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BROMINATION OF 3-PHENYLINDOLES

T. HINO,* M. TONOZUKA and M. NAKAGAWA
Faculty of Pharmaceutical Sciences, Chiba University, Yayoi, Chiba-shi, 280, Japan

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Abstract—Brominations of 3-phenylindole (**1a**) and its 1-methyl-(**1b**) and 1-acetyl-(**1c**) derivatives with NBS in AcOH and CCl_4 have been carried out. In AcOH **1** gave 2-bromo derivatives (**2**) in high yields and the relative reactivity was found to be NH > NMe ≫ NAc by competitive reactions. In boiling CCl_4, **1a** and **1b** gave **2** but bromination of **1c** did not proceed. Bromination of **1a** with 2 moles of NBS in AcOH gave 2,6-(major) and 2,5-dibromides (**8** and **9**). Reaction of **2a** with thiourea gave **19**. Selective reduction of the bromine atom at the 2-position in 2,6-dibromide (**10**) was achieved by Zn—Cu—NaOH, and irradiation of **8** in EtOH-alkali reduced 2,6-dibromide to **1a**.

The bromination of 3-methylindole and 3-indolealkanoic acids with NBS was reported to give oxindole derivatives in aqueous media,[1] whereas 2-bromo derivatives were obtained in anhydrous media.[2] On the other hand, in the presence of pyridine 3-methylindole or 3-phenylindole produced N-(2-indolyl)pyridinium salts by the reaction with dioxane dibromide[3] or NBS.[4] The bromination of 3-indolecarboxyaldehyde and carboxylate with Br_2—AcOH is known to give 5- or 6-bromo derivatives.[5] However, the effect of substituents at the 1-position and bromination with NBS—CCl_4-benzoyl peroxide(BPO), a typical reagent system for radical bromination, have not been studied.[6]

We report here an examination of the bromination of 3-phenylindole and its 1-methyl and 1-acetyl derivatives with NBS in AcOH and CCl_4.

1. *Reactions with one mole of NBS.* The reaction of 3-phenylindole (**1a**) with one mole of NBS in AcOH at 20°, according to Hinman's condition,[2] gave the 2-bromo derivative (**2a**) in 88% yield and the oxindole (**3a**) in 4% yield (Table 1). The bromination of 1-methyl-3-phenyl-indole (**1b**) under similar reaction conditions gave the 2-bromo derivative

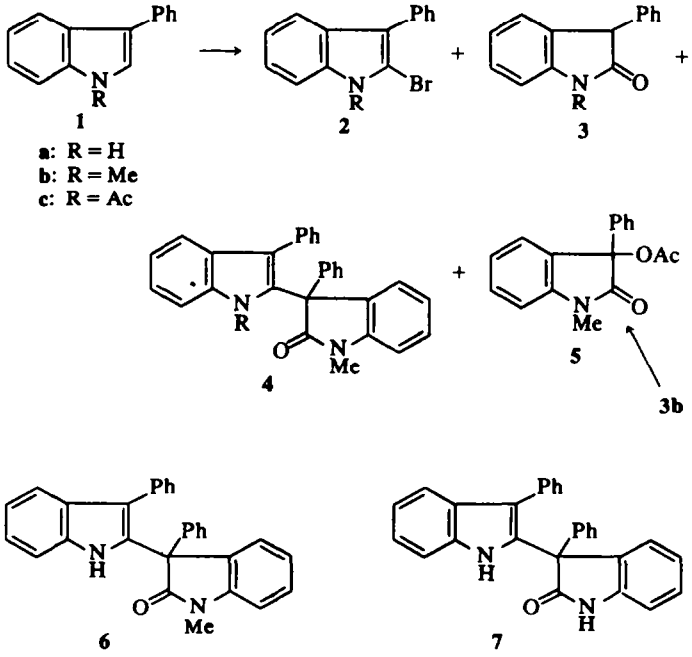


CHART 1.

Table 1. Bromination of 3-phenylindoles with NBS in AcOH at 20°

Indoles	Reaction time, hr	Yield of 2	Other products	Recovered 1
1a	1	**2a**, 88%	**3a** (4%)	4%
1b	2	**2b**, 61%	**4** (20%), **5** (5%)	8%
1c	4·5	**2c**, 95%	—	—

(**2b**) as the main product. Presence of a 1-Me group favoured formation of the dimeric product (**4**) as a by-product, similarly as has been observed in the chlorination of 3-(*p*-methoxyphenyl)-1-methylindole with NCS in AcOH.[7] The 1-acetyl derivative (**1c**) gave **2c** in high yield, though prolonged reaction time was required to complete the reaction; no other by-product was isolated. 2-Bromo-3-phenylindoles (**2**) are more stable than 2-bromo-3-methylindoles, which partly decompose during purification. The structures of these compounds were confirmed by spectral data and elemental analysis. Furthermore, **2a** and **2b** were converted to the known **3a** and **3b**[8] by acid hydrolysis, and **2c** was converted to **2a** by alkaline hydrolysis. The structure **5** was further confirmed by direct comparison with a sample obtained by the reaction of **3b** with NBS in AcOH.

To evaluate the effect of 1-Me and 1-Ac groups on the bromination two competitive reactions, between **1a** and **1b**, and **1a** and **1c**, were carried out under similar conditions using 5 mmoles of each indole and NBS. The results (Table 2) clearly show that the order of reactivity of the bromination was NH > NMe ≫ NAc. It is interesting to note that two dimeric products (**6** and **7**), which were not isolated in the bromination of a single indole, were obtained in the competitive reactions.

We previously reported that the bromination of 1-methyl-indole with Br_2 in ether at − 60° gave 2-bromo-3-methylindole in good yield.[3a] The bromination of **1a** under similar reaction conditions gave **2a** in 72%, **3a** in 2·5%, and recovered **1a** in 22% yield.

The bromination of 1-benzoylindole with NBS in CCl_4 was reported to give 3-bromoindole.[9] Since the bromination with NBS—CCl_4—BPO is generally considered to proceed by a bromine radical,[10] in contrast to bromination with NBS-AcOH which is believed to proceed via an ionic mechanism,[6] bromination of **1** under radical conditions was examined to find out the difference between the two reactions. The results (Table 3) demonstrate that

Table 3. Bromination of 3-phenylindoles with NBS in CCl_4—BPO

Indoles	Refluxing time, hr	Yield of 2	Other products
1a	2·5	**2a**, 98%	**1a** (1%)
1b	2·5	**2b**, 96%	**1b** (0·5%), **3b** (0·8%)
1c	5	**2c**, 8%	**1c** (90%)

under radical conditions a 1-Ac group strongly inhibited the bromination, while presence of a 1-Me group no longer encouraged production of a dimeric product, instead a small amount of **3b** was obtained. These results may be interpreted by the reaction path via **a** as shown in Chart 2. Initial abstraction of the indolic NH by Br is excluded by the fact that the bromination of the 1-methyl compound occurred in 96% yield. Addition of Br to the 2-position instead of 3-position was supported by the inhibition of bromination of **1c**, where 3-Ph and 1-Ac groups will cause steric hindrance to the attack of Br at the 2-position. Conversely, the mechanism of the formation of the dimeric products (**4**, **6**, and **7**) in AcOH can be drawn as shown in Chart 2.

