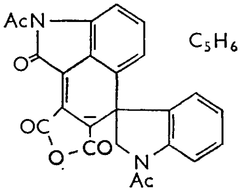
256. *The Condensation of Isatin with Propionic Anhydride.*

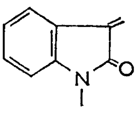
By A. W. Johnson and A. S. Katner.

Condensation of isatin and propionic anhydride in presence of pyridine yields a mixture of the geometrical isomers of 1,2-di-(*N*-propionyl-2-oxo-3-indolinylidene)-ethane. Isomers of the corresponding di-*N*-acetyl compound as well as the parent diamide have also been prepared. One set of these derivatives have been assigned the *cis-trans*-configuration on the basis of dipole moment measurements.

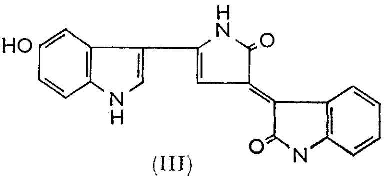
Our investigations on the structure of the purple product (I) formed from the condensation of isatin with acetic anhydride in the presence of pyridine [1] led us to examine the reaction of isatin with propionic anhydride under similar conditions. In this case, however, the product A, which was first obtained by Dr. J. C. Tebby in this laboratory, was formed in good yield, and was a red crystalline compound. An appreciable amount of carbon dioxide was liberated during the reaction. Unlike (I), the propionic anhydride condensation product was neither a pyridinium salt nor an anhydride.



(I)



(II)



(III)

Thin-layer chromatographic examination of A showed that it was a mixture of three closely related isomeric components, A_1, A_2, and A_3, $C_{24}H_{20}N_2O_4$, and although one of these could be eliminated by repeated crystallisation of the mixed product from benzene or chloroform, more convenient methods, described below, have been found for the isolation of the pure components. The formation of the same mixture of products from *N*-propionylisatin with propionic anhydride and pyridine suggested that the *N*-propionyl compound was a probable intermediate in the reaction. Treatment of *N*-acetylisatin with propionic anhydride and pyridine gave a somewhat similar mixture, B, again containing three components, each $C_{22}H_{16}N_2O_4$, B_1, B_2, and B_3, corresponding to A_1, A_2, and A_3, and also a fourth component, C, $C_{23}H_{18}N_2O_4$, which could be isolated from the mixture by column chromatography and which appeared to be a mixed *N*-acetyl-*N'*-propionyl derivative formed by acyl interchange. Hydrolysis of either of the mixtures A or B with hot ethanolic potassium hydroxide, followed by decomposition of the dark blue crystalline potassium derivative with dilute hydrochloric acid, yielded a dark red solid, D, $C_{18}H_{12}N_2O_2$, which again was a mixture of isomers. Treatment of D with hot *NN*-dimethylformamide or hot ethanolic sulphuric acid gave bright red needles of a single isomer, formulated as D_2 because acetylation or propionylation gave the pure isomers B_2

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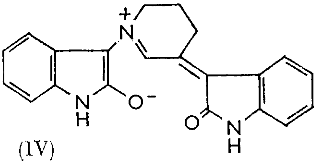
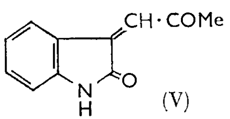
[1] J. A. Ballantine, A. W. Johnson, and A. S. Katner, *J.*, 1964, 3323.

and A_2, respectively. Under similar conditions D gave mixtures of either isomers B_1 and B_3 or A_1 and A_3, which could be separated by column chromatography, suggesting that D itself was a mixture of isomers D_1 and D_3. Treatment of D_2 with ethanolic potassium hydroxide also gave a mixture of isomers D_1 and D_3 corresponding to the original mixture.

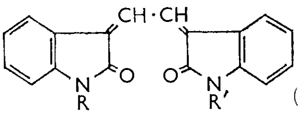
It therefore appeared that in the products A, B, and C, there were contained *N*-acyl-2-oxo-3-indolinylidene units (II) and this was confirmed by ozonolysis of the *N*-acetyl condensation product, B, when *N*-acetylisatin was obtained. Furthermore, permanganate oxidation of the same condensation product gave *N*-acetylanthranilic acid and similar oxidations of the *N*-propionyl condensation product gave *N*-propionylisatin and *N*-propionylanthranilic acid, respectively. Pyrolysis of the *N*-acetyl condensation product gave *N*-acetyloxindole, a reaction which appears to be associated with 2-oxo-3-indolinylidene (II) derivatives, *e.g.*, violacein[2] (III), Isatin Blue[3] (IV) and, as is now shown, 2-oxo-3-indolinylideneacetone[4] (V).



