On 1,2-Benzisoxazole-3-acetic Acid and 3-Methyl-1,2-benzisoxazole: a Restatement.

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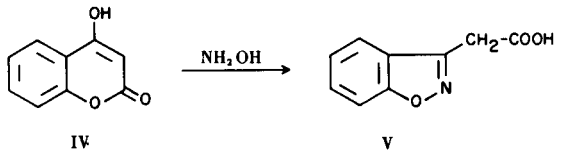
A compound formulated in the literature as 4-hydroxylaminocoumarin is now recognized to be the isomeric 1,2-benzisoxazole-3-acetic acid. Therefore, a preceding paper by the authors describing this acid is proved incorrect due to inexact data in the previous literature on the preparation of 3-methyl-1,2-benzisoxazole.

In 1965 we presented a note entitled "On 1,2-benzisoxazole-3-acetic Acid" (1), in which we proposed a synthesis of the title compound, not yet cited by that time.

Unfortunately we were then misled by two distinct errors in the previous literature which brought us to an erroneous conclusion.

First, the starting material used in our synthesis, a liquid described as 3-methyl-1,2-benzisoxazole (I) (2), proved on further examination to be a rough mixture in which the isomeric 2-methyl-benzoxazole (II), apparently formed by a Beckmann type rearrangement (3), was often predominant (4). Under the reaction conditions used in our former paper (1), the only reactive compound in the mixture was found to be II, which underwent the Claisen condensation to give the already known series of products leading to benzoxazole-2-acetic acid (III) (5). For these reasons all the compounds described in our former paper as benzisoxazole derivatives are to be considered identical to the corresponding members of the isomeric benzoxazole series: a comparison of the physical constants confirms this restatement.

Secondly, a compound described by Mustapha *et al.* (6) as 4-hydroxylaminocoumarin was found to be 1,2-benzisoxazole-3-acetic acid (V), apparently formed by a rearrangement of the coumarin nucleus during the reaction of 4-hydroxycoumarin (IV) with hydroxylamine.



IV V

This conclusion follows from three distinct groups of data collected by us for Mustapha's compound:

1. Formation of Functional Derivatives.

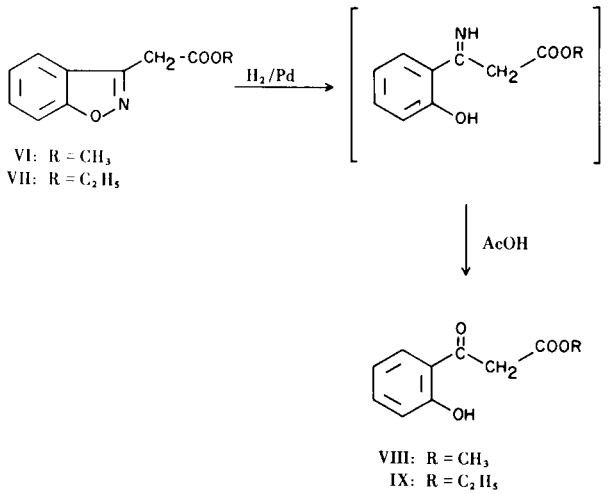
Mustapha's compound forms all the functional derivatives that can be obtained from a carboxylic acid (Table 1), including those impossible to obtain from an oxime or a hydroxylamine (*e.g.* the amide, the hydrazide and the benzimidazole). Some of these can also be changed back to the starting material: the hydrazide can be dehydrazinated to the ester (7), and this in turn can be hydrolyzed to the free acid.

2. Ultraviolet Spectra.

The UV spectra of Mustapha's compound and of pure 3-methyl-1,2-benzisoxazole (I) are substantially identical and quite different from those of 4-hydroxycoumarin (IV) (8) and of the benzoxazole isomers (II, III) (Table 2).

