Pakistan J. Sci. Ind. Res., Vol. 23, Nos. 1-2, February-April, 1978

A FACILE ONE-STEP SYNTHESIS OF 2-SKATYL BENZIMIDAZOLE AND ITS REACTIONS WITH GRAMINE AND N,N-DIMETHYL AMINOPROPIOPHENONE HYDROCHLORIDE

IZHAR, H. QURESHI, SOOFIA SHAHID and NAHEED SULTANA,

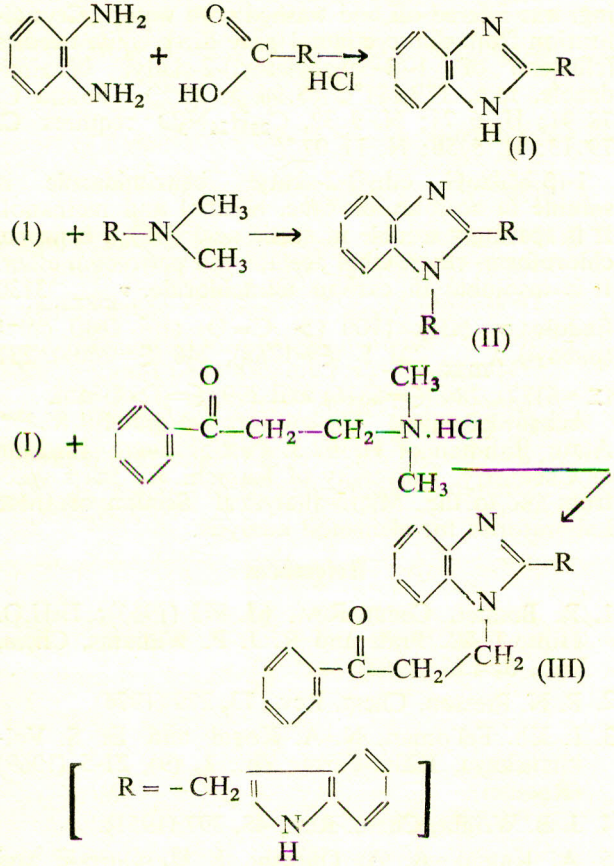
PCSIR Laboratories, Karachi-39.

(Received June 26, 1978; revised July 31, 1978)

Abstract. A simple one-step synthesis of 2-skatyl-benzimidazole (I) is described. Reaction of (I) with gramine afforded 1,2 diskatyl benzimidazole (II) while treatment of (I) with N,N-dimethyl amino-propiophenone hydrochloride furnished 1-(β-benzoyl ethyl)-2-skatyl benzimidazole (III). Compounds (II) and (III) have not been described previously.

The discovery that 5, 6-dimethyl-1-(α-D-ribofuranosyl) benzimidazole is an integral part of the chemical structure[1] of vitamin β_{12} has added interest to the benzimidazole chemistry. Consequently, massive research effort has been directed towards synthesizing new benzimidazole compounds for pharmacological screening. In fact, several synthetic benzimidazoles were found useful therapeutic agents[2] to combat human and veterinary diseases (see Table 1).

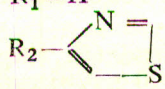
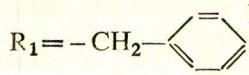
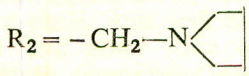
For the synthesis of 2-skatyl benzimidazole (I), the only method[3] available in literature is by the condensation of *ortho*-phenylene diamine and indole-3-acetonitrile *via* indole-3-iminoacetate. However, using Phillip's procedure,[4] we were able to accomplish the synthesis of (I) by the direct condensation of *ortho*-phenylene diamine and indole-3-acetic acid in hydrochloric acid.



A number of methods[2] are available for alkylating benzimidazoles; of these the interaction of benzimidazole and an appropriate Mannich base provides a convenient method. In the case of 2-substituted benzimidazoles, alkylation takes place on nitrogen at position 1. Thus 2-methyl- and 2-benzyl benzimidazoles on reaction with gramine (Mannich base) have been shown to furnish the corresponding N-skatyl derivatives.[5] In the present studies, N-alkylation of 2-skatyl benzimidazole (I), using different Mannich bases, are described.

Thus the reaction of 2-skatyl benzimidazole (I) with gramine in aqueous medium readily furnished a crystalline compound, m.p. 190°. It analyzed for $C_{25}H_{20}N_4$; (M+376). Its ir spectrum showed bands at 3490, 3470 (>NH), 1616 and 1580 $cm.^{-1}$ (phenyl). On the basis of the above analytical and spectral data, the compound was formulated as 1,2-diskatyl benzimidazole (II).

TABLE 1

Approved name	Structure	Use
Thiabendazole	R_1=H, R_2= 	Human and veterinary anthelmintic
Diabazole	R_1=H, R_2= $-CH_2$-Ph (HCl)	Vasodilator, spasmolytic and hypotensive
Clemizole	R_1=  , R_2= 	Bactericide antihistamine

Similarly 2-skatyl benzimidazole (I) when allowed to react with β-dimethyl amino-propiophenone

hydrochloride in aqueous medium afforded a crystalline compound, m.p. 179-81°. Its elemental analysis coupled with mass measurements (M^+ 379) agreed with the molecular formula, $C_{25}H_{21}N_3O$. ν_{max} 3130 (>NH, indole), 1700 (>C=O), 1610 cm^{-1} (phenyl). The above mentioned analytical and spectral data for this compound led to its formulation as N-(β-benzoylethyl)-2-skatyl benzimidazole (III) which is also compatible with its mass spectrum (Table 2).