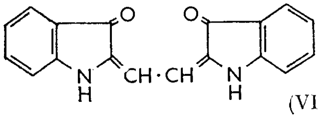
(IV)



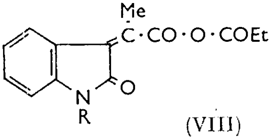
(V)



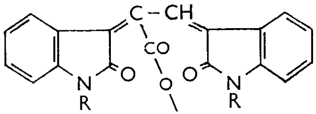
(VI)



(VII)



(VIII)



(IX)

Reduction of any of the isomers B_1, B_2, or B_3 with zinc and acetic acid gave the same colourless product, $C_{22}H_{20}N_2O_4$, the spectra of which strongly suggested that it was a derivative of *N*-acetyloxindole. All this evidence supported the supposition that the condensation products A and B each contained two *N*-acyl-2-oxo-3-indolinylidene units and hence it was concluded that the individual compounds A_1, A_2, and A_3 and B_1, B_2, and B_3 were the theoretically possible geometrical isomers of (VI; in the isomers of A, $R = R' =$ CO·Et; in the isomers of B, $R = R' =$ CO·Me).

The formation of one isomer, D_2, of the hydrolysis product D (VI; $R = R' = H$) by condensation of two moles of oxindole with glyoxal under acidic conditions provided confirmation of structure (VI; $R = R' = H$). Although this compound had not been synthesised previously, the related condensation of indoxyl with glyoxal is known[5] to yield compound (VII).

The mode of formation of the acyl derivatives (VI; R = CO·Me or CO·Et) from isatin or its *N*-acyl derivatives is regarded as involving an initial condensation with propionic anhydride to form (VIII) which then undergoes further reaction with isatin to (IX). This product, the vinylogue of a β-keto-anhydride, decomposes with elimination of carbon dioxide and propionic acid to give (VI).

The condensation products (VI; $R = R' =$ H, CO·Me, or CO·Et) can each exist in three geometrical forms, designated *cis-cis*, *cis-trans*, and *trans-trans*, taking the central hydrogen atoms and the amide carbonyl groups as reference points, and there should be four geometrical isomers of the *N*-acetyl-*N*-propionyl derivative. Each of these forms can also exist theoretically in *s-cis* and *s-trans* forms although an examination of Dreiding models shows that it is impossible for the *cis-cis* isomer to assume the *s-cis* conformation. The remaining five isomers of (VI) are shown, (X)—(XIV). However, the similarity of

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[2] R. J. S. Beer, K. Clarke, H. G. Khorana, and A. Robertson, *J.*, 1949, 885.

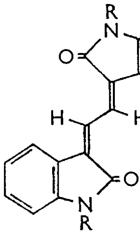
[3] A. W. Johnson and D. J. McCaldin, *J.*, 1957, 3470.

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

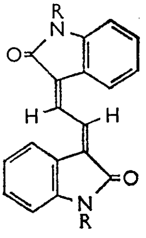
[5] P. Friedländer and F. Risse, *Ber.*, 1914, **47**, 1919.

the visible spectra of the three isomers isolated suggests that all exist in the most stable *s-trans* conformation.

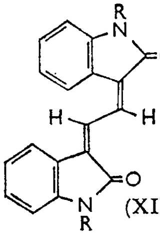
Examination of the three possible configurations of the *s-trans*-isomers of A, B, and D suggested that the *cis-trans* form ought to have a larger dipole moment than the other two isomers because it is not centrosymmetrical. The dipole moments of isomers A_1, A_2, and A_3, in benzene solution, were A_1, 26·2 D; A_2, 0·0 D; A_3, 8·1 D, with an estimated error of 20—30% because of the sparing solubility of the compounds. However the results show clearly that A_1 is the *cis-trans* isomer which is also suggested by the fact that A_1 is rather more soluble than A_2 or A_3. In related substituted butadiene systems where the structures of the individual isomers have been determined, *e.g.*, the 1,4-diphenylbutadienes [6] and the muconic acids,[7] the *trans-trans*-form has the highest melting point, is the least soluble, and absorbs in the ultraviolet or visible regions with the greatest intensity at usually the longest wavelength. Irradiation of these isomers with light of wavelength which the compound can absorb usually results in the formation of a mixture in which the least stable isomer predominates, *e.g.*, *cis-trans* in the case of diphenylbutadiene.[6] However when the irradiation is carried out in presence of iodine, a radical-catalysed isomerisation ensues and the most stable isomer (*trans-trans* with diphenylbutadiene [6] or muconic acid [7]) is the main product.


