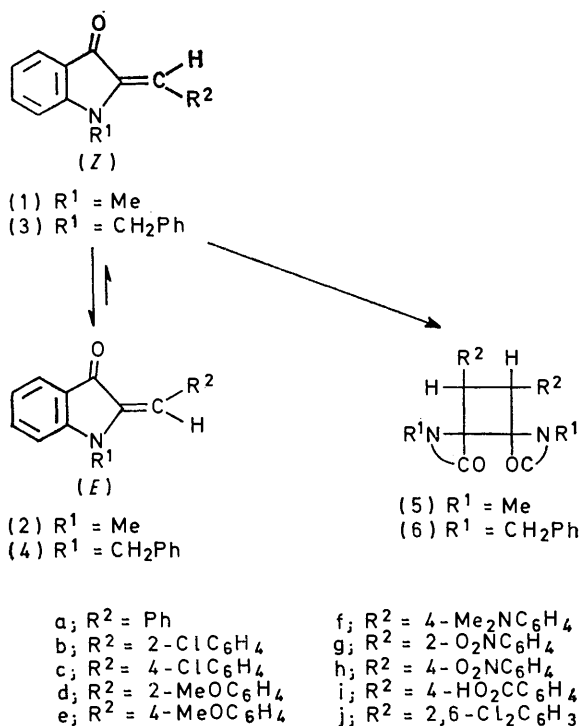# 2-Arylmethyleneindolin-3-ones:† Photodimerisation to Cyclobutane Derivatives

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

$N$-Alkyl-2-arylmethyleneindolin-3-ones have been shown to give rigid cyclobutane derivatives upon irradiation. These compounds were identified using analytical and spectroscopic data. Detailed n.m.r. studies have enabled the configuration and conformation of the photodimers to be established. It is suggested that the reaction may proceed *via* a triplet biradical intermediate. The cyclobutanes undergo thermal cycloreversion probably by a concerted $[\sigma 2_s + \sigma 2_a]$ mechanism.

WE have previously reported the isolation of yellow compounds as by-products in the synthesis of certain $N$-alkyl-2-arylmethyleneindolin-3-ones (1)—(4).[1] These



(1) $R^1$ = Me
(3) $R^1$ = CH₂Ph

(2) $R^1$ = Me
(4) $R^1$ = CH₂Ph

(5) $R^1$ = Me
(6) $R^1$ = CH₂Ph

a; $R^2$ = Ph
b; $R^2$ = 2-ClC₆H₄
c; $R^2$ = 4-ClC₆H₄
d; $R^2$ = 2-MeOC₆H₄
e; $R^2$ = 4-MeOC₆H₄
f; $R^2$ = 4-Me₂NC₆H₄
g; $R^2$ = 2-O₂NC₆H₄
h; $R^2$ = 4-O₂NC₆H₄
i; $R^2$ = 4-HO₂CC₆H₄
j; $R^2$ = 2,6-Cl₂C₆H₃

yellow compounds have now been identified as cyclobutanes (5) and (6). When the synthesis of $N$-methyl-2-

phenylmethyleneindolin-3-one was performed in the absence of light, at 0° or at reflux temperature, only the orange $(Z)$-isomer (1a) was formed. Irradiation of solutions of either the $(Z)$- (1a) or the $(E)$-isomer of $N$-methyl-2-phenylmethyleneindolin-3-one (2a) with u.v. light gave in each case the same yellow product as that obtained in the synthesis of the indolinone. The reactions leading to the yellow compounds were therefore photochemical rather than thermal.

The nature of the aryl substituent ($R^2$) of the indolinone was found to influence the formation of the cyclobutanes. When the substituent was strongly electron-attracting [(1g—j) and (3h)] no yellow product was obtained. As the effect of the substituent in the aryl ring changed from electron withdrawing to electron releasing the yield of cyclobutane increased in the irradiation experiments and also from the synthesis of the corresponding indolinones. Indeed when very strongly electron releasing substituents, *e.g.* OMe or NMe₂, were present only the cyclobutanes (5e and f) were formed but in low yield. Most of the starting aldehydes were recovered unchanged. The formation of the indolinones would be made more difficult by these substituents but it appears that the subsequent dimerisation is facilitated by electron release to such an extent that the indolinones cannot be isolated.