2. *Reactions with two moles of NBS.* The dibromination of 3-methylindole was reported to give 2,6-dibromide as a sole product,[1] but little data is reported on the dibromination of other 3-alkylindoles. Since 3-phenylindoles gave clear results in the mono-bromination as described above, bromination of **1a** with 2 moles of NBS in AcOH was carried out to find out the isomer distribution in the dibromides. A mixture of dibromides, **8** and **9**, was obtained in over 90% yield, but attempt at separation of these compounds by preparative layer or gas chromatography failed. The mixture of dibromides was therefore acetylated with Ac_2—AcONa to give a mixture of **10** and **11**. Fractional recrystallizations of the mixture gave 2,6-dibromide (**10**), mp 91–92° as main product and 2,5-

Table 2. Competitive bromination

Reaction	Products % 2a	2b	2c	Recovered indoles 1a	1b	1c	Other products
1a + **1b**	50	35	—	45	57	—	**4** (2%), **6** (5%)
1a + **1c**	85	—	0	7	—	98	**7** (8%)

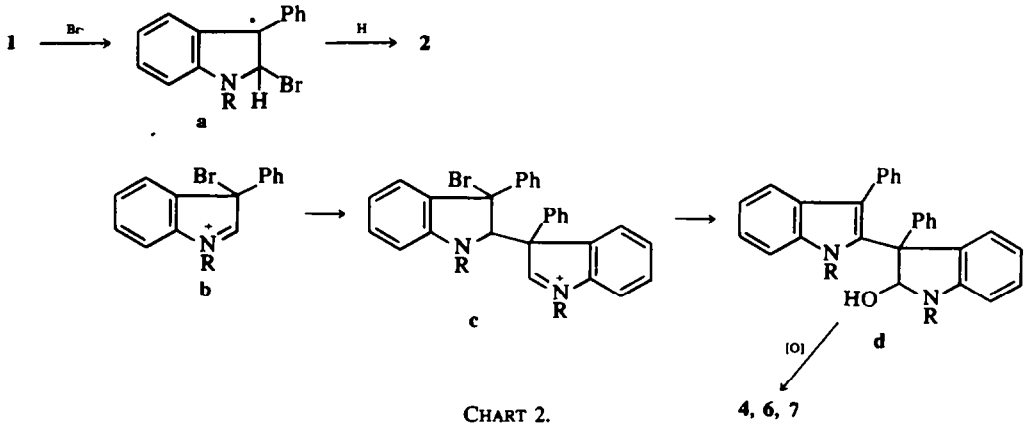


CHART 2.

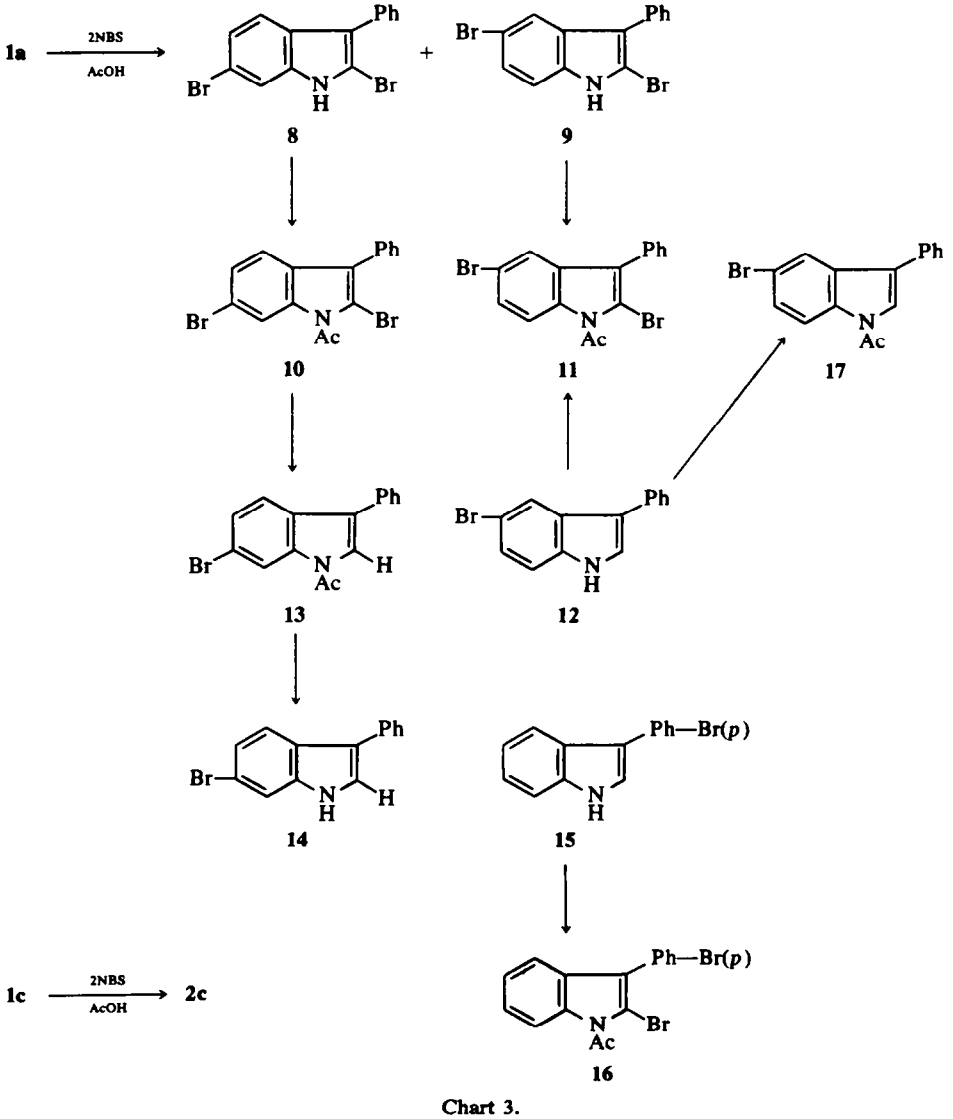


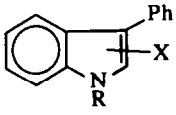
Chart 3.

