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THE STRUCTURE OF METHYLISATOID

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Abstract—The formation of methylisatoid from O-methylisatin has been re-examined and evidence obtained for its formulation as (III).

THE alkylisatoids have had a long and chequered history. The formation of methylisatoid when solid O-methylization was exposed to the atmosphere was first observed by Baeyer and Oekonomides,[1] who assigned to the product the correct molecular formula, $C_{17}H_{12}N_2O_4$, and prepared similar compounds from the O-ethyl, O-propyl and O-isobutyl derivatives of 5-bromoisatin. Later Hantzsch[2] reported that some of the products obtained by Heller[3] from the methylation of silver isatins were impure samples of methylisatoids. This initiated a long controversy between the two groups of workers in the course of which a variety of O-alkylisatoids were prepared,[6–11] as well as the apparently related isatoids. The latter are obtained by the action of benzoyl chloride on silver isatins and were at one stage mistakenly claimed by Hantzsch[2,9] to be identical with the alkylisatoids. This, together with the confusing names assigned to products of doubtful purity has further complicated the position. The names isatol, isatinone and β-isatol have been used for substances that appear to have been essentially methylisatoid.

For a time, at least, Heller favoured an O-methylisatin-isatin complex structure for methylisatoid but this was rejected[12] finally on the basis of crystallographic and X-ray investigations. Hantzsch[11] suggested structures II and III preferring the latter as he was apparently able to obtain a phenylhydrazone derivative. The structural evidence has remained fragmentary and inconclusive. For example, exposure of a solution of "isatinone" in 0·5N sodium hydroxide to air and light gave IV.[4] Treatment of alkylisatoids with hydrobromic acid in acetic acid gave a compound, formulated as V which also gave IV on oxidation with chromium trioxide in acetic acid.[7] The observed formation of IV is of doubtful significance since it may even be obtained by the oxidation of isatin.[13] As non-photochemical reactions of organic compounds in the solid state are relatively rare it seemed desirable to attempt to clarify the position.

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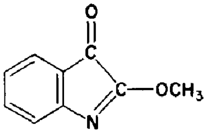
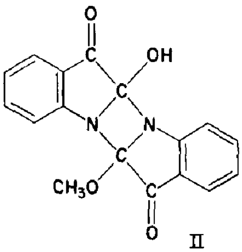
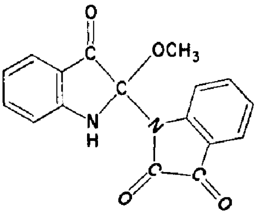


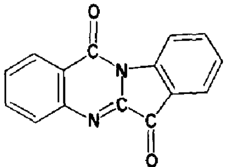
I



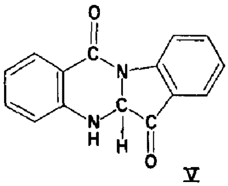
II



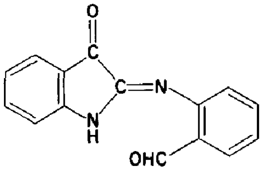
III



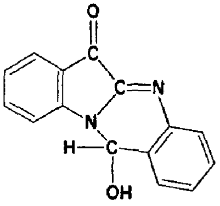
IV



V



VIa



VIb

Methylisatoid was obtained pure, m.p. 245–246° either by repeated crystallization from acetonitrile or by chromatography. This corresponds to γ-methylisatoid obtained by acidifying an alkaline solution of β-methylisatoid. The metastable α-form m.p. 238–240°, formed by exposure of O-methylisatin to moisture, and the β-form m.p. 226°, obtained either by treating the α-form with solvents or recrystallizing the γ-form from acetic acid, appear to be impure samples of methylisatoid. Pure methylisatoid dissolves in dilute alkali giving initially an orange–red solution which slowly fades on standing. Acidification of the freshly prepared solution gives unchanged methylisatoid. The U.V. spectrum in ethanol shows absorption maxima at 232 mμ (ε 13,900), 256 mμ (ε 18,600), 319 mμ (ε 7,350) and 447 mμ (ε 6,850) supporting the formulation of methylisatoid as III. For comparison the spectra of N-methylisatin,[14] with maxima at 245 mμ (ε 22,400), 299 mμ (ε 2,350) and 420 mμ (ε 500), and of spiro-[cyclopentane-1,2^1-indoxyl],[15] with maxima at 235 mμ (ε 18,900) and 400 mμ (ε 3,700), which contain similar chromophores may be noted. The I.R. spectrum of methylisatoid shows diagnostic bands at 3,150 cm^{-1} (N—H), 1755 and 1720 cm^{-1} ($>$C = O), 1080 cm^{-1} (—O—CH$_3$) and 755 cm^{-1} (*o*-disubstituted benzene).

