SYNTHESIS OF 3-PHENYL- AND 3-PHENYL-1-METHYLLIMIDAZO [5, 1-b] BENZOXAZOLES

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Reduction of 2-benzoylbenzoxazole oxime gives 2-(α-aminobenzyl) benzoxazole, converted to the formyl or acetyl derivative by treatment with, respectively, ethyl formate or acetic anhydride. Thiourea derivatives are obtained by treating 2-(α-aminobenzyl) benzoxazole with arylisothiocyanates. Heating the above formyl or acetyl derivative with phosphorus oxychloride converts them to 3-phenyl- and 3-phenyl-1-methylimidazo [5, 1-b]-benzoxazole, which are representative members of a new tricyclic system. It did not prove possible to cyclize 1-[α-(benzoxazolyl-2)benzyl]-3-phenylthiourea.

Hitherto the imidazobenzoxazole system has not been described. The starting compound for preparing 3-phenylimidazo [5, 1-b] benzoxazole was 2-benzylbenzoxazole [1], converted by amyl nitrite into 2-benzoylbenzoxazole oxime [2]. Reduction of the oxime with zinc dust in ammonia gives the amine I. Treatment of this amine with phenylisothiocyanate and p-butoxyphenylisothiocyanate in benzene gives respectively the thiourea derivatives II and III. However compound II, unlike the analogous benzothiazole derivative [3], cannot be cyclized by heating in high-boiling solvents, or in the absence of a solvent.

![Fig. 1. UV spectra: 1) 2-(α-formamidobenzyl)-benzoxazole (V); 2) 2-(phenyl)-(formamido)-acetyl aminophenol (IV); 3) 3-phenylimidazo [5, 1-b] benzoxazole (VI).](image)

![Fig. 2. UV spectra: 1) 2-(α-acetamidobenzyl)-benzoxazole (VII); 2) 3-phenyl-1-methyl-imidazo [5, 1-b] benzoxazole (VIII).](image)

Formylation of I with 88% formic acid gives compound IV, whose analysis and properties (solubility in alkalies) correspond to those of an o-aminophenol derivative, i.e., the benzoxazole ring is obviously opened under the conditions used.

Formylation of I with ethyl formate gives a formyl derivative V, whose UV spectrum differs sharply from that of IV (Fig. 1). Heating V with phosphorus oxychloride in benzene converts it into 3-phenylimidazo [5, 1-b] benzoxazole (VI).

Acetylation of I with acetic anhydride gives its acetyl derivative VII, converted by phosphorus oxychloride into 3-phenyl-1-methylimidazo [5, 1-b] benzoxazole (VIII).
The UV spectra of the imidazo [5, 1-b]benzoxazole derivatives prepared differ sharply from those of the acyl derivatives of the starting amine (Figs. 1 and 2), and closely resemble those of the recently described imidazo [5, 1-b] benzothiazole [4].

Experimental

2- (α-Aminobenzyl) benzoxazole (I). A suspension of 8.83 g 2-benzoylbenzoxazole oxime was heated to 60°C [2], and 6.83 g NH₄OAc, 8.83 g Zn dust, and 544 ml aqueous ammonia added. The mixture was heated for 40 min at 80°C, then 4.42 g Zn dust and 270 ml aqueous ammonia added. After heating the mixture for 4 hr at the same temperature, a further 4.42 g Zn dust and 270 ml ammonia were added, and the whole stirred for 1 hr. The reaction products were left overnight, next day 4.42 g Zn was added, the mixture heated for 40 min at 80°C, then filtered hot. The precipitate which formed after cooling was filtered off, yield 5.43 g (67%) long needle-shaped crystals, mp 83.5°C-86°C (ex petrol ether). Found: C 75.16; H 5.50; N 12.54%. Calculated for C₁₇H₁₇N₂O₃: C 74.98; H 5.39; N 12.49%.

1-[α-(Benzoxazol-2-yl) benzyl]-3-phenylthiourea (II). 1 g I was dissolved in 9 ml dry benzene, 1 g phenylisothiocyanate added, and the whole refluxed for 4 hr. After cooling, the precipitate was filtered off. Yield 1.36 g (85%) slightly yellowish compound, readily soluble in EtOH and AcOH, moderately soluble in ether, insoluble in water. Mp 197.5°C-199°C (ex BuOH). The compound crystallized with 1 molecule of BuOH, For analysis it was vacuum-dried at 100°C. Found: C 70.10; H 4.65; S 9.19%. Calculated for C₁₉H₁₇N₂SOS: C 70.17; H 4.77; S 8.95%.

1-[α-(Benzoxazol-2-yl) benzyl]-3-(p-butoxyphenyl) thiourea (III.). The reaction was carried out as in the preceding experiment. 1 g I and 1.6 g p-butoxyphenylisothiocyanate gave 1.9 g (yield about 100%) substance mp 187.5°C-194°C, insoluble in water and benzene, readily soluble in EtOH. Attempts to recrystallize it from 50% EtOH led to a drop in mp. For analysis the substance was washed with boiling benzene, mp 191°C-194°C. Found: C 69.61; H 5.84; N 9.41; S 7.53%. Calculated for C₂₆H₂₅N₃O₃S: C 69.56; H 5.84; N 9.74; S 7.43%.

2- [(Phenyl) (formamido) acetyl] aminophenol (IV). A mixture of 0.75 g I and 1.05 ml 88% formic acid was heated for 3 hr at 100°C. The solid mass obtained after cooling was ground with 5 ml aqueous ammonia, the solid filtered off, and washed with water, to give 0.84 g orange-brown substance. Recrystallization from aqueous MeOH gave pale-pink needles, readily soluble in alkali, slightly soluble in water, moderately soluble in EtOH and MeOH. Decomposed at 192.5°C. Found: C 66.51; H 5.36; N 10.58%. Calculated for C₁₅H₁₄N₂O₃: C 66.65; H 5.22; N 10.36%.

2- (α-Formamidobenzyl) benzoxazole (V). A suspension of 2 g I in 12 ml freshly-prepared ethylformate was heated at 100°C for 3 hr 30 min. Excess ethylformate was vacuum-distilled off, and the residue recrystallized from aqueous...