dibromide (**11**), mp 139–140°, as minor product. The ratio **10** to **11** was estimated as about 6:1 from the relative intensity of the 7-H proton signal in the NMR spectrum of the mixture. The structure of **11** was confirmed by an unambiguous synthesis from **12**, prepared from *p*-bromophenylhydrazine and phenylacetaldehyde. The position of the 6-bromo in **10** was confirmed by the fine doublet (J = 1 Hz) of 7-H at 8·47 ppm (in CCl_4) compared with that of 7-H in **2c** where double doublets (J = 1 and 7 Hz) were observed at 8·32 ppm. Another possible dibromide isomer, 1-acetyl-2-bromo-3-(*p*-bromophenyl)-indole (**16**), was synthesized from **15**[7] and proved not to be identical with **10**. Compound **10** was converted to mono bromide (**13**) by the reduction with Zn—Cu—NaOH, which selectively removed the Br at the 2-position; hydrolysis then gave **14**. Compound **14** was shown to be different from **12** and **15**. Formation of the 2,6-dibromide from 3-methylindole has been reported and the 6-position is known to be the most reactive site in the benzene ring of indoles in electrophilic substitution.[1,6] Although, in general the 4-position is known to be the second favoured position in electrophilic substitution, here the 3-phenyl group inhibited attack at the 4-position and the second bromination occurred at the 5 position.

The bromination of **1c** with 2 moles of NBS in AcOH at 20° gave the 2-bromide (**2c**) in 97% yield and no dibromide was isolated, indicating strong inhibition of bromination in the benzene ring by the 1-Ac group.

The analytical data and the UV, NMR, and mass spectral data of these compounds obtained by the bromination are summarized in Tables 4–11. The UV spectrum of **8** in EtOH showed maxima at 233, 275, and 297[sh] nm which shifted to 292 and 313[sh] nm on the addition of 10% NaOH. Similar but smaller bathochromic shifts were observed with **2a** and **9**. Since such shifts were not observed with **12** and **14**, they might be caused by removal of the NH proton due to the increased acidity brought about by the

Table 4. Brominated 3-phenylindoles



Compd. No.	R	X	m.p.	Recryst solv[a]	Formula	Analytical data Calcd. C	H	N	Br	Found C	H	N	Br
2a	H	2-Br	57–58·5	A	$C_{14}H_{10}NBr$	61·79	3·70	5·15	29·36	61·79	3·76	5·11	29·21
2c	Ac	2-Br	115–116°	A	$C_{16}H_{12}NOBr$	61·16	3·85	4·43	25·46	61·13	3·88	4·46	25·04
10	Ac	2,6-diBr	91–92°	B	$C_{16}H_{11}NOBr_2$	48·89	2·82	3·56	40·66	48·97	2·83	3·57	40·93
11	Ac	2,5-diBr	139–140°	A	$C_{16}H_{11}NOBr_2$	48·89	2·82	3·56	40·66	49·11	2·85	3·53	40·74
12	H	5-Br	88–89°	B	$C_{14}H_{10}NBr$	61·79	3·70	5·15	29·36	61·88	3·63	5·11	29·34
17	Ac	5-Br	137–138	B	$C_{16}H_{12}NOBr$	61·16	3·85	4·43	25·46	61·15	3·80	4·40	25·21
16	Ac	2,p-diBr	127–128·5°	A	$C_{16}H_{11}NOBr_2$	48·89	2·82	3·56	40·66	48·82	2·79	3·61	40·42
13	Ac	6-Br	124–125°	B	$C_{16}H_{12}NOBr$	61·16	3·85	4·43	25·46	61·05	3·96	4·35	25·23
14	H	6-Br	109–110°	B	$C_{14}H_{10}NBr$	61·79	3·70	5·15	29·36	61·94	3·72	5·10	29·46

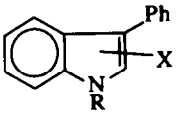
[a] A; cyclohexane, B; benzene–hexane.

Table 5. 3-Phenylindole derivatives

Compd. No.	m.p.	Recryst solvent	Formula	Calcd. C	H	N	Found C	H	N
4	203–204°	benzene–hexane	$C_{30}H_{24}N_2O$	84·08	5·65	6·54	84·10	5·67	6·93
5	145·5–146·5°	benzene–hexane	$C_{17}H_{15}NO_3$	72·58	5·37	4·98	72·71	5·38	4·92
18	86–87°	cyclo-hexane	$C_{14}H_{10}NCl$[a]	73·85	4·43	6·15	73·68	4·52	6·20
19a	252–253°	EtOH—Et_2O	$C_{22}H_{21}N_3S_2O_3H_2O$[b]	57·75	5·07	9·18	57·36	4·76	9·21
19b	208–210°	i-PrOH—Et_2O	$C_{15}H_{14}N_3SBr$[c]	51·73	4·05	12·07	51·35	4·06	12·21

[a] Cl calcd. 15·57, Found 15·76%.
[b] S, calcd. 14·01 Found 13·98%.
[c] S, calcd. 9·21, Found 8·99%; Br, calcd. 22·94, Found 22·81%.

Table 6. UV spectra of brominated 3-phenylindoles



Compd. No.	R	X	EtOH λ_{max} nm($\epsilon \times 10^{-3}$)	EtOH λ_{min} nm ($\epsilon \times 10^{-3}$)
1a	H	H	225 (31·6), 270 (15·1)	245 (5·4)
2a	H	2-Br[a]	225 (37·3), 277 (14·4), 290[sh] (11·8)	247 (7·0)
12	H	5-Br	225 (29·7), 268 (16·8)	249 (10·9)
14	H	6-Br	231 (29·3), 270 (18·3)	249 (10·1)
10	H	2,6-diBr[b]	233, 275, 297[sh]	252
11	H	2,5-diBr[c]	229, 269, 290[sh], 301	253
18	H	2-Cl	225 (35·4), 276 (14·8), 289 (11·6)	247 (6·0)
1b	Me	H	227, 269, 283[sh]	248
2b	Me	2-Br	227, 285, 293[sh]	250
1c	Ac	H	246 (25·1), 305 (12·0)	224 (18·6), 284 (7·8)
2c	Ac	2-Br	245 (21·4), 284 (9·8), 303 (9·3)	225 (15·3), 269 (9·2), 292 (9·1)
17	Ac	5-Br	232[sh](24·8), 247 (29·8), 302 (9·3)	215 (21·7), 294 (7·3)
13	Ac	6-Br	248 (33·4), 275 (10·3), 300 (8·4), 308 (8·6)	218 (17·3), 294 (7·8)
11	Ac	2,5-diBr	245 (26·1), 288 (11·3), 299 (9·7), 309 (8·0)	227 (20·2), 272 (10·1)
10	Ac	2,6-diBr	246 (21·4), 290 (12·2)	226 (18·8), 270 (10·3)
16	Ac	2,p-diBr	250 (23·6), 285 (10·1), 296 (10·1), 304 (10·6)	225 (16·1), 280 (10·0) 290 (10·0)

[a] $\lambda_{max}^{EtOH—NaOH}$ 284, 291[sh]; λ_{min} 255.
[b] $\lambda_{max}^{EtOH—NaOH}$ 292, 313[sh]; λ_{min} 267.
[c] $\lambda_{max}^{EtOH—NaOH}$ 238, 292, 300[sh]; λ_{min} 225, 266.

