COMPOUNDS WITH POTENTIAL ANTITUBERCULAR ACTION

XIV. (Benzoxazolyl-2)-Hydrazines

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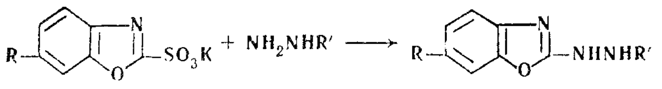
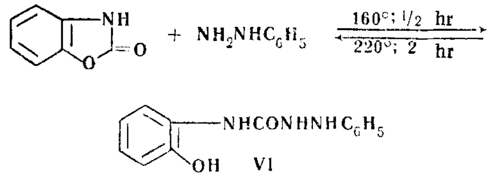
Reaction of potassium 2-benzoxazole sulfonate, and its 6-nitro and 6-acetylamino derivatives with hydrazine hydrate, or with aryl or arylalkyl substituted hydrazines, gives a series of (benzoxazolyl-2)hydrazines. Reaction of benzylhydrazine and phenylethylhydrazine with potassium 2-benzoxazolyl sulfonate gives 2 isomers: a 1,1-disubstituted hydrazine, and 1,2-disubstituted hydrazine. The reaction of 2-benzoxazolone with phenylhydrazine at 180° is accompanied by ring opening and formation of an o-aminophenol derivative.

The present work aimed at the synthesis of some (benzoxazolyl-2) hydrazines with a view to investigating their chemical properties and antibacterial activities. A patent [1] indicates that the action of hydrazine hydrate on potassium 2-benzoxazole sulfonate gives (benzoxazolyl-2) hydrazine. On investigating this reaction we found that at about 100°, no (benzoxazolyl-2-)hydrazine is formed, but that the benzoxazole ring opens and the main reaction product is o-aminophenol, similar to what obtains when hydrazine hydrate acts on 2-mercaptobenzoxazole [2]. If the reaction is run at 5–10°, (benzoxazolyl-2-) hydrazine (I) is obtained in up to 93% yield [1]. From it were prepared the hydrochloride and the hydrazones derived from anisaldehyde and benzaldehyde. Reaction of (benzoxazolyl-2) hydrazine with acetylacetone gives 1-(benzoxazolyl-2')-3,5-dimethylpyrazole. Treatment of potassium 2-benzoxazole sulfonate with phenylhydrazine gives 1-phenyl-2-(benzoxazolyl-2') hydrazine (II) melting point 137–139°. The literature states [3] that 1-phenyl-2 (benzoxazolyl-2') hydrazine is obtained by reacting 2-benzoxazolone with phenylhydrazine, but the recorded melting point of that compound (208°) differs markedly from that of ours. When we carried out the reaction between 2-benzoxazolone and phenylhydrazine under the conditions given by one author [3] (equimolecular amounts, 160°), we also obtained a compound with melting point 207–208°, but its analysis and properties (solubility in alkalies) corresponded to the phenylhydrazide of 2-hydroxyphenylcarbamic acid (VI), i.e. the benzoxazole ring opened. Longer heating led to splitting out of phenylhydrazine, and reformation of 2-benzoxazolone. Similar transformations were previously observed [4] when 2-benzoxazolone was heated with aniline.



I R = R' = H; II R = H, R' = C$_6$H$_5$; III R = NO$_2$, R' = H;

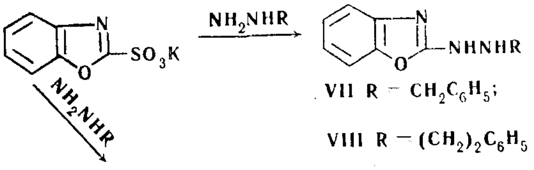
IV R = NO$_2$, R' = C$_6$H$_5$; V R = CH$_3$CONH; R' = H



VI

Owing to the presence of a nitro group, the reaction of potassium 6-nitro-2-benzoxazole sulfonate [5] with hydrazine hydrate proceeds very readily, at low temperature, to give (6-nitrobenzoxazolyl-2) hydrazine (III). A like reaction was carried out with phenylhydrazine, using a short heating time, and the product was 1-(6-nitrobenzoxazolyl-2')-2-phenylhydrazine (IV). The reaction of hydrazine hydrate with potassium 6-acetylamino-2-benzoxazole sulfonate [5] gave (6-acetaminobenzoxazolyl-2)-hydrazine (V).

