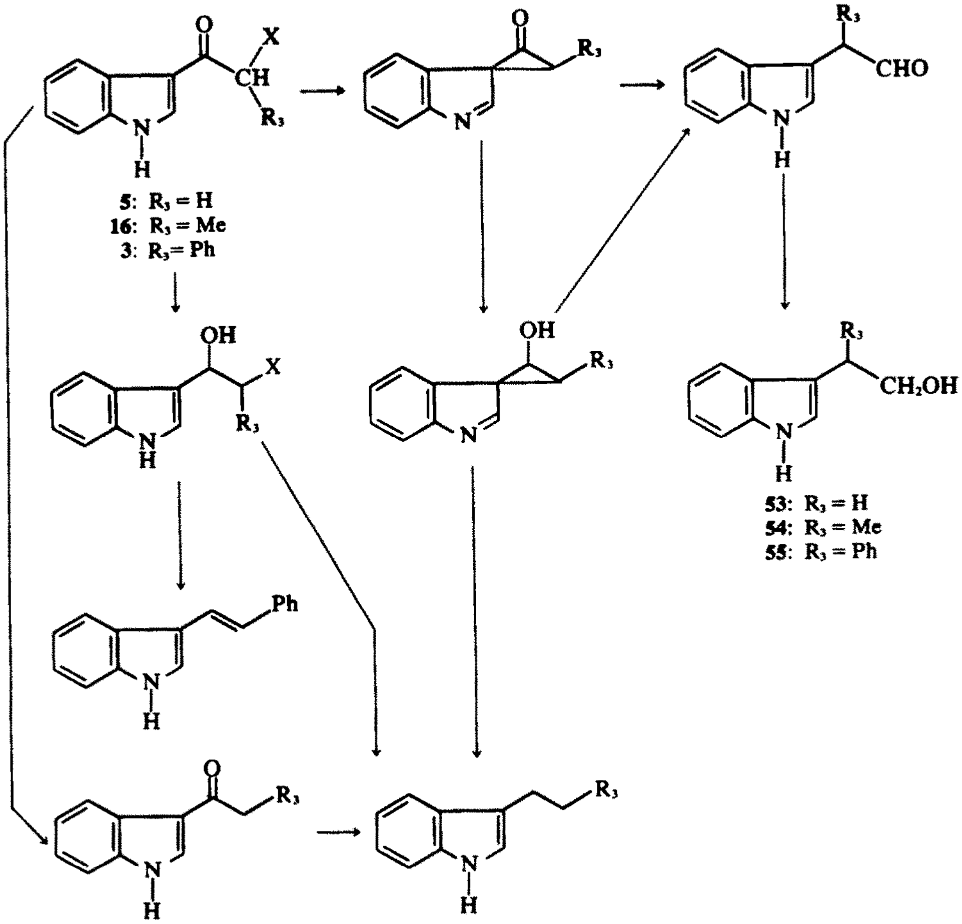
A mechanism for the reduction of 3-(α-haloacyl)indoles

Table 3. Reaction of 3-(α-haloacyl)indoles with LAH

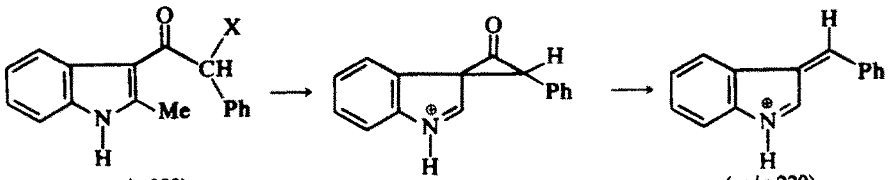
Starting material	Substance	Yield of tryptophole %	Yield of 3-alkylindole
5a (X = Cl)	$R_3 = H$	73[a]	3[a]
5b (X = Br)	$R_3 = H$	70[a]	5[a]
5c (X = I)	$R_3 = H$	8[a]	54[a]
1b (X = Br)	$R_3 = CH_3$	67[b]	—
3 (X = Cl)	$R_3 = C_6H_5$	73[b]	1[b]

[a] Determined by GLC using benzyl ether as internal standard.
[b] Isolated yield.

with LAH is proposed in Scheme 4. N-Deprotonation followed by expulsion of halogen would give a cyclopropanone intermediate. The cyclopropanone is then reductively cleaved to the aldehyde, which on further reduction gives the 3-(2-hydroxyalkyl)indole. The isomeric 3-(1-hydroxyalkyl)indole could not be detected.[33] A halohydrin intermediate followed by formation of a cyclopropanol would also lead to the open aldehyde. Rearrangement of 3-chloroacetylindole (**5a**) induced by $LiAlD_4$ giving α,α-dideuterated tryptophole ($ArCH_2CD_2OH$) confirmed this mechanism. The formation of alkylindole is likely to proceed via a halohydrin



Scheme 4.



10 (m/e 283)

(m/e 220)

	Relative abundance (%)*	
	$M^{+\cdot}$	$(M\text{-halogen-}28)^+$
4	5	7
9	9	3
10	2	8
11	6	10
13	1	6

*Relative abundance to the $ArC{\equiv}O^+$ ion (the most abundant ion in all of the spectra; see Ref. 10).

which on prolonged reduction should give the 3-alkylindole. Accordingly, the 3-ethylindole formed from $LiAlD_4$-reduction of **5a** was deuterated as follows—$ArCD_2CH_2D$.

The product distribution varied markedly in the series **5a–c** (X = Cl, Br, I) as shown in Table 2. The high yield of 3-ethylindole observed when X = I is probably due to the facilitated hydride substitution.

Mass spectra of 3-(*α-haloacyl*)*indoles*. It is noteworthy that the mass spectra of 3-(α-haloacyl)indoles show a peak at M-halogen-28, indicating elimination of carbon monoxide from a cyclopropanone.

Thermal elimination of carbon monoxide from cyclopropanone normally requires high temperature (150°).[12,22] The facile carbon monoxide elimination observed in the base-induced rearrangement of some α-haloacylindoles, e.g. **10** and **11**, indicates a low-lying transition state, which may thus permit the addition of carbon monoxide to **34**. This would constitute a useful preparative route to indole-3-acetic acids.

Similar reactions are also conceivable with other types of α-haloacyl substituted aromatics, notably α-haloacylphenols (see Ref. 32). If successful a new route to quinone methides will be opened.

EXPERIMENTAL

M.ps are corrected. NMR spectra were recorded on a Varian A-60 spectrometer unless otherwise stated. IR spectra were obtained with a Perkin-Elmer 421 spectrophotometer. Mass spectra were recorded on an LKB 9000 spectrometer. Preparative TLC was done on silica gel GF plates (Analtech). GLC analyses were obtained from a Hewlett-Packard 402 gas chromatograph, using a 4 ft × 1/8 in. (i.d.) column of 3·8% UC-W98 on Chromosorb W. All the base-induced reactions were conducted under N_2.

