

2-Arylmethylideneindolin-3-ones: Stereochemistry and Reduction with Sodium Borohydride

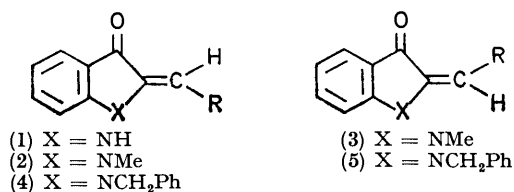
By M. Hooper* and W. N. Pitkethly, School of Pharmacy, Sunderland Polytechnic, Sunderland SR1 3SD

The synthesis of 2-arylmethylideneindolin-3-ones and their 1-substituted analogues is described. The syntheses of the latter, with some exceptions, produced mixtures of *cis*- and *trans*-isomers which were separated by preparative t.l.c.: the products were characterised by spectroscopic methods. The ratio of the isomers varied with the structure of the indolinone; an explanation in terms of the opposing effects of orbital overlap control and steric crowding in the reaction intermediates and products is suggested. Reduction of the indolinones with sodium borohydride led to benzylindoles *via* intermediate indolinols, which were isolated from two of the reactions. A mechanism is proposed which differs from the one already advanced by other workers.

THE title compounds¹ were prepared by acid- or base-catalysed condensation of aromatic aldehydes with indoxyl (Table 2) or 1-substituted indoxyls² (Table 3). For the preparation of the *N*-substituted indolinones (2a, c, and d) it was necessary to reduce the temperature of the reaction to 0–5° to avoid the formation of tarry products. T.l.c. of these reaction mixtures showed the presence, in varying amounts, of three compounds, coloured orange, red, and yellow, respectively. The reactions leading to the indolinones (2h and j) and (3f) were, however, satisfactorily carried out at reflux temperature and each gave rise to only one product. The reaction between 2-chlorobenzaldehyde and 1-methylindoxyl was satisfactorily carried out at either temperature but at 0–5° a mixture of products resulted whereas at reflux temperature only the red compound was formed.

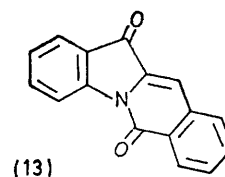
Elemental analysis and mass measurements indicated that the orange and red compounds were isomeric indolinones. The structure of the yellow compounds, at present uncertain, will be the subject of a separate paper. When solutions of the orange indolinones (2a–d) were exposed to u.v. light for several hours both red and yellow compounds were formed. The relative amounts of the orange, red, and yellow compounds present after this time varied with the structure of the indolinone and the solvent used but with one exception each of these compounds was present in significant amounts (Table 4). Only the red compounds were formed when the orange isomers were heated at about 180° in an inert solvent. These observations suggested that the orange and red

compounds were geometrical isomers in which the ring carbonyl group is either *trans* (2) or *cis* (3) to the aryl group attached to the carbon-carbon double bond.



For structures (1)–(5), R =

- | | |
|--|--|
| a; Ph | h; 4-O ₂ N·C ₆ H ₄ |
| b; 2-ClC ₆ H ₄ | i; 2-HO ₂ C·C ₆ H ₄ |
| c; 4-ClC ₆ H ₄ | j; 4-HO ₂ C·C ₆ H ₄ |
| d; 2-MeOC ₆ H ₄ | k; 4-Me ₂ N·C ₆ H ₄ |
| e; 4-MeO·C ₆ H ₄ | l; 2-Pyridyl |
| f; 2-HO·C ₆ H ₄ | m; 3-Pyridyl |
| g; 4-HO·C ₆ H ₄ | n; 4-Pyridyl |
| | o; 2,6-Cl ₂ C ₆ H ₃ |
| (6) X = CH ₂ , R = Ph | (7) X = CH ₂ , R = Ph |
| (8) X = CMe ₂ , R = Ph | (9) X = CMe ₂ , R = Ph |
| (10) X = O, R = aryl | (11) X = O, R = Ph |
| (12) X = S, R = aryl | |



Dreiding models and scale projection diagrams (Figure 1) clearly show that the steric interactions between the *N*-methyl group and the aryl ring in the *trans*-isomer are greater than those between the carbonyl oxygen atom and the aryl ring in the *cis*-isomer. The

¹ W. C. Sumpter and F. M. Miller, 'Heterocyclic Compounds with Indole and Carbazole Systems,' ed. A. Weissberger, Interscience, New York, 1954, p. 166; P. J. Julian, E. W. Meyer, and H. C. Printy in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1952, p. 186.

² S. J. Holt and P. W. Sadler, *Proc. Roy. Soc. (B)*, 1958, **148**, 481.

trans-configuration will, therefore, be less planar than the *cis*-configuration. This was confirmed by spectroscopic studies (Table 1). The more planar structure of

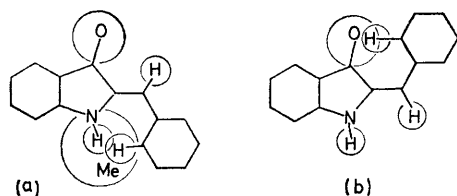


FIGURE 1 Scale drawing of *trans*- and *cis*-2-arylmethylideneindolin-3-ones based on the following dimensions (E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 1955, 3755): bond lengths C-C 1.53, C=C 1.33, aromatic C-C 1.39, C-H 1.08, C=O 1.23, C-Cl 1.70, N-Me 1.47, N-H 1.01 Å; bond angles aromatic ring 120°, five-membered ring 108°, C=C-H 120°, C-C=O 126°, C-N-Me 126°; atomic radii H 0.60, CH₃ 1.70, =O 1.1 Å

the red *cis*-compounds was in agreement with the longer wavelength and greater intensity of their u.v. absorption, and the lower i.r. carbonyl and double bond stretching frequencies. The n.m.r. spectra of the orange *trans*-isomers showed the vinylic proton resonances at lower

reduced, also show similar changes in their i.r. and n.m.r. spectra but have almost identical u.v. spectra. In all the reactions leading to these compounds the *trans*-isomer was formed preferentially, although there was a significant amount of the *cis*-isomer in the case of the 3,3-dimethylindan-1-one derivatives. In each of these cases the *trans*-isomers were converted into the *cis*-isomers on irradiation.

