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On 1,2-Benzisoxazole-3-acetic Acid (I)

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The proposed 6- and 7-methyl-1,2-benzisoxazole-3-acetic acids (3) have been shown to be 6- and 7-methyl-4-hydroxyimino-2-oxo-chromans. The method of preparation of these unknown acids was demonstrated by the synthesis of 1,2-benzisoxazole-3-acetic acid, starting from 3-methyl-1,2-benzisoxazole. Comparative results of the auxin test are reported.

1,2-Benzisoxazole-3-acetic acid (VII) has not yet been described, although its two 6- and 7-methyl derivatives were mentioned by Posner and Hesse (3), who had tentatively assigned these structures to the by-products of the reaction of 6- or 7-methylcoumarin and hydroxylamine.

As an intermediate for other purposes 4-hydroxyaminocoumarin (4) was required, better formulated as 2-oxo-4-hydroxyiminochroman (I) on the basis of its proton magnetic resonance spectrum. Compound I was strongly acidic and gave alkylhydroxyimino derivatives (Ia, Ib and Ic) with diazomethane or dimethylsulfate, *p*-bromophenacyl bromide and *p*-nitrobenzyl bromide, respectively. Moreover 2-oxo-4-hydroxyiminochroman (I) was converted into the known 3-methyl-1,2-benzisoxazole (IV) (5) on heating in quinoline.

All these properties could well be referred to 1,2-benzisoxazole-3-acetic acid, but the n.m.r. spectrum (6) of I in deuterochloroform, in addition to the signals of the four aromatic protons and of the two equivalent protons of the methylene group (singlet at $\delta = 4.08$ p.p.m.), shows a signal for one proton at $\delta = 8.52$ p.p.m., that is too highly shielded to be due to a carboxylic proton, clearly establishing the substance to be an oxime. The opening of the coumarin ring that must be involved in the decarboxylation reaction in quinoline in spite of the anhydrous environment, can be imagined as effected by the base itself.

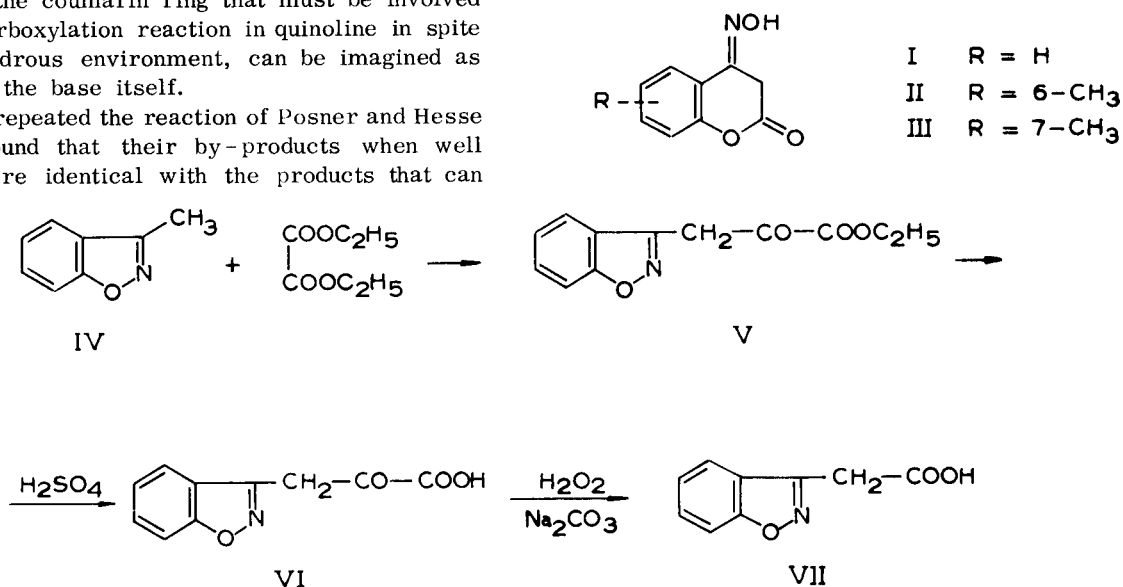
We have repeated the reaction of Posner and Hesse (3a) and found that their by-products when well purified were identical with the products that can

be obtained from reaction between 6- or 7-methyl-4-hydroxycoumarin and hydroxylamine by the procedures used in the preparation of I, therefore structures II and III were assigned to them, by considering the similarities in acidity, I. R. and U. V. spectra when compared with this data on I.