General procedure for the preparation of 3-(*α-haloacyl*)*indoles*. Following the method described earlier* the α-haloacyl halide (0·1 mol) was added during 1 hr to a well-stirred soln of the appropriate indole (0·1 mol) and pyridine (0·1 mol) in toluene (250 ml) at 50–60°. The mixture was stirred for another hr, cooled, poured into water (300 ml) and allowed to stand at 0° *ca.* 30 min. The crude product which separated from the toluene–water mixture was collected, triturated with MeOH and recrystallized from MeOH or acetonitrile.

Compounds **1a** (m.p. 210–212°), **1b** (m.p. 193–194°), **2** (m.p. 190–191°), **3** (m.p. 218–220°), **12** (m.p. 220–221°) and **5a** (m.p. 230–232°) have been synthesized earlier by the method described.[10]

3-*Bromoacetylindole* (**5b**) yield: 40%. Recrystallization from MeOH m.p. 229° (lit.[37] 230°).

3-(2-*Bromopropionyl*)-5-*methoxyindole* (**6**), yield: 65% recrystallized from acetonitrile, m.p. 181–182°; IR (KBr) 3180 (NH), 1614 (C=O), 1480, 1435, 1274, 1218, 915 cm⁻¹; mass spectrum *m/e* (relative intensity) 283 (13), 281 (13), 174 (100), 159 (10). (Found: C, 50·87; H, 4·31; N, 5·07; Br, 28·57. Calc. for $C_{12}H_{12}NO_2Br$: C, 51·09; H, 4·29; N, 4·96; Br, 28·32%).

3-(*α-Chlorophenylacetyl*)-5-*methoxyindole* (**7**), yield: 83%, recrystallized from acetonitrile, m.p. 210°; IR (KBr) 3240 (NH), 1640, 1635 (C=O), 1470, 1437, 1205, 717 cm⁻¹; mass spectrum *m/e* (relative intensity) 301 (2), 299 (5), 236 (5), 175 (11), 174 (100), 159 (6). (Found: C, 68·25; H, 4·76; N, 4·70; Cl, 11·87. Calc. for $C_{17}H_{14}NO_2Cl$: C, 68·12; H, 4·71; N, 4·67; Cl, 11·83%).

3-(2-*Bromopropionyl*)-2-*methylindole* (**8**), yield: 85%, recrystallized from acetonitrile m.p. 162°; IR (KBr) 3180 (NH), 1600 (C=O), 1455, 1440, 760 cm⁻¹; NMR (DMSO-d_6) δ 1·88 (d, 3, CH_3), 2·80 (s, 3, CH_3), 5·35 (q, 1, CH), 7·0–8·3 (m, 4, aromatic), 12·01 (s, 1, NH). (Found: C, 54·05; H, 4·60; N, 5·31; Br, 30·15. Calc. for $C_{12}H_{12}NOBr$: C, 54·16; H, 4·54; N, 5·26; Br, 30·02%).

3-(2-*Bromobutyryl*)-2-*methylindole* (**9**), yield: 93%, recrystallized from MeOH m.p. 135–136°; IR (KBr) 3300 (NH), 1610 (C=O), 1488, 1456, 1430, 1270, 745, 720 cm⁻¹; NMR (DMSO-d_6) δ 1·85 (t, 3, CH_3), 2·17 (m, 2, CH_2), 2·77 (s, 3, CH_3), 5·18 (t, 1, CH). (Found: C, 55·47; H, 4·87; N, 5·13; Br, 28·31. Calc. for $C_{13}H_{14}NOBr$: C, 55·73; H, 5·04; N, 5·00; Br, 28·52%).

3-(*α-Chlorophenylacetyl*)-2-*methylindole* (**10**). The oil formed when pouring the toluene phase into water did not crystallize when triturated with MeOH, but on standing in MeOH overnight in a refrigerator, the crystals formed were recrystallized from MeOH–water (85:15), yield: 53% m.p. 145°; IR (KBr) 3310 (NH), 3280, 1638 (C=O), 1605, 1458, 1430, 751, 740, 730 cm⁻¹; NMR (DMSO-d_6) δ 2·58 (s, 3, CH_3), 6·57 (s, CH); mass spectrum *m/e* (relative intensity) 285 (0·5), 283 (1·5), 220 (8), 159 (11), 158 (100), 130 (7). (Found: C, 72·01; H, 4·94; N, 5·10; Cl, 12·48. Calc. for $C_{17}H_{14}NOCl$: C, 71·96; H, 4·97; N, 4·94; Cl, 12·49%).

3-*Bromoacetyl*-2-*methylindole* (**12b**), yield: 50%, recrystallized from MeOH; m.p. 202–203° (lit.[34] 204°).

3-(*α-Chlorophenylacetyl*)-2-*ethylindole* (**13**). The oil was treated as described for **10**, yield: 20%; m.p. 133–134° (MeOH); IR (KBr) 3260 (NH), 1615 (C=O), 1450, 1410, 1237, 731 cm⁻¹; mass spectrum *m/e* (relative intensity) 297 (1), 234 (6), 173 (12), 170 (100), 143 (6), 129 (7). (Found: C, 72·62; H, 5·44; N, 4·55. Calc. for $C_{18}H_{16}NOCl$: C, 72·60; H, 5·42; N, 4·70%).

3-(2-*Iodopropionyl*)*indole* (**1c**). 3-(2-Chloropropionyl)indole[10] (5·18 g, 0·025 mol) and NaI (29·8 g, 0·2 mol) in acetone (100 ml) were refluxed for 5 hr. The NaCl formed was removed by filtration and the clear solution was poured into water (200 ml). The precipitated 3-(2-iodopropionyl)indole gave 6·56 g (92%) m.p. 202–204°. (Found: C, 44·50; H, 3·43; N, 4·64. Calc. for $C_{11}H_{10}NOI$: C, 44·17; H, 3·37; N, 4·68%).

3-*Iodoacetylindole* (**5c**). The same method as for **1c** was used treating 3-chloroacetylindole with NaI, yield: 90% m.p. 200–201° (lit.[34] 211°).

3-*Isobutyrylindole* from indole, N,N-dimethyl isobutyramide and $POCl_3$, m.p. 126–27° (lit.[35] 126–127·5°).

3-*Isobutyryl*-2-*methylindole* from 2-methylindole by the method for 3-isobutyrylindole, yield: 50%; m.p. 160–61° (EtOH); IR (KBr) 3200–3000 (NH), 2970, 1600 (C=O), 1455, 1435, 1369, 760 cm⁻¹; mass spectrum *m/e* (relative intensity) 201 (16), 159 (11), 158 (100), 130 (12). (Found: C, 77·64; H, 7·48; N, 6·93. Calc. for $C_{13}H_{15}NO$: C, 77·58; H, 7·51; N, 6·96%).

3-(2-*Bromoisobutyryl*)*indole* (**4**). A mixture of 3-isobutyrylindole (1·40 g, 7·5 mmol) and trimethylphenylammonium tribromide (2·82 g, 7·5 mmol) in THF (60 ml) was stirred at 25° for 24 hr. After evaporation of the solvent at room temp. under vacuum, water (75 ml) was added and the mixture was stirred for 1 hr. The crystals formed were carefully washed with water, yield: 1·97 g (99%). Recrystallization from toluene–light petroleum (3:1) m.p. 172–174° (lit.[36] 176–178°).