Elemental analysis and mass measurements (Table 1)

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† This name is preferred to the name 2-arylmethylidene-indolin-3-one which has been used in previous papers in this series.

[1] M. Hooper and W. N. Pitkethly, *J.C.S. Perkin I*, 1972, 1607.

of the yellow compounds indicated that they were dimers of the corresponding $N$-alkylindolinones. The i.r. spectra (Table 2) showed the absence of an olefinic bond and an increase in the carbonyl stretching frequency of ca. 20 cm$^{-1}$ compared with that of the parent indolinone.[1] These observations indicated that the photodimers were cyclobutane derivatives formed by the union of two carbon–carbon double bonds, i.e. [2 + 2 ⟶ 4]. Dimerisations of this kind are well known and are characteristic of many αβ-unsaturated ketones.[2]

The n.m.r. spectra of the yellow compounds (Table 2) were all very similar and confirmed their dimeric structure. Two signals at τ ca. 7 were each assigned to an $N$-methyl group and two doublets, each integrating for one

clearly established that head to head dimerisation had occurred. Theoretically six such isomers A–F are possible (Figure). However the size of the coupling constants



(7)　　　　　　　　　　(8)
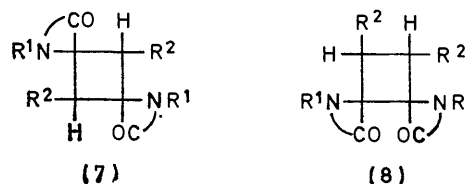
alone cannot be used to assign the adjacent ring protons to a cis- or trans-configuration.[3]

In many cyclobutanes the ring is known to be folded and to rapidly 'flip' between two equivalent geometries

TABLE 1

Cyclobutane derivatives formed by photodimerisation of $N$-alkyl-2-arylmethyleneindolin-3-ones

| Compound | Yield * (%) | M.p. (°C) | Formula | Found (%) | | | | Required (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | $M^{+}$ | C | H | N | M |
| (5a) | 12 | 197—198 $^a$ | $C_{32}H_{26}N_2O_2$ | 81·6 | 5·95 | 5·8 | 470·1939 | 81·7 | 5·5 | 5·95 | 470·1994 |
| (5b) | 4 | 184—185 $^b$ | $C_{32}H_{24}Cl_2N_2O_2$ | 70·9 | 4·6 | 5·1 | | 71·2 | 4·45 | 5·2 | |
| (5c) | 8 | 186—187 $^c$ | | 71·2 | 4·6 | 5·15 ‡ | | | | | |
| (5d) | 11 | 180—181 $^a$ | $C_{34}H_{30}N_2O_4$ | 77·1 | 5·8 | 5·1 | | 77·0 | 5·7 | 5·3 | |
| (5e) | 100 † | 169—170 $^a$ | | 76·5 | 5·8 | 5·2 | | | | | |
| (5f) | 100 † | 176—177 $^d$ | $C_{36}H_{36}N_4O_2$ | 77·5 | 6·8 | 10·3 | | 77·7 | 6·5 | 10·1 | |
| (6a) | 8 | 185—186 $^e$ | $C_{44}H_{34}N_2O_2$ | | | | 622·2634 | | | | 622·2620 |
| (6b) | 11 | 172—173 $^e$ | $C_{44}H_{32}Cl_2N_2O_2$ | 76·3 | 4·3 | 3·75 | | 76·4 | 4·6 | 4·0 | |

* Expressed as a percentage of the total yield of the corresponding (Z) and (E)-indolinones (see Table 3 of ref. 1).　† Only 300 mg (11%) of (5e) and 250 mg (9%) of (5f) were isolated from the attempted synthesis of the corresponding indolinones.　‡ Found: Cl, 12·85.　Required: Cl, 13·15%.

$^a$ From benzene.　$^b$ From ethanol.　$^c$ From ether.　$^d$ From chloroform.　$^e$ From acetone.