(X)

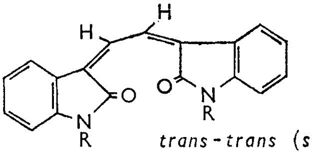
trans-trans (s-trans)


(XII)

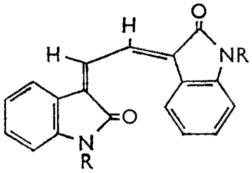
cis-cis (s-trans)


(XIII)

cis-trans (s-trans)


(XI)

trans-trans (s-cis)


(XIV)

cis-trans (s-cis)

Unfortunately, in the present case the melting points of the individual isomers were not sharp because in each case isomerisation to give a mixture of all three forms occurred somewhat below the melting point. Nuclear magnetic resonance has not proved of value in this problem because of the sparing solubility of all the isomers. For the same reason, infrared spectra were determined on the compounds in the solid phase and the results have not helped in assignment of conformations. However, two of the *N*-acyl derivatives, A_3 and B_3, did not absorb above 1722 cm.$^{-1}$ in the carbonyl region (amide groups) whereas the other four compounds (two from each group) all showed absorbance above 1740 cm.$^{-1}$. There were also slight differences in the ultraviolet and visible absorptions of the various geometrical isomers but these were not sufficiently pronounced as to permit structural deductions to be made on this basis. Irradiation of benzene solutions of the *NN*-dipropionyl (A) or *NN*-diacetyl (B) isomers gave products, the composition of which (A_3 or B_3 contaminated with traces of A_1 and A_2 or B_1 and B_2, respectively) was not apparently

[6] J. H. Pinckard, B. Wille, and L. Zechmeister, *J. Amer. Chem. Soc.*, 1948, **70**, 1938.

[7] J. A. Elvidge, R. P. Linstead, P. Sims, and B. A. Orkin, *J.*, 1950, 2235.

affected by the presence of iodine. Irradiation of the single isomer (C_3) of the *N*-acetyl-*N*-propionyl derivative available gave a mixture of three components in which the original C_3 predominated. It is suggested therefore that the geometrical configuration of C_3 corresponds to those of A_3 and B_3. As described above, isomerisation of the non-acylated isomers, D (VI; R = R′ = H), could also be achieved by heating the isomers in *NN*-dimethylformamide or by heating with ethanolic sulphuric acid, when the main product was isomer D_2. Further work is required before the configuration of all of the various isomers can be settled unequivocally.

EXPERIMENTAL

Ultraviolet and visible absorption spectra were determined on benzene solutions and infrared spectra on potassium bromide discs except where otherwise stated. Neutralised silica gel (Kieselgel " G," Merck; 275 μ layer) was used for thin-layer chromatography.

1,2-*Di*-(N-*propionyl*-2-*oxo*-3-*indolinylidene*)-*ethane* (VI; R = R′ = CO·Et). (*Mixture A*).—Isatin (9 g.), propionic anhydride (30 ml.), and pyridine (10 ml.) were heated under reflux for 30 min. After cooling, the dark red needles (5·2 g., 40%), m. p. 250—270° (decomp.) were separated, washed with acetone and then ether, and dried in air at 100°. Thin-layer chromatographic examination of the product on silica in benzene revealed the presence of three components: A_1, R_F 0·18, very faint yellow; A_2, R_F 0·24, faint yellow; A_3, R_F 0·36, intense yellow. After three crystallisations of the crude product from either benzene or chloroform, dark red needles were obtained which were shown to be a mixture of components A_2 and A_3 only.

The mixture A (10 g.) was treated with a hot ethanolic solution of potassium hydroxide (200 ml.; 10%) and the suspension heated under reflux for 20 min. The dark blue crystalline product (8·9 g.) was separated, washed with acetone and ether, and the potassium derivative decomposed with dilute hydrochloric acid (200 ml.; 2N). The red solid (6·6 g.), mixture D (VI; R = R′ = H), was separated, washed with water, and dried at 100°. It formed small purple crystals, m. p. >360° (from acetone).