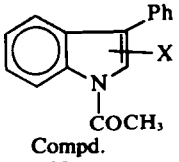
Table 7. UV spectra of 3-phenylindole derivatives

Compd. No.	λ_{max}^{EtOH} nm($\epsilon \times 10^{-3}$)	λ_{min} nm($\epsilon \times 10^{-3}$)
4	222 (45·6), 269 (13·8), 289 (12·3)	218 (44·5), 249 (13·6)
5	260 (6·5), 270[sh] (4·8), 290[sh] (1·2)	249 (5·8)
6	268, 285[sh], 294	256, 292
7	260[sh], 286, 294	282, 292
19a	220 (42·7), 265[sh] (8·4), 293 (14·1)	257 (8·3)
19b	217 (31·7), 293 (14·0)	258 (8·0)

presence of bromine at the 2-position. The NMR spectra of 1-Ac derivatives (Table 8) showed that the Me signal of the Ac group is shifted down field (0·3 ppm) by the presence of Br at the 2-position. The proton at the 2-position of 3-phenylindole derivatives was not observed at a field above 7 ppm, and cannot be used as an indication of substitution at the 2-position.

3. *Reactions of 2-bromo-3-phenylindoles.* 2-Bromo-3-methylindole is hydrolyzed with acid to the oxindole, while it is very stable towards bases.[2,3a] We have now examined the reactivity of 2-bromo-3-phenylindole (**2a**). When a solution of **2a**

Table 8. NMR spectra of 1-acetyl-3-phenylindoles

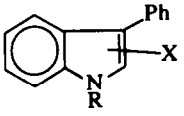


Compd. No.	X	Solv.	CH_3CO	7-H (ppm)
1c	H	$CDCl_3$	2·65	8·52 (m)
2c	2-Br	$CDCl_3$	2·92	8·32 (d – d, J = 2 and 7 Hz)
17	5-Br	CCl_4	2·59	8·28 (d, J = 8 Hz)
14	6-Br	CCl_4	2·56	8·58 (d, J = 1 Hz)
11	2,5-diBr	CCl_4	2·88	8·17 (d, J = 8 Hz)
10	2,6-diBr	CCl_4	2·87	8·47 (d, J = 1 Hz)
16	2, *p*-diBr	CCl_4	2·86	8·23 (d – d, J = 1 and 8 Hz)

Table 9. NMR spectra of 3-phenylindole derivatives

Compd. No.	NMR in $CDCl_3$, σ
3a	4·58 (s, 3-H), 6·8–7·4 (m, arom H), 9·10 (br.s, NH)
3b	3·23 (s, NMe), 4·58 (s, 3-H), 6·8–7·4 (m, arom H)
4	2·97 (s, oxindolic NMe), 3·42 (s, indolic NMe), 6·65–7·4 (m, arom H)
5	2·12 (s, $COCH_3$), 3·18 (s, NMe), 6·8–7·5 (m, arom H)
6	2·91 (s, oxindolic NMe), 6·6–7·5 (m, arom H)), 8·27 (br.s, oxindolic NH)
8	6·57–7·40 (m, arom H), 8·47 (br.s, indolic NH), 8·77 (br.s, oxindolic NH)

Table 10. Mass spectral data of brominated 3-phenylindoles



Compd. No.	R	X	Main peaks, m/e (relative abundance, %)
2a	H	2-Br	273 (97, M + 2), 271 (100, M^+), 192 (26, M—Br), 165 (32)
2b	Me	2-Br	287 (99, M + 2), 285 (100, M^+), 272, 270 (8, M—Me), 204 (17), 190 (49, M—(Me + Br), 165 (22)
2c	Ac	2-Br	315 (17, M + 2), 313 (17, M^+), 273, 271 (100, M—CH_2CO), 192 (21), 190 (31), 165 (25)
8	H	2,6-diBr	353 (51, M + 4), 351 (100, M + 2), 349 (53, M^+), 273, 271 (18, M—Br + H), 190 (37), 164 (28)
10	Ac	2,6-diBr	395 (11, M + 4), 393 (20, M + 2), 391 (10, M^+), 353 (42), 351 (100), 349 (57, M—CH_2CO), 272 (19), 270 (20, M—(Br + CH_2CO)), 190 (50), 163 (31)
11	Ac	2,5-diBr	395 (8, M + 4), 393 (16, M + 2), 391 (8, M^+), 353 (50), 351 (100), 349 (50, M—CH_2CO) 272 (7), 270 (7, M—(Br + CH_2CO)), 190 (36), 163 (16)
16	Ac	2,p-diBr	395 (6, M + 4), 393 (10, M + 2), 391 (7, M^+) 353 (47), 351 (100), 349 (50, M—CH_2CO) 272 (11), 270 (10, M—(Br + CH_2CO)), 190 (25)
13	Ac	6-Br	315 (44, M + 2), 313 (44, M^+), 273 (100), 271 (100, M—CH_2CO), 192 (29, M—(Br + CH_2CO)) 190 (23), 165 (34)
17	Ac	5-Br	315 (35, M + 2), 313 (35, M^+), 273 (100), 271 (100, M—CH_2CO), 192 (26, M—(Br + CH_2CO)), 190 (32), 165 (57)
14	H	6-Br	273 (93, M + 2), 271 (100, M^+), 192 (34, M—Br), 165 (40)
12	H	5-Br	273 (99, M + 2), 271 (100, M^+), 192 (23, M—Br), 165 (36)

Table 11. Mass spectral data of 3-phenylindole derivatives

Compd. No.	Main peaks, m/e (relative abundance, %)
4	428 (100, M^+), 399 (26, M—HCO), 370 (15), 351 (20), 323 (52), 307 (21), 214 (18)
5	281 (100, M^+), 239 (85, M—CH_2CO), 222 (35), 210 (24), 194 (30), 165 (17), 152 (14), 105 (43)
6	414 (100, M^+), 337 (75, M—Ph), 309 (36, M—(Ph + CO))
7	400 (88, M^+), 372 (6, M—CO), 324 (100, M—Ph + H), 296 (56), 200 (10, M^{++})
18	229 (35, M + 2), 227 (100, M^+), 192 (18, M—Cl), 165 (21)
19a	255 (24), 235 (55), 193 (100), 172 (47), 165 (37), 91 (98)
19b	225 (100), 193 (31), 165 (23), 42 (100)
3b	223 (100, M^+), 209 (7, M—CH_2), 195 (67, M—CO), 180 (10), 166 (12)

in dioxane saturated with HCl was refluxed for 3 h, the 3-chloro derivative (**18**) was obtained in 67% yield. The reaction of **2a** with thiourea in boiling *i*-PrOH in the presence of *p*-toluenesulfonic acid or in boiling EtOH-concHBr, afforded 2-indolylpseudothioureas (**19a** and **b**) in good yield. Alkalline hydrolysis of **19a** afforded the diindolyl disulfide.[7] These reaction may proceed via protonated intermediates (**20a** and **20b**).