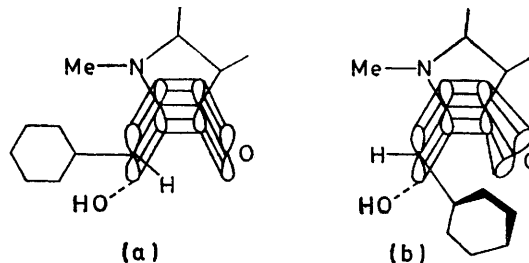


FIGURE 2

The problem remains that in all these reactions the isomer with the least favourable stereochemistry is the one preferentially formed. The stereochemistry of the

TABLE 1
Spectroscopic properties of 2-arylmethylideneindolin-3-ones

Compound	$\lambda_{\max.}$ (EtOH)/nm (ϵ)	$\nu_{\max.}/\text{cm}^{-1}$ (Nujol)			τ				
		C=O	C=C	Aryl	=CH	NMe			
(1a) ^a	231 (12,500)	241 (12,420)	299 (21,600)	470 (9880)	1685	1630	1600		
(1b)	233 (12,210)		300 (22,800)	469 (9837)	1690	1630			
(1c)	234 (14,380)		309 (24,120)	466 (11,880)	1690	1630			
(1d)	233 (12,930)	296 (19,600)	350 (10,420)	477 (11,800)	1680	1630			
(2a)	241 (14,800)		299 (17,160)	478 (5594)	1680	1630	1605	3.17	6.93
(3a)	249 (21,620)		302 (26,310)	504 (6130)	1665	1620		3.44	6.68 ^b
(2b)	241 (17,970)		292 (19,000)	476 (5390)	1700	1635	1605	3.23	7.00
(3b)	242 (19,090)		297 (25,020)	497 (5094)	1685	1630	1600	3.48	6.67
(2c)	240 (20,880)		303 (28,300)	474 (9750)	1695	1635	1602	3.22	6.94
(3c)	237 (16,090)		314 (28,780)	503 (6469)	1680	1630		3.45	6.70
(2d)	241 (14,333)	285 (14,260)		477 (5644)	1695	1635	1610		6.95 ^c
(3d)	237 (18,770)		300 (23,410)	508 (7681)	1670	1625	1600	3.40	6.70
(3o)	239 (18,090)	274 (17,230)		465 (4180)	1700	1635	1610	3.70	6.65
(4a)	247 (15,970)	280 (19,070)	301 (22,810)	471 (6377)	1690	1635	1610		5.12 ^d
(5a)	248 (21,440)	263 (19,320)	307 (30,750)	496 (7698)	1675	1625		3.35	4.80 ^d
(4b)	241 (20,540)	281 (21,500)	296 (20,730)	468 (5476)	1695	1640	1610		5.20 ^d
(5b)	240 (15,540)	281 (22,170)	301 (21,940)	495 (5332)	1685	1620	1600	3.45	4.85 ^d

(3f) $\nu_{\max.}$ 3300—2300 (very broad bonded O-H), 1655 (chelated C=O), 1625 (C=C); (2h) $\nu_{\max.}$ 1685 (C=O), 1630 (C=C); (2j) $\nu_{\max.}$ 3500—2400 (very broad, satellite dimer peaks of carboxylic acid OH), 1685br (C=O of acid and ring), 1625 cm⁻¹ (C=C).

^a Ref. a, Table 2. ^b All the *cis*-isomers had a multiplet at low field (τ 1.80—2.10) corresponding to the single proton in the 2-position of the aryl ring which lies in the deshielding cone of the carbonyl group. ^c OMe at τ 6.15. ^d CH₂.

field than in the case of the red *cis*-isomers, owing to deshielding by the ring carbonyl group. The *N*-methyl resonances showed the opposite behaviour. In the *trans*-isomers the *N*-methyl group lies in the shielding cone of the inclined aryl ring and the absorption is upfield of the corresponding resonances in the *cis*-isomers where this effect cannot operate. The assignment of these configurations is in agreement with results reported for related systems. The *trans*- and *cis*-3,3-dimethylindan-1-ones (8 and 9)³ show corresponding changes in their u.v., i.r., and n.m.r. spectra. The isomeric unsubstituted indan-1-ones (6) and (7)³ and auronones (10) and (11),⁴ in which steric hindrance is

³ D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, 1964, **29**, 1276.

products resulting from carbanionoid reactions between active methylene and carbonyl compounds has been shown to be governed by 'overlap control' in the developing $\alpha\beta$ -unsaturated system.⁵ In the less flexible indolinones, where rotation round the $\alpha\beta$ carbon-carbon bond is more restricted than in acyclic systems, this principle is still a major factor in determining the stereochemistry of the products. In the *trans*-isomers overlap of the adjacent *p* orbitals is maximal (Figure 2a) whereas in the *cis*-isomers overlap is reduced by the

⁴ B. A. Brady, M. M. Healey, J. A. Kennedy, W. I. O'Sullivan, and E. M. Philbin, *Chem. Comm.*, 1970, 1434; W. I. O'Sullivan, personal communication.