3. Hydrogenolysis.

The esters VI and VII of Mustapha's compound absorbed one mole of hydrogen on hydrogenation with palladium at room temperature and atmospheric pressure. The resulting products easily decompose to ammonia and to nitrogen-free compounds still containing the ester linkage, shown by analytical data and n.m.r. spectra to be, respectively, the methyl (VIII) and ethyl (IX) esters of the already known *o*-hydroxybenzoylacetic acid (9). Their formation is not explained by the formulation of Mustapha's compound as 4-hydroxylaminocoumarin, but can be interpreted on the basis of the carboxylic acid structure (V) with hydrogenolytic ring cleavage of the N-O bond, followed by hydrolysis of the ketimine function, according to the following scheme.



VI: R = CH_3
VII: R = C_2H_5

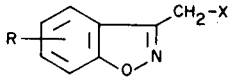
VIII: R = CH_3
IX: R = C_2H_5

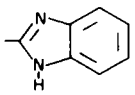
We must note here that the discussion of the IR spectrum of the compound as presented by Mustapha is not imperative, and that all the data used therein can as well be referred to structure V. In addition, n.m.r. spectra taken in concentrated hexadeuterioacetone solution gave shift values for the acidic proton that were in agreement with what is known for carboxylic acids in such a solvent at comparable concentration (10). The previously reported (1) anomalous shift value was due to low concentration (owing to low solubility) of the deuteriochloroform solution (11,12).

It is also interesting to note that the assignment of structure V to the compound explains much better its chemical properties (acidity, easy esterification and decarboxylation) and is also in agreement with the formulas

TABLE I

Physical Constants of 1,2-Benzisoxazole-3-acetic Acids and Their Functional Derivatives (a)



R \ X	-COOH	$-COOCH_3$	$-COOC_2H_5$	$-CONH_2$	$-CO-NH-NH_2$	
-H	V (6) m. 125°	VI (1) eb. 85° 0.05 mm Hg	VII eb. 120-122° 1 mm Hg	m. 150-151° dec.	m. 185-187° dec.	m. 174-176° dec.
$-5CH_3$	X (1, 13) m. 154-155°	eb. 124-125° 0.7 mm Hg	eb. 110-112° 0.1 mm Hg	m. 147-149° dec.	m. 165-166° dec.	m. 182-184° dec.
$-6CH_3$	XI (1,13) m. 172-173°	eb. 130-132° 0.8 mm Hg m. 48-49°	eb. 116-118° 0.1 mm Hg	m. 178-180° dec.	m. 199-201° dec.	m. 192-195° dec.

(a) IR and UV spectra for all the compounds included in this table are in agreement with the proposed structures.

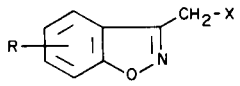
TABLE II

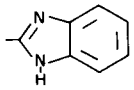
Comparison of U. V. Spectra of Benzisoxazole and Benzooxazole Derivatives: λ max in mμ (log ε).

A) 1,2-Benzisoxazole derivatives		B) Benzoxazole derivatives	
3-methyl (I)	3-acetic acid (V)	2-methyl (II)	2-acetic acid (III)
236.5 (3.92)	237.5 (3.78)	232.0 (3.89)	234.0 (3.92)
243.0 (3.86)	244.0 (3.67)	262.5 (3.40)	265.0 (3.41)
282.0 (3.49)	283.0 (3.40)	270.0 (3.59)	272.0 (3.58)
292.0 (shoulder)	293.0 (shoulder)	276.5 (3.64)	279.0 (3.59)

TABLE III

Elementary Analysis of New Derivatives of 1,2-Benzisoxazole-3-acetic Acids.