The n.m.r. spectra of II and III could not be taken in chloroform because of lack of solubility in that solvent. Moreover dimethylsulfoxide- d_6 was not a suitable solvent since the hydroxyimine proton gave a broad and not very clear signal in this case.

1,2-Benzisoxazole-3-acetic acid (VII) was obtained starting from IV as outlined in the reaction scheme. It was an unstable compound and was very easily decarboxylated, even when kept dry at room temperature. This compound was very sparingly soluble in deuterochloroform. When dissolved in DMSO- d_6 , it gave an n.m.r. spectrum that could be recognized as that of the decarboxylation product, which was found in the solution.

1,2-Benzisoxazole-3-acetic acid (VII) has been investigated for possible heteroauxin activity by the Went's method (7) and found to be one hundred times less active than indole-3-acetic acid.



EXPERIMENTAL

Unless otherwise indicated, melting points were determined in capillary tubes on a Büchi apparatus and are uncorrected. The infrared spectra were recorded with an Unicam SP 200 spectrometer in nujol or as the pure liquid in the case of oils; the U. V. spectra were taken in ethanol with an Unicam SP 800 spectrometer.

Ethers of 4-Hydroxyimino-2-oxochroman (Ia-c).

Methyl ether (Ia).

This compound was obtained by allowing diazomethane or dimethyl sulfate to react with 4-hydroxyimino-2-oxochroman (I) which was prepared by the method of Mustafa (4) or, in 70% yield, by the method described for compounds II and III. For instance an excess of an ethereal diazomethane solution was used. After the first vigorous reaction in an ice bath had subsided, the mixture was allowed to stand for 1 hour at room temperature and then evaporated. The resulting yellow oil distilled at 85° (0.05 mm.), $n_D^{18} = 1.5421$. It did not give a color reaction with ferric chloride, C=O band absorption at 1727 cm^{-1} . There was no absorption band for the OH group.

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NO}_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.98; H, 4.62; N, 7.50.

Like the other ethers of I it was easily hydrolyzed and gave I on short heating in 2 N sodium hydroxide solution followed by acidification.

p-Bromophenacyl ether (Ib).

An aqueous-alcoholic solution of the sodium salt of I was refluxed 1 hour with the stoichiometric amount of *p*-bromophenacyl bromide in ethanol, white needles from ethanol, m.p. 116-118°, keto C=O absorption band at 1685; lactonic C=O absorption band at 1723 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{BrNO}_4$: C, 54.56; H, 3.23; N, 3.74. Found: C, 54.45; H, 3.22; N, 3.81.

p-Nitrobenzyl ether (Ic).

This compound was prepared as described above using *p*-nitrobenzyl bromide. White leaflets were obtained from ethanol, m.p. 106-107°; C=O absorption band was at 1728 cm^{-1} .

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_5$: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.67; H, 3.89; N, 9.17.

Conversion of 4-Hydroxyimino-2-oxochroman (I) into 3-Methyl-1,2-benzisoxazole (IV).

Cupric oxide (0.3 g.) and 3 g. of I in 15 ml. of anhydrous quinoline were gradually heated to 180°. After 0.5 hour at 180-185°, the evolution of gas ceased. The reaction mixture was allowed to cool and poured into 2 N hydrochloric acid. The acidic solution was extracted with ether, the ethereal layer washed with sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated, leaving an oil which distilled at 93-95° (10 mm.), $n_D^{20} = 1.5490$. The analysis, IR and UV spectra, as well as gas-chromatographic behavior on comparison with an authentic sample of 3-methyl-1,2-benzisoxazole obtained by Lindemann's method (5) confirmed the identity of the two products.

Preparation of 6-Methyl-4-hydroxyimino-2-oxochroman (II) and 7-Methyl-4-hydroxyimino-2-oxochroman (III).

The reaction between the 4-hydroxycoumarins and hydroxylamine was carried out by heating at 70-80° for 8 hours one mole of the hydroxycoumarin dissolved in ethanol with 4.5 moles of hydroxylamine hydrochloride and 4.5 moles of sodium acetate dissolved in water. Ethanol was evaporated, the aqueous solution made alkaline with sodium bicarbonate and extracted with ether. In the ethereal extract small amounts of the corresponding *o*-hydroxyacetophenone oxime was found, and from the aqueous solution a small amount of the starting materials separated at pH 4. By further acidification, the 4-hydroxyimino-2-oxochroman (II) crystallized from water as white silky needles, m.p. 154-155°.

UV: λ max (log ϵ): 239 (3.87) 246 (3.77) 292 (3.46) (8). IR: ν max 2680, 2600 (bound OH), 1700 (lactone C=O), 1533 (C=N), 1340 cm^{-1} (OH bending).