⁵ H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, 1959, **81**, 2086.

repulsion between the carbonyl oxygen atom and the aryl ring (Figure 2b). However, steric changes in other parts of the molecule do alter the relative amounts of the two isomers. When the aryl ring carries no substituents or a substituent in the 4-position, then the major (2a and c) or only products (2h and j) were the *trans*-isomers predicted by 'overlap control.' When a 2-substituent was introduced then the *cis*-isomers were formed either exclusively (3f and o) or in much greater yields (3b and d). The larger the substituent the greater the amount of the *cis*-isomer (3b and d). The reaction leading to the indolinones (2b) and (3b) was temperature-dependent: at 0° the *trans*-isomer was the major product but at reflux temperature only the *cis*-isomer was formed. It seems, therefore, that at low

u.v. and i.r. absorption characteristic of the less planar structure (Table 1). Whereas overlap control would be expected to favour the formation of the *trans*-isomer, the considerable increase in steric interactions would be expected to favour the formation of the *cis*-isomer. In both cases, however, the 2,6-dichlorophenyl ring would be twisted out of the plane of the indoline ring. The indolinone was not isomerised by u.v. light and in the n.m.r. spectrum the vinylic proton and *N*-methyl group resonances appeared in similar positions to those of these groups in the *cis*-isomers. We have therefore assigned to it the *cis* configuration (3o). The configurations of the indolinones (2h and j) and (3f) were assigned on the basis of their i.r. spectra. The isolation of the *cis*-isomer (3f) as the only product of the reaction would

TABLE 2
2-Arylmethylideneindolin-3-ones

Compound	Method	Yield (%)	Colour	M.p. (°C)	Formula	Found (%)			Required (%)		
						C	H	N	C	H	N
(1a) ^a	B	90	Orange	176—178 ^b	C ₁₅ H ₁₁ NO						
(1b)	A	94	Orange	214—215 ^c	C ₁₅ H ₁₀ ClNO	70.3	4.1	5.3*	70.5	3.9	5.5
(1c)	A	85	Orange	260—261 ^d		70.5	3.9	5.4†			
(1d)	A	86	Bronze	205—206 ^b	C ₁₆ H ₁₃ NO ₂	76.3	5.2	5.6	76.5	5.2	5.6
(1e)	A	93	Orange	180—181 ^b		76.7	5.4	5.8			
(1f)	B	93	Orange	174—175 ^b	C ₁₅ H ₁₁ NO ₂	76.1	4.9	6.0	76.0	4.6	5.9
(1g) ^e	B	95	Bronze	267—269 ^b							
(1h) ^f	A	94	Dark red	273—274 ^d	C ₁₅ H ₁₀ N ₂ O ₃						
(1i)	B	81	Orange-red	See expt.	C ₁₆ H ₁₁ NO ₃	72.4	4.0	5.5	72.5	4.15	5.3
(1j)	A	94	Orange	334—335 ^g		72.8	4.3	5.2			
(1k) ^a	B	94	Purple	236—238 ^d	C ₁₇ H ₁₆ N ₂ O						
(1l)	A	68	Orange	157—158 ^b	C ₁₄ H ₁₀ N ₂ O	75.7	4.5	12.7	75.7	4.5	12.6
(1m)	B	91	Yellow	229—230 ^b		75.4	4.6	12.9			
(1n)	A	72	Orange	205—206 ^b		75.6	4.7	12.7			

* Found: Cl, 13.6. † Found: Cl, 13.85. Required: Cl, 13.9%.

^a R. A. Abramovitch and A. M. Marko, *Canad. J. Chem.*, 1960, **38**, 131. ^b From methanol. ^c From ethanol. ^d From acetone. ^e Beilstein, XXI, p. 593. ^f Beilstein, XXI, p. 349. From water-dimethylformamide.

temperatures the reaction is governed by 'overlap control' whereas at higher temperatures steric crowding in the products is the determining factor. This temperature effect apparently involves the intermediates shown (Figure 2) since thermal isomerisation of the *trans*-compounds only takes place at much higher temperatures and to a smaller extent. These observations indicate that this reaction proceeds under both kinetic and thermodynamic control. The reaction intermediates (Figure 2) are in equilibrium; at low temperatures the energetically favoured intermediate (Figure 2a) predominates and the major product is the *trans*-isomer (2b), whereas at higher temperatures the reaction proceeds through the higher energy intermediate (Figure 2b) to the more planar *cis*-isomer (3b). It is probable that all the above reactions are governed by the same principle. We are now extending this study to indolinones [(4a and b) (5a and b)] with bulkier substituents on the nitrogen atom but preliminary results are conflicting.

The reaction between 1-methylindoxyl and 2,6-dichlorobenzaldehyde gave only a single compound, analysis of which agreed with the indolinone structure. The configuration of this compound was difficult to assign. The compound was orange and showed both

not be expected on steric grounds alone but intramolecular hydrogen bonding in both the intermediate state and the product would be an additional factor favouring the formation of this isomer.