When benzylhydrazine was treated with potassium 2-benzoxazole sulfonate, two substances were obtained. One of them, melting point 107–109°, gave a hydrazone with anisaldehyde, and readily dissolved in dilute hydrochloric acid. Its elementary analysis and properties corresponded to those of 1-benzyl-1-(benzoxazolyl-2') hydrazine (IX), i.e. addition of the benzoxazole ring took place at the secondary nitrogen atom of the benzylhydrazine. The other substance, melting point 207–209°, did not give a hydrazone, and did not dissolve in hydrochloric acid. It was 1-benzyl-2-(benzoxazolyl-2') hydrazine (VII). To prove its structure, 1-benzal-2-(benzoxazolyl-2') hydrazine was hydrogenated in the presence of platinum oxide; the produce gave an undepressed mixed melting point with the compound, melting point 207–209°. Reaction of potassium 2-benzoxazole sulfonate with phenylethylhydrazine also gave two isomers (VIII and IX), and the main product, as with benzylhydrazine, was a disubstituted hydrazine with a free NH$_2$ group (X).



VII R = CH$_2$C$_6$H$_5$;

VIII R = (CH$_2$)$_2$C$_6$H$_5$

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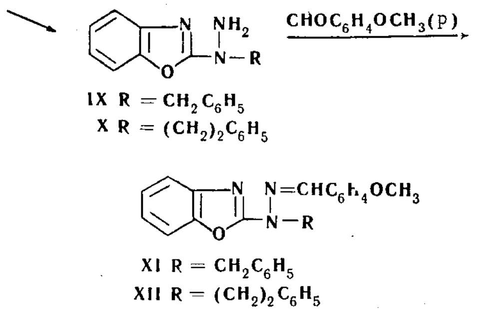
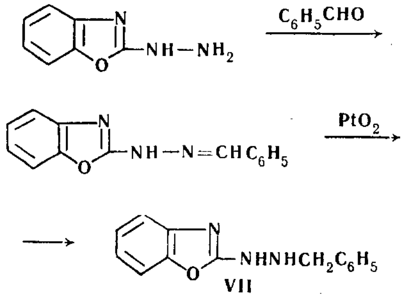


IX R = $CH_2C_6H_5$
X R = $(CH_2)_2C_6H_5$

XI R = $CH_2C_6H_5$
XII R = $(CH_2)_2C_6H_5$



VII

Thus reaction of potassium 2-benzoxazole sulfonate with monosubstituted hydrazines proceeds analogously to alkylation of monoalkylhydrazines, where it has been established [6,7] that introduction of the second alkyl group takes place at the secondary nitrogen atom.

The simultaneous formation of 1, 2-disubstituted hydrazines with benzylhydrazine and phenylethylhydrazine is possibly due to that reaction proceeding more readily than alkylation, and even the insignificant electron density at the NH_2 group of the hydrazine is sufficient for addition of the benzoxazole group. On the other hand, in the case of phenylhydrazine, the effect of the electron-accepting phenyl group leads to a decrease in the density of the electrons at the secondary nitrogen atom, so that the main reaction product is a 1,2-disubstituted hydrazine.

When an attempt was made to react the potassium 2-benzoxazole sulfonate with unsymmetrical dimethylhydrazine by heating them together in aqueous ethanolic solution at 60°, or 100°, only the starting potassium salt was isolated.

It is of interest to note that all the 1,2-disubstituted hydrazines which we prepared, as well as the hydrazones, impart a green color to a flame when burnt on copper wire. Hydrazines with a free NH_2 group do not exhibit that property.

All the benzoxazolylhydrazines were checked for tuberculostatic activity and for ability to inhibit the action of monoamine oxidase.* Compounds II and III showed rather considerable in vitro tuberculostatic activity in the presence of serum (minimum bacteriostatic concentration 4 γ/ml); benzoxazolyl-2)hydrazine hydrochloride inhibited growth of tubercular bacilli at a concentration of 8 γ/ml, without serum. However in the presence of horse serum the activity of these preparations drops to 15 γ/ml, and to 250 γ/Ml in the case of III. The other preparations had low activities. (Benzoxazolyl-2)hydrazines and their substitution products have not been found to show any antimonoamine oxidase activity.

EXPERIMENTAL

(Benzoxazolyl-2)hydrazine (I). 10 ml (0.2 mole) hydrazine hydrate was dropped into a mixture of 5 g (0.021 mole) potassium 2-benzoxazole sulfonate in 10 ml water which was stirred and cooled in ice-water. The mixture was stirred for 4 hr at 20°, then cooled, and the precipitate filtered off and washed with ice-water. Yield 2.93 g (93%), colorless crystalline compound in the form of plates, mp 152-143° [1].

The hydrochloride was prepared by passing a current of dry HCl into an ether solution of base I. Colorless crystals, soluble in water and hot methanol, decomp 164-169°. Found: Cl 19.49%. Calculated for $C_7H_7N_3O \cdot HCL$: Cl 19.10%.