TABLE 2

Spectroscopic properties of the photodimers of $N$-alkyl-2-arylmethyleneindolin-3-ones

| Compound | λ$_{max.}$(dioxan)/nm (ε) | | | $v_{max.}$/cm$^{-1}$ (Nujol) | | τ (100 MHz) * | | |
|---|---|---|---|---|---|---|---|---|
| | | | | C=O | Aryl | NCH$_3$ | CHCH† | Aromatic |
| (5a) | 240 (63,400) | 307 (6,600) | 419 (3020) | 1700 | 1620 | 6·89, 7·03 | 4·94, 6·39 | 2·48—3·6 |
| (5b) | 240 (86,560) | | 420 (3490) | 1700 | 1620 | 6·91, 6·93 | 4·17, 5·39 | 2·48—3·5 |
| (5c) | 240 (87,460) | | 418 (3460) | 1700 | 1615 | 6·87, 7·05 | 4·92, 6·47 | 2·48—3·52 |
| (5d) | 240 (71,830) | 307 (6,830) | 418 (3030) | 1700 | 1620 | 6·9, 7·02 | 4·23, 5·46 | 2·48—3·56 |
| (5e) | 238 (92,210) | | 421 (3350) | 1700 | 1615 | 6·83, 7·01 | 4·95, 6·62 | 2·48—3·64 |
| (5f) | 242 (71,830) | | 418 (2980) | 1700 | 1620 | 6·84, 7·02 | 5·04, 6·53 | 2·45—3·55 |
| (6a) | 239 (88,410) | | 417 (3460) | 1700 | 1615 | | | |
| (6b) | 239 (79,270) | | 415 (3460) | 1700 | 1610 | | 4·22, 5·31 | 2·4—3·36 |

* Extra signals for (5d) at τ 6·7 (6H, s, 2 × OMe), for (5e) at τ 6·28 (3H, s, OMe), and 6·33 (3H, s, OMe), and for (5f) at τ 7·15 (6H, s, NMe$_2$) and 7·20 (6H, s, NMe$_2$).　† J 11 Hz.

proton at τ ca. 5 and 6·5 respectively, were assigned to the two cyclobutane ring protons. A multiplet in the low field region integrated for the corresponding number of aromatic protons in each dimer.

A head to tail (7) or head to head (8) combination of two $N$-alkylindolinone molecules would place the two cyclobutane ring protons in the 1,3- or 1,2-relationship. The J values reported for 1,3-interactions in cyclobutanes are much smaller (0·4—2·3 Hz)[3] than those observed for 1,2-couplings (4—13 Hz)[4a] and as the spectra of the yellow compounds showed J values of 11 Hz this

in which the angle θ is ca. 18—20° but can be as high as 51° [equilibrium (9)]. An equilibrium exists between the resulting 'axial' and 'equatorial' conformations the position of which varies with the nature of the ring substituents.[3] Cyclobutane derivatives with rigid stereochemistry are also reported to have folded ring structures.[5]

The folding of a cyclobutane ring can give rise to two effects which influence the chemical shifts of ring protons as well as those of protons contained in substituent groups. The first of these effects can be attributed to the

[2] A. Mustafa, Chem. Rev., 1952, 51, 1; S. T. Reid, 'The Photochemistry of Drugs and Related Substances,' in 'Progress in Drug Research,' ed. E. Jucker, Birkhäuser Verlag, Basel and Stuttgart, 1968, vol. 11, p. 48; S. T. Reid, Adv. Heterocyclic Chem., 1970, 11, 61.
[3] I. Fleming and D. H. Williams, Tetrahedron, 1967, 23, 2747.

[4] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 2nd edn., 1969 (a) p. 287; (b) p. 281; (c) p. 227.
[5] N. Nakagawa, S. Saito, A. Suzuki, and M. Itch, Tetrahedron Letters, 1967, 1003.

