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FORMATION OF 3-METHYLISOINDOLENINE-1-CARBOXYLIC ACID

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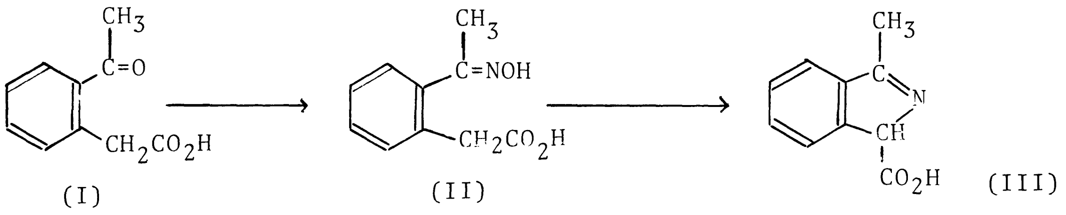
It was found that 3-methylisoindolenine-1-carboxylic acid(III) was obtained by heating o-acetylphenylacetic acid with hydroxylamine. This compound was also obtained by the reaction of o-acetylphenylacetic acid oxime with hydroxylamine or semicarbazide under similar reaction conditions. From these results a probable process of formation has been suggested.

Treatment of o-acetylphenylacetic acid(I) with hydroxylamine in aqueous alcoholic solution at room temperature for 2-3 days afforded o-(1-hydroxyiminoethyl)phenylacetic acid(o-acetylphenylacetic acid oxime)(II), but the reaction in the boiling solution afforded an unexpected product predominantly. Molecular weight of this product was 175 by mass spectrometry and this value agreeded with that of dehydration product of the oxime(II). By this finding we have assumed that the unexpected product might be a derivative of isoindole, namely, 3-methylisoindolenine-1-carboxylic acid(III). The structure of this product was confirmed by the results of elementary analysis, IR and NMR spectra. III was unstable even at room temperature but was converted by catalytic reduction to the corresponding stable isoindoline derivative(mol. weight 177).

III: mp 171-172°C; Anal. Found: C, 69.02; H, 5.46; N, 8.21%. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00%. IR(nujol): 1650 cm^{-1}(CO_2H), 1625 cm^{-1}(C=N). NMR(DMSO-d6,δ): 2.9(3H, s), 6.8(1H, s), 7.4(4H, m), 10.2(1H, s).

At first, the compound III seemed to be formed directly by the dehydration of the oxime II as follows.



When heated with hydroxylamine, o-acetylphenylacetic acid oxime(II) also afforded the compound III in a moderate yield, but in the absence of hydroxylamine or under alkaline conditions, it was not affected.

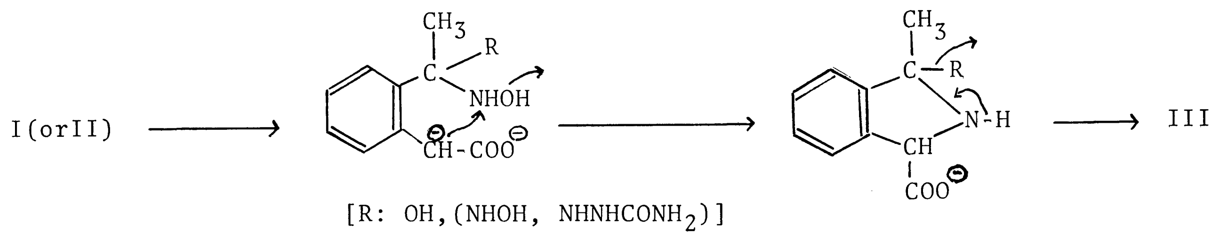
Treatment of o-acetylphenylacetic acid(I) with 2 moles hydroxylamine in aqueous alcoholic solution under reflux for 6 hours gave the compound III as hydroxylammonium salt. After decomposition of this salt by the addition of hydrochloric acid, III was obtained in an 80% overall yield. On the other hand, only 48% yield of III was obtained when the oxime II was treated under similar reaction conditions. These results showed that the oxime II is not an intermediate for the formation of isoindole derivative from I. Of particular interest was the fact that the compound III was also obtained in a 37% yield by the reaction of II with 2 moles of semicarbazide under similar condition, while by the use of the compound I as starting material, only semicarbazone of I was obtained. The experimental results are summarized in table 1.

Table 1. Yields of III under varying conditions.

starting material	reagents(2 moles)	III(%)
I	NH_2OH	80
II	NH_2OH	48
II	$NH_2NHCONH_2$	37
I	$NH_2NHCONH_2$	0

From these results a probable course of formation of III from I is presumed to be as follows.

As the first step, a nucleophilic addition of primary amines takes place to the C=O bond of I(or to the C=N bond in case of the reaction of II with hydroxylamine or semicarbazide); subsequent ring formation will be effected by the S_N2 type attack of the carbanion derived from α-carbon on the nitrogen atom of the hydroxyamino group, the hydroxyl being a good leaving group, followed by elimination of water(or the corresponding amine in case of the reaction of II).



[R: OH,(NHOH, $NHNHCONH_2$)]

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