Although **2a** in AcOH was stable at room temperature, on refluxing the 6-bromo derivative (**14**) and the dimeric product (**7**) were obtained in 21% and in

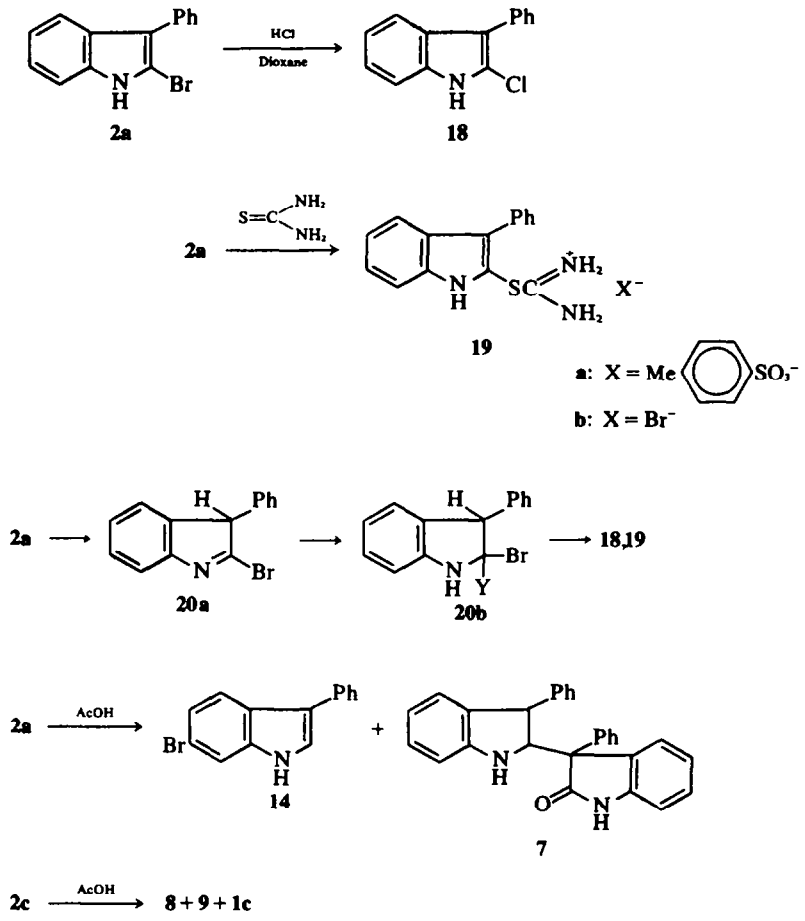


Chart 4.

35% yields, respectively. On the other hand, **2c** was converted to a mixture of **8**, **9**, and **1c** under similar conditions. Their mechanism is not yet clear, but these reactions are the first examples of migration in a 2-bromoindole.

2-Bromo-3-phenylindole (**2a**) was not reduced with $NaBH_4$ in boiling EtOH to **1a**. However, **2a** was reduced to **1a** (17%), and in addition **7** was formed (40%), when **2a** was refluxed in *i*-PrOH in the presence of *p*-toluenesulfonic acid. The reduction of **2a** with Zn—AcOH gave **1a** in 37% yield, but the main product was the hydrolyzed oxindole (**3a**) in 54% yield. However, **2a** was reduced to **1a** in 83% yield with Zn—Cu-10% NaOH, which is known to reduce a reactive halogen.[11] On the other hand 5-, 6-bromo and 2,6-dibromo derivatives were reduced to **1a** by photoreduction (254 nm) in EtOH-alkali.

EXPERIMENTAL

All m.p. are uncorrected. The IR spectra were taken with a Hitachi-G3 spectrophotometer, the UV spectra were measured with a Hitachi EPS-3-T spectrophotometer, the NMR spectra were recorded on a JEOL-4H-100 spectrometer and the mass spectra were taken with a Hitachi RMU-6 spectrometer.

Bromination of **1a** *with NBS (1 mole) in* AcOH. A soln of NBS (1·78 g, 10 mmole) in AcOH (68 ml) was added to a soln of **1a**[12] (1·93 g, 10 mmole) in AcOH (16 ml) at 20° under N_2 during 30 min. The mixture was stirred at 20° for a further 1 h to give a bluish-purple soln. The mixture was poured into a soln of NaOH (54·5 g) in H_2O (100 ml) with ice cooling and adjusted to pH 9 by the addition of 10% NaOH. The mixture was extracted with CH_2Cl_2, which was then washed with $NaHCO_3$ aq and H_2O, and dried. The CH_2Cl_2 soln was evaporated to leave a yellow oil (2·72 g) which was chromatographed over silica gel (40 g). Elution with benzene–hexane (1 : 1) gave **2a** (2·4 g, 88%) as a colorless oil. Recrystallization from cyclohexane gave **2a**, m.p. 57–58·5°. The second elution with the same solvent gave **1a** (78 mg, 4%). Elution with CH_2Cl_2 gave **3a** (74 mg, 4%) which was identical with an authentic sample (mmp and IR).

Bromination of **1b** *with NBS (1 mole) in* AcOH. N-Methylation of **1a** with $NaNH_2$–CH_3I in liq. NH_3[13] gave **1b**, m.p. 65–66°[14], in 83% yield.

A soln of NBS (1·78 g, 10 mmole) in AcOH (70 ml) was added to a soln of **1b** (2·07 g, 10 mmole) in AcOH (30 ml) at 20° under N_2 during 40 min. The mixture was stirred for 2 h at 20° and worked up as above to give a yellow oil

(2·76 g), which was chromatographed over silica gel (40 g). Elution with benzene–hexane (1:9) gave **2b** (1·76 g, 61%) as a colorless oil. NMR ($CDCl_3$) 3·80 (s, NMe). Elution with benzene–hexane (1:4) gave **1b** (165 mg), m.p. 65–66°, which was identical with an authentic sample (mmp). Elution with benzene gave **4** (430 mg, 20%). Further elution with CH_2Cl_2 gave **5** (140 mg, 5%).