A suspension of this hydrolysis product (770 mg.) in propionic anhydride (20 ml.) was treated with perchloric acid (1 drop; 60%) and stirred at room temperature for 12 hr. The brownish-red product (680 mg.) was separated and washed with acetone and then ether. Thin-layer chromatography of the product showed that it consisted of components A_1 and A_3 only. The mixed propionyl derivatives (150 mg.) in chloroform (200 c.c.) were adsorbed on neutral silica gel (15 g.) and then added to a column of neutral silica gel (40 × 1·5 cm.) in benzene. The chromatogram was developed with benzene, when separation of the two isomers was achieved. *Isomer* A_3 was eluted first and was thus obtained as dark red needles (39 mg.), m. p. 254—262° (decomp.) (from benzene) (Found: C, 71·9; H, 4·9; N, 7·05. $C_{24}H_{20}N_2O_4$ requires C, 72·0; H, 5·05; N, 7·0%), $\lambda_{max.}$ 395, 415, and 469 mμ (ε 17,370, 19,000, and 22,150), respectively, $\nu_{max.}$ 1722, 1704, and 1686 cm.$^{-1}$ (*N*-propionyl and cyclic amide stretching). *Isomer* A_1 formed scarlet needles (90 mg.), m. p. 254—262° (decomp.) (from benzene) (Found: C, 71·6; H, 4·85; N, 7·3%), $\lambda_{max.}$ 389, 410, and 461 mμ (ε 14,620, 15,570, and 19,080), $\nu_{max.}$ 1745, 1722, and 1711 cm.$^{-1}$ (amide C:O).

1,2-*Di*-(N-*acetyl*-2-*oxo*-3-*indolinylidene*)-*ethane* (VI; R = R′ = Ac) (*Mixture B*) *and* 1-(N-*acetyl*-2-*oxo*-3-*indolinylidene*)-2-(N-*propionyl*-2-*oxo*-3-*indolinylidene*)-*ethane* (VI; R = Ac, R′ = CO·Et) (*Mixture C*).—*N*-Acetylisatin (9 g.), propionic anhydride (30 ml.), and pyridine (10 ml.) were treated as in the previous experiment, and the crude product, B (5·5 g.), m. p. 260—280° (decomp.), was separated. Thin-layer chromatography as before showed the presence of four components (R_F values using benzene then chloroform as solvents): B_1, R_F 0·18, 0·65 (intense yellow); C_1, R_F 0·26, 0·75 (faint yellow). Crystallisation of the crude product from benzene or chloroform gave bright red needles which were shown to be a mixture of B_2 and B_3 only.

The crude condensation product (1·5 g.) in chloroform (1500 ml.) was adsorbed on neutral silica gel (100 g.) and this was added to a column of neutral silica gel (40 × 5 cm.) in benzene. The chromatogram was developed with benzene and the fastest-running coloured band was collected and shown by thin-layer chromatography to consist only of component C_1. Separation of the other components of the mixture was not achieved by this method. Removal of solvent from the fractions of the eluate containing component C_1 and crystallisation of the residual solid from benzene gave the N-*acetyl*-N′-*propionyl derivative* (37 mg.) as dark red needles, m. p. 253—267° (decomp.) (Found: N, 7·05. $C_{23}H_{18}N_2O_4$ requires N, 7·25%), $\lambda_{max.}$

395, 416, and 470 mμ (ε 15,730, 17,280, and 20,300), $\nu_{max.}$ 1724, 1704, and 1690 cm.$^{-1}$ (*N*-acetyl, *N*-propionyl, and cyclic amide stretching).