3-(2-*Bromoisobutyryl*)-2-*methylindole* (**11**). The same method as for preparation of **4** was used, yield: 100% m.p. 124°. After recrystallization from toluene–light petroleum (2:1) the m.p. was unchanged;; mass spectrum (relative intensity) 281 (3), 279 (3), 172 (10), 159 (11), 158 (100), 130 (14), 102 (11), 77 (12), 41 (9). (Found: C, 56·00; H, 4·83; N, 4·93. Calc. for $C_{13}H_{14}NOBr$: C, 55·73; H, 5·04; N, 5·00%).

3-(2-*Bromoisobutyryl*)-1,2-*dimethylindole* (**17**). The same method was used starting from 1,2-dimethyl-3-isobutyrylindole (described below), yield: 88% m.p. 130° (benzene–light petroleum); mass spectrum *m/e* (relative intensity) 295 (3), 293 (3), 186 (8), 173 (12), 172 (100), 115 (6). (Found: C, 57·07; H, 5·44; N, 4·69. Calc. for $C_{14}H_{16}NOBr$: C, 57·15; H, 5·48; N, 4·76%).

Preparation of N-*substituted acylindoles by methylation*

3-(2-*Bromopropionyl*)-1,2-*dimethylindole* (**14**). Following the procedure described by Jackson and Smith,[37] 3-(2-bromopropionyl)-2-methylindole (7·9 g), MeBr (6 g) and K_2CO_3 (8 g) in acetone (80 ml) were refluxed for 36 hr. The mixture was filtered, the filtrate was evaporated and the residue was recrystallized from EtOH to give 5·5 g (66%) of **14** m.p. 118–119°; IR (KBr) 1635 (C=O), 1505, 1400, 1170, 756 cm⁻¹; mass spectrum *m/e* (relative intensity) 281 (8), 279 (8), 173 (12), 172 (100). (Found: C, 55·91; H, 5·05; N, 5·14. Calc. for $C_{13}H_{14}NOBr$: C, 55·73; H, 5·04; N, 5·00%).

3-(2-*Bromopropionyl*)-1-*methylindole* (**15**). The same method as

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*See * footnote on p. 2066.

above was used starting from 3-(2-bromopropionyl)indole, yield: 90% m.p. 114–116° (EtOH); IR (KBr) 1630 (C=O), 1530, 1468, 1375, 750 cm^{-1}; mass spectrum *m/e* (relative intensity) 267 (9), 265 (9), 157 (11), 158 (100). (Found: C, 54·50; H, 4·56; N, 5·39. Calc. for $C_{12}H_{12}NOBr$: C, 54·16; H, 4·54; N, 5·26%).

3-Bromoacetyl-1,2-dimethylindole (**16**), from 3-bromoacetyl-2-methylindole by the same procedure m.p. 120–121° (MeOH); IR (KBr) 1640 (C=O), 1510, 1470, 1450, 1400, 1075, 738 cm^{-1}; mass spectrum *m/e* (relative intensity) 267 (16), 265 (16), 186 (13), 173 (12), 172 (100). (Found: C, 54·10; H, 4·50; N, 5·20. Calc. for $C_{12}H_{12}NOBr$: C, 54·16; H, 4·54; N, 5·26%).

1,2-Dimethyl-3-isobutyrylindole. Prepared by methylation of 3-isobutyryl-2-methylindole with MeI/K_2CO_3, recrystallization from light petroleum, yield: 80%; m.p. 62–63°; IR (KBr) 2960, 1630 (C=O), 1460, 1400, 1070, 745 cm^{-1}; mass spectrum *m/e* (relative intensity) 215 (14), 173 (12), 172 (100), 115 (8). (Found: C, 77·77; H, 7·88; N, 6·43. Calc. for $C_{14}H_{17}NO$: C, 78·10; H, 7·96; N, 6·51%).

3-(2-Bromobutyryl)-1,2-dimethylindole (**18**) from 3-(2-bromobutyryl)-2-methylindole, yield: 85%; m.p. 107–108°. (Found: C, 57·25; H, 5·49; N, 4·56. Calc. for $C_{14}H_{16}NOBr$: C, 57·15; H, 5·48; N, 4·76%).

3-(α-Chlorophenylacetyl)-1,2-dimethylindole (**19**) by the same method from 3-(α-chlorophenylacetyl)-2-methylindole, yield: 97%; m.p. 157° NMR (DMSO-d_6) δ 2·74 (s, 3, CH_3), δ 3·70 (s, 3, CH_3), 6·63 (s, 1, CH), 7·1–8·2 (4, m, aromatic) mass spectrum *m/e* (relative intensity) 299 (0·5), 297 (1·3), 234 (6), 173 (12), 172 (100). (Found: C, 72·83; H, 5·42; N, 4·68. Calc. for $C_{18}H_{16}NOCl$: C, 72·60; H, 5·42; N, 4·70%).

Reaction of 3-haloacylindoles with sodium hydroxide

α-Methylindole-3-acetic acid (**20**). To a well-stirred soln of NaOH (2·4 g, 0·06 mol) in EtOH (160 ml) and water (40 ml), was added 3-(2-bromopropionyl)indole (5·04 g, 0·02 mol) in ten portions during 1 hr. The soln was refluxed for another hr, cooled and neutralized with HCl. The slightly yellow soln was concentrated under vacuum to a small volume (30 ml). Ether (50 ml) was added and the organic phase was extracted three times with 1 M $NaHCO_3$ (3 × 30 ml). The alkaline water phases were combined and washed with ether. The water phase was treated with activated carbon, titrated with HCl to pH 3 and extracted three times with ether. The combined ether phases were washed with water and dried ($MgSO_4$). Evaporation under vacuum gave a semisolid mass of α-methylindole-3-acetic acid which crystallized when treated with benzene–light petroleum (3 ml, 1:1), yield: 0·55 g 15% m.p. 105–107° (lit.[38] 111–112°); NMR ($CDCl_3$) δ 1·41 (d, 3, CH_3), 3·87 (q, 1, CH).

The organic phase from above was dried ($MgSO_4$) to give an oily residue (3·00 g). This mixture was dissolved in MeOH and 300 mg was separated by preparative TLC (eluent CH_2Cl_2). The first component was identified as 3-(2-*ethoxypropionyl*)*indole* (51 mg; 12%) m.p. 137–138° (MeOH) IR (KBr) 3210 (NH), 1625 (C=O), 1415, 1095, 1110, 760 cm^{-1} mass spectrum *m/e* (relative intensity) 217 (4), 173 (13), 145 (15), 144 (100), 117 (10). (Found: C, 72·25; H, 6·80; N, 6·40. Calc. for $C_{13}H_{15}NO_2$: C, 71·87; H, 6·96; N, 6·45%).

The second fraction gave 151 mg 3-(2-*hydroxypropionyl*)*indole* (40%) m.p. 154–156° (lit.[39] 152–153°).