The hydrolysis of **2b** *to* **3b**. A soln of **2b** (570 mg), dioxane (3 ml), and conc HCl (10 ml) was refluxed for 3·5 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated. The residue (450 mg) was chromatographed over silica gel. Elution with benzene-hexane (1:9) gave a colorless oil (110 mg) which was found to be 2-chloro-1-methyl-3-phenylindole containing a small amount of **2b** from mass data (*m/e*; 285(6), 287(6) for **2b**; 243(33), 241(100) for 2-chloro derive). Elution with benzene–hexane (1:4) gave an oil (15 mg) which was identical with **1b** on TLC. Elution with benzene gave **3b** (300 mg, 72%), m.p. 110–116°, which was recrystallized from benzene–hexane gave colorless needles, m.p. 117·5–118·5° (reported m.p. 119–120°[7]). The hydrolysis of **2a** for 8 h gave **3b** in 91% yield.

Reaction of **3b** *with NBS in* AcOH

Formation of **5**. A soln of NBS (712 mg, 4 mmole) in AcOH (30 ml) was added to a soln of **3b** (892 mg, 4 mmole) in AcOH (15 ml) at room temp during 30 min. The mixture was further stirred for 22 h. Work-up as above gave a mixture (1·14 g). Separation of the mixture by silica gel column and preparative layer chromatography gave 407 mg of **3b** contaminated with a benzene brominated oxindole and 170 mg of **5**. The latter was recrystallized from benzene–hexane to give **5**, m.p. 145–146·5°, which was identical with the sample obtained above (mmp).

Bromination of **1c** *with NBS* (1 *mole*) *in* AcOH. A soln of NBS (890 mg) in AcOH (40 ml) was added to a soln of **1c**[7] (1·17 g) in AcOH (40 ml) at 20° during 30 min under N_2. The mixture was stirred for 3 h at 20° and for 1·5 h at 30°. The solvent was evaporated *in vacuo* (under 40°), and the residue was extracted with CH_2Cl_2. The extracts were washed with NaCl aq, dried, and evaporated to leave a pale yellow solid (1·56 g), which was chromatographed over silica gel (20 g). Elution with benzene–hexane (1:4) gave **2c** (1·45 g, 92%). Elution with benzene–hexane (1:1) gave **1c** (64 mg).

A soln of **2c** (2·25 g) in EtOH (50 ml)–10% NaOH (10 ml) was stirred for a few min at room temp, and worked up as usual to give crude **2a** (1·97 g) which was recrystallized from cyclohexane to give **2a**, m.p. 56–58°, which was identical with the sample obtained above (IR and mmp).

Competitive reactions. To a soln of **1a** (965 mg, 5 mmole) and **1b** or **1c** (5 mmole) in AcOH (30 ml) was added NBS (890 mg, 5 mmole) in AcOH (40 ml) at 20° under N_2 during 20 min. The mixture was stirred for 1 h at 20° and worked up as above. The product mixture was separated by silica gel column. The results are summarized in Table 2.

Bromination **1a** *with* Br_2 *in ether*. Br_2 (0·52 ml, 10 mmole) was added to a soln of **1a** (1·93 g, 10 mmole) in anhyd ether (30 ml) at − 70° (dry ice–acetone) with vigorous stirring during 5 min. The mixture was stirred for 15 min, then 10% NaOH (4 ml) was added. The ethereal soln was separated and the aqueous soln was extracted with ether. The ethereal soln was washed with H_2O, dried, and evaporated to leave a yellow oil (2·58 g) which was chromatographed over silica gel (40 g). Elution with benzene–hexane (1:3) gave **2a** (1·94 g, 72%) as a colorless oil which was identical with an authentic sample (IR and TLC). Elution with benzene–hexane (1:1) gave **1a** (430 mg, 22%), m.p. 85–87°. Elution with CH_2Cl_2 gave **3a** (51 mg, 2·5%) which was identical with an authentic sample (TLC).

Bromination of **1** *with NBS* (1 *mole*) *in* CCl_4. To a soln of **1** (10 mmole) in CCl_4 (40 ml) was added NBS (1·78 g, 10 mmole) and benzoyl peroxide (8 mg). The mixture was refluxed under N_2. After cooling, insoluble succinimide was filtered and the filtrate was evaporated to leave a brown oil which was chromatographed over silica gel. The results are summarized in Table 3.

Bromination of **1a** *with NBS* (2 *mole*) *in* AcOH. NBS (17·8 g, 0·1 mole) was added to a soln of **1a** (9·56 g, 0·05 mole) in AcOH (300 ml) at 20° during 30 min under N_2. The mixture was stirred for 3 h at 20°, then evaporated to half volume at below 40° *in vacuo*. The condensed mixture was poured into a soln of NaOH (80 g) in H_2O (200 ml) under ice cooling and adjusted to pH 9–10 by the addition of 10% NaOH. The mixture was extracted with CH_2Cl_2 and the extracts were washed with H_2O, dried and evaporated to leave an oil (17·8 g), which was chromatographed over silica gel (150 g). Elution with benzene–hexane (3:17–1:2) gave a colorless oil (17·36 g, 98% as dibromides), whose TLC showed a main spot accompanied with a minor spot which could not be isolated, but the mass spectrum of this mixture showed *m/e* 349, 351, and 353 peaks in the ratio 1:2:1 corresponding to dibrimides (**8** and **9**). Elution with CH_2Cl_2–MeOH (19:1) gave a mixture (730 mg) which was further separated by preparative layer chromatography to give a colorless powder (275 mg). Recrystallization from benzene–hexane afforded a powder, m.p. 206–208°. IR (KBr); 3400, 3260 (NH), 1733 (C=O). Mass; *m/e* 560(6), 558(10), 556(6), 352(24), 350(45), 348(25), 208(100), 190(20), 180(20). Its structure was tenatively assigned as dibrominated **7**.

Acetylation of the mixture of **8** *and* **9**. A mixture of the mixed dibromides (**8** and **9**, 16·0 g) obtained above, AcOH (250 ml), and AcONa (25 g) was refluxed for 6 h. The mixture was filtered to remove insoluble materials and evaporated *in vacuo* to give colorless crystals (17·4 g). The ratio of products, **10**:**11**, was estimated to be about 6:1 from the intensities of the down field signals of 7-H protons in the NMR spectrum. Recrystallization from benzene–hexane gave **10** (10·88 g, 56%), m.p. 86·5–90°. Further recrystallization from the same solvent gave **10**, m.p. 91–92°, as colorless needles. The mother liquor of the first recrystallization was condensed to give **11** (353 mg), m.p. 127–135°, as a colorless powder. Recrystallization from cyclohexane gave **11**, m.p. 139–140°, as colorless needles, which were identical with a sample obtained from 5-bromo-3-phenylindole (see below) (IR and mmp). Both **10** and **11** were hydrolysed respectively with EtOH–10% NaOH at room temperature for 5 min to give pure **8** and **9** as colorless oils.