The mixture of N-acetyl compounds, B, was hydrolysed with hot ethanolic potassium hydroxide as described above and the same mixture D (VI; R = R′ = H) obtained. Mixture D (387 mg.) was acetylated with acetic anhydride (20 ml.) in presence of perchloric acid (1 drop; 60%) in the manner described above for the *N*-propionyl compounds, and the product (400 mg.), consisting of components B_1 and B_3 only, was separated by chromatography on silica gel as before. From the mixed *N*-acetyl derivatives (200 mg.) there was obtained *isomer B_3* (65 mg.), red needles, m. p. 272—282° (decomp.) (from benzene) (Found: C, 71·0; H, 4·25; N, 7·5. $C_{22}H_{16}N_2O_4$ requires C, 71·0; H, 4·35; N, 7·5%), $\lambda_{max.}$ 395, 414, and 470 mμ (ε 15,440, 16,880, and 20,500), $\nu_{max.}$ 1722, 1708, and 1687 cm.$^{-1}$ (amide C:O), and *isomer B_1* (95 mg.), scarlet needles, m. p. 285—292° (decomp.) (from benzene) (Found: C, 70·8; H, 4·35; N, 7·55%), $\lambda_{max.}$ 390, 411, and 465 mμ (ε 14,060, 15,000, and 18,870) $\nu_{max.}$ 1741, 1725, and 1712 cm.$^{-1}$ (amide C:O).

1,2-*Di*-(2-*oxo*-3-*indolinylidene*)*ethane* (*Isomer D_2*).—(*a*) The crude hydrolysis product, D, (160 mg.), derived either from the di-*N*-acetyl or di-*N*-propionyl derivatives, was dissolved in warm *NN*-dimethylformamide (1 ml.) and heated under reflux for 5 min. A red crystalline precipitate was formed and, after cooling, bright red needles of *isomer D_2* (140 mg.), m. p. >360°, were obtained which were separated, washed with acetone, and dried at 100°. The product was recrystallised from *NN*-dimethylformamide (Found: C, 74·9; H, 4·15; N, 9·8; C–Me, 0·0. $C_{18}H_{12}N_2O_2$ requires C, 75·0; H, 4·2; N, 9·7; C–Me, 0%), $\lambda_{max.}$ (*NN*-dimethylformamide) 269, 362, 380, 400, and 474 mμ (ε 17,120, 18,080, 21,950, 17,720, and 9770), $\nu_{max.}$ 3270 (NH), 1698, and 1678 cm.$^{-1}$ (amide C:O). The original mixture of isomers, D, was formed from isomer D_2 on treatment with ethanolic potassium hydroxide.

(*b*) The crude hydrolysis product (100 mg.) was suspended in ethanol (180 ml.) and concentrated sulphuric acid (10 ml.) was added. The mixture was heated under reflux for 48 hr. and the red needles (30 mg.) separated, washed, dried, and shown (spectra) to be identical with isomer D_2 (above).

(*c*) Glyoxal monohydrate (76 mg.; 0·001M) and oxindole (266 mg.; 0·002M) in acetic acid (10 ml.) and hydrochloric acid (0·5 ml.; 12N) were heated under reflux for 2 hr. The mixture was cooled to −5° and kept overnight at this temperature, when the red crystalline product (50 mg.) was separated, washed, dried, and shown (spectra) to be identical with isomer D_2.

Acetylation of isomer D_2 (180 mg.) gave a single *isomer, B_2* (100 mg.) of 1,2-*di*-(N-*acetyl* 2-*oxo*-3-*indolinylidene*)-*ethane*, as shown by thin-layer chromatography. Crystallisation of the product from benzene gave orange laths, m. p. 272—280° (decomp.) (Found: C, 71·2; H, 4·6; N, 7·45. $C_{22}H_{16}N_2O_4$ requires C, 71·0; H, 4·35; N, 7·5%), $\lambda_{max.}$ 390, 411, and 461 mμ (ε 13,500, 14,400, and 16,410), $\nu_{max.}$ 1740, 1732, 1710, and 1703 cm.$^{-1}$ (*N*-acetyl and cyclic amide C:O).

Propionylation of isomer D_2 (270 mg.) gave a single *isomer, A_2*, of 1,2-*di*-(N-*propionyl*-2-*oxo*-3-*indolinylidene*)-*ethane*, as shown by thin-layer chromatography. The product (270 mg.) formed brownish-red laths, m. p. 246—264° (decomp.) (from benzene) (Found: C, 71·8; H, 4·95; N, 7·05. $C_{24}H_{20}N_2O_4$ requires C, 72·0; H, 5·05; N, 7·0%), $\lambda_{max.}$ 389, 408, and 458 mμ (ε 14,960, 15,710, and 17,420), $\nu_{max.}$ 1740, 1730, 1710, and 1701 cm.$^{-1}$ (amide C:O).