R	X	Formula		C%	H%	N%
5-CH_3	-$COOCH_3$	$C_{11}H_{11}NO_3$	Calcd.	64.38	5.40	6.83
			Found	64.51	5.50	6.70
6-CH_3	-$COOCH_3$	$C_{11}H_{11}NO_3$	Calcd.	64.38	5.40	6.83
			Found	63.98	5.40	6.52
H	-$COOC_2H_5$	$C_{11}H_{11}NO_3$	Calcd.	64.38	5.40	6.83
			Found	64.49	5.63	7.06
5-CH_3	-$COOC_2H_5$	$C_{12}H_{13}NO_3$	Calcd.	65.74	5.98	6.39
			Found	65.36	6.34	6.01
6-CH_3	-$COOC_2H_5$	$C_{12}H_{13}NO_3$	Calcd.	65.74	5.98	6.39
			Found	66.03	6.04	6.25
H	-$CONH_2$	$C_9H_8N_2O_2$	Calcd.	61.36	4.58	15.90
			Found	61.34	4.58	15.79
5-CH_3	-$CONH_2$	$C_{10}H_{10}N_2O_2$	Calcd.	63.15	5.30	14.73
			Found	63.41	5.48	14.42
6-CH_3	-$CONH_2$	$C_{10}H_{10}N_2O_2$	Calcd.	63.15	5.30	14.73
			Found	63.01	5.57	15.01
H	-$CONHNH_2$	$C_9H_9N_3O_2$	Calcd.	56.54	4.75	21.98
			Found	56.34	4.60	21.96
5-CH_3	-$CONHNH_2$	$C_{10}H_{11}N_3O_2$	Calcd.	58.53	5.40	20.48
			Found	58.22	5.38	20.20
6-CH_3	-$CONHNH_2$	$C_{10}H_{11}N_3O_2$	Calcd.	58.53	5.40	20.48
			Found	58.45	5.35	20.21
H		$C_{15}H_{11}N_3O$	Calcd.	72.27	4.45	16.86
			Found	71.98	4.50	16.69
5-CH_3		$C_{16}H_{13}N_3O$	Calcd.	72.98	4.98	15.96
			Found	72.60	5.10	15.61
6-CH_3		$C_{16}H_{13}N_3O$	Calcd.	72.98	4.98	15.96
			Found	72.90	5.04	15.91

that Posner and Hess (13) had tentatively assigned to their by-products (X and XI) of the reaction of 6- and 7-methylcoumarins and hydroxylamine, which in our hands gave derivatives analogous to those of V (See Table I). These formulas must therefore be considered correct and in our former paper (1) the title "Preparation of 5-Methyl- and 6-Methyl-1,2-benzisoxazole-3-acetic Acids" should be put in place of "Preparation of 6-Methyl-4-hydroxyimino-2-oxochroman and 7-Methyl-4-hydroxyimino-2-oxochroman", preceding the synthesis of the mentioned by-products by a different route. Also the derivatives of Mustapha's compound described therein as 4-hydroxyimino-2-oxochromane ethers are, instead, esters of V.

We have submitted 1,2-benzisoxazole-3-acetic acid (V) to the auxine test by Went's method and found it to possess 1/20 of the activity of indole-3-acetic acid, which is a stronger activity than that of benzoxazole-2-acetic acid (1). The 4- and 5-methyl homologues of V show lower activities. The auxine activity of V is noteworthy in view of its easy preparation and higher stability in comparison with indole-3-acetic acid.

EXPERIMENTAL

Unless otherwise indicated, melting points were determined in capillary tubes on a Büchi apparatus and are uncorrected. The IR spectra were recorded with an Unicam SP 200 spectrometer, in nujol or as pure liquid in the case of oils; the UV spectra were taken in ethanol with an Unicam SP 800 spectrometer; gas chromatographic separations were effected with an Aerograph P 705 apparatus; n.m.r. measurements were achieved with a Varian A 60 spectrometer, using TMS as an internal standard.

Separation of the Mixtures of 3-Methyl-1,2-benzisoxazole (I) and 2-Methylbenzoxazole (II).

Fractional distillation of these mixtures left the ratio of the two components practically unchanged. Their analytical separation can be achieved by thin layer chromatography (on silica gel Merck GF 254, eluting with ethyl acetate-cyclohexane mixture, 1:4) or by gas chromatography (SE 30, column temperature 187° using nitrogen as carrier).

Preparative separation can be effected by gas chromatography, using a preparative column (6 m. length, 3/8" diameter) under the above conditions, or by column chromatography on silica gel, eluting with the above solvent mixture.

Cyclization of *o*-Hydroxyacetophenone Oxime Acetate.

a) Ten g. of the oxime acetate were stirred in an equimolar amount of 10% aqueous sodium hydroxide until the solid material completely changed to an oil (2b). The mixture was then ether-extracted and the oil obtained (6.8 g.) was subjected to the above separation procedure resulting in mainly (90%) II with only 10% of I.