1-(p-Methoxybenzal)-2-(benzoxazolyl-2')hydrazine. A mixture of 0.5 g (3.3 mole) I, 5 ml ethanol, and 0.4 ml (3.3 mole) anisaldehyde was refluxed for 2 hr. The precipitate which separated from the hot solution was, after cooling, filtered off, washed with cold ethanol, and dried. Yield 0.74 g colorless crystalline substance which turned yellow in air, mp 202-204° (ex butanol). Found: C 67.14; H 4.87; N 15.53%. Calculated for $C_{15}H_{13}N_3O_2$: C 67.40; H 4.90; N 15.72%.

1-Benzal-2-(benzoxazolyl-2')hydrazine was prepared similarly, mp 204-205° (ex ethanol). Found: C 70.35; H 4.90; N 17.46%. Calculated for $C_{14}H_{11}N_3O$: C 70.86; H 4.67; N 17.71%.

1-(Benzoxazolyl-2')-3, 5-dimethylpyrazole. A mixture of 1.49 g (0. 01 mole] I, 1 ml (0.01 mole) freshly-distilled acetylacetone, and 15 ml dry ethanol was refluxed for 2 hr, then vacuum evaporated. The residue was treated with 5 ml 10% aqueous NaOH solution, filtered off, and washed with water. Yield 1.4 g colorless crystalline material, insoluble in water, soluble in hot ethanol. Mp 119.5-121° (ex ethanol). Found: C 67.57; H 5.18; N 20.00%. Calculated for $C_{12}H_{11}N_3O$: C 67.58; H 5.19; N 19.70%.

1-Phenyl-2-(benzoxazolyl-2')hydrazine (II). 2.2 g (20.4 mmole) phenylhydrazine was added to a mixture of 2 g (8.4 mmole) potassium 2-benzoxazole sulfonate, 10 ml water, and 10 ml ethanol. The mixture was then held for 5 hr 30 min at 60°, cooled, the precipitate filtered off, and washed with warm water. Yield 1.2 g (63%) colorless crystalline material, insoluble in water, dilute alkalies, and dilute acids, readily soluble in warm ethanol, mp 137-139° (ex benzene). It gave a green flame when burnt on copper wire, and did not form a hydrazone with anisaldehyde. Found: C 69.65; H 4.93%. Calculated for $C_{13}H_{11}N_3O$: C 69.31; H 4.92%.

Phenylhydrazide of 2-hydroxyphenylcarbamic acid (VI). A mixture of 5 g (0.037 mole) 2-benzoxazolone and 3.5 ml (0.037 mole) freshly-distilled phenylhydrazine was heated at 160°. When the hot solution was rubbed with a rod, a precipitate formed, and in 30 min the entire mass solidified. Heating was stopped, the reaction products transferred in a small amount of 50% ethanol, the precipitate filtered off, washed with cold aqueous ethanol, dried, and treated with boiling benzene. Yield 4.53 g almost colorless substance, readily soluble in aqueous alkalies. Mp 207-208° (ex aqueous ethanol). Found: C 64.25; H 5.41; N 17.23%. Calculated for $C_{13}H_{13}N_3O_2$: C 64.18; H 5.38; N 17.27%.

2 g of the phenylhydrazide of 2-hydroxyphenylcarbamic acid was heated at 200° in a vacuum for about 2 hr, which led to partial decomposition, and a small amount of oily material collected in the receiver. When triturated with ether the charred residue crystallized. Mass 0.96 g. The material was recrystallized from water

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*The investigations were carried out in this institute by T. N. Zykova and S. N. Milanovanova in the chemotherapy division, and in the biochemistry laboratory (director L. I. Grebennik).

using decolorizing charcoal, and then treated with alkali. Acidification of alkaline solutions with acetic acid gave 0.38 g almost colorless crystals mp 139.5–141. 5° (ex water). Undepressed mixed mp with 2-benzoxazole. The oily material which collected in the receiver was triturated with a small amount of dry ethanol, and a few drops of anisaldehyde added to the solution. Rubbing with a glass rod led to the separation of crystals mp 119.5–122.5° (ex EtOH), undepressed mixed mp with anisaldedyde phenylhydrazone.

Reaction of potassium 2-benzoxazole sulfonate with benzylhydrazine. A solution of 3 g (0.0248 mole) benzylhydrazine in 13 ml ethanol was dropped into a mixture of 2.73 (0.01 mole) potassium 2-benzoxazole sulfonate and 13 ml water. The mixture was kept at 70° for 5 hr, cooled, the precipitate filtered off, and washed with cold aqueous ethanol. Yield 2.66 g, mp 71–85°, two recrystallizations from 50% dimethylformamide gave 1.43 g colorless crystalline substance, mp 107–109°, readily soluble in ethanol and dilute hydrochloric acid, which was 1-benzyl-1-(benzoxazolyl-2')hydrazine IX. Found: C 70.35; H 5.48; N 17.60%. Calculated for $C_{14}H_{13}N_3O$: C 70.25; H 5.45; N 17.55%.