paramagnetic anisotropy associated with the carbon atoms of the cyclobutane ring which gives rise to a de-shielding of the axial substituents and a relative shielding
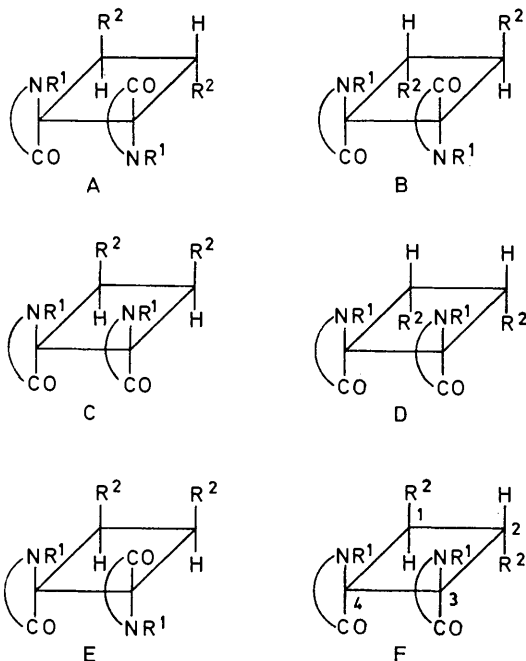


The six possible isomers from head to head dimerisation
of $N$-alkyl-2-arylmethyleneindolin-3-ones

of the equatorial substituents.[6] The second effect stems from the degree of folding of the ring which alters the dihedral angle between vicinal protons thereby influenc-ing the magnitude of their coupling constants. Varia-tions in the size of the vicinal coupling constants can also
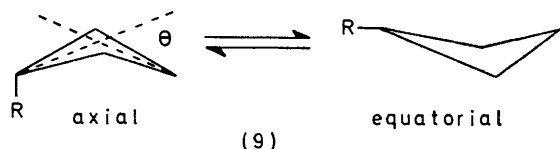


be caused by other factors such as electronegativity, orientation of substituents, and bond lengths. The magnitude of the coupling constants is therefore not a reliable guide to the configuration of cyclobutane derivatives.[4b]



(10)
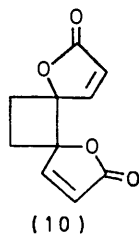
Anaemonin (10) is a cyclobutane derivative resulting from the head to head dimerisation of protoanaemonin.[7] X-Ray crystallography has clearly shown that the lactone

rings, which have approximately the same size and shape as the five-membered rings of the indolinones, are attached to adjacent ring carbon atoms at right angles to the plane of the cyclobutane ring; one lactone ring being inverted in relation to the other. The molecule is thought to be rigidly held in one conformation with the ring folded at an angle of 28°. The dihedral angles between the two sets of vicinal protons differ giving rise to two *trans*-coupling constants $J_{e,e}$ 2·24, $J_{a,a}$ 10·72 Hz, and a *cis*-coupling constant $J_{a,e}$ 10·19 Hz. The coupling constant $J_{a,a}$ 10·72 Hz is in very close agreement with the value of 11 Hz observed for the ring protons in the yellow compounds.

By analogy with anaemonin the $N$-alkyl-2-aryl-methyleneindolin-3-one dimers may reasonably be assumed to have a rigid but folded cyclobutane ring in which the disposition of the substituent groups is fixed. The difference in the chemical shifts of the $N$-methyl groups can be accounted for by ring folding but the difference in the chemical shifts of the ring protons is much greater than that expected from ring folding alone (Table 2). The ring protons must therefore lie in sub-stantially different magnetic environments.

In the isomers (Figure, A and B) the ring protons being *trans* and adjacent to identical substituents, are in the same environment and would therefore be expected to give a single absorption band in the n.m.r. spectrum. In the isomers C and D the two $N$-methyl groups are attached to the cyclobutane ring in a *cis*-relationship which places each group of methyl protons in different environments arising from the magnetic anisotropy of the ring. Similarly the two ring protons exist in a *cis*-relationship and for the same reason would be expected to be in different magnetic environments. However there are no other factors to account for the much greater difference in the chemical shift of the ring protons compared with that between the $N$-methyl groups in these isomers C and D. All four isomers A—D may therefore be dis-counted.

An aromatic ring attached to a cyclic compound normally tends to assume an average conformation which places the adjacent *cis*-substituent in its shielding zone.[4c] In agreement with this observation the n.m.r. spectra of the yellow compounds show that the shielding effect experienced by both the cyclobutane ring protons increases as the electron density of the aryl ring is in-creased by electron-releasing substituents in the 4-position. However, the introduction of a substituent in the 2-position of the aryl rings, irrespective of its elec-tronic properties causes a pronounced downfield shift of both the ring protons (Table 2). The 2-substituent must therefore alter the conformation of the aryl ring so that the adjacent cyclobutane ring proton no longer lies in its shielding zone. Indeed the size of the shift suggests that the aryl ring is now deshielding the cyclobutane ring proton. These effects can only arise when the cyclo-

[6] G. R. Bedford, *Ann. Reports N.M.R. Spectroscopy*, 1971, **4**, 40.