The reactions between indoxyl and aromatic aldehydes also gave only a single product, the indolinone (Table 2), to which we have assigned the *trans*-configuration (1). The u.v. and i.r. spectra of compounds (1a—d) were similar to those of the corresponding *trans*-*N*-methylindolinones (Table 1). When 2-carboxybenzaldehyde was condensed with indoxyl under alkaline conditions, at reflux temperature, an unexpected yellow compound was formed in high yield. The compound had a molecular ion corresponding to C₁₆H₉NO₂, i.e. the expected indolinone less one molecule of water. The i.r. spectrum showed the absence of carboxylic acid and NH absorption and the presence of an amide as well as a ring carbonyl group. It was therefore assigned the tetracyclic lactam structure (13). The expected indolinone (1i), which readily cyclised to the lactam, was obtained when the reaction was carried out at 0°. Furthermore, the reduced steric influence of the nitrogen substituent would be expected to favour the *trans*-isomer. A refluxing solution of the indolinone (1a) on prolonged irradiation (48 h) gave only traces of a red

compound, which its mass spectrum indicates is probably not the isomeric compound. This resistance to photochemical isomerisation is in agreement with the known photostability of indigo and related compounds.⁶ Other workers have proposed the *trans*-configuration for 2-alkylideneindolin-3-ones derived from steroidal compounds.⁷

The indolinones (1a, b, e—h, j—n), (2h and j), and (3f) in methanolic solution were readily reduced by an excess of sodium borohydride to the corresponding 2-aryl-methylindoles (Table 5). The indoles (16a and l) were identical with authentic samples.

It was necessary to carry out the reduction of the 1-substituted indolinones (2h and j) and (3f) under nitrogen in order to obtain high yields of the corresponding indoles. The nitro-group present in (2h) was at the same time reduced to an azoxy-group in the product (17h).^{8*} This synthetic route now makes available a class of compounds few of which have so far been reported.

The mechanism indicated is consistent with all our experimental data. The first step involves the 1,4-addition of hydrogen across the $\alpha\beta$ -unsaturated carbonyl system⁹ of the indolinones to give the tautomeric indoxyls (14). The keto-tautomers would undergo further reduction to the indolinols (15) which by loss of water would give the indoles (16) and (17). Hassner and his co-workers⁷ have postulated an alternative mechanism involving 1,2-addition of hydrogen to steroidal indolinones followed by isomerisation of the intermediate alkylideneindolinol (20) to an alkylindolenine (21) which was further reduced by addition of hydrogen across the azomethine linkage. Hassner did not detect or isolate any of these suggested intermediates. Our proposals are supported by the observation that when the indolinones (2h and j) and (3b and f) were reduced in the presence of air the colour of the reaction mixture first faded then slowly returned to that of the original indolinone. This is consistent with the presence of the proposed indoxyls, which would be expected to undergo ready aerial oxidation, especially in alkaline solution.¹ Secondly, the indolinol (15b) isolated from the reduction of the indolinone (3b), was easily dehydrated to the corresponding indole (17b). When air was bubbled through an alkaline solution of the indolinol (15b), no change occurred; this provides further evidence in support of an indoxyl intermediate (14) and also indicates that the second reduction step is irreversible. Despite careful examination of the other reaction mixtures no other indolinols were isolated except in the case of the reduction of the lactam (13)

* The reduction of aromatic nitro-compounds to azoxy-compounds with sodium borohydride has not previously been reported although such reductions are known to occur with lithium aluminium hydride.

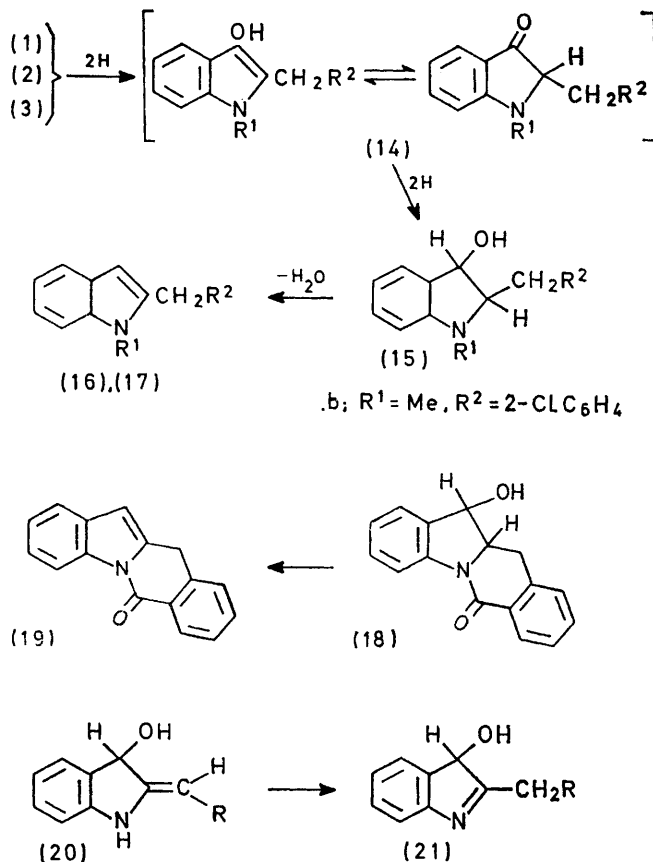
† We thank a referee for drawing our attention to this paper.

⁶ G. M. Wyman, *Chem. Comm.*, 1971, 1332.

⁷ A. Hassner, M. J. Haddadin, and P. Catsoulacos, *J. Org. Chem.*, 1966, **31**, 1363.