Reduction of **10** *with* Zn-Cu-10% NaOH. To a suspension of Zn—Cu couple (prepared by the addition of Zn powder (2·74 g) to 20% $CuSO_4$ (1·5 ml) diluted with H_2O (7 ml)) in 10% NaOH (10 ml) was added **10** (393 mg) in benzene (5 ml). The mixture was refluxed for 5 h with stirring, then filtered and extracted with benzene. The extracts were washed with H_2O, dried, and evaporated to leave yellow crystals (303 mg) which were chromatographed over silica gel. Elution with benzene–hexane (3:7) gave **14** (31 mg, 10%). Recrystallization from cyclohexane gave **14**, m.p. 107–109°, which was identical with a sample

obtained from **13**. A second elution with the same solvent gave **1a** (13 mg, 6%), while a third elution with the same solvent gave **13** (250 mg, 80%). Recrystallizations from benzene–hexane gave **13**, m.p. 124–125°, as colorless prisms. Hydrolysis of **13** with EtOH-10% NaOH at room temp gave **14**, m.p. 109–110°, as colorless plates.

Preparation of 5-bromo-3-phenylindole (**12**). A soln of *p*-bromophenylhydrazine (4·68 g) and phenylacetaldehyde (3·0 g) in benzene (30 ml) was refluxed for a few h. The residue left after evaporation of the solvent was dissolved in AcOH (20 ml) to which BF_3 etherate (3·6 g) was added, and the whole mixture was refluxed for 2 h. The solvent was evaporated *in vacuo* and the residue was diluted with H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave a brown oil (6·88 g) which was chromatographed over silica gel. Elution with benzene–hexane (3:17) gave a solid (3·89 g) which showed a single spot on TLC. Recrystallization from benzene–hexane gave **12**, m.p. 88–89°, as colorless plates.

Acetylation of **12** with Ac_2O—AcONa gave 1-acetyl-5-bromo-3-phenylindole, m.p. 137–138° (from benzene–hexane, in 82% yield.

An alternative synthesis of **11** *from* **12**. A mixture of **12** (816 mg, 3 mmole), NBS (534 mg, 3 mmole), and BPO (2 mg) in CCl_4 (15 ml) was refluxed for 1·5 hr under N_2. After cooling, the mixture was filtered to remove succinimide and the filtrate was evaporated. The oil (1·24 g) was dissolved in Ac_2O (16 ml) and AcONa (1·5 g) was added to the soln. The mixture was refluxed for 1 h, cooled, then filtered to remove insoluble material. The filtrate and benzene washings were evaporated to leave a pale brown solid (1·19 g), m.p. 139–140°. Recrystallization from benzene–hexane gave **11**, m.p. 139–141°, as colorless prisms which were identical with the sample obtained above.

Preparation of 1-acetyl-2-bromo-3-(p-bromophenyl)-indole (**16**). A mixture of 3-(*p*-bromophenyl)indole (150 mg)[15], NBS (98 mg), and BPO (1 mg) in CCl_4 (10 ml) was refluxed for 1·5 hr. Work up as above gave a crude 2-bromo-3-(*p*-bromophenyl)indole. This indole was acetylated with Ac_2O—AcONa to give crude **16** (250 mg) which was purified through a silica gel column. Recrystallizations from cyclohexane gave **16**, m.p. 127–128·5°, as colorless prisms.

Bromination of **1c** *with NBS* (2 *mole*) *in* AcOH. A soln of NBS (1·78 g, 10 mmole) in AcOH (90 ml) was added to a soln of **1c** (1·17 g, 5 mmole) in AcOH (940 ml) at 20° under N_2 during 30 min. The mixture was stirred for 3 h at 20°, then concentrated *in vacuo* at below 40° until NBS and succinimide began to precipitate. The mixture was diluted with CCl_4 (60 ml) and filtered to remove insoluble materials (NBS and succinimide). The filtrate was evaporated to leave a yellow solid (1·60 g) which gave **2c** (1·52 g, 97%) on recrystallization and preparative layer chromatography of the mother liquor. Recrystallizations from benzene–hexane gave **2c**, m.p. 114–115·5°, which was identical with the sample obtained above (mmp). A trace of **1c** (12 mg, 1%) was recovered.

Reaction of **2a** *with thiourea*

(1) *Formation of* **19a**. A soln of **2a** (272 mg, 1 mmole), thiourea, (760 mg, 10 mmole) and *p*-toluenesulfonic acid (1·72 g, 10 mmole) in *i*-PrOH (10 ml) was refluxed for 6 h. The mixture was kept in a refrigerator and separated ppt (1·49 g) was collected. The filtrate was again kept in a refrigerator to precipitate colorless needles (**19a**, 267 mg), m.p. 252–253°, which were collected by filtration. The filtrate and the ppt (1·49 g) were again dissolved in hot *i*-PrOH. The soln was cooled, separated crystals (1·05 g) were removed by filtration, and the filtrate was evaporated to leave a residue (1·39 g) which was chromatographed over silica gel (20 g). Elution with CH_2Cl_2 gave **1a** (8 mg). Elution with CH_2Cl_2—MeOH (19:1) gave **19a** (130 mg, total 397 mg, 90%). Recrystallizations from EtOH—Et_2O gave **19a**, m.p. 252–253°, as colorless needles.

(2) *Formation of* **19b**. A mixture of **2a** (350 mg) and thiourea (1·0 g) in EtOH (10 ml)-47% HBr (1 ml) was refluxed for 1 h. The mixture was cooled, separated thiourea (70 mg) was removed by filtration, and the filtrate was evaporated *in vacuo*. The residue (1·3 g) was chromatographed over silica gel. Elution with CH_2Cl_2 gave **1a** (13 mg, 5%). Elution with CH_2Cl_2—MeOH (19:1) gave **19b** (400 mg, 88%) which showed a single spot on TLC. Recrystallization from *i*-PrOH—Et_2O gave **19b**, m.p. 208–210°, as pale yellow needles.

Hydrolysis of **19a**. A soln of **19a** (94 mg) in EtOH (10 ml)-10% NaOH (5 ml) was refluxed for 5 h. The EtOH was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave crude di(3-phenyl-2-indoly) disulfide (37 mg) which was recrystallized from benzene–hexane to give the disulfide, m.p. 186–191°, identical with an authentic sample[8] (mmp and IR).