α-Ethylindole-3-acetic acid (**21**). The same procedure as above was utilized. 3-(2-Bromobutyryl)indole (5·28 g, 0·02 mol) was reacted with NaOH in 80% EtOH. The product was recrystallized from benzene–light petroleum to give white crystals m.p. 106–107° (lit.[11a] 106°), yield: 0·50 g (12%); NMR (DMSO-d_6) δ 0·88 (t, 3, CH_3), 1·90 (m, 2, CH_2), 3·66 (t, 1, CH).

α-Phenylindole-3-acetic acid (**22**) from 3-chlorophenylacetylindole (3·90 g, 0·0145 mol). Recrystallized from MeOH:water (3:2), yield: 0·65 g (18%) m.p. 184–186° (lit.[40] 175–176·5°); IR (KBr) 3439 (NH), 3200–2500 (OH), 1705 (C=O), 1207, 749, 705 cm^{-1}; mass spectrum *m/e* (relative intensity) 251 (29), 207 (17), 206 (100), 204 (17), 144 (30).

α,α-Dimethylindole-3-acetic acid (**23**). (A) Prepared from 3-(2-bromoisobutyryl)indole (532 mg) by the standard method as described for **20**, yield: 15 mg (4%); m.p. 135–136° (lit.[38] 135°). (B) The reaction was performed at 25° in 2·4 M NaOH in 80% EtOH. 3-(2-bromoisobutyryl)indole (0·443 g) was added to a soln of NaOH (1·6 g) in 80% EtOH (16·7 ml) during 1 hr. The reaction was allowed to continue for 2 hr after the addition was complete, yield: 63 mg (19%); m.p. 135–136°.

5-Methoxy-α-methylindole-3-acetic acid (**25**) from 3-(2-bromopropionyl)-5-methoxyindole (0·75 g, 2·66 mmol), yield: 65 mg (11%); m.p. 114–116° (benzene–light petroleum); IR (KBr) 3405 (NH), 1718 (C=O) cm^{-1}; mass spectrum *m/e* (relative intensity) 219 (37), 175 (24), 174 (100), 160 (23), 159 (17), 158 (30), 131 (10), 130 (14). (Found: C, 65·80; H, 5·70; N, 6·20. Calc. for $C_{12}H_{13}NO_3$: C, 65·74; H, 5·98; N, 6·39%).

5-Methoxy-α-phenylindole-3-acetic acid (**26**) from 3-chlorophenylacetyl-5-methoxyindole (2·20 g, 7·35 mmol), yield: 0·21 g (10%); m.p. 180–182° (benzene–light petroleum); IR (KBr) 3420 (NH), 3200–2500 (OH), 1700 (C=O), 1486, 1219, 1203, 1175, 704; mass spectrum *m/e* (relative intensity) 281 (32), 236 (100), 220 (16), 204 (13). (Found: C, 72·30; H, 5·20; N, 4·60. Calc. for $C_{17}H_{15}NO_3$: C, 72·56; H, 5·37; N, 4·98%).

α,2-Dimethylindole-3-acetic acid (**27**). (A) The same procedure was used starting from 3-(2-bromopropionyl)-2-methylindole. The oil formed was treated with benzene–light petroleum (1:1). Recrystallization from MeOH–water (2:3), yield: 0·80 g (20%); m.p. 135–137° (lit.[9] 135–137°); IR (KBr) 3400 (NH), 3200–2500 (OH), 1700 (C=O), 1465, 1300, 1250, 1245, 750 cm^{-1}; mass spectrum *m/e* (relative intensity) 203 (27), 159 (13), 158 (100), 144 (15), 143 (18).

(B) As A but the reaction was performed at 40° in 4·8 M NaOH in 80% ethanol. Addition during 1 hr followed by 4 hr stirring, yield: 25%.

α-Ethyl-2-methylindole-3-acetic acid (**28**) from 3-(2-bromobutyryl)indole (4·0 g, 0·0143 mol), yield: 0·55 g (18%); m.p. 100–102°; IR (KBr) 3385 (NH), 3200–2500 (OH), 1694 (C=O), 1460, 1300, 750 cm^{-1}; mass spectrum *m/e* (relative intensity) 217 (37), 188 (29), 173 (14), 172 (100), 157 (18). (Found: C, 71·90; H, 6·70; N, 6·40. Calc. for $C_{13}H_{15}NO_2$: C, 71·86; H, 6·96; N, 6·45%).

2-Methyl-α-phenylindole-3-acetic acid (**29**). (A) Prepared from 3-chlorophenylacetyl-2-methylindole (4·21 g, 0·015 mol) as described for **20**. Recrystallized from benzene, yield: 0·74 g (19%); m.p. 168–169°; IR (KBr) 3420 (NH), 3200–2500 (OH), 1705 (C=O), 1464, 1310, 750, 722 cm^{-1}; mass spectrum *m/e* (relative intensity) 265 (27), 221 (18), 220 (100). (Found: C, 76·81; H, 5·75; N, 5·36. Calc. for $C_{17}H_{15}NO_2$: C, 76·96; H, 5·70; N, 5·28%).

(B) Preparation was performed in 2·4 or 4·8 M NaOH as described for **23**. Extraction was performed with 1 M NaOH, yields see Table 2.

α,α,2-Trimethylindole-3-acetic acid (**30**). (A) Prepared from 3-(2-bromoisobutyryl)-2-methylindole (470 mg) by the standard method (0·3 M NaOH), yield: 33 mg (9%) m.p. 138–139°. (B) Preparation was performed in 2·4 M NaOH as described for **23**. After the addition the solution was stirred for 1 hr at 25°, yield: 157 mg (47%) m.p. 138–139° (benzene–light petroleum); IR (KBr) 3435 (NH), 3100–2500 (OH), 1690 (C=O), 1460, 1305, 1290, 735 cm^{-1}. (Found: C, 71·44; H, 6·90; N, 6·36. Calc. for $C_{13}H_{15}NO_2$: C, 71·86; H, 6·96; N, 6·45%).

2-Ethyl-α-phenylindole-3-acetic acid (**32**). (A) Prepared from 3-chlorophenylacetyl-2-ethylindole (1·19 g, 4·0 mmol) by the standard method (0·3 M NaOH), yield: 0·24 g (23%). (B) Preparation was performed in 2·4 or 4·8 M NaOH as described for **23**. Extraction was performed with 1 M NaOH, yields see Table 2; m.p. 80–81° (benzene–light petroleum 4:1); IR (KBr) 3380 (NH), 3200–2500 (OH), 1700 (C=O). (Found: C, 77·73; H, 6·23; N, 4·87. Calc. for $C_{18}H_{17}NO_2$: C, 77·40; H, 6·13; N, 5·01%).

Indole-3-acetic acid methyl ester. The crude acid mixture obtained from **5a** was treated with diazomethane. Separation of the esters obtained by preparative TLC using CH_2Cl_2 as eluent gave indole-3-acetic acid methyl ester (0·5%) and indole-3-carboxylic acid methyl ester (0·8%). The esters were identified by comparison with authentic samples (see Refs 41 and 42, respectively).

