UDC 547.78 + 543.422

SYNTHESIS OF 3-PHENYL- AND 3-PHENYL-1-METHYLIMIDAZO [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-phenyl-imidazo [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.

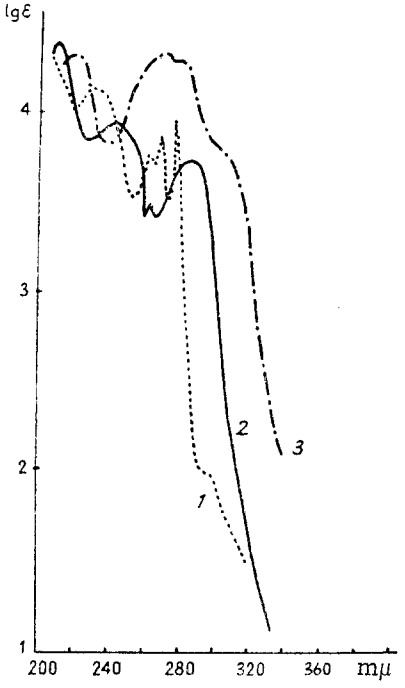


Fig. 1. UV spectra: 1) 2-(α-formamidobenzyl)-benzoxazole (V); 2) 2-[(phenyl)-(formamido)-acetyl] aminophenol (IV); 3) 3-phenylimidazo-[5, 1-b] benzoxazole (VI).

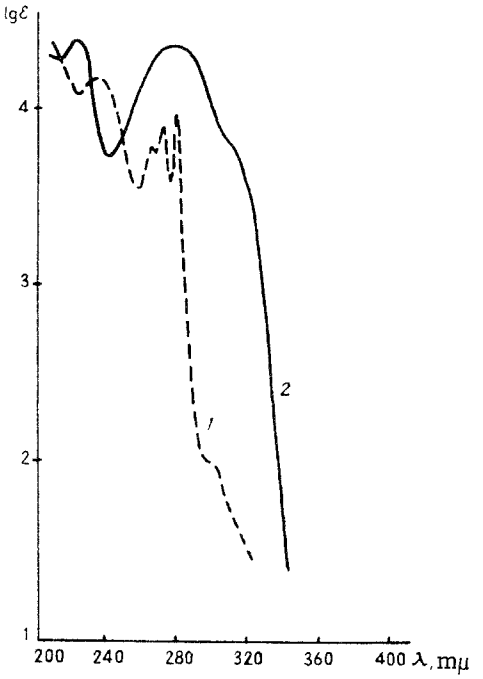
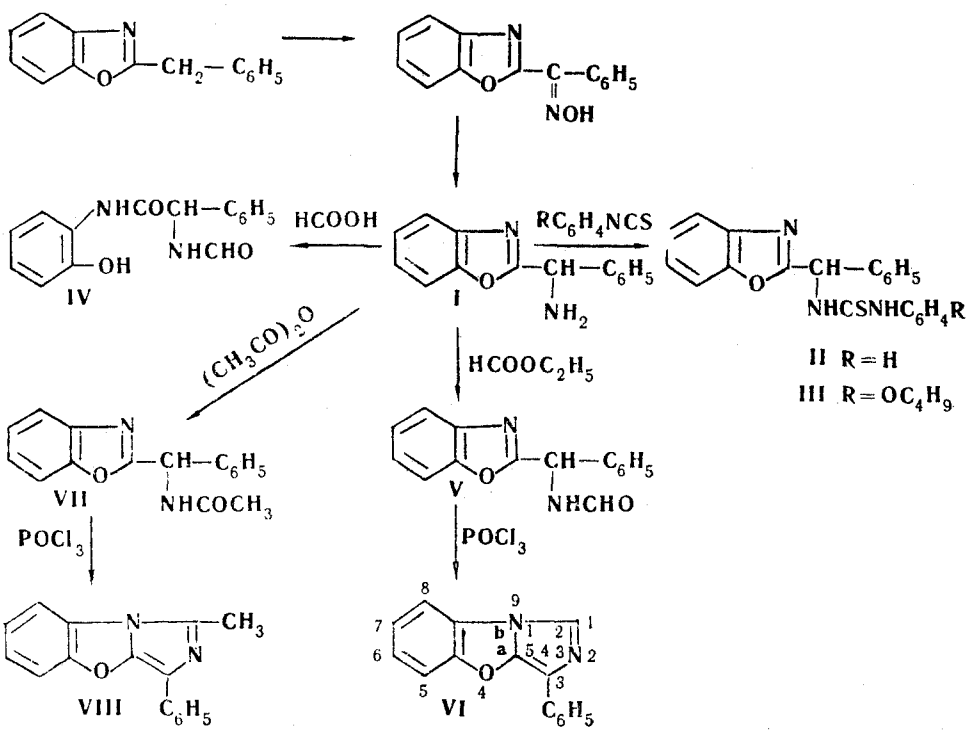