Reaction of **2a** *with dry* HCl *in dioxane*

Formation of **18**. A soln of **2a** (544 mg) in dioxane (25 ml) saturated with dry HCl gas was refluxed for 2·5 h and evaporated *in vacuo*. The residue was dissolved in dioxane (35 ml) saturated with HCl gas and refluxed again for 1·5 h. The mixture was evaporated *in vacuo* to leave an oil (468 mg) which was chromatographed over silica gel. Elution with benzene–hexane (1:3) gave **18** (425 mg) as a colorless oil which showed a single spot on TLC. Recrystallization from cyclohexane gave **18** (305 mg, 67%), m.p. 83–85°. Repeated recrystallizations from the same solvent gave colorless pillars, m.p. 86–87°. Refluxing of **2a** in dioxane-conc HCl (1:1) for 2·5 h gave **18** in 12% and **3a** in 82% yields; a small amount of **1a** was also isolated.

Reaction of **2a** *in* AcOH. A soln of **2a** (272 mg) in AcOH (5 ml) was refluxed for 1·5 h. The mixture was evaporated *in vacuo*, and the residue was diluted with H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave a residue (245 mg) which was chromatographed over silica gel. The fractions eluted with benzene were further separated by preparative thin layers to give **14** (59 mg, 21%), m.p. 85–100°, and a mixture (51 mg) of **1a** and **12**, which could not be separated. Compound **14** was recrystallized from benzene–hexane to give colorless crystals, m.p. 107–109°, which was identical with the sample obtained above (IR). The second fraction from the column eluted with CH_2Cl_2 gave a yellow solid (70 mg, 35%), m.p. 150–160°, which was identical with **7** obtained above (IR and TLC).

Reaction of **2c** *in* AcOH. A soln of **2c** (157 mg) in AcOH (5 ml) was refluxed for 6 h and the solvent was evaporated to leave a residue (154 mg), which was chromatographed over silica gel. Elution with benzene–hexane (1:9) gave colorless oil (30 mg, 15%) which was a mixture of **8** and **9** (IR and TLC). A second elution with the same solvent gave recovered **2c** (33 mg,

20%). Elution with benzene–hexane (1:3) gave a solid (52 mg, 37%). Recrystallization from benzene–hexane gave colorless crystals, m.p. 134–136·5° which were identical with **1c** (IR).

Reduction of **2a** *to* **1a**

(1) TsOH—*i*-PrOH. A soln of **2a** (150 mg, 0·55 mmole) and *p*-toluenesulfonic acid (950 mg, 5·5 mmole) in i-PrOH (10 ml) was refluxed for 17 h, and evaporated *in vacuo* to leave a residue (1·36 g) which was chromatographed over silica gel. Elution with benzene–hexane (1:1) gave **1a** (18 mg, 17%), m.p. 82–88°, recrystallized from benzene–hexane to give colorless crystals, m.p. 86–88°, whose IR spectrum was superimposable with that of **1a**. Elution with CH_2Cl_2 gave a solid (43 mg, 40%) which was recrystallized from benzene–hexane to give **7**, m.p. 215–217°, whose IR spectrum was superimposable with that of the sample obtained above.

(2) Zn—AcOH. To a mixture of **2a** (272 mg) in AcOH (5 ml) was added Zn powder (300 mg), and the mixture was refluxed for 2·5 h. Further Zn powder (500 mg) was added and the mixture was refluxed for a further 10 h. The mixture was filtered to remove Zn and the filtrate was evaporated *in vacuo* to leave a residue which was extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to leave a pale yellow solid (204 mg) which was chromatographed over silica gel. Elution with benzene–hexane (1:2) gave **1a** (72 mg, 37%) which was identical with an authentic sample (IR and mmp after recrystallization). Elution with CH_2Cl_2 gave **3a** (120 mg, 54%), which was recrystallized from EtOH to give colorless crystals, m.p. 190–191°, whose IR spectrum was superimposable with that of an authentic sample.

(3) Zn—Cu-10% NaOH. To a suspension of Zn—Cu (prepared from 2·75 g of Zn powder) in 10% NaOH (10 ml) was added a soln of **2a** (272 mg) in benzene (7 ml) with stirring. The mixture was refluxed for 16 h and filtered to remove insoluble materials. The filtrate was extracted with benzene and the extracts were washed with H_2O, dried, and evaporated to leave a residue (217 mg) which was chromatographed over silica gel. Elution with benzene–hexane (1:4) gave **2a** (25 mg, 9%). Elution with benzene–hexane (3:7) gave **1a** (160 mg, 83%). Recrystallization from benzene–hexane gave colorless crystals, m.p. 86–87·5°, which were identical with an authentic sample (mmp).

Reduction of **2c** *to* **1c**

A soln of **2c** (314 mg) in benzene was added to a suspension of Zn—Cu (prepared from 2·75 g of Zn) in 10% NaOH (10 ml) and the mixture was refluxed for 5 h. Work up as above 3 gave **1a** (46 mg, 24%) and **1c** (147 mg, 62%) besides recovered **2c** (21 mg, 6·5%).

Photochemical reaction of **14**

(1) In EtOH-10% KOH. A soln of **14** (100 mg) in EtOH (70 ml)-10% KOH (10 ml) was irradiated with a low pressure Hg lamp (10 W) for 1 h under N_2. The EtOH was evaporated *in vacuo* and the residue was neutralized with 10% HCl and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave a residue (79 mg) which was separated by preparative thin layer (silica gel). From the less polar fraction **1a** (66 mg, 93%) was obtained. Recrystallization from cyclohexane gave colorless crystals, m.p. 85–88°, which were identical with **1a** (IR). The more polar fraction gave 3 mg of an unknown compound.

(2) MeOH—MeONa. A soln of **14** (100 mg) in MeOH—MeONa (prepared from Na (800 mg) and MeOH (80 ml)) was irradiated with a low pressure lamp for 1·25 h under N_2. Similar work-up to that above gave **1a** (65 mg, 91%) and two unknown compounds.

(3) In MeOH. A soln of **14** (100 mg) in MeOH (80 ml) was irradiated with a low pressure lamp for 1·25 h under N_2. The mixture was evaporated to leave a residue which was separated by preparative layer chromatography to give **1a** (52 mg, 73%).

Photochemical reaction of **8**. A soln of **8** (100 mg) in MeOH (60 ml)-10% KOH (20 ml) was irradiated with a low pressure lamp for 1 h. The mixture was treated as above (1) to give **1a** (34 mg, 48%) and **8** (10 mg, 10%).

Photochemical reaction of **12**. A soln of **12** (100 mg) in MeOH—MeONa (prepared from Na (800 mg) and MeOH(80 ml)) was irradiated with a low pressure lamp for 1·5 h. Work-up as above gave **1a** (25 mg , 37%) and a mixture of unknown compounds (23 mg) which could not be purified.

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