Reaction of 3-chloroacetyl-2-methylindole (**12**) *with* NaOH. To a refluxing soln of NaOH (2·4 g, 0·06 mol) in 200 ml 80% EtOH was added 3-chloroacetyl-2-methylindole (4·14 g, 0·02 mol) in ten portions during 1 hr. After another hr of reflux the soln was cooled and neutralized. Evaporation gave a crude product which was dissolved in ether and extracted three times with 1 M $NaHCO_3$.

The $NaHCO_3$ extract was acidified and extracted with ether.

The ether soln was dried ($MgSO_4$) and evaporated. The residue (54 mg) was separated by preparative TLC (eluent CH_2Cl_2–MeOH 20:1) giving *2-methylindole-3-carboxylic acid* (20 mg, 0·6%); m.p. 181–183° (lit.[46] 180°) and *2-methylindole-3-acetic acid* (20 mg, 0·5%); m.p. 190–195° (lit.[44] 197–199°).

Reaction of 3-(*α-chlorophenylacetyl*)-2-*methylindole* (**10**) *with* NaOH. The reaction was performed as above starting from 400 mg of **10**. After neutralization the soln was cooled and left at 0° overnight. The crystals formed were collected to give 84 mg (34%) of **35**; m.p. 241–243° (lit.[15] 243°).

The remaining EtOH–water phase was reduced to a small volume, diluted with ether and extracted with $NaHCO_3$ to remove the acid (see above). The ether phase was evaporated to give an oily residue which was separated by preparative TLC to give 50 mg (13%) of **42** m.p. 120–121° (MeOH–water 4:1); IR (KBr) 3255, 3050, 2965, 1494, 1461, 1192, 1062, 747, 702 cm^{-1}; mass spectrum *m/e* (relative intensity) 265 (20), 220 (100), 219 (22), 218 (27), 204 (10), 188 (17). (Found: C, 76·96; H, 5·70; N, 5·28. Calc. for $C_{17}H_{15}NO_2$: C, 76·96; H, 5·70; N, 5·28%).

GLC analysis of the reaction mixture showed that 20% *benzaldehyde* had been formed.

Reaction of 3-(2-*bromobutyryl*)-2-*methylindole* (**9**) *with* NaOH. The reaction was performed as described above for **12** starting from **9** (4·0 g). After evaporation, the crude product was dissolved in ether and extracted with $NaHCO_3$ to remove the acid (0·55 g, see above). A solid was formed in the ether phase during the extractions. This solid (0·18 g, 6%) was found to be **45** m.p. 208°; IR (KBr) 3150 (NH), 2955, 2870, 1650 (C=O), 1465, 1430, 1160, 780, 740 cm^{-1}; mass spectrum *m/e* (relative intensity) 200 (9), 199 (60), 184 (15), 172 (12), 171 (100), 170 (58), 156 (11), 129 (11), 115 (11); NMR (DMSO-d_6) δ 0·94 (t, 3, CH_3), 1·63 (m, 2, CH_2), 2·50–3·67 (m, 3, CH and CH_2), 7·1–7·9 (m, 4, aromatic). (Found: C, 78·20; H, 6·59; N, 7·20. Calc. for $C_{13}H_{13}NO$: C, 78·36; H, 6·58; N, 7·03%).

The remaining clear ether phase was evaporated and one-tenth of the semi-solid mass was separated by preparative TLC (eluent CH_2Cl_2). It was shown to contain 86 mg (30%) of **45** (total yield 36%).

Reaction of 3-(2-*bromoisobutyryl*)-2-*methylindole* (**11**) *with* NaOH. The reaction was performed as described above for **12** starting from **11** (470 mg). The ether was extracted with $NaHCO_3$ to remove the acid (see above). The remaining ether phase was evaporated to give a semi-solid residue (261 mg) which was separated by preparative TLC (eluent CH_2Cl_2–MeOH 20:1 then light petroleum–ether 4:1). The first component was identified as 2-*methylindole* 40 mg (18%). The second component 101 mg (36%) was determined to be **36** m.p. 160–161° (MeOH); IR (KBr) 3405 (NH), 2970, 1615 ($C{=}CH_2$), 1460, 1432, 1420, 890, 742 cm^{-1}; NMR (DMSO-d_6) δ 1·37 (s, 6, $2CH_3$), 2·22 (s, 3, CH_3), 2·29 (s, 3, CH_3), 3·14 (s, 2, CH_2), 4·87 and 4·98 (AB pattern $J = 3$ Hz, 2, $C{=}CH_2$), 6·9–7·9 (m, 8, aromatic), 4·18 (s, 1, NH), 4·52 (s, 1, NH); mass spectrum *m/e* (relative intensity) 342 (6), 287 (21), 173 (13), 172 (100), 171 (35), 157 (11), 156 (35), 131 (10), 130 (12), 129 (11), 128 (11). (Found: C, 83·98; H, 7·60; N, 7·97. Calc. for $C_{24}H_{26}N_2$: C, 84·17; H, 7·65; N, 8·18%).

2,4-*Bis*-(2-*methylindol*-3-*yl*)-4-*methyl*-1-*pentene* (**36**). 2-Methyl-3-isopropylideneindolenine sulfate[18] (4·2 g) and water (25 ml) was mixed and allowed to stand for 1 min. 2 M NaOH (30 ml) was added and the mixture was stirred for 10 min at room temp. The ether extracts (50 ml) were washed with water, dried ($MgSO_4$) and evaporated. The residue was crystallized from EtOH, yield: 1·02 g (40%) m.p. 159–160°.

Reaction of 2-*methyl*-3-*isopropylideneindolenine sulfate* (**34c**) *with* 0·3 M NaOH *in* 80% *refluxing ethanol*. The reaction was performed under the conditions used for the base-induced reaction of **11**. 0·45 g of **34c** was added to the refluxing alkaline EtOH–water soln (17 ml). The products were separated by preparative TLC (the same eluent as above). Fraction 1 (25 mg) consisted of 2-methylindole (12%).

The second component (56 mg) was identified as 2,4-*bis*-(2-*methylindol*-3-*yl*)-4-*methyl*-1-*pentene* (**36**) (20%) m.p. 156–158°.

The third fraction (66 mg) consisted of 2-(2-*methylindole*-3-*yl*)-3,4,4a,9a-*tetrahydro*-4,4,9a-*trimethylcarbazole* (**39a**; 23%) m.p. 184–185° (lit.[20a] 182–183°).

Reaction of 2,4-*bis*-(2-*methylindol*-3-*yl*)-4-*methyl*-1-*pentene* (**36**) *with* NaOH. Compound **36** was refluxed for 2 hr in 0·3 M NaOH in 80% EtOH. **36** was recovered unchanged.

Reaction of **36** *with* HCl. Compound **36** (88 mg) was stirred for 90 min in a mixture of EtOH (2 ml) and conc HCl (0·5 ml). Neutralization with 2 M NaOH gave the free base of **39** in 100% yield m.p. 184–185°.

