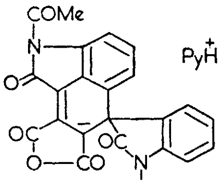
Diels–Alder Reactions of Oxindolylideneacetone

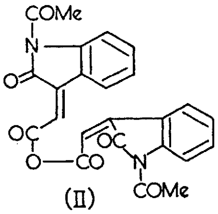
By P. Bamfield, A. W. Johnson, and A. S. Katner

Oxindolylideneacetone has been shown to react with a variety of acetylenic dienophiles to yield derivatives of naphthostyril. The dimerisation of oxindolylideneacetone is also a Diels–Alder addition reaction and a probable structure is advanced for the dimer.

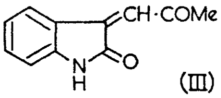
We have previously shown [1] that the purple condensation product (I) derived from isatin, acetic anhydride, and pyridine is derived by an internal Diels–Alder reaction of the precursor (II) followed by rearrangement and oxidation. We have now studied the behaviour of simpler oxindolylidene compounds as dienes in Diels–Alder reactions and have found that oxindolylideneacetone (III) [2] reacts with dimethyl acetylenedicarboxylate in dry acetic anhydride to give a pale yellow crystalline solid, $C_{17}H_{13}NO_6$, which has been formulated as dimethyl *N*-acetylnaphthostyril-4,5-dicarboxylate (IV; R = Ac). No adduct was formed when ether, benzene, toluene, or acetic acid were used as solvents, or in the absence of solvent. The infrared (i.r.) spectrum of the adduct contained amide and ester carbonyl stretching bands at 1750 and 1735 (broad) cm.$^{-1}$ and no NH stretching bands, which suggested that it might possess either an *N*-acetyloxindolyl or *N*-acetyloxindolylidene grouping. When it was hydrolysed with methanolic hydrochloric acid a bright yellow crystalline derivative, $C_{15}H_{11}NO_5$ (IV; R = H) was obtained, indicating the loss of an acetyl group. The hydrolysis product contained bands at 1731 (C=O), 3233 (bonded NH), and 3451 (NH) cm.$^{-1}$ and the n.m.r. spectra (Experimental section) were in accord with the assigned structures.



(I)

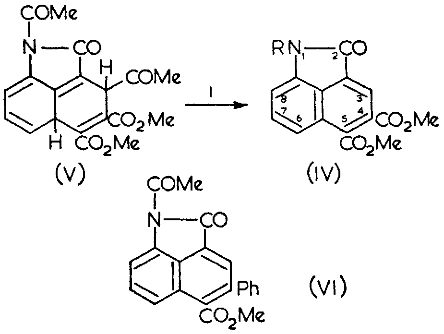


(II)



(III)

Further hydrolysis of the ester (IV; R = H) gave naphthostyril-4,5-dicarboxylic acid, which was purified as the anhydride. The formation of the naphthostyril derivatives is regarded as a Diels–Alder addition reaction followed by loss of the acetyl group from the extended β-keto-ester system in the initial adduct (V) by a reverse Claisen reaction. Condensation of oxinodolylideneacetone with methyl phenylpropiolate in acetic anhydride gave a product which was related to compound (IV). The elimination of the *C*-acetyl group requires the presence of an electron-attracting group at C_5, and consequently the adduct is formulated as (VI) rather than as the isomer with the phenyl and methoxycarbonyl groups reversed. On the other hand, benzoylacetylene and oxindolylideneacetone in boiling acetic anhydride gave a yellow crystalline adduct, $C_{22}H_{15}NO_4$, which was shown by its n.m.r. spectrum to contain two acetyl groups (*N*-acetyl and *C*-acetyl), and is therefore represented as structure (VII). The reaction of benzoylacetylene with a substituted styrene recalls the formation of 3-benzoyl-*meso*benzanthrones from methyleneanthrone and benzoylacetylenes.[3]



1. AcO$^-$; rearrangement and oxidation

When oxindolylideneacetone was kept at 100° in

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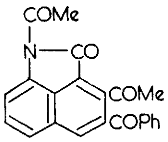
[1] J. A. Ballantine, A. W. Johnson, and A. S. Katner, *J. Chem. Soc.*, 1964, 3323.

