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Condensation of *o*-Phenylenediamine with Cinnamic Acid

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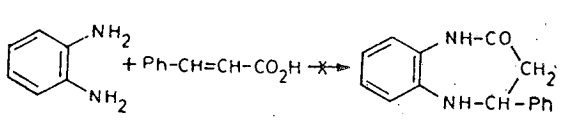
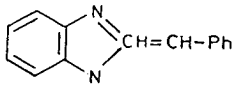
The condensation of *o*-phenylenediamine with cinnamic acid has been shown to give 2-styrylbenzimidazole and not a benzdiazepinone as reported by S. H. Dandegaonker and G. B. Desai [*Indian J. Chem.*, 1 (1963), 298].

IN a recent communication[1] the formation of the benzdiazepinone (I), m.p. 195-6°, from the condensation of *o*-phenylenediamine with cinnamic acid was reported. The reaction was extended to substituted phenylenediamines and cinnamic acids. However, the evidence provided for the structures of the products was utterly inadequate. Only nitrogen analysis was reported, although analysis of carbon and hydrogen would have clearly and adequately distinguished between benzdiazepinone (I) and the styryl-imidazole structure (II), which was a distinct possibility for the product. The ultraviolet absorption spectrum did not seem to be consistent with (I); infrared data were not given; the formation of a semicarbazone by (I) appeared to be strange.

Hence it was considered worthwhile to repeat the reaction. Equimolecular amounts of the diamine hydrochloride and cinnamic acid were heated at 200° for 4 hr and the product worked up as described later in this communication. A 57 per cent yield of the compound, m.p. 199-201°, was obtained which was clearly identified as the well-known 2-styrylbenzimidazole, by elemental analysis, m.p. and m.m.p. determination with an authentic sample[2] and comparison of infrared spectra. The benzimidazole was further characterized as the hydrochloride, m.p. 258-63° (decomp.), and by catalytic reduction to the known 2-β-phenylethylbenzimidazole[3]. As expected (II) was found to be unreactive towards semicarbazide. Heating cinnamic acid with free *o*-phenylenediamine and working up the reaction as reported in the literature failed to give a crystalline compound, but thin-layer chromatography over silica-chloroform-methanol (2 per cent) clearly showed (II) to be the major product and this was eventually isolated as the



I



II

hydrochloride in about 50 per cent yield. The reaction of *o*-phenylenediamine hydrochloride with *p*-methoxycinnamic acid resulted in the formation of amorphous phenolic products; the free base under these conditions led to a gummy mixture, from which a crystalline compound could not be isolated. The reaction of 4-chloro-1,2-diaminobenzene dihydrochloride with cinnamic acid again gave 5(6)-chloro-2-styrylbenzimidazole in *c.* 30 per cent yield.

It should be noted that the diazepinone (I), reported to have been obtained by earlier workers[1] by the reaction of *o*-phenylenediamine with cinnamic acid has been synthesized by Reid and Stahlhofen[4] by a different route and these workers reported it to melt at 167°.

2-Styrylbenzimidazole (II) — The hydrochloride from *o*-phenylenediamine (2·2 g.) and cinnamic acid (3 g.) were heated at 200° for 4 hr. The dark blue mass was dissolved in ethanol and poured into excess aqueous sodium bicarbonate. The violet crystalline precipitate (3·1 g.) was filtered and chromatographed in chloroform solution through a column of neutral alumina (60 g.). Elution with chloroform and removal of eluate by evaporation followed by trituration with ether gave 2-styrylbenzimidazole which was crystallized from ethanol; yield 2·6 g. (57 per cent); m.p. and m.m.p.[2] 199-201°; $\lambda_{max.}^{EtOH}$ 262, 322, 334, 350 (sh) mμ (log ε 4·05, 4·43, 4·43, 4·20); $\lambda_{min.}$ 241, 271-328 mμ (log ε 3·85, 3·87, 4·41) (Found: C, 81·51; H, 5·62; N, 12·57. $C_{15}H_{12}N_2$ requires C, 81·79; H, 5·49; N, 12·72%).

The hydrochloride of (II) was crystallized from ethanol-ether; m.p. 258-63° (decomp.) (Found: C, 69·76; H, 5·51. $C_{15}H_{13}ClN_2$ requires C, 70·21; H, 5·10%).