⁸ N. G. Gaylord, 'Reduction with Complex Metal Hydrides,' Interscience, New York, 1956, p. 776.

when the indolinol (18) was the only product. Dehydration of this compound to the indole (19) proved difficult, but was finally achieved by warming with concentrated sulphuric acid. The isolation of the indolinols (15b) and (18) does not exclude Hassner's



mechanism for the reduction of the indolinones (1; X = NH), however, the 1,3-tautomeric shift in 2-aryl-methylideneindolin-3-ols [(20) \rightarrow (21); R = aryl] is less probable in view of the conjugation of the lone pair of the nitrogen atom with the aromatic ring and the conjugation of the exocyclic double bond with the 2-aryl substituent.¹⁰ Such a shift is impossible in the reduction of the indolinones (2), (3), and (13). The reduction of these indolinones would not be predicted by Hassner's mechanism.

The reductions of the analogous oxygen¹¹ (10; R = Ph or MeO·C₆H₄) and sulphur (12)^{12†} compounds have also been reported. In the case of the aurones selective reduction of the carbonyl group took place, followed by a rearrangement to a benzofuran (22;

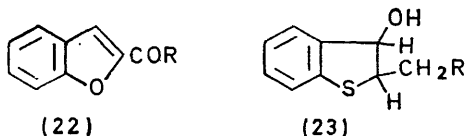
⁹ S. B. Kadin, *J. Org. Chem.*, 1966, **31**, 620; H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965, pp. 39 and 40; S. W. Chaikin and W. C. Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.

¹⁰ K. Bláha and O. Cěrvinka, *Adv. Heterocyclic Chem.*, 1966, **6**, 150.

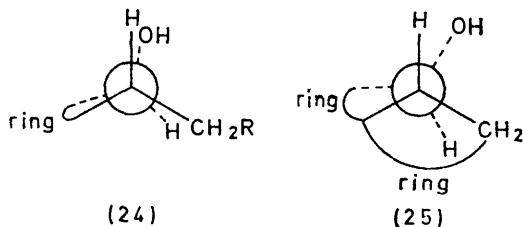
¹¹ A. Holý and A. Vystrčil, *Coll. Czech. Chem. Comm.*, 1962, **27**, 1861.

¹² N. Kucharczyk and V. Horák, *Coll. Czech. Chem. Comm.*, 1968, **33**, 92.

R = Ph or MeO·C₆H₄). The dihydrobenzothiophens (12) were, in most cases, reduced directly to the corresponding alcohols (23) but when the aryl ring carried 4-chloro- or 3,4-dichloro-substituents selective reduction of the carbonyl group was observed, and further reduction, in these cases only, gave a mixture of *cis*- and *trans*-isomers of the corresponding alcohols (23; R = 4-ClC₆H₄ or 3,4-Cl₂C₆H₃). The production of the alcohols (23) would be facilitated by the larger size and greater flexibility of the dihydrothiophen ring. In each case the alcohols were easily dehydrated to the corresponding 2-arylmethylbenzothiophens regardless of their stereochemistry.

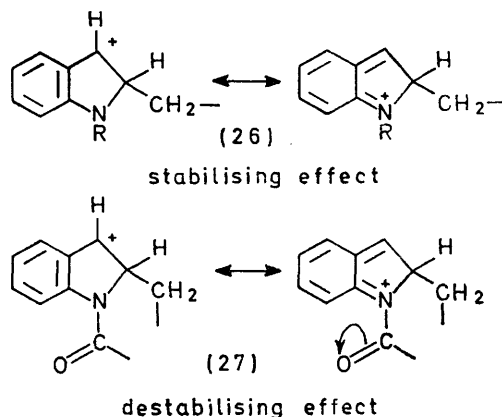


There remains to be explained the marked difference in conditions required for dehydration of the indolinols (15b) and (18). The possibility of steric factors controlling the reaction was examined. On the assumption that the ring nitrogen atom is *sp*² hybridised, for maximum interaction of the lone pair with the adjacent unsaturated system, Dreiding models show that the substituents in the 2- and 3-positions of the indolinol (15b) are eclipsed (24), whereas the corresponding substituents in the lactam (18) are more skewed owing to the fusion of the extra rings to the indoline system (25). The n.m.r. spectra were in agreement with this stereochemistry¹³ (see Experimental section). Although the



more readily dehydrated indolinol showed the greatest crowding, the steric differences are too small to account for the large difference in reactivity. In both cases dehydration would be expected to take place very readily both to reduce steric crowding and to increase the resonance energy of the system by formation of the indole ring. In our view the considerable difference in the ease of dehydration of the indolinols (15b) and (18) reflects the great difference in electronic properties of the groups substituted on the indolinol nitrogen atom. Dehydration involves protonation of the hydroxy-group and subsequent loss of water and a proton in one or two steps. The electron-releasing methyl group would

facilitate the reaction by stabilising the intermediate carbonium ion (26; R = Me), or incipient carbonium ion, whereas the electron-withdrawing carbonyl group would hinder the reaction by destabilising the intermediate carbonium ion (27).



