On the Reaction between Coumarins and Hydroxylamine

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The Posner reaction between coumarin and hydroxylamine was studied and extended to several substituted coumarins. Isolation of some significant reaction intermediates permitted rationalization of a possible reaction pathway.

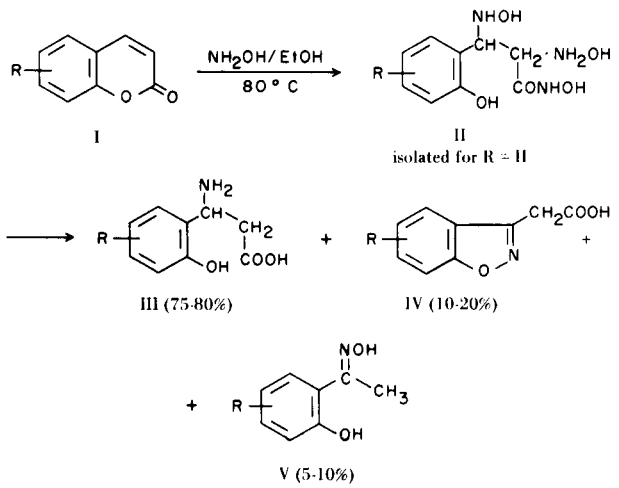
Introduction.

The synthesis of several substituted 1,2-benzisoxazole-3-acetic acids as analogues of heteroauxin was previously reported (1) as having been carried out by reaction between 4-hydroxycoumarins and hydroxylamine.

Because of difficulties encountered in the synthesis of some of the starting materials, the Posner reaction between coumarins and hydroxylamine (2,3) was considered as a possible alternative route to 1,2-benzisoxazole-3-acetic acids. Although this reaction leads mainly to β-amino-β-(2-hydroxyphenyl)propionic acids, in the case of 6-methyl- and 7-methylcoumarin, Posner isolated two by-products to which he tentatively assigned the structure of 5-methyl- and 6-methyl-1,2-benzisoxazole-3-acetic acids (3). These structures were later proved to be correct (4).

This paper reports the results obtained using the Posner reaction under different conditions and extended to several substituted coumarins. On the basis of these results a possible reaction pathway is proposed.

CHART I



Results.

The Posner reaction is represented in Chart I. The substituted 1,2-benzisoxazole-3-acetic acids (IV) were obtained as by-products from most of the coumarins examined (I; R = H, 8-CH_3, 6-NO_2, 6-$NHCOCH_3$, 6-I, 8-OCH_3, 8-NO_2). When the coumarin substituents were 6-Cl, 6-Br, and 8-OH, and the reaction was carried out under the conditions described by Posner, compounds IV were not isolated; however the substituted 2-hydroxyacetophenone oximes (V) were formed in every case in 5-10% yields.

When the reaction was performed at room temperature a 1:3 coumarin-hydroxylamine "adduct" (II) was isolated which usually was so unstable that it could not be purified except in the case of the unsubstituted coumarin. This adduct (II; R = H), already isolated by Posner, was purified and properly characterized.

Prolonged boiling in ethanol of all of the 1:3 adducts gave the same products as obtained by the direct reaction. However an increase in the yields of compounds IV was observed, thus permitting the isolation of 5-bromo-1,2-benzisoxazole-3-acetic acid (IV; R = 5-Br) which could not be accomplished with the direct procedure.

Furthermore, treatment of the 1:3 adducts of coumarin and 6-nitrocoumarin (II; R = H, 5-NO_2) with water gave 1:2 adducts to which was assigned structure VI on the basis of analytical, chemical and spectroscopic evidence (see Chart II). The yield of the 1,2-benzisoxazole-3-acetic

CHART II

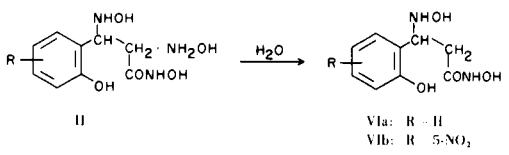
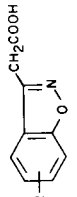