[2] F. Braude and H. G. Lindwall, *J. Amer. Chem. Soc.*, 1933, **55**, 325.

[3] F. Irving and A. W. Johnson, *J. Chem. Soc.*, 1948, 2037.

toluene for 24 hr. an almost quantitative yield of a pale yellow crystalline compound was obtained; it was purified by crystallisation from methanol (Soxhlet) to give high-melting colourless needles. Analysis showed that this was a dimer, which was confirmed by spectral measurements, and by the formation of a *NN*-diacetyl derivative and a bis-2,4-dinitrophenylhydrazone. If, as seems most likely, the dimer is formed by a Diels–Alder addition reaction, then two structures (VIII) and (IX) have to be considered. It is of interest in this connection that 2-methyleneoxindole (X) has also been stated to form a "polymer" and although no structure was advanced,[4] it was stated not to be an analogue of the 2-methylenecyclohexanone dimer (XI). In view of the ultraviolet (u.v.) and i.r. absorptions quoted for the 2-methyleneoxindole "polymer," which are similar to those observed (allowing for the presence of the *C*-acetyl groups) for the present dimer, it seems probable that they possess related structures. The nuclear protons of the cyclohexene ring of the oxindolylidene-dimer are vicinal (1,2,3-) in (VIII) but are in the 1,2,4-positions in (IX). The signal in the n.m.r. spectrum of a solution in trifluoroacetic acid (TFA) corresponding to these protons is a symmetrical multiplet and the expected singlet from the isolated proton in structure (IX) was not apparent. Structure (VIII) is therefore favoured for the dimer of oxindolylideneacetone. In view of the ease of dimerisation of oxindolylideneacetone, we were tempted to investigate the possible application of derivatives of dihydronicotinic acid as dienophiles in the reaction, which could have given adducts containing a ring system related to that of lysergic acid (XII), but attempts to cause the derivatives, 1,4-dihydro-*N*-methylnicotinamide (XIII)[5] or 1-methyl-2-pyridone-3-carboxamide (XIV)[6] to react with oxindolylideneacetone were unsuccessful.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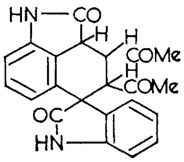
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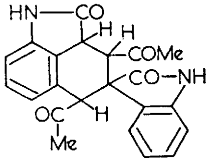
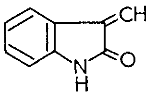
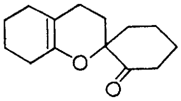

(IX)


(X)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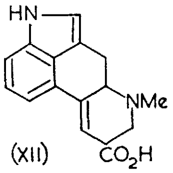
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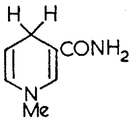
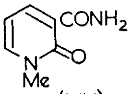
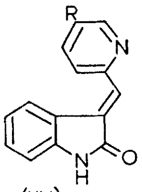

(XIII)


(XIV)


(XV)

Attempts were also made to cyclise the oxindolylidene-2-picolines (XV; R = H or CO_2Et) or the corresponding methiodides, but this also failed. At the time this work was carried out, compound (XV; R = H) had been reported as having m. p. 205—207° (ref. 7) and also 154—155° (ref. 8) both groups of workers having effected the preparation by the condensation of isatin and α-picoline. We prepared compound (XV; R = H) by condensation of oxindole and 2-formylpyridine and find that the product has m. p. 204—205°, and this condensation has since been reported from another laboratory.[9] The molecular weight (mass spectrometer) of the product, m. p. 154—155°, was 222, showing that it was an isomer, probably the geometrical isomer, of the compound, m. p. 204—205°.

Reaction of oxindolylideneacetone with a variety of ethylenic dienophiles, *e.g.*, acrylonitrile, acrylic acid, and maleic anhydride, all failed to yield crystalline adducts.

EXPERIMENTAL

U.v. spectra were determined for ethanolic solutions and i.r. spectra for chloroform solutions, except where otherwise stated. N.m.r. spectra were determined on a Perkin-Elmer R10 60 Mc. spectrometer using tetramethylsilane as internal reference and solutions in methylene dichloride except where otherwise stated.