EXPERIMENTAL

U.v. spectra were determined for ethanolic solutions with a Unicam SP 500 spectrophotometer. I.r. spectra were determined with Perkin-Elmer 225 [compounds (2a) and (3a)] and Unicam SP 200 spectrophotometers. N.m.r. spectra were determined for solutions in [2H₆]dimethyl sulphoxide (indolinones) or [2H]chloroform (indoles) (tetramethylsilane as an internal standard) with Perkin-Elmer R12 (60 MHz) and Varian Ha-100 [(2a), (3a), (15b), and (18)] spectrophotometers. Preparative thin-layer chromatography (p.l.c.) was carried out on 100 cm plates with 1.0 mm layers of kieselgel PF₂₅₄ (Merck).

2-Arylmethylideneindolin-3-ones (Table 2).—1-Acetyl-indoxyl (0.01 mol) was heated under reflux for 1 h, in an atmosphere of nitrogen, with either (A) 50% aqueous ethanol (50 ml) containing concentrated hydrochloric acid (1 ml) or (B) 1.5N-sodium hydroxide (55 ml). The appropriate aldehyde (0.01 mol) in ethanol (2 ml) was then added through the condenser and heating was continued for a further 2 h. The indolinone which separated on cooling was collected, washed, dried, and crystallised from a suitable solvent. All the indolinones showed characteristic NH, C=O, and C=C stretching frequencies in the i.r. (see examples in Table 1). Satisfactory n.m.r. spectra (CDCl₃) could only be obtained for compounds (1a, e, h, l, and n) in which the vinylic proton resonances occurred at τ 3.15, 3.15, 3.11, 3.24, and 3.36 respectively.

2-(2-Carboxyphenyl)methylideneindolin-3-one (1i).—The general method (B) was followed except that the solution of indoxyl was cooled to 0° before the addition of 2-carboxybenzaldehyde (0.01 mol) in methanol (5 ml). The mixture was stirred for a further 5 h at 0–5° and the lactam (13) (0.21 g) was filtered off. The filtrate was washed with ether until the washings were colourless, filtered through Celite to remove traces of indigo, cooled to 0°, and acidified by the dropwise addition of concentrated hydrochloric acid. The orange-red *indolinone* which separated was recrystallised from methanol (2.15 g, 81%), but had no definite m.p.; at 209–210° the colour changed from red to yellow and the substance finally melted at 241–242°, the m.p. of the lactam (13). The product showed ν_{\max} 3350 (N–H), 3300–2300 (satellite at 2600) (O–H of carboxylic acid),

¹³ D. H. Williams and I. Fleming, 'Spectroscopic Methods in Organic Chemistry,' McGraw-Hill, London, 1966, p. 104; L. M. Jackmann and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 2nd edn., 1969, p. 280.

TABLE 3
1-Substituted 2-arylmethylideneindolin-3-ones

Com- pound	Colour	Yield (%)	M.p. (°C)	Formula	Found (%)			Required (%)		
					C	H	N	C	H	N
(2a) ‡	Orange	80 *	131—132 ^a	C ₁₆ H ₁₃ NO	81.6	5.5	6.1	81.7	5.5	6.0
(3a)	Red	8	109—110 ^a		<i>M</i> - 1, 234.0915			234.0919		
(2b) ‡	Orange	57 *	103—104 ^b	C ₁₆ H ₁₂ ClNO	71.3	4.45	5.2 †	71.25	4.45	5.2
(3b)	Red	39	155—156 ^a		71.4	4.6	5.4 †			
(2c) ‡	Orange	76 *	159—160 ^a		71.4	4.6	5.1 †			
(3c)	Red	16	131—132 ^a		71.3	4.7	5.1 †			
(2d) ‡	Orange	52 *	113—114 ^c	C ₁₇ H ₁₅ NO ₂	76.7	5.7	5.1	77.0	5.7	5.3
(3d)	Red	37	100—101 ^c		77.2	5.6	5.4			
(3f)	Red	88	134—136 ^d	C ₁₆ H ₁₃ NO ₂	76.3	5.3	5.5	76.5	5.2	5.6
(2h)	Dark red	96	217—218 ^e	C ₁₆ H ₁₂ N ₂ O ₃	68.8	4.05	10.2	68.6	4.3	10.0
(2j)	Orange red	90	250—251 ^f	C ₁₇ H ₁₃ NO ₃	73.7	4.9	5.1	73.1	4.7	5.0
(3o)	Orange	98	160—161 ^b	C ₁₆ H ₁₁ Cl ₂ NO	63.1	3.8	4.55 †	63.2	3.6	4.6
(4a) ‡	Orange	20 *	94—95 ^a	C ₂₂ H ₁₇ NO	84.7	5.4	4.5	84.9	5.5	4.5
(5a)	Red	71	122—123 ^a		85.1	5.5	4.4			
(4b) ‡	Orange	50 *	119—120 ^a	C ₂₂ H ₁₆ ClNO	76.45	4.7	3.9 †	76.4	4.6	4.05
(5b)	Red	38	87—88 ^a		76.15	4.8	3.75 †			

* The percentage of yellow compound is that required to make up the total yield to 100%. † Chlorine analyses: Found: (2b) 12.95; (3b) 13.4; (2c) 12.9; (3c) 12.8. Required: Cl, 13.2%. Found: (3o) 23.1. Required: Cl, 23.35%. Found: (4b) 10.5; (5b) 10.4. Required: Cl, 10.3%. ‡ P.l.c. separations were carried out under the following conditions: running solvents benzene [(2a), (2b), (4a)], dichloromethane (2c), dichloromethane with 10% carbon tetrachloride (2d), and carbon tetrachloride with 20% dichloromethane (4b). Number of runs two [(2a, c, d), (4a)] and four [(2b), (4b)]. The mobility of the bands on the plates was always yellow > red > orange.