Alkaline hydrolysis of **36**. NaOH (4·0 g) in water (10 ml) was added to a soln of **36** (0·34 g) in dioxane–EtOH (1:1, 10 ml). The resulting soln was refluxed for 6 hr and after concentration extracted with CH_2Cl_2. This extract was concentrated and **40** was isolated by preparative TLC using CH_2Cl_2 as eluent. The product obtained (91 mg (39%) m.p. 44–46°) was identical with an authentic sample.[20a]

Reaction of 1-*methylated haloacylindoles with* NaOH

Reaction of 3-(2-*bromopropionyl*)-1-*methylindole* (**15**) *with* NaOH. The reaction was carried out in 80% EtOH in the manner described for the other haloacylindoles. Compound **15** (1·32 g, 0·005 mol) was added to a refluxing soln of NaOH (0·6 g) in 80% EtOH. After neutralization and evaporation the crude product was dissolved in ether and extracted 3 times with 1 M $NaHCO_3$ to remove acidic products. The ethereal soln was dried over $MgSO_4$ and evaporated under reduced pressure to give 1·01 g of a light-brown oil. The oil was chromatographed on silica gel using light petroleum–diethyl ether (1:1) as the eluent. The first fraction (145 mg (15%)) consisted of 3-(2-ethoxypropionyl)-1-methylindole m.p. 111–113°. Recrystallization from light petroleum–benzene (3:1); IR (KBr) 3115 (w), 2968, 1630 (C=O), 1518, 1468, 1375, 1235, 1102, 758 cm^{-1}; mass spectrum *m/e* (relative intensity) 231 (4), 187 (8), 159 (11), 158 (100), 130 (8). (Found: C, 72·70; H, 7·40; N, 6·08. Calc. for $C_{14}H_{17}NO_2$: C, 72·70; H, 7·41; N, 6·06%).

The second component was identified as 3-(2-hydroxypropionyl)-1-methylindole (447 mg (44%)), m.p. 91–93° (recrystallization from benzene); IR (KBr) 3420, (OH), 1630 (C=O), 1532, 1470, 1364, 1138, 1081, 881, 759; mass spectrum *m/e* (relative intensity) 203 (12), 159 (12), 158 (100), 130 (12), 103 (11), 78 (17), 77 (15). (Found: C, 70·83; H, 6·44; N, 6·84. Calc. for $C_{12}H_{13}NO_2$: C, 70·92; H, 6·45; N, 6·89%).

The $NaHCO_3$ extract from above was acidified and extracted with ether. The ether soln was dried over $MgSO_4$ and evaporated. The residue (25 mg) was separated by preparative TLC. No α,1-dimethylindole-3-acetic acid could be detected. The main product (15 mg) was identified by its mass spectrum and IR[45] as 1-methylindole-3-carboxylic acid m.p. 214–215° (lit.[43,45] 214°, 205–206°).

Reaction of 3-(2-*bromopropionyl*)-1,2-*dimethylindole* (**14**) *with* NaOH. Compound **14** (3·7 g, 0·014 mol) was added in 10 portions to a refluxing soln of NaOH (1·7 g) in 140 ml 80% aqueous EtOH. The soln was refluxed for 45 min and then worked up as described for **15** (above). No acidic rearrangement product could be detected. The ether phase was dried ($MgSO_4$) and evaporated to give a yellow residue, which was crystallized from MeOH m.p. 135–136°, yield: 1·41 g (54%) of **46**; IR (KBr) 1665 (C=O), 1531, 1509, 1481, 1454, 1428, 754 cm^{-1}; NMR ($CDCl_3$) δ 1·31 (d, 3, CH_3), 2·2–3·3 (m(ABC part of an $ABCY_3$-system), 3, CH_2, CH; addition of $Eu(DPM)_3$ simplified the spectrum and gave an AB part of a pseudo ABX-system: $J_{AB} = 17·9$, $J_{AX} = 6·7$, $J_{BX} = 2·8$), 3·54 (s, 3, N–CH_3). (Found: C, 78·23; H, 6·60; N, 6·92. Calc. for $C_{13}H_{13}NO$: C, 78·36; H, 6·58; N, 7·03%).

Reaction of 3-*bromoacetyl*-1,2-*dimethylindole* (**16**) *with* NaOH. The above procedure was used starting from 3-bromoacetyl-1,2-dimethylindole (1·32 g, 0·005 mol) and 0·6 g NaOH in 80% aqueous EtOH. The crude mixture was separated on a silica gel column (eluent CH_2Cl_2–MeOH (98:2)). The second fraction was collected and purified by preparative TLC, giving 36 mg (4%) of **47** m.p. 209–210°; IR (KBr) 1668 (C=O), 1470, 1455, 1078, 755 cm^{-1}, mass spectrum *m/e* (relative intensity) 186 (13), 185 (100), 184 (31), 157 (44), 156 (38), 142 (15), 130 (14), 129 (15), 128 (15), 115 (22). (Found: C, 77·50; H, 5·90; N, 7·30. Calc. for $C_{12}H_{11}NO$: C, 77·81; H, 5·99; N, 7·56%).

5-*Oxo*-6-*ethyl*-8-*methyl*-6,7-*dihydrocyclopent*(b)*indole* (**48**). Prepared from 3-(2-bromobutyryl)-1,2-dimethylindole (5·88 g) by the procedure described for prep of **46**, yield: 3·87 g (91%) (MeOH) m.p. 127–129°; IR (KBr) 2955, 1670 (C=O), 1540, 1481, 1452, 1421, 1140, 814, 765 cm^{-1}; NMR ($CDCl_3$) δ 0·92 (t, 3, CH_3), 1·46 (m, 2, CH_2), 2·30–3·10 (m, 3, CH_2 and CH), 3·47 (s, 3, N–CH_3); mass spectrum *m/e* (relative intensity) 213 (50), 198 (14), 186 (14), 185 (100), 184 (39), 170 (10). (Found: C, 78·51; H, 7·06; N, 6·50. Calc. for $C_{14}H_{15}NO$: C, 78·84; H, 7·09; N, 6·57%).

5-*Oxo-6-phenyl-8-methyl-6,7-dihydrocyclopent*(b)*indole* (**49**). The method was as described for prep of **46** starting from **19** (2·97 g). During the reaction a solid was formed. The mixture was cooled, neutralized, and the white crystals collected, giving **49**: 2·09 g (80%); m.p. 215–216°; IR (KBr) 1673 (C=O), 1537, 1515, 1485, 1455, 1422, 1076, 760 cm^{-1}; NMR (DMSO-d_6; JEOL MH-100) δ 4·0–4·7 (AB part of ABX-system,* 2, $\delta_A = 4·11$, $\delta_B = 4·63$, $J_{AB} = 17·7$ Hz, $J_{AX} = 2·6$ Hz, $J_{BX} = 7·1$ Hz, CH_2), 4·77 (s, 3, N–CH_3), 5·12 (q, 1, CH); mass spectrum *m/e* (relative intensity) 262 (21), 261 (100), 260 (24), 233 (14), 232 (50), 217 (36), 184 (19), 172 (14). (Found: C, 82·71; H, 5·76; N, 5·25. Calc. for $C_{18}H_{15}NO$: C, 82·73; H, 5·79; N, 5·36%).