Dimethyl N-*acetylnaphthostyril*-4,5-*dicarboxylate* (IV; R = Ac).—A solution of oxindolylideneacetone[2] (1 g.) and dimethyl acetylenedicarboxylate (1 ml.) in freshly distilled acetic anhydride (5 ml.) was heated under reflux for 1 hr. The solution was concentrated (to 2 ml.) and on keeping, pale yellow crystals of the *adduct* (300 mg.) formed, which were separated and washed with ether. After crystallisation from chloroform–methanol they had m. p. 187—188° (decomp.) (Found: C, 62·5; H, 4·05; N, 4·4. $C_{17}H_{13}NO_6$ requires C, 62·4; H, 4·0; N, 4·3%). $\lambda_{max.}$ 233, 255, and 346 mμ; $\varepsilon_{max.}$ 41,800, 17,880, and 3850 with λ_{infl} 229, 274, 330, and 363 mμ; ε 38,400, 13,430, 3020, and 3620, respectively. $\nu_{max.}$ 1750 (amide CO) and 1735 (ester and amide CO) cm.$^{-1}$. The n.m.r. spectrum contained signals at τ 7·25 (s; 3 protons of *N*-acetyl), 6·03, 5·96 (both s and each 3 protons of methyl esters), 2·47 (d; C_6 and C_8 aromatic protons) 1·93 (t; C_7 aromatic proton), and 1·69 (s; C_3 aromatic proton adjacent to electron-withdrawing groups).

Dimethyl Naphthostyril-4,5-*dicarboxylate* (IV; R = H).—The foregoing product (90 mg.) was suspended in methanol (7 ml.) and concentrated hydrochloric acid (1 ml.) was added. The mixture was heated under reflux until a clear yellow solution was produced (10 min.) which was poured into water (50 ml.) and the precipitated yellow solid separated and dried. After crystallisation from chloroform–light

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[4] R. L. Hinman and C. P. Baumann, *J. Org. Chem.*, 1964, **29**, 2431.

[5] P. Karrer and F. Blumer, *Helv. Chim. Acta*, 1947, **30**, 1157.

[6] H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, 1951, **16**, 73.

[7] A. M. Akkerman and A. Veldstra, *Rec. Trav. chim.*, 1954, **73**, 629.

[8] R. M. Abramovitch and D. H. Hey, *J. Chem. Soc.*, 1954, 1697.

[9] I. W. Elliott and P. Rivers, *J. Org. Chem.*, 1964, **29**, 2438.

petroleum it formed yellow needles (54 mg.), m. p. 208—209° (decomp.) (Found: C, 62·7; H, 3·8; N, 4·85. $C_{15}H_{11}NO_5$ requires C, 63·2; H, 3·9; N, 4·9%). $\lambda_{\text{max.}}$ 222, 271, 350, and 383 mμ; $\varepsilon_{\text{max.}}$ 46,010, 13,850, 2420, and 3190, respectively; λ_{infl} 332 mμ, ε 1900. $\nu_{\text{max.}}$ 3451 (NH), 3233 (bonded NH), and 1731 (broad; ester and amide CO) cm.$^{-1}$. The n.m.r. spectrum (dimethyl sulphoxide) contained signals at τ 5·93 and 5·89 (both s and each 3 protons of methyl esters), 2·80 to 1·52 (multiplet, aromatic protons), and −1·13 (s; NH).

Naphthostyril-4,5-*dicarboxylic Acid Anhydride*.—Dimethyl *N*-acetylnaphthostyril-4,5-dicarboxylate (above; 0·5 g.) was suspended in a mixture of ethanol (25 ml.) and aqueous sodium hydroxide (5 ml. of 10%). The mixture was heated under reflux for 2 hr., cooled, and poured into water (50 ml.). The product was acidified with concentrated hydrochloric acid and the hot solution filtered. On cooling, the crystalline product which separated was removed, washed with water, and dried (350 mg.). It was sublimed at 210°/1 mm. to give orange-red prisms of the *anhyhride*, m. p. 315° (Found: C, 65·1; H, 2·2; N, 5·8. $C_{13}H_5NO_4$ requires C, 65·25; H, 2·1; N, 5·85%). $\lambda_{\text{max.}}$ 223, 269, 334, 350, and 379 mμ; $\varepsilon_{\text{max.}}$ 46,100, 15,500, 2700, 3280, and 3820; λ_{infl} 280 mμ, ε 12,800. $\nu_{\text{max.}}$ 1710 (amide CO), 1760 and 1835 (anhydride CO) cm.$^{-1}$.