^a From methanol. ^b From ethanol. ^c From diethyl ether. ^d From chloroform. ^e From acetone. ^f From glacial acetic acid.

TABLE 4
Yield (%) *

Compound	Yield (%) *		
	Orange	Red	Yellow
(2a)	49	29	22
(2b)	22	70	9
(2c)	20	25	55
(2d) †			ca. 95
(3o)	Extensive decomposition		

* P.l.c. conditions as in Table 3. † Easily converted into the yellow compound which was the major product of photoisomerisation.

gentle warming for 10 min with either 0.5N-sodium hydroxide or methanol containing a few drops of dilute hydrochloric acid gave a product identical with the lactam (13) (m.p., mixed m.p., i.r. spectrum).

Indolo[1,2-*b*]isoquinoline-6,12-dione (13).—This lactam was prepared from 1,3-diacetylindoxyl and 2-carboxybenzaldehyde by method (B). The product separated (67%) as green-yellow prisms, m.p. 241—242° (from benzene or glacial acetic acid) (Found: C, 77.4; H, 3.4; N, 5.45. C₁₆H₉NO₂ requires C, 77.7; H, 3.6; N, 5.7%), ν_{\max} 1700 (indolinone C=O), 1665 (lactam C=O), and 1640 cm⁻¹ (C=C).

1-Substituted 2-Arylmethylideneindolin-3-ones (Table 3).—1-Benzyl- or 1-methyl-3-acetoxyindole (0.01 mol) was hydrolysed by heating with N-sodium hydroxide solution

1700 (ring C=O), 1660 (C=O of aromatic carboxylic acid), and 1625 cm⁻¹ (C=C).

Conversion into the lactam (13). Although the indolinone was recovered unchanged after boiling with water for 1 h,

TABLE 5
2-Arylmethylindoles

Com- pound	R ¹	R ²	Yield (%)	M.p. (°C)	Formula	Found (%)			Required (%)		
						C	H	N	C	H	N
(16a) *	H	Ph	94	85—86 ^a	C ₁₅ H ₁₃ N						
(16b)	H	2-ClC ₆ H ₄	91	62—63 ^b	C ₁₅ H ₁₂ ClN	74.7	5.3	6.0 †	74.55	5.0	5.8
(16c)	H	4-MeO-C ₆ H ₄	93	107—108 ^b	C ₁₆ H ₁₅ NO	80.8	6.2	5.7	81.0	6.3	5.9
(16f)	H	2-HO-C ₆ H ₄	91	109—110 ^b	C ₁₅ H ₁₃ NO	80.45	5.9	6.0	80.7	5.8	6.3
(16g)	H	4-HO-C ₆ H ₄	91	142—143 ^b		80.45	5.95	6.45			
(16h)	H	4-O ₂ N-C ₆ H ₄	95	110—111 ^b	C ₁₅ H ₁₂ N ₂ O ₂	71.3	4.8	11.3	71.45	4.8	11.1
(16j)	H	4-HO ₂ C-C ₆ H ₄	90	213—214 ^c	C ₁₆ H ₁₃ NO ₂	76.3	5.3	5.7	76.5	5.2	5.6
(16k)	H	4-Me ₂ N-C ₆ H ₄	85	129—130 ^b	C ₁₇ H ₁₈ N ₂	81.9	7.3	10.9	81.6	7.2	11.2
(16l) ‡	H	2-Pyridyl	96	95—96 ^b	C ₁₄ H ₁₂ N ₂						
(16m)	H	3-Pyridyl	94	150—151 ^d		80.8	6.0	13.7	80.8	5.8	13.5
(16n)	H	4-Pyridyl	93	141—142 ^b		80.95	5.9	13.35			
(17b)	Me	2-ClC ₆ H ₄	93	118—119 ^e	C ₁₆ H ₁₄ ClN	75.3	5.4	5.3	75.15	5.5	5.5
(17f)	Me	2-HO-C ₆ H ₄	84	119—120 ^f	C ₁₆ H ₁₅ NO		<i>M</i> ⁺ , 237.1160			237.1155	
(17h)	Me	4,4'-Azoxy §	83	158—159 ^d	C ₃₂ H ₂₈ N ₄ O		<i>M</i> ⁺ , 484.2263			484.2263	
(17j)	Me	4-HO ₂ C-C ₆ H ₄	56	205—206 ^e	C ₁₇ H ₁₅ NO ₂		<i>M</i> ⁺ , 265.1104			265.1103	

All the 1-unsubstituted indoles showed characteristic NH i.r. absorption at 3300 cm⁻¹. Characteristic absorption was seen in all n.m.r. spectra at τ 5.95—5.75 (CH₂) and 3.70—3.60 (H-3 of indole ring).

* P. L. Julian and J. Pikel, *J. Amer. Chem. Soc.*, 1933, **55**, 2105. † Found: Cl, 14.8. Required: Cl, 14.7%. ‡ G. R. Clemon and J. C. Seaton, *J. Chem. Soc.*, 1954, 2582. § 4,4'-Bis-(1-methylindol-2-ylmethyl)azoxybenzene.

^a From light petroleum (b.p. 40—60°). ^b From light petroleum (b.p. 60—80°). ^c From water-dimethylformamide. ^d From methanol. ^e From ethanol. ^f From benzene.