TABLE 2

m/e	Relative abundance	m/e	Relative abundance
379	100	131	18
303	18	130	40
274	40	129	17
259	36	122	17
258	54	110	39
248	25	109	23
247	62	106	30
246	50	105	74
245	20	103	18
219	17	91	23
212	20	78	20
157	17	77	51
149	30	51	30
132	25		

Attempts to react (I) with 2-morpholinomethyl *cyclo*hexanone hydrochloride in aqueous medium were not successful and the starting materials were recovered. Even drastic conditions failed to induce the reaction to take place.

Experimental

Melting points were taken on Kofler Block and are corrected. Uv spectra were measured on a Beckmann Model D.B. spectrophotometer in methanol. Ir spectra were recorded on Perkin-Elmer 137 spectrophotometer in KBr, unless otherwise stated. Mass spectra were measured on Micromass MM 12 instrument at 70 e.v. Petroleum ether used had the boiling range 40-60°.

2-Skatyl benzimidazole (*I*). A mixture of *ortho*-phenylene diamine (1.0 g, 0.01 mole), indole-3-acetic acid (2.6g, 0.015 mole), ethanol (20ml.) and 4NHCl (20 ml.) were taken in a 100 ml round-bottom flask and refluxed on a water bath for 24 hr. The mixture on cooling (in ice bath) and neutralization with 20% ammonia solution afforded a dark brown oil which was decanted off. This oily material, which congealed to a solid on standing, was taken up in ethyl acetate, washed first with dilute sodium bicarbonate solution, then with water and finally dried over sodium sulphate (anhydrous). Removal of the solvent and crystallization from dilute ethanol gave 2-skatyl benzimidazole (I), m.p. 193-4° (lit.[3] m.p. 193-4°) 0.85 g, (35%); ν_{max} (KBr), 3469 (indole > NH), 3071 (benzimidazole > NH) and 1616 $cm.^{-1}$ (benzenoid stretching vibration) λ_{max} 224 (ε=68336), 275 (ε=37461), 281 (ε=40343) and 290 nm (ε=16466).

1,2-Diskatyl benzimidazole (*II*). A mixture of gramine (0.21 g, 0.0012 mole) and 2-skatyl benzimidazole (0.3g, 0.0012 mole) was taken up in distilled water (50 ml.) and refluxed (9 hr.) The slightly pink solid obtained was filtered off and washed with hot petroleum ether to remove any unreacted gramine. Crystallization of the solid with aqueous ethanol furnished 1,2-diskatyl benzimidazole as pale-white clusters, m.p. 190°. (0.22 g. ; 49%). Found C, 80, 23; H, 8.43; N, 15.09 $C_{25}H_{20}N_4$ requires C, 79.76; H, 5.35; N, 14.88%.

1,2-diskatyl benzimidazole (II) is soluble in acetone, methanol, ethanol, dioxane, ethyl acetate and ether. It is sparingly soluble in acetic acid (10%), hot water, benzene, petroleum-ether and chloroform. It is insoluble in carbon tetrachloride, ν_{max} 3490, 3470 (> NH), 1616 and 1580 cm^{-1} (phenyl). λ_{max} 223.5 (ε=20930), 277 (ε=1520) 283 (ε=1645) and 289 n.m. (ε=5013).

1-(β-benzoylethyl)-2-skatyl benzimidazole (*III*). 2-Skatyl benzimidazole (2.47 g, 0.01 mole), N,N-dimethylaminopropiophenone hydrochloride (2.13g; 0.01 mole) and distilled water (70 ml.) were refluxed (12 hr.). The cream coloured solid, obtained on cooling, was filtered off and washed with water. Crystallization from dilute ethanol gave dirty white needles (clusters) of 1-(β-benzoylethyl)-2-skatyl benzimidazole, m.p. 179-181°C (0.94 g, 25%). Found C, 78.91; H, 6.71; N, 9.32, $C_{25}H_{21}N_3O$ requires C, 79.13; H, 5.58; N, 11.07%.

1-(β-benzoyl ethyl)-2-skatyl benzimidazole is soluble in acetone, dioxane, ethanol and methanol. It is sparingly soluble in acetic acid (10%), benzene, chloroform, ether, ethyl acetate and petroleum ether. It is insoluble in carbon tetrachloride. $\nu_{max.}$ 3130 (indole > NH), 1700 (> C=O) and 1610 cm^{-1} (phenyl). λ_{max} 221.5 (ε=1768), 248 (ε=9601), 277 (Σ=6127), 284 (ε=6316) and 290 (ε=3284) nm.

Acknowledgment. The authors are grateful to Dr. Ataur Rahman of H. E. J. Post-graduate Institute of Chemistry, University of Karachi for mass spectrum and to the Micro-analytical Section of these Laboratories for elemental analysis.

References

1. R. Bonnet, Chem. Rev., **63,** 573 (1963); H.H.O. Hills, J. W. Pratt and R. J. P. Williams, Chem. Brit., **5,** 156 (1969).
2. P. N. Preston, Chem. Rev., **73,** 279 (1974).
3. I. Kh. Fel'dman, N. A. Kogal and E. S. Volkhanskaya, Khim-Farm. Zh., **1,** (9), 21-5 (1969) (Russian).
4. J. B. Wright, Chem. Rev., **48,** 397 (1951).
5. A. Kamal, A. A. Qureshi, I. H. Qureshi and Massarat Anjum, Pakistan J. Sci. Ind. Res., **13,** 4, 341-7 (1970).