Methyl N-*Acetyl-4-phenylnaphthostyril-5-carboxylate* (VI).—A solution of oxindolylideneacetone (2 g.) and methyl phenylpropiolate (3 ml.) in acetic anhydride (5 ml.) were heated under reflux for 6 hr. The pale yellow crystals of the *product* (420 mg.) which separated on cooling were removed, washed with ether, and then crystallised from chloroform–methanol to give pale yellow needles, m. p. 189—192° (decomp.) (Found: C, 72·9; H, 4·3; N, 4·05. $C_{21}H_{15}NO_4$ requires C, 73·05; H, 4·4; N, 4·05%). $\lambda_{\text{max.}}$ 206, 251, and 358 mμ; $\varepsilon_{\text{max.}}$ 41,200, 23,600, and 6050, respectively; λ_{infl} 222, 298, 329, and 347 mμ; ε 36,000, 6140, 5510, and 6080. $\nu_{\text{max.}}$ 1755, 1710 (amide carbonyls), 1740 (ester carbonyl) cm.$^{-1}$. The n.m.r. spectrum showed signals at τ 7·26 (s; 3 protons of acetyl group), 6·36 (s; 3 protons of methyl ester), and 2·80 to 1·62 (multiplet; 9 aromatic protons).

N,3-*Diacetyl-4-benzoylnaphthostyril* (VII).—A solution of oxindolylideneacetone (2 g.) and benzoylacetylene (2 g.) in acetic anhydride (10 ml.) was heated under reflux for 8 hr. The yellow crystals of the *adduct* which formed on cooling were separated, washed with ether, and crystallised from chloroform–methanol to yield yellow rhombs, m. p. 214—216° (decomp.) (Found: C, 73·6; H, 4·15; N, 3·6. $C_{22}H_{15}NO_4$ requires C, 73·9; H, 4·25; N, 3·9%). $\lambda_{\text{max.}}$ 210, 261, and 386 mμ; $\varepsilon_{\text{max.}}$ 37,100, 28,400, and 3540, respectively; λ_{infl} 224, 286, and 357 mμ; ε 27,600, 13,100, and 2600. $\nu_{\text{max.}}$ 1745, 1710 (amide carbonyls), 1700, and 1664 (ketonic carbonyls) cm.$^{-1}$. The n.m.r. spectrum ($CDCl_3$) showed signals at τ 7·03 and 6·92 (both s and each 3 protons of acetyl groups) and τ 2·72 to 1·59 (multiplet; 9 aromatic protons).

Dimerisation of Oxindolylideneacetone.—A stirred suspension of oxindolylideneacetone (12 g.) in toluene (150 ml.) was heated on the steam-bath for 24 hr. After cooling, the yellow crystalline precipitate (11·5 g.) was separated and washed with ether. Crystallisation from methanol (Soxhlet) gave colourless needles, m. p. 245—247° (decomp.) (Found: C, 70·4; H, 4·5; N, 7·2. $C_{22}H_{18}N_2O_4$ requires C, 70·6; H, 4·85; N, 7·5%). $\lambda_{\text{max.}}$ 250 (main band) and 290 mμ with an inflection at 265 mμ. Intensities could not be measured because of the lack of solubility of the product. $\nu_{\text{max.}}$ 1715—1730 (broad; amine and ketone carbonyls) cm.$^{-1}$. The n.m.r. spectrum (TFA) showed signals at τ 7·96 (s; protons of 2*C*-acetyl groups), 5·0—6·4 (diffuse multiplet; aliphatic protons), 2·05—3·10 (diffuse multiplet; aromatic protons), and τ 0·86 and 0·29 (both s; NH groups).