Similar results were obtained when cyclization was effected in boiling sodium carbonate solution.

b) The melt of the oxime acetate was kept at 160° for some hours (2a) giving a low yield of a liquid mixture containing variable proportions of I (50-80%) and II (20-50%).

The pure I and II obtained by either of the above reaction conditions were found to be identical with authentic specimens obtained by different routes, *i.e.*, acetylation of *o*-aminophenol (or commercial source) for II, and decarboxylation of V (1) for I.

1,2-Benzisoxazole-3-acetic Acids and Their Functional Derivatives.

Unsubstituted 1,2-benzisoxazole-3-acetic acid (V) was prepared from 4-hydroxycoumarin and hydroxylamine using the conditions given by Mustapha (6) or better by following the procedure in our former paper (1). Its melting point (Table 1) was given by Mustapha, and its UV spectrum is reported in Table 2: n.m.r. shift values for the carboxylic proton are δ, 8.5 (in 0.2 *M* deuteriochloroform solution), and 6.5 (broad) and 8.2 p.p.m. (respectively, in 0.4 *M* and 0.8 *M* hexadeuterioacetone solution) (10, 11, 12). Its decarboxylation was already described (1) under the heading "Conversion of 4-Hydroxyimino-2-oxo-chroman into 3-Methyl-1,2-benzisoxazole".

The 5- and 6-methyl derivatives were prepared according to Posner and Hess (13) or by following our former paper (1); melting points are mentioned in Table 1 (X and XI).

Several functional derivatives of the three mentioned 1,2-benzisoxazole-3-acetic acids were obtained by conventional methods. Their physical constants are collected in Table 1, and their analytical data in Table 3.

Hydrogenolysis of 1,2-Benzisoxazole-3-acetic Acid Methyl Ester (VI) and Ethyl Ester (VII).

An ethanolic solution of the ester (2.1 g.) was hydrogenated at room temperature and atmospheric pressure using 0.5 g. of 10% palladium on charcoal. A rather slow hydrogen absorption occurred, and after 5-6 hours about 1.3 moles of hydrogen had been consumed.

Filtration and evaporation left a yellow oil with an ammonia-like odor, which could not be purified as such by column chromatography due to its easy hydrolysis to ammonia. Treatment with diluted acetic acid overnight at room temperature followed by further dilution with water gave a colorless oil which was ether-extracted and washed with sodium bicarbonate solution.

The oil could not be distilled because formation of 4-hydroxycoumarin occurs on heating. However it could be purified by column chromatography on silica gel eluting with ethyl acetate-cyclohexane mixture (3:7), giving 0.7 g. of a pure fraction consisting of the ester of *o*-hydroxybenzoylacetic acid. The pure methyl ester (VIII) was easily crystallized from *n*-hexane, m.p. 48-50°. IR, ν max, 1640 (C=O ketone), 1735 cm^{-1} (C=O ester); n.m.r.: (deuteriochloroform) δ, 3.65 (singlet, CH_3-O), 3.86 (singlet, CO-CH_2-COO), 6.6 - 7.8 (4 aromatic protons), 11.6 p.p.m. (singlet, phenolic OH).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.98; H, 5.29.

The pure ethyl ester (IX) was a liquid whose boiling point could not be determined because of the fore mentioned decomposition. IR, ν max, 1638 (C=O ketone), 1730 cm^{-1} (C=O ester); n.m.r.: (deuteriochloroform) δ, 1.2 (triplet, CH_3-C), 3.99 (singlet, CO-CH_2-COO), 4.22 (quadruplet, C-CH_2-O), 6.7 - 7.8 (4 aromatic protons), 11.8 p.p.m. (singlet, phenolic OH).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.22; H, 6.05.

Both the methyl and the ethyl esters dissolved in 2 *N* sodium hydroxide and the solutions, when acidified with 2 *N* hydrochloric acid, gave a precipitate of 4-hydroxycoumarin. The ethanolic solution of either gave a violet color with ferric chloride.

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Received October 25, 1968 Camerino, Italy