Heating 0.2 g of this compound with 0.1 ml anisaldehyde in 5 ml dry ethanol gave the hydrazone XI, yield 0.17 g, mp 166.5–168.5 165.5° (ex aqueous EtOH). Found: C 74. 05; H 5.44; N 11.93%. Calculated for $C_{22}H_{19}N_3O_2$: C 73.93; H 5.48; N 17.60%.

The dimethylformamide mother liquors from the recrystallization of IX were diluted with water, the precipitate filtered off, and treated with hot petrol ether (bp 100–120°). On cooling to room temperature 0.13 g colorless crystalline material separated[*] mp 207–209°, insoluble in hydrochloric acid, and not forming a hydrazone with anisaldehyde. This was 1-benzyl-2-(benzoxazolyl-2') hydrazine (VII), and it gave a green flame when burnt on copper wire. Found: C 70.50; H 5.68; N 17.67%. Calculated for $C_{14}H_{13}N_3O$: C 70.25; H 5.45; N 17.55%.

The same compound (mp 202°) was obtained by hydrogenating a solution of 0.75 g 1-benzal-2-(benzoxazolyl-2')hydrazine in 70 ml dry ethanol in the presence of 0.1 g Pt oxide. The two compounds gave an undepressed mixed mp.

Reaction of potassium 2-benzoxazole sulfonate with phenylethylhydrazine. A mixture of 2 g (8.4 mmole) potassium 2-benzoxazole sulfonate, 2 g (14.7 mmole) freshly-distilled phenylhydrazine, 10 ml water, and 10 ml ethanol was held at 60° for 5 hr. The mixture of oily and crystalline material obtained on cooling was filtered off, and the solid washed with water, yield 1.66 g, mp 65–76°, after recrystallizing from hexane it had mp 86–87.5°. Colorless crystals, readily soluble in benzene and ethanol, soluble in dilute hydrochloric acid. It was 1-phenylethyl-1-(benzoxazolyl-2')hydrazine (X). Found C 71.17; H 6.11; N 16.75%. Calculated for $C_{15}H_{15}N_3$; C 71.12; H 5.96; N 16.59%.

With anisaldehyde it gave a hydrazone XII, mp 128–129.5° (ex MeOH). Found: C 74.14; H 5.25; N 11.36%. Calculated for $C_{23}H_{21}N_3O_2$: C 74.37; H 5.69; N 11.31%.

The aqueous ethanol solutions after removal of X gave, on standing, 0.19 g material mp 110–111.5° (ex hexane), insoluble in hydrochloric acid, and it does not give a hydrazone with anisaldehyde. The mixed mp with X was 69°. It was 1-phenylethyl-2-(benzoxazolyl-2') hydrazine (VIII). Found: C 71.31; H 6.13; N 16.33%. Calculated for $C_{15}H_{15}N_3O$: C 71.12; H 5.96; N 16.59%.

(6-Nitrobenzoxazolyl-2) hydrazine (III). 1 ml (20.6 mmole) hydrazine hydrate was added, with cooling in ice-water, to a mixture of 0.4 g (1.4 mmole) potassium 6-nitro-2-benzoxazolyl sulfonate [5] and 4 ml water; suddenly a bulky reddish precipitate separated, and quickly turned yellow. Stirring was continued for 2 hr more at room temperature, the precipitate filtered off, and washed with water, yield 0.26 g, decomp 180–181° (ex MeOH; accompanied by slow melting, then the melt suddenly solidified, and did not remelt up to 365°). Bright yellow crystals, soluble in hot water. Found: C 43.40; H 3.15; N 29.23%. Calculated for $C_7H_6N_4O_3$: C43.21; H 3.11; N 28.86%.

1-(6-Nitrobenzoxazolyl-2')-2 phenylhydrazine (IV) was prepared by reacting potassium 6-nitro-2-benzoxazolyl sulfonate and phenylhydrazine in aqueous ethanol (held at 60–80° for 1 hr), mp 165–166° (ex toluene). Found: C 57.87; H 3.83; N 20.74%. Calculated for $C_{13}H_{10}N_4O_3$: C 57.77; H 3.73; N 20.73%.

(6-Acetylaminobenzoxazolyl-2)hydrazine (V). Prepared by reacting potassium 6-acetylamino-2-benzoxazolyl sulfonate [5] and hydrazine hydrate in aqueous solution. Quantitative yield, mp 201° (ex water). Found: N 27.31 %. Calculated for $C_9H_{10}N_4O_2$: N 27.20%.

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[*] Cooling the solution with ice led to precipitation of a mixture with a wide melting range.