2-β-Phenylethylbenzimidazole was obtained from (II) by prolonged catalytic reduction at 50° in methanol solution using 10 per cent Pd-C catalyst. It was crystallized from aqueous ethanol; m.p. 188-9° (lit.[3] m.p. 189-90°); $\lambda_{max.}^{EtOH}$ 248, 274, 280 (log ε 3·68, 4·02, 3·98); $\lambda_{min.}$ 227, 259, 278 mμ (log ε 3·68, 3·75, 3·81) (Found: C, 81·02; H, 6·57. $C_{15}H_{14}N_2$ requires C, 81·05; H, 6·35%).

5-(6)-Chloro-2-styrylbenzimidazole — The dihydrochloride of 4-chloro-1,2-diaminobenzene (6·4 g.) and cinnamic acid (4·5 g.) were heated together and the product worked up as before; purification by chromatography gave the benzimidazole, 2·25 g. (30 per cent); m.p. 158-62°; $\lambda_{max.}^{EtOH}$ 263, 324, 336, 352 (sh) (log ε 4·03, 4·43, 4·44, 4·22); $\lambda_{min.}$ 242, 276, 329 (log ε 3·77, 3·86, 4·42) (Found: C, 70·89; H, 4·63. $C_{15}H_{11}ClN_2$ requires C, 70·76; H, 4·35%).

References

1. Dandegaonker, S. H. & Desai, G. B., *Indian J. Chem.*, **1** (1963), 298.
2. Weidenhagen, R., *Chem. Ber.*, **69B** (1936), 2263.
3. Hoffmann, K., *Imidazoles & derivatives* (Interscience Publishers Inc., New York), 1953, 381.
4. Reid, W. & Stahlhofen, P., *Chem. Ber.*, **90** (1957), 815.

von Salzsäure praktisch keine Veränderung. – IR.-Spektrum ($CHCl_3$): 3436, 1730, 1681, 1605, 1597; in $3{,}3 \cdot 10^{-4}$ M CCl_4-Lösung: 3458.

Fruticosamin liess sich mit Pyridin-Essigsäureanhydrid bei 20° nicht acetylieren.

Umlagerung von Fruticosamin in Fruticosin: 25 mg Fruticosamin in 2 ml Methanol liess man mit 3 Tropfen konz. Ammoniak 41 Std. bei 20° stehen. Nach dieser Zeit liessen sich dünnschichtchromatographisch nur mehr Spuren von Fruticosamin nachweisen; Hydrolyseprodukte mit gelboranger Cer(IV)-sulfat-Reaktion traten nicht auf. Die Lösung wurde eingedampft und der Rückstand aus Methanol und Methanol-Wasser umkristallisiert. Das erhaltene Produkt stellte auf Grund von übereinstimmenden Smp., Misch-Smp., IR.-Spektren und Dünnschichtchromatogrammen reines Fruticosin dar.

Ca. 1 mg Fruticosamin wurde mit 1 ml Glycerin 1 Min. auf 220–230° erhitzt. Nach dem Abkühlen wurde mit wäss. Natriumhydrogencarbonatlösung verdünnt, mit Chloroform ausgeschüttelt und der eingedampfte Chloroformauszug dünnschichtchromatographisch analysiert: Neben ca. 5% decarbomethoxylierten Produkten enthielt das Produkt ca. 20% Fruticosamin und ca. 75% Fruticosin.

Unter denselben Bedingungen erhitzt, ergab Fruticosin ein Produkt (ca. 20–25% Fruticosamin und ca. 70–75% Fruticosin), welches dem aus Fruticosamin erhaltenen sehr ähnlich war.

Auch beim kurzen Schmelzen von Fruticosin bzw. Fruticosamin trat neben Decarbomethoxylierung gegenseitige Umlagerung der beiden Alkaloide ein (Analyse durch Dünnschichtchromatographie).

Anm. bei der Korrektur: Die Arbeit von BATTERSBY & GREGORY [2]) ist inzwischen erschienen (J. chem. Soc. *1963*, 22). Die Identität der in verschiedenen polymorphen Formen kristallisierenden, als Fruticosamin bezeichneten Pflanzenbasen wurde u. a. dünnschichtchromatographisch und IR.-spektroskopisch erwiesen.

ZUSAMMENFASSUNG

Unter sehr milden Aufarbeitungsbedingungen liessen sich aus getrockneten Blättern von *Kopsia fruticosa* (KER.) A. DC., neben Kopsin, Fruticosin und Fruticosamin, Decarbomethoxy-kopsin und Decarbomethoxy-isokopsin isolieren. Fruticosin und Fruticosamin sind Isomere der Formel $C_{22}H_{24}O_4N_2$ und lassen sich gegenseitig ineinander umwandeln; das chromophore System und die Natur der funktionellen Gruppen dieser beiden Alkaloide wurden abgeklärt.

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