[7] R. M. Moriarty, C. R. Romain, I. L. Karle, and J. Karle, *J. Amer. Chem. Soc.*, 1965, **87**, 3251; E. Lustig and R. M. Moriarty, *ibid.*, p. 3252.

butane ring protons exist in a *trans*-relationship each being adjacent to an aryl ring. This evidence eliminates isomer E in which the ring protons are *cis* and consequently would only be influenced by inductive effects arising from substituents in the aryl rings. It would be difficult to explain the large downfield shift of the ring protons in derivatives of isomer E which contained a substituent in the 2-position of the aryl ring.

In isomer F however the magnetic environment of each ring proton is the same with respect to the influence of the adjacent aryl ring and the anisotropy of the cyclobutane ring but whether they are axial (deshielding) or equatorial (shielding) is dependent on the conformation of the folded cyclobutane ring. Steric interaction between the two N-methyl groups and the *cis*-aryl ring on C-1 would be expected to cause the cyclobutane ring (11) to fold so that the 1-aryl ring and 3-N-methyl group are directed into the equatorial region. This conformation places the two ring protons in the axial direction which is the deshielding zone of the cyclobutane ring. The proton attached to C-1 would be expected to experience the strong deshielding effects of the adjacent carbonyl groups



( 11 )
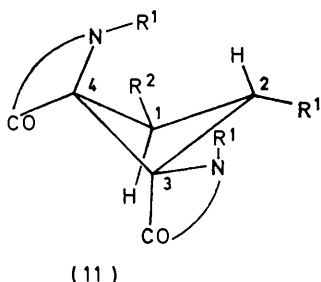
on C-3 and C-4 resulting in a significant downfield shift relative to the *trans*-orientated ring proton on C-2. The only difference between the magnetic environment of the N-methyl groups is that, being in a *cis*-relationship, one of the groups (on C-3) lies in the shielded (equatorial) region of the cyclobutane ring and the other N-methyl group on C-4 lies in the deshielded (axial) region. The aryl ring on C-1 would be expected to have a much greater influence on the chemical shift of the ring proton on C-2 than on the more remote N-methyl protons on C-4.[8]

Photodimerisations of αβ-unsaturated carbonyl compounds are well known[2] and may proceed *via* intermediate singlet or triplet excited states.[9a] The following evidence indicates that an intermediate biradical triplet state is probably involved in these reactions. The influence of substituents in the aryl ring of the indolinone on both the ease and extent of cyclobutane formation accords with the formation of such an intermediate.[10,11]

The reactions were independent of changes in solvent polarity.[12] The specific stereochemistry of the final products is readily rationalised by the intermediacy of a diradical triplet state (12) in which the electronic interactions and steric effects are minimal. Rotation round the carbon–carbon bond linking the indolinone rings would lead only to the formation of the cyclobutane F. The ring closure step would be expected to be sensitive to steric factors; indolinones in which the vinylic proton



( 12 )
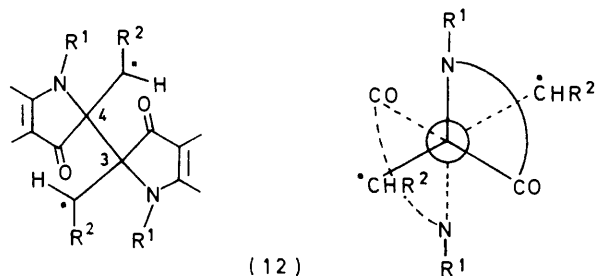
has been replaced by bulky groups, such as phenyl or bromine, did not dimerise.[13] The presence of carbonyl groups within a molecule is known to induce triplet formation and it has been suggested that photodimerisation of the related chalcones would be expected to proceed *via* triplet intermediates.[14]