Reaction of 3-(2-*bromoisobutyryl*)-1,2-*dimethylindole* (**17**) *with* NaOH. The reaction was carried out as described starting from **17**. No cyclized product was formed but 1,2-*dimethyl*-3-(-2-*hydroxypropionyl*)*indole* was formed in high yield (90%); m.p. 133–134° (benzene): IR (KBr) 3430 (OH), 1604 (C=O), 1480, 1470, 1450, 1392, 1375, 1069, 941, 741 cm^{-1}; NMR ($CDCl_3$) δ 1·52 (s, 6, 2CH_3), 2·66 (s, 3, CH_3), 3·72 (s, 3, CH_3). (Found: C, 72·15; H, 7·43; N, 5·98. Calc. for $C_{14}H_{17}NO_2$: C, 72·70; H, 7·41; N, 6·06%).

Reduction of 5-oxo-8-methyl-6,7-dihydrocyclopent(b)*indole* (**47**) with LAH–$AlCl_3$.† A soln of **47** (12·0 mg, 0·064 mmol) and $AlCl_3$ (8·5 mg, 0·064 mmol) in THF (0·5 ml) was carefully added to a slurry of LAH in THF (1 ml). The mixture was refluxed for 20 hr. Excess of LAH was destroyed by addition of $Na_2SO_4 \cdot 10H_2O$ followed by water. The ppt was collected and washed several times with ether. The ether–THF phase was washed with water, dried (Na_2SO_4) and evaporated to give 9·4 mg of an oily residue, which was purified by preparative TLC. The product was identified as 8-methyl-6,7-dihydro-5H-cyclopent(*b*)indole, which was independently prepared according to the method described by Perkin and Plant.[29]

General procedure for the reaction of 3-(α-*haloacyl*)*indoles with* LAH. The appropriate 3-(α-haloacyl)indole (1·5 mmol) was added in 5 portions during 15 min to LAH (0·152 g, 4 mmol) in dry ether (20 ml). The mixture was stirred for 45 min and then refluxed for 5 hr. Excess of LAH was destroyed by careful addition of water. The ether phase was dried and evaporated to give a residue which was worked up with preparative TLC.

3-(2-*Hydroxyethyl*)*indole* (**53**). Prepared from 3-chloroacetylindole in 73% yield m.p. 57–58° (lit.[48] 57–58°). 3-Ethylindole was a minor by-product (3%).

3-(2-*Hydroxy*-1-*methylethyl*)*indole* (**54**). Prepared from 3-(2-bromopropionyl)indole, yield: 67%. Identified as the 3,5-dinitrobenzoyl derivative m.p. 187–188° (lit.[49] 187–188°).

3-(2-*Hydroxy*-1-*phenylethyl*)*indole* (**55**). Prepared from 3-chlorophenyl-acetylindole (**3**), yield: 73% m.p. 120° (benzene–light petroleum 3:1); IR (KBr) 3410 (OH), 3370 (NH), 3050, 3010, 2930, 2875, 1450, 1046, 1010, 743, 700 cm^{-1}; mass spectrum *m/e* (relative intensity) 237 (12), 207 (17), 206 (100), 205 (6), 204 (13), 179 (6), 178 (10). (Found: C, 81·08; H, 6·40; N, 5·74. Calc. for $C_{16}H_{15}NO$: C, 80·98; H, 6·37; N, 5·90%).

From this reaction, 3-styrylindole (8%) and a minor fraction of 3-(2-phenylethyl)indole (1%) were isolated and identified by means of authentic samples prepared by independent routes.[50]

Reduction of 3-*chloroacetylindole with* LAD. The reaction was performed as described. 3-(2-Dideuterio-2-hydroxyethyl)indole was identified by its NMR spectrum in which the CH_2–O protons were absent. The 3-ethylindole-d_3 was shown to be deuterated as 1,1-dideuterio-1-(indol 3-yl)-2-deuterioethane; mass spectrum *m/e* (relative intensity) 149 (7), 148 (34), 147 (8), 146 (3), 133 (16), 132 (100), 131 (7).

2-*Methyl*-3-*formylindole* was prepared from 2-methylindole by a Vilsmeyer reaction[51,52] m.p. 206–208° (lit.[52] 206–208°).

1,2-*Dimethyl*-3-*formylindole* (**51a**) was obtained by methylation of 2-methyl-3-formylindole with MeI as described[37] (see above; reaction time 5 hr). Recrystallization from EtOH m.p. 133–134° (lit.[52] 131–132°).

Deuterium exchange of the 2-*methyl group in* 1,2-*dimethyl*-3-*formylindole* (**51a**). (A) Compound **51a** (86 mg) was refluxed in 5 ml 80% EtOH-d_1 (4 ml EtOD, 1 ml D_2O) for 20 min. The soln was concentrated to dryness. NMR showed that no D exchange had occurred. (B) **51a** (100 mg) was refluxed in 6 ml 0·3 M NaOD in 80% EtOH-d_1 (4·8 ml EtOD, 1·2 ml D_2O and 0·072 g NaOD) for 20 min. The soln was cooled, concentrated under vacuum to 2 ml, and diluted with D_2O. The crystals were filtered and washed with D_2O. NMR showed that complete D exchange had occurred in the 2-Me group.

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REFERENCES

[1] B. Tchoubar and V. Sackur, *C.R. Acad. Sci., Paris* **208**, 1020 (1939).

[2] C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.* **74**, 5352 (1952).

[3a] C. L. Stevens and E. Farkas, *Ibid.* **74**, 618 (1952); [b] C. L. Stevens, W. Malik and R. Pratt, *Ibid.* **72**, 4758 (1950).

[4] E. E. Smissmann and G. Hite, *Ibid.* **82**, 3375 (1960).

[5] E. E. Smissmann and J. L. Diebold, *J. Org. Chem.* **30**, 4005 (1965).

[6] H. H. Wasserman, N. E. Aubrey and H. E. Zimmermann, *J. Am. Chem. Soc.* **75**, 96 (1953); and refs cited.

[7a] D. J. Pasto, K. Garves and M. P. Serve, *J. Org. Chem.* **32**, 774 (1967); [b] D. J. Pasto and K. Garves, *Ibid.* **32**, 778 (1967).

[8a] N. H. Cromwell and P. H. Hess, *J. Am. Chem. Soc.* **83**, 1237 (1961); [b] D. N. Kevill and N. H. Cromwell, *J. Org. Chem.* **29**, 499 (1964).

[9] J. Bergman and J.-E. Bäckvall, *Tetrahedron Letters* 2899 (1973).

[10] J. Bergman, J.-E. Bäckvall and J. O. Lindström, *Tetrahedron* **29**, 971 (1973).

[11a] K. K. Schlender, M. J. Bukovac and H. M. Sell, *Phytochemistry*, **5**, 133 (1966); [b] Å. Jönsson, *Encyclopedia in Plant Physiology*, (Edited by W. Ruhland), Vol. 14, pp. 959–1006. Springer Verlag, Berlin (1961).

[12a] For a recent review on cyclopropanones see ref. 12*b*; [b] H. H. Wasserman, G. C. Clark and P. C. Turley, *Topics in Current Chemistry* **47**, 73 (1974); [c] J. F. Pazos, J. G. Pacifici, G. O. Pierson, D. B. Sclove and F. D. Greene, *J. Org. Chem.* **39**, 1990 (1974); and refs cited.