Fig. 2. UV spectra: 1) 2-(α-acetamidobenzyl)-benzoxazole (VII); 2) 3-phenyl-1-methyl-imidazo [5, 1-b] benzoxazole (VIII).

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 8.83 g NH_4OAc, 8.83 g Zn dust, and 544 ml aqueous ammonia added. The mixture was heated for 40 min at 80°, 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°, then filtered hot. The precipitate which formed after cooling was filtered off, yield 5.43 g (67%) long needle-shaped crystals, mp 83.5°–86° (ex petrol ether). Found: C 75.16; H 5.50; N 12.54%. Calculated for $C_{14}H_{12}N_2O$: 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°–199° C (ex BuOH). The compound crystallized with 1 molecule of BuOH. For analysis it was vacuum-dried at 100°. Found: C 70.10; H 4.65; S 9.19%. Calculated for $C_{21}H_{17}N_3OS$: 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°–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°–194°. Found: C 69.61; H 5.84; N 9.41; S 7.53%. Calculated for $C_{25}H_{25}N_3O_2S$: 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°. Found: C 66.51; H 5.36; N 10.50%. Calculated for $C_{15}H_{14}N_2O_3$: 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

MeOH, using decolorizing charcoal. Yield 1.85 g colorless crystalline substance, insoluble in alkali and in water, moderately soluble in EtOH. Mp 131°–133°. Found: C 71.37; H 4.74; N 11.27%. Calculated for $C_{15}H_{12}N_2O_2$: C 71.41; H 4.79; N 11.11%.

3-Phenylimidazo [5, 1-b] benzoxazole (VI). 2 g V was suspended in 26.4 ml dry benzene, 6.2 ml $POCl_3$ added, and the mixture heated for 6 hr, then left overnight. The solvent was vacuum-distilled off, benzene added to the dry residue, and the whole again evaporated to dryness. The caramel-like residue was treated with cooling, with water, the solid filtered off, washed with water, carefully ground with 10% Na_2CO_3 solution, and recrystallized from MeOH, to give 1.16 g (62.5%) yellowish crystalline substance, mp 179.5°–180.5°C, insoluble in dilute mineral acids and alkalies. Found: C 76.77; H 4.30; N 12.23%. Calculated for $C_{15}H_{10}N_2O$: C 76.91; H 4.30; N 11.96%.

2-(α-Acetamidobenzyl) benzoxazole (VII). A mixture of 1 g I, 5 ml glacial AcOH, and 2 ml Ac_2O was heated at 100° C for 1 hr 30 min, then vacuum-evaporated to dryness. The crystalline residue was ground with cold water, washed with water, and filtered off. Yield 1.18 g (quantitative) substance forming colorless needles mp 156.5°–158° (ex aqueous MeOH), insoluble in water and petrol ether, readily soluble in EtOH and benzene. Found: C 72.48; H 5.24; N 10.72%. Calculated for $C_{16}H_{14}N_2O_2$: C 72.16; H 5.30; N 10.52%.

3-Phenyl-1-methylimidazo [5, 1-b] benzoxazole (VIII). A mixture of 0.5 g VII, 6.6 ml benzene, and 1.55 ml $POCl_3$ was refluxed for about 4 hr, and left overnight. The crystalline precipitate which formed was filtered off, washed with water, and ground with 10% Na_2CO_3 solution, then again washed with water. Yield 0.41 g (88%) colorless needles mp 144.5°–146.5° C (ex 50% EtOH). Found: C 77.38; H 4.64%. Calculated for $C_{16}H_{12}N_2O$: C 77.40; H 4.87%.

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