The *bis*-2,4-*dinitrophenylhydrazone* formed yellow needles (MeOH; Soxhlet), m. p. 272—273° (Found: C, 55·5; H, 3·65; N, 18·6. $C_{34}H_{26}N_{10}O_{10}$ requires C, 55·6; H, 3·6; N, 19·05%). $\lambda_{\text{max.}}$ 362 mμ; $\varepsilon_{\text{max.}}$ 16,530; λ_{infl} 251, 274, and 415 mμ; ε 13,100, 8390, and 5330, respectively. $\nu_{\text{max.}}$ 1725 (amide CO) cm.$^{-1}$.

The NN-*diacetyl* derivative was crystallised from methanol and formed pale yellow needles, m. p. 245—248° (decomp.) (Found: C, 67·7; H, 4·8; N, 6·2. $C_{26}H_{22}N_2O_6$ requires C, 68·1; H, 4·85; N, 6·1%). $\nu_{\text{max.}}$ 1760, 1740 (amide CO), 1705—1700 (ketone and amide CO) cm.$^{-1}$. The n.m.r. spectrum (TFA) showed signals at τ 7·94, 7·95 (both s and each 3 protons of $C-CO-CH_3$ groups), 7·36, 6·94 (both s and each 3 protons of $N-CO-CH_3$ groups,) 6·2—6·6 and 5·1—5·9 (diffuse multiplets of aliphatic protons), and τ 2·5—3·3 (diffuse multiplet of aromatic protons).

Condensation of Oxindole and 2-*Formylpyridine*.—Piperidine (0·15 g.) was added to a solution of oxindole (0·33 g.) and 2-formylpyridine (0·3 g.) in methanol (3 ml.), and the mixture was heated under reflux for 30 min. After cooling, the crystalline precipitate (0·455 g.; 83%) was separated and washed with methanol. For analysis a sample was sublimed at 170°/1 mm. to give orange prisms, m. p. 204—205° (lit.,[7] 205—207°) (Found: C, 75·1; H, 4·75; N, 12·25. Calc. for $C_{14}H_{10}N_2O$: C, 75·7; H, 4·5; N, 12·6%). $\lambda_{\text{max.}}$ 259, 336, and 400 mμ; $\varepsilon_{\text{max.}}$ 15,600, 15,700, and 2840; λ_{infl} 325 and 347 mμ, ε 13,800 and 12,200, respectively. $\nu_{\text{max.}}$ 1700 (amide CO) cm.$^{-1}$.

The methiodide formed orange-red plates, m. p. 238—240° (lit.,[9] 232—233°) (Found: C, 49·0; H, 3·6; N, 7·25. Calc. for $C_{15}H_{13}IN_2O$: C, 49·5; H, 3·55; N, 7·7%). $\lambda_{\text{max.}}$ 215, 253, 338, and 429 mμ; $\varepsilon_{\text{max.}}$ 34,800, 16,400, 8660, and 2060, respectively; λ_{infl} 258 and 272 mμ; ε 15,300 and 8660. $\nu_{\text{max.}}$ 1710 (amide CO) cm.$^{-1}$.

Condensation of Isatin and Ethyl 6-*Methylnicotinate*.—Isatin (4·2 g.) and ethyl 6-methylnicotinate [10] (4·5 g.) were mixed and heated to 175° in an oil-bath over 45 min. This temperature was maintained for 30 min., and then the reaction product was cooled and ethanol (20 ml.) added at 60°. Unreacted isatin was separated from the hot solution and, on cooling, the filtrate yielded the *product* (XV; R = CO_2Et) (800 mg.) which crystallised from ethanol as orange prisms, m. p. 190—193° (Found: C, 69·2; H, 4·75; N, 9·6. $C_{17}H_{14}N_2O_3$ requires C, 69·4; H, 4·8; N, 9·5%). $\lambda_{\text{max.}}$ 220, 262, 265, 346, and 421 mμ; $\varepsilon_{\text{max.}}$ 20,800, 13,800, 13,800, 18,300, and 3600, respectively; λ_{infl} 335 and 359 mμ; ε 15,900 and 14,600. $\nu_{\text{max.}}$ 1705 (amide CO) and 1735 (ester CO) cm.$^{-1}$.

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The University, Nottingham.

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