[13] W. D. Closson, S. A. Roman, G. T. Kwiatkowski and D. A. Corvin, *Tetrahedron Letters* 2271 (1966).

[14] G. Yagil, *Tetrahedron*, **23**, 2855 (1967).

[15] G. O. Burr and R. A. Gortner, *J. Am. Chem. Soc.* **46**, 1224 (1924).

[16a] K. Griesbaum and R. Kibar, *Chem. Ber.* **106**, 1041 (1973); [b] B. Lindström, *Chem. Commun. University of Stockholm*, No. 8, 25 (1973).

[17] T. L. Ho and C. M. Wong, *J. Org. Chem.* **39**, 562 (1974).

[18] A. H. Cook and J. R. Majer, *J. Chem. Soc.* 486 (1944).

[19] J. A. Joule and G. F. Smith, *Proc. Chem. Soc.* 322 (1959).

[20a] W. E. Noland, M. R. Venkiteswaran and C. G. Richards, *J. Org. Chem.* **26**, 4241 (1961); [b] R. C. Simurdak, Ph.D. Thesis, Univ. of Minnesota, Minneapolis (1972).

[21] L. J. Dolby and G. W. Gribble, *Tetrahedron* **24**, 6377 (1968).

[22a] N. J. Turro, W. B. Hammond and P. A. Leermakers, *J. Am. Chem. Soc.* **87**, 2774 (1965); [b] D. B. Sclove, J. F. Pazos, R. L. Camp and F. D. Greene, *Ibid.* **92**, 7488 (1970); [c] N. Schamp and M. Verzele, *Bull. Soc. Chim. Belg.* **73**, 81 (1964).

[23a] G. Büchi and B. Egger, *J. Org. Chem.* **36**, 2021 (1971); [b] G. Büchi, U. Hochstrasser and W. Pawlak, *Ibid.* **38**, 4348 (1973); [c] F.

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*The parameters were optimized by an iterative procedure using the program UEAITR.[46]

†Reduction of similar systems with LAH–$AlCl_3$ has been reported.[47]

Kienzle, G. W. Holland, J. L. Jernow, S. Kwoh and P. Rosen, *Ibid.* **38**, 3440 (1973); [d] T. Wakui, Y. Otsuji and E. Imoto, *Bull. Chem. Soc. Japan* **47**, 1522 (1974).

[24] D. M. Hayes, C. A. Zeiss and R. Hoffmann, *J. Phys. Chem.* **75**, 340 (1971).

[25] J. F. Liebman and A. Greenberg, *J. Org. Chem.* **39**, 123 (1974).

[26a] R. C. Fuson and J. Corse, *J. Am. Chem. Soc.* **61**, 975 (1939); [b] R. C. Fuson, C. H. Keever and J. Corse, *Ibid.* **62**, 600 (1940).

[27a] J. P. Schaefer and J. L. Bertran, *Ibid.* **89**, 4121 (1967); [b] H. Hensel, *Angew. Chem.* **65**, 491 (1953); [c] R. B. Moll, E. J. Poziomek and W. A. Mosher, *J. Org. Chem.* **36**, 1056 (1971); [d] C. A. Buehler and J. O. Harris, *J. Am. Chem. Soc.* **72**, 5015 (1950).

[28a] A. A. Akhrem, T. K. Ustynyuk and Yu. A. Titov, *Russ. Chem. Rev.* **39**, 732 (1970); and refs cited; [b] A. Sacks and J. G. Aston, *J. Am. Chem. Soc.* **73**, 3902 (1951); [c] M. W. Carlsson, Ph.D. Thesis, Northwestern Univ. Evanston, Illinois (1969).

[29] W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.* **123**, 3242 (1923).

[30a] Preliminary studies on attempted CH-insertion of **52** (R = H), generated from 1,2-dimethylindol-3-yl diazomethyl ketone, in aqueous methanol in the presence of copper bronze failed to give **47**. Products formed by OH-insertion predominated (see Ref. 30*b*); [b] K. S. Bhandari and V. Snieckus, *Can. J. Chem.* **49**, 2354 (1971).

[31] F. Bohlmann and H. Kapteyn, *Tetrahedron Letters* 1895 (1972).

[32a] L. H. Schwartz and R. V. Flor, *Chem. Commun.* 1129 (1968); [b] L. H. Schwartz and R. V. Flor, *J. Org. Chem.* **34**, 1499 (1969); [c] R. V. Flor, Ph.D. Thesis, The City Univ. New York (1972); [d] L. H. Schwartz and R. V. Flor, *J. Org. Chem.* **39**, 219 (1974).

[33a] In the reduction of 3-(chlorophenylacetyl)indole with $NaBH_4$ in THF 3-(1-hydroxy-2-phenylethyl)indole[33b] was, however, found to be a minor product in the complex reaction mixture. J. Bergman and J.-E. Bäckvall, unpublished; [b] W. Carruthers and N. Evans, *J. Chem. Soc. Perkin I*, 421 (1974).

[34] G. Sanna, *Gazz. Chim. Ital.* **59**, 838 (1929).

[35] J. Szmuszkovicz, *J. Org. Chem.* **27**, 515 (1962).

[36] R. F. Parcel and J. P. Sanchez, U.S. Pat. 3,562,294 (1971), *Chem. Abstr.* **74**, 125423 (1971).

[37] A. H. Jackson and A. E. Smith, *J. Chem. Soc.* 5510 (1964).

[38] H. Erdtman and Å. Jönsson, *Acta Chem. Scand.* **8**, 119 (1954).

[39] D. E. Ames and G. Hall, *J. Chem. Soc.* (C), 2647 (1967).

[40] V. N. Rusinova, Yu. I. Smushkevich, O. V. Telenkova, M. V. Vasin and N. N. Suvorov, *Khim. Get. Soedin* 211 (1974).

[41] R. Stauffer, *Helv. Chim. Acta* **49**, 1199 (1966).

[42] A. Michael, *Chem. Ber.* **38**, 2091 (1905).

[43] G. Hart and K. T. Potts, *J. Org. Chem.* **27**, 2940 (1962).

[44] H. E. Johnson and D. G. Crosby, *Ibid.* **28**, 1246 (1963).

[45] F. Millich and E. J. Becker, *Ibid.* **23**, 1096 (1958).

[46] R. B. Johannessen, J. A. Ferretti and R. K. Harris, *J. Magn. Resonance* **3**, 84 (1970).

[47] K. T. Potts and D. R. Liljegren, *J. Org. Chem.* **28**, 3202 (1963).

[48] R. C. Elderfield, B. Fischer and J. M. Lagovski, *J. Org. Chem.* **22**, 1376 (1957).

[49] M. Julia, H. Igolen and J. Lenzi, *Bull. Soc. Chim. Fr.* 2291 (1966).

[50] J. Bergman, *Acta Chem. Scand.* **25**, 1277 (1971).

[51] G. F. Smith, *J. Chem. Soc.* 3842 (1954).

[52] E. Leete, *J. Am. Chem. Soc.* **81**, 6023 (1959).