(55 ml) under nitrogen and the solution was cooled to 0–5°. The appropriate aldehyde (0.01 mol) in methanol (4 ml) was added through the condenser and the mixture stirred at 0–5° for 2 h. The ice-bath was removed and stirring was continued overnight. The products which separated were collected, dried, and dissolved in benzene, and a sample containing 0.25–0.90 g was subjected to p.l.c.

In the preparation of the indolinones (2h and j) and (3b and f) the cooling of the indoxyl solution was omitted and after the addition of the aldehyde the mixture was refluxed for 4 h.

Photoisomerisations.—The indolinone (2a–d) (0.5 g) was dissolved in dry benzene (50 ml) and irradiated for ca. 12 h in a Hanovia II photochemical reactor using a water-cooled medium-pressure mercury arc tube (main emissions 254, 265, 297, 313, and 366 nm). The solution was concentrated to 10–15 ml and subjected to preparative t.l.c. (Table 4).

When methanol was used as solvent for the indolinone (2a) the yield of yellow compound was increased at the expense of the orange and red compounds. The results for reactions in carbon tetrachloride solution were very similar to those in benzene.

Thermal Isomerisations.—The indolinone (20 mg) in biphenyl (ca. 0.5 g) was heated to about 180° in an oil-bath. The reaction was monitored by t.l.c. The time required for the appearance of a well-defined red spot was recorded:

Compound	T/°C	t/min
(2a)	180	40
(2b)	170	45
(2c)	160	45
(2d)	160	15

2-Arylmethylindoles (16) (Table 5).—Sodium borohydride (4 g) was added in portions, with stirring, to a solution of the indolinone (0.5 g) in methanol (40 ml). The mixture was set aside for 12 h and the bulk of the solvent was then removed under reduced pressure. The residue was diluted with warm water (200 ml) and the solution acidified with dilute hydrochloric acid. The product which slowly separated was collected and crystallised from the appropriate solvent.

When the product was basic (16k–n) the acidic solution was set aside for 3–4 h then made alkaline with 10% ammonia solution; the product was extracted with ether.

1-Methyl-2-arylmethylindoles (17f, h, and j) (Table 5).—Nitrogen was passed through a solution of the indolinone (1.0 g) in ethanol (30 ml). Sodium borohydride (1.5 g) was then added in portions and the mixture was heated on a boiling water bath overnight. The bulk of the solvent was removed under reduced pressure and the residue was diluted with water (200 ml). Acidification with dilute hydrochloric acid gave the indole.

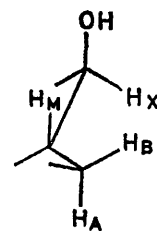
2-(o-Chlorobenzyl)-1-methylindolin-3-ol (15b).—Nitrogen gas was bubbled through a solution of the indolinone (3b) (1.0 g) in ethanol (30 ml) and sodium borohydride was added in portions. The mixture was heated overnight on a boiling water-bath and water (50 ml) was added slowly.

The *indolinol* separated as a white precipitate (0.85 g, 84%) on cooling; m.p. 147–148° (from ethanol) (Found: C, 70.1; H, 5.8; Cl, 12.7; N, 4.9. C₁₆H₁₅ClNO requires C, 70.2; H, 5.85; Cl, 13.0; N, 5.1%), ν_{\max} 3300br cm⁻¹ (O–H); τ (100 MHz) 8.42 (1H, exchangeable OH), 7.18 (3H, s, NMe), 6.72 (overlapping signals, 3H, m, CH·CH₂), 5.31br (1H, d, J 2.5 Hz, CH·O), and 3.4–2.3 (8H, m, aromatic). A complete analysis of the n.m.r. spectrum was not possible (even at 220 MHz).

2-(o-Chlorobenzyl)-1-methylindole (17b).—The indolinol (15b) (30 mg) heated under reflux for 1 h in ethanol (15 ml) containing one drop of dilute hydrochloric acid gave the *indole* (17b) (26 mg) (Table 5).

11a,12-Dihydro-12-hydroxyindolo[1,2-b]isoquinolin-6(11H)-one (18).—Nitrogen was bubbled through a solution of the indolinone (13) (2.25 g) in methanol (80 ml) for 10 min. The solution was cooled to 0° and sodium borohydride (2.5 g) was added in portions. The mixture was stirred for 24 h at room temperature and poured into water (300 ml). The *indolinol* separated as a white precipitate (2.1 g, 93%), m.p. 195–196° (from methanol) (Found: C, 76.5; H, 5.15; N, 5.4%; M⁺, 251.0946. C₁₆H₁₃NO₂ requires C, 76.5; H, 5.2; N, 5.6%; M, 251.0941), ν_{\max} 3380br (bonded O–H) and 1640 cm⁻¹ (lactam C=O).

N.m.r. Spectra.—The spin-spin interactions between the aliphatic protons H_A, H_B, H_M, and H_X were determined by calculation from the results of double-resonance studies.



Proton	τ	J/Hz	ϕ (°) (approx.)
H _A } septet	6.84	AB 15	180
H _B }			
H _M octet	5.88	AM 13	60
		BM 4	155
H _X doublet	4.82	XM 7.5	

Indolo[1,2-b]isoquinolin-6(11H)-one (19).—The indolinol (18) (0.5 g) was dissolved in the minimum volume of concentrated sulphuric acid and the solution gently warmed on a water-bath. The cooled solution was poured, with stirring, into water (60 ml), to give the *indole* (19) (0.4 g, 88%), m.p. 201–202° (from methanol) (Found: M⁺, 233.0839. C₁₆H₁₁NO requires M, 233.0840).

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