Permanganate Oxidation of 1,2-*Di*-(N-*acetyl*-2-*oxo*-3-*indolinylidene*)-*ethane*.—A mixture of isomer B_2 of the di-*N*-acetyl derivative (2 g.), finely ground potassium permanganate (7 g.), and sodium carbonate (1 g.) in water (250 ml.) was heated under reflux for 1 hr., cooled, filtered, and the filtrate acidified with concentrated sulphuric acid. Sulphur dioxide was bubbled through the solution until all the colour was discharged and the resulting solution was extracted with chloroform (6 × 50 ml.). The combined extracts were dried and the solvent was removed, leaving a pale yellow crystalline residue (300 mg.) which was crystallised from aqueous methanol to give colourless prisms of *N*-acetylanthranilic acid, identified by mixed m. p. 184—185°.

A similar oxidation of the mixed isomers of the di-*N*-propionyl analogue, mixture A (2 g.), gave *N*-propionylanthranilic acid (320 mg.), identified by mixed m. p.[8] 117°.

Ozonolysis of 1,2-*Di*-(N-*acetyl*-2-*oxo*-3-*indolinylidene*)*ethane*.—A stream of ozonised oxygen was passed through a suspension of isomer B_2 of the di-*N*-acetyl derivative (1·5 g.) in methylene chloride (400 ml.) at −5° for 4 hr. The solvent was cautiously removed at 20° under reduced pressure and the partly crystalline residue dissolved in ethanol (30 ml.) at 60°. After the

[8] A. Pictet and L. Duparc, *Ber.*, 1887, **20**, 3415.

effervescence had ceased, the solution was kept at 0° when yellow needles (0·7 g.), m. p. 139—140°, of *N*-acetylisatin were obtained, identified by mixed m. p. and comparison of spectra.

A similar ozonolysis of the mixed isomers of the di-*N*-propionyl analogue, mixture A (2 g.), gave *N*-propionylisatin (0·8 g.), identified by mixed m. p.[9] 141°.

Pyrolysis of 1,2-*Di*-(N-*acetyl*-2-*oxo*-3-*indolinylidene*)-*ethane*.—Isomer B_2 (20 mg.) of the di-*N*-acetyl derivative was heated at 245°/0·1 mm. for 24 hr. in a sublimation tube. Several volatile products were formed but the colourless crystals of the most volatile sublimate were separated and resublimed at 90°/0·1 mm. to give *N*-acetyloxindole (3 mg.), m. p. 124°, identified by mixed m. p. and ultraviolet and infrared spectra.

Reduction of the Isomers of 1,2-*Di*-(N-*acetyl*-2-*oxo*-3-*indolinylidene*)-*ethane*.—Each of the isomers B_1, B_2, and B_3 (30 mg.) of the 1,2-di-*N*-acetyl compound in acetic acid (5 ml.) containing hydrochloric acid (0·5 ml.; 12N), was mixed with zinc (4 g.) and heated under reflux for 15 min. The resulting pale yellow solutions were filtered into water (30 ml.) and the colourless precipitates collected, washed with water, and dried at 70° in air, when they (25 mg. of each) had m. p. 220—227° raised to 227—229° (colourless needles) by crystallisation from chloroform (Found: C, 70·4; H, 5·2; N, 7·65. $C_{22}H_{20}N_2O_4$ requires C, 70·2; H, 5·35; N, 7·45%), $\nu_{max.}$ 1761, 1755 (*N*-acetyl C:O), and 1709 and 1700 cm.$^{-1}$ (cyclic amide C:O), $\lambda_{max.}$ (ethanol) 231 mμ, $\lambda_{infl.}$ 270 and 285 mμ. *N*-Acetyloxindole has $\lambda_{max.}$ 231 mμ, $\lambda_{infl.}$ 270 and 283 mμ.

Pyrolysis of 2-*Oxo*-3-*indolinylideneacetone* (V).—The base[4] (20 mg.) was heated at 240°/0·1 mm. for 12 hr. Several products could be discerned in the sublimate but the most volatile was easily separated from the others. Resublimation of this colourless fraction at 80°/0·1 mm. gave oxindole (2 mg.), identified by mixed m. p. 125°.

We acknowledge the award of a Maintenance Grant from the D.S.I.R. (to A. S. K.), and we are grateful to Mrs. R. M. Canadine, Petrochemical and Polymer Laboratory, Imperial Chemical Industries Limited, for measurements of dipole moments.

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[*Received, July* 8*th*, 1964.]

[9] H. Meyer, *Monatsh.*, 1905, **26**, 1311.