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PYRROLIDINE AS A COMMON CONTAMINANT OF Δ^3-PYRROLINE: CORRECT STRUCTURE OF THE PRODUCT FROM ISATIN AND Δ^3-PYRROLINE

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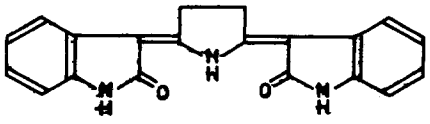
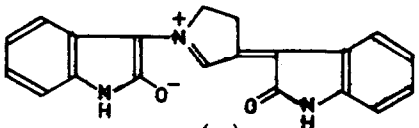
The pigments formed by the interaction of isatin or ninhydrin with certain heterocyclic amines were first isolated by Grassmann and Arnim (1,2). They recognized that pyrrolidine and proline gave the same blue pigment with isatin (1). The structure (I) they proposed for this pigment ($C_{20}H_{15}N_3O_2$) was later revised to (II) by Johnson and McCaldin (3). Grassmann and Arnim also reported the formation of a blue pigment from isatin and Δ^3-pyrroline (2). Elementary analysis suggested its molecular formula to be $C_{20}H_{13}N_3O_2$, and structure (III) was proposed by analogy with (I).

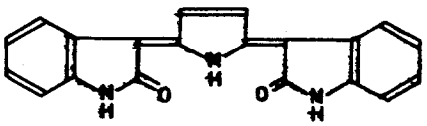
Three facts indicate that structure (III) is incorrect. Firstly, the revised structure (II) for the pyrrolidine pigment renders invalid the analogy used in formulating (III). Secondly, the visible absorption spectra for the pyrrolidine and pyrroline pigments as recorded by Grassmann and Arnim are identical. Thirdly, we recently proved that the product from the interaction of isatin and 3,4-dehydroproline was 3-(1-pyrrolyl)oxindole (IV) (4). Since proline and pyrrolidine both give (II) with isatin, it was anticipated that 3,4-dehydroproline and Δ^3-pyrroline should both yield (IV). The mechanism of formation of (IV) from pyrroline would be the same as that proposed from dehydroproline (4), except that deprotonation at a pyrroline α-carbon would replace the amino acid decarboxylation step. A problem to be resolved on this hypothesis was that (IV) is colourless whereas Grassmann and Arnim's product from the pyrroline reaction was blue.



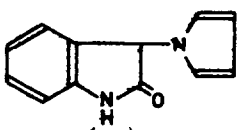
(I)



(II)



(III)



(IV)

We prepared Δ^3-pyrroline by the standard method, reduction of pyrrole with zinc dust and 20% hydrochloric acid for 7 hr. (5). Examination by g.l.c. (6) and n.m.r. (7) revealed that the pyrroline contained 15 ± 2% of pyrrolidine. This hitherto unrecognized contaminant from zinc/acid reductions of pyrrole is inseparable by ordinary distillation techniques: pyrrolidine has b.p. 88.5 - 89.5 and Δ^3-pyrroline has b.p. 90 - 91°. The impure pyrroline certainly gave a blue coloration with isatin in hot acetic acid (conditions of Grassmann and Arnim), and a low yield of the pigment crystallized when the reaction mixture was kept at 0°. Comparison of its i.r. and mass spectra (8) with those of authentic material proved the blue solid was (II). Furthermore, dilution of the mother liquor with water, and chloroform-extraction gave a high yield of (IV), identified by m.p., mixed m.p. and i.r. spectrum.

The pyrrolidine impurity was removed by fractional crystallization of the hydrochlorides. Two recrystallizations from ethanol afforded pure Δ^3-pyrroline hydrochloride. The liberated free base gave no blue colour with isatin in acetic acid, and an 81% yield of (IV). It is clear, therefore, that Grassmann and Arnim had been misled by their microanalytical results, and the Δ^3-pyrroline used must have contained at least 35% of pyrrolidine to produce their yield of blue pigment (II).

Pure Δ^3-pyrroline and ninhydrin react rapidly in 2N acetic acid at 80° to generate (80%) the di-adduct obtained previously (4) from 3,4-dehydroproline and ninhydrin.

No pyrrolidine formed when pure Δ^3-pyrroline was stirred with zinc dust in 20%

hydrochloric acid for 2 days. Both compounds therefore arise directly from pyrrole, and their formation can be rationalized in terms of the alternative modes of pyrrole protonation. Protonation at an α-carbon, and reduction of the azomethinium double bond gives pyrroline with the isolated 3,4-olefinic group. The less-favoured protonation at a β-carbon, and reduction of the azomethinium double bond yields Δ^2-pyrroline. Further β-protonation of this enamine and reduction to pyrrolidine is reasonable. Although zinc/acid reduction of pyrroles is undoubtedly a convenient route to pyrrolines (e.g. 9, 10, 11), we have found no mention of the definite identification of pyrrolidines as by-products. Our results demonstrate the need for product analyses by modern techniques.

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(5) L. H. Andrews and S. M. McElvain, J. Am. Chem. Soc., 51, 887 (1929).

(6) Perkin-Elmer 154 Fractometer, 1 m. column containing 20% Carbowax 20M on acid-washed Embacel at 70°; retention times: pyrroline, 7.0 min; pyrrolidine, 4.2 min.

(7) Varian A-60; δ-values of centre of multiplets for α-H and β-H respectively are: Δ^3-pyrroline, 3.61, 5.88 (D_2O), 4.13, 5.94 (D_2O/HCl); pyrrolidine, 2.75, 1.65 (D_2O), 3.30, 2.00 p.p.m. (D_2O/HCl); internal sodium 3-trimethylsilylpropyl-1-sulphonate reference.

(8) AEI MS9 instrument.

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