When the cyclobutane (5a) was heated in the absence of light, at >130°, equal quantities of the (Z)- (1a) and (E)-N-methylindolinone (2a) were isolated in very high yield. (Z)-N-Methylindolinone (1a) heated under the same conditions gave only 15% of the (E)-isomer (2a). The high yield of (E)-isomer from the cyclobutane was therefore not the result of the thermal isomerisation (Z) ⟶ (E). It would appear that fission of the cyclobutane ring is influenced by the steric interaction between the N-methyl groups together with the electronic interaction between the adjacent carbonyl groups which result in strain on the intervening C-3–C-4 bond. A similar result was observed in the mass spectrum of the cyclobutanes (5a) and (6a); no peak could be detected corresponding to a stilbene derivative or an NN'-dialkylindigo which would have been produced if fission of the C-1–C-4 and C-2–C-3 bonds had taken place.

Thermal cycloreversions of cyclobutanes may proceed by either a radical or concerted *supra-antara*-facial [σ2_s + σ2_a] mechanism.[15] The concerted reaction would be expected to give two molecules of the (Z)-N-alkylindolinone or two molecules of the (E)-isomer from one molecule of a cyclobutane. The observed 50% yield of each isomer agrees with the theoretical predictions. Recent papers have generally agreed that cycloreversions of cyclobutanes involve radical intermediates,[16,17] and no

[8] A. Lewis and J. Meinwald, *J. Amer. Chem. Soc.*, 1961, **83**, 2769.

[9] D. C. Neckers, 'Mechanistic Organic Photochemistry,' Reinhold, New York, 1967, (a) p. 116; (b) p. 112.

[10] P. D. Bartlett, *Science*, 1968, **159**, 833.

[11] P. D. Bartlett, *Pure Appl. Chem.*, 1971, **27**, 597.

[12] C. J. M. Stirling, 'Radicals in Organic Chemistry,' ed. M. F. Grundon, Oldbourne, London, 1965, p. 14.

[13] W. N. Pitkethly, Ph.D. Thesis, C.N.A.A., 1972, pp. 83 and 98.

[14] H. Wynberg, N. B. Groen, and R. M. Kellogg, *J. Org. Chem.*, 1970, **35**, 2828.

[15] R. B. Woodward and R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8**, 781.

[16] H. M. Frey and R. M. Walsh, *Chem. Rev.*, 1969, **69**, 103.

[17] A. J. Cocks, H. M. Frey, and I. D. R. Stevens, *Chem. Comm.*, 1969, 458.

[$\sigma 2_s + \sigma 2_a$] cycloreversion has been clearly demonstrated experimentally.[18,19] It may well be that the rigid cyclobutane structure (11), in which there is already considerable twisting of the C-2–C-3 bond, facilitates the concerted process which requires a 180° rotation of one of the terminal atoms in the system. Further studies are being carried out to establish whether this reaction belongs to this very rare [$\sigma 2_s + \sigma 2_a$] class of cycloreversions.[19] The N-unsubstituted indolinones were virtually unaffected by irradiation. It has been reported [20] that in the presence of a photosensitiser (acetone) a yellow polymeric material of uncertain structure is formed.

## EXPERIMENTAL

U.v. spectra were determined for solutions in dioxan with a Unicam SP 500 spectrophotometer. I.r. spectra were determined with a Unicam SP 200 spectrophotometer. N.m.r. spectra were determined for solutions in [$^2$H]-chloroform using tetramethylsilane as an internal standard with Perkin-Elmer R12 (60 MHz) [(5e and f)] and Varian HA-100 spectrophotometers. Mass spectra were determined using an A.E.I. MS 902 spectrometer operating at 70 eV.