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NO}_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.86; H, 4.92; N, 7.58.

7-Methyl-4-hydroxyimino-2-oxochroman (III) crystallized from water as white needles, m.p. 172-173°.

UV: λ max (log ϵ): 243 (3.94) 283 (3.53) (8). IR: ν max 2650, 2550 (bound OH), 1715 (C=O) 1530 (C=N) 1328 cm^{-1} (OH bending).

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{NO}_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.81; H, 5.04; N, 7.12.

Both these products were highly acidic and did not give a color reaction with ferric chloride. They did not depress the melting point of the products obtained from 6-methylcoumarin and 7-methylcoumarin, respectively (3). The IR and UV spectra were identical.

Ethyl 1,2-benzisoxazole-3-pyruvate (V).

To an ethanol-ether solution of potassium ethoxide prepared from 2.5 g. of potassium, 4.4 g. of diethyl oxalate was added and the mixture stirred for 0.5 hour. A solution of 4 g. of 2-methyl-1,2-benzisoxazole (IV) in 20 ml. of anhydrous ether was added and stirring was continued for about 12 hours. The potassium salt which separated was collected, washed with ether and suspended in water. After acidification with 2 N hydrochloric acid, the suspension was stirred for 1 hour. The ester was filtered, washed thoroughly with water and crystallized from water-ethanol, m.p. 68-70° (Kofler). It gave a dark green color with ferric chloride. The ester C=O band was at 1700 and the keto C=O band was at 1622 cm^{-1} ; λ max (log ϵ) 332 (4.19).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{NO}_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 62.04; H, 4.86; N, 5.98.

Compound V with sodium acetate buffered hydroxylamine hydrochloride gave the oxime (Va), m.p. 134-136° from water; this compound did not give a color with ferric chloride; C=O band at 1697. C=N band at 1570 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.88; H, 4.63; N, 11.50.

1,2-Benzisoxazole-3-pyruvic acid (VI).

(a) A solution of the ester (V) in ten volumes of concentrated sulfuric acid was kept 20 minutes on a steam bath and then 40 minutes at 60-70°. The cooled solution was added to crushed ice with vigorous stirring. The white precipitate was filtered and thoroughly washed with water. Recrystallization of the product from water-ethanol avoiding prolonged heating, afforded white needles melting at 145-147° (dec.) in 85% yield, which became yellow when dried. The substance gave a red color with ferric chloride, and with sodium hydroxide solution a yellow salt was formed (probably the disodium salt of the enol form) which is slightly soluble in water while with sodium carbonate a water soluble monosodium salt was obtained.

(b) To a solution of 0.39 g. of potassium in 20 ml. of absolute ethanol was added 1.16 g. of V. The suspension of the potassium salt was stirred and refluxed for 18 hours. The solid was filtered from the cold solution, dissolved in water and acidified from the aqueous solution. A solid, m.p. 138-140° separated, which after recrystallization, afforded the product (VI) in poorer yield than by method (a).

UV: λ max (log ϵ) 316 (4.18); IR, 1710 (carboxylic C=O), 1618 cm^{-1} (keto C=O).

Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{NO}_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.53; H, 3.09; N, 7.20.

1,2-Benzisoxazole-3-acetic acid (VII).

To a solution of 0.4 g. of VI in 20 ml. of 2 N sodium carbonate solution, 2 ml. of 3.5% hydrogen peroxide was added and the mixture was kept at 0° overnight and then one hour more at room temperature. By treatment with dilute hydrochloric acid a solid was obtained, which crystallized from ethanol in needles, m.p. 106-108° (dec.), yield 60%.

UV: λ max (log ϵ) 239 (3.92) 272 (3.58) 278.5 (3.59) (9). IR: 2450 (carboxylic OH stretching), 1700 cm^{-1} (carboxylic C=O).

Anal. Calcd. for $\text{C}_9\text{H}_7\text{NO}_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 61.15; H, 4.13; N, 8.10.

The odor of the product was peculiar and similar to that of 3-methyl-1,2-benzisoxazole (IV) into which it slowly changed at room temperature, even when kept dry. It was converted very quickly into IV by heating.

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- (8) UV spectrum of (I), λ max (log ϵ) 237.5 (3.86) 244 (3.67) 283 (3.40).
- (9) UV spectrum of (IV), λ max (log ϵ) 237 (3.95) 271 (3.41) 277 (3.68).

Received September 21, 1965

Camerino, Italy