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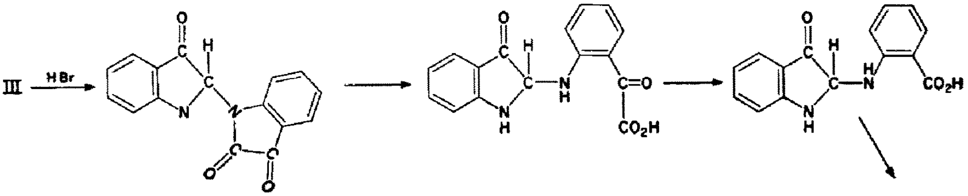
III



+ CH_3OH

V

Treatment of methylisatoid with hydrobromic acid in acetic acid gave a compound, $C_{15}H_{10}N_2O_2$, apparently identical with that obtained by Heller[7] and assigned structure V. It was also obtained when sulphuric acid was substituted for the hydrobromic but the only likely route by which the conversion of III to V could be conceived is as above where HBr is acting as a reducing agent and it is unlikely that sulphuric acid could bring about this reaction. This compound was readily oxidized to IV in good yield by chromic acid and also by air. As the structure V proposed for this compound requires the postulation of an unattractive mode of formation the alternative formula (VIa or b) appeared more reasonable. This was confirmed by the synthesis of (VIa or b) from *o*-aminobenzaldehyde and O-methylisatin and unambiguously demonstrates the position of the internuclear linkage. This compound appears to exist predominantly as VIb as indicated by the I.R. spectral evidence. Only one carbonyl band at 1725 cm^{-1} is discernible and there is also a strong band at 1020 cm^{-1} attribute to a C—O-grouping. The weak band at 2,750 cm^{-1}, which could be an aldehyde C—H, probably belongs to the band centered at 3,100 cm^{-1} arising from a hydrogen bonded O—H.

Finally one or two incidental observations throw some light on the mode of formation of methylisatoid. Several unsuccessful attempts were made to prepare a monobromo-methylisatoid by heating 5-bromoisatin with O-methylisatin in nitrobenzene at 100°, although a similar solution of the latter slowly deposited methylisatoid when exposed to the atmosphere. Thus the hydrolysis and coupling are probably a concerted process. In accord with this conclusion the crystallographic data available[12] suggest that in the O-methylisatin crystal the appropriate reaction centres are in close proximity.

EXPERIMENTAL

I.R. spectra were recorded for Nujol mulls on a Perkin Elmer model 137E spectrophotometer.

Methylisatoid. Crude methylisatoid was prepared as described by Hantzsch and purified by chromatography on silica gel in chloroform, followed by elution with chloroform–ethanol mixtures. Isatin is eluted first under these conditions. Pure methylisatoid was finally recrystallized from acetonitrile, m.p. 245–246°. (Found: C, 66·1; H, 4·0; N, 21·1. Calc. for $C_{17}H_{12}N_2O_2$: C, 66·3; H, 3·9; N, 20·8%).

Action of acid on methylisatoid. Methylisatoid (0·5 g) in acetic acid (20 ml) and sulphuric acid (50%, 2 ml) was heated under reflux for 3 hr. The solution was cooled and the sulphuric acid neutralized by addition of sodium acetate. Dilution with an equal volume of water caused the product (0·3 g) to crystallize out. Recrystallization from aqueous alcohol gave *isatin-α-(2-formylanil)* (VI) m.p. 216–217° (Found: C, 71·9; H, 4·2; N, 10·8. $C_{15}H_{10}N_2O_2$ requires C, 72·0; H, 4·0; N, 11·2%).

An identical product was obtained when hydrobromic acid was used instead of sulphuric acid.

Synthesis of isatin-α-(2-formylanil) (VI). O-Methylisatin (0·81 g) and *o*-aminobenzaldehyde (0·60 g) were each dissolved separately in dry benzene (10 ml). The solutions were combined, refluxed with magnetic stirring for 5 hr and then allowed to stand overnight. The orange material (1·1 g), which had immediately started to separate, was collected and recrystallized from aqueous alcohol to give isatin-α-(2-formylanil) identical with the previously obtained sample.

Oxidation of isatin-α-(2-formylanil). The anil (VI; 0·3 g) was dissolved in acetic acid (10 ml) and a solution of chromium trioxide (50 mg) in water (1 ml) added. The solution was allowed to stand overnight. Dilution with water gave fluffy yellow crystals of 6,12-dihydro-6,12-dioxo-indolo [2, 1-b] quinazoline (IV) (0·16 g) which was recrystallized from xylene, m.p. 262–263°, identical with an authentic specimen.