1-Alkyl-2-arylmethyleneindolin-3-ones and the Dispiro-[1-alkyl-3-oxoindoline-2,1'-(3,4-diarylcyclobutane)-2',2''-(1-al-kyl-3-oxoindoline)] Photodimers.—These were prepared according to the methods described previously.[1] (Z)-N-Methyl-2-(2-nitrophenylmethylene)indolin-3-one was obtained as a red precipitate (43%), m.p. 167—168° (from methanol) (Found: C, 68·1; H, 4·5; N, 9·55. $C_{16}H_{12}N_2O_3$ requires C, 68·55; H, 4·3; N, 10·0%), $\nu_{max.}$ 1690 (indolinone C=O), 1635 (C=C), 1605 (aryl), 1525 (NO$_2$), and 1350 cm$^{-1}$ (NO$_2$). (Z)-N-Benzyl-2-(2-nitrophenylmethylene)indolin-3-one was obtained as a purple precipitate (96%), m.p. 205—206° (from acetone) (Found: C, 74·1; H, 4·6; N, 7·9. $C_{22}H_{16}N_2O_3$ requires C, 74·15; H, 4·5; N, 7·8%), $\nu_{max.}$ 1680 (indolinone C=O), 1630 (C=C), 1590 (aryl), 1520 (NO$_2$), and 1340 cm$^{-1}$ (NO$_2$). When the synthesis of the N-methyl-indolinone (1a) was protected from light only the orange (Z)-isomer (1a) was isolated (2·2 g, 93%) and examination of the reaction mixture on t.l.c. showed only one spot corresponding to this compound. When the reaction was carried out at reflux temperature a gummy product was formed in which only the (Z)-isomer could be detected using t.l.c.

The indolinones (1g—j) and (3h) did not dimerise. They were the only products formed during the synthesis and were recovered unchanged from the irradiation experiments. The indolinone (1a) gave similar yields of the cyclobutane (5a) in the irradiation experiments when the solvent was benzene, carbon tetrachloride, or methanol. At reflux temperature the yield of cyclobutane was increased in methanol.[1] The indolinone (1d) readily dimerised on exposure to daylight either in benzene, ethanol, ether or methanol.

Attempted Thermal Dimerisation of (Z)- and (E)-N-Methyl-2-phenylmethyleneindolin-3-one.—The indolinones (1a) (100 mg) and (2a) (100 mg) and a mixture of the two isomers (1a) and (2a) (50 mg of each), were each dissolved in biphenyl (0·5 g). The three solutions were protected from light and heated at 100° in a silicone fluid bath. The progress of each reaction was monitored on t.l.c. Each solution gave three spots coloured orange, red, and yellow respectively. The yellow spot was always very faint even after heating for 2 h. Comparison of the spots on t.l.c. with authentic samples indicated that they were the (Z)-N-methylindolinone (1a) (orange), the (E)-isomer (2a) (red), and probably the cyclobutane (5a) (yellow), respectively.

It was not possible to isolate the yellow product in sufficient quantity for further examination because at this temperature the compound broke down into its constituent monomeric units almost as rapidly as it was formed.

Effect of Heat on the Cyclobutane Derivatives.—The cyclobutane derivative (10 mg) was heated in biphenyl (0·5 g), in a silicone fluid bath, in the absence of light. The reaction was monitored on t.l.c. after every 10° rise in temperature. At 130° all the cyclobutane derivatives (5a—f) and (6a and b) gave orange, red, and yellow spots. The intensity of the orange and red spots increased as the heating continued. They were shown, by comparison on t.l.c. with authentic samples, to be the corresponding (Z)- and (E)-indolinones.

Quantitative Study of the Effect of Heat on Dispiro-[1-methyl-3-oxoindoline-2,1'-(3,4-diphenylcyclobutane)-2',2''-(1-methyl-3-oxoindoline)] (5a).—A solution of the photodimer (5a) (0·4 g) in biphenyl (2·0 g) was heated at 150°, in a silicone fluid bath in the absence of light, for 15 min. At the same time a solution of the (Z)-N-methylindolinone (1a) (0·1 g) in biphenyl (1 g) was heated under the same conditions. The two solutions were diluted with benzene (15 ml) and the products separated using p.l.c. The solution of the photodimer (5a) gave the (Z)-N-methylindolinone (1a) (160 mg), the (E)-N-methylindolinone (2a) (160 mg), and starting material (5a) (31 mg). The solution of the (Z)-N-methyl-indolinone (1a) gave the (E)-isomer (2a) (17 mg) and unchanged starting material (75 mg).

[18] J. E. Baldwin and P. W. Ford, J. Amer. Chem. Soc., 1969, 91, 7192.

[19] R. Grigg, Ann. Reports, 1971, 68B, 154.
[20] E. J. Rothery, personal communication.