TABLE I

Ring Substituted 1,2-Benzisoxazole-3-acetic Acids (a)



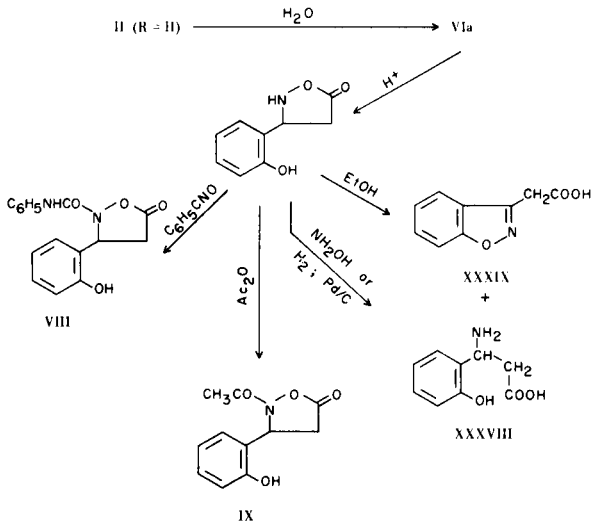
Compound No.	R	Recryst. Solvent	M.p. °C (dec.)	% Yield (b)	Molecular Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
XVI	7-OCH_3	H_2O	176-178	12	$C_{10}H_9NO_4$	57.97	4.38	6.76	57.67	4.45	6.90
XVII	5-NO_2	EtOH-H_2O	198-201	17	$C_9H_6N_2O_5$	48.66	2.72	12.61	48.83	3.00	12.88
XVIII	7-NO_2	H_2O	180-182	5	$C_9H_6N_2O_5$	48.66	2.72	12.61	48.85	2.55	12.80
XIX	5-$NHCOCH_3$	H_2O	202-206	16	$C_{11}H_{10}N_2O_4$	56.41	4.30	11.96	56.20	4.57	11.78

(a) Ir and uv spectra of the compounds reported in the table are in agreement with the proposed structures. (b) Based on pure compound.

acids (IV; R = H, $5NO_2$) from VI was further increased by its prolonged boiling in ethanol.

Careful treatment of VIa with dilute acetic acid gave a product, corresponding to a 1:1 ratio of coumarin and hydroxylamine (VII), for which the structure shown in Chart III is proposed. The ir spectrum of VII shows a typical carbonyl band (ν = 1780 cm^{-1}) and the nmr spectrum is similar to that reported for some isoxazolidines (5,6). Furthermore, hydrogenation of VII with palladium on charcoal at room temperature and atmospheric pressure, readily gave β-amino-β-(2-hydroxyphenyl)propionic acid (XXXVIII). When VII was refluxed in ethanol for several hours, equivalent amounts of XXXVIII and 1,2-benzisoxazole-3-acetic acid (XXXIX) were obtained while use of an excess of hydroxylamine gave mainly the amino-acid XXXVIII with just a small amount of XXXIX. Derivatives VIII and IX afforded further evidence on the structure of VII.

CHART III

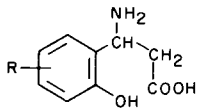


Both of the 5-nitro substituted adducts (II and VIb; R = 5-NO_2) yielded compound X (see Chart IV) on treatment with dilute hydrochloric acid. The cyclization took place differently from that of VII giving a benzisoxazoline ring possibly due to the mesomeric effect of the *p*-nitro group on nucleophilic substitution. Compounds of this kind were unknown until the report of Seidl and coworkers (7), which claimed that the benzene ring stabilizes the otherwise unstable Δ^4-isoxazoline nucleus, making possible the isolation of the products.

As with VII, compound X was quantitatively reduced to β-amino-β-(2-hydroxy-5-nitrophenyl)propionic acid (XXVI) by hydrogenation with palladium on charcoal at room temperature and atmospheric pressure, while boiling in ethanol for several hours gave XXVI and 5-nitro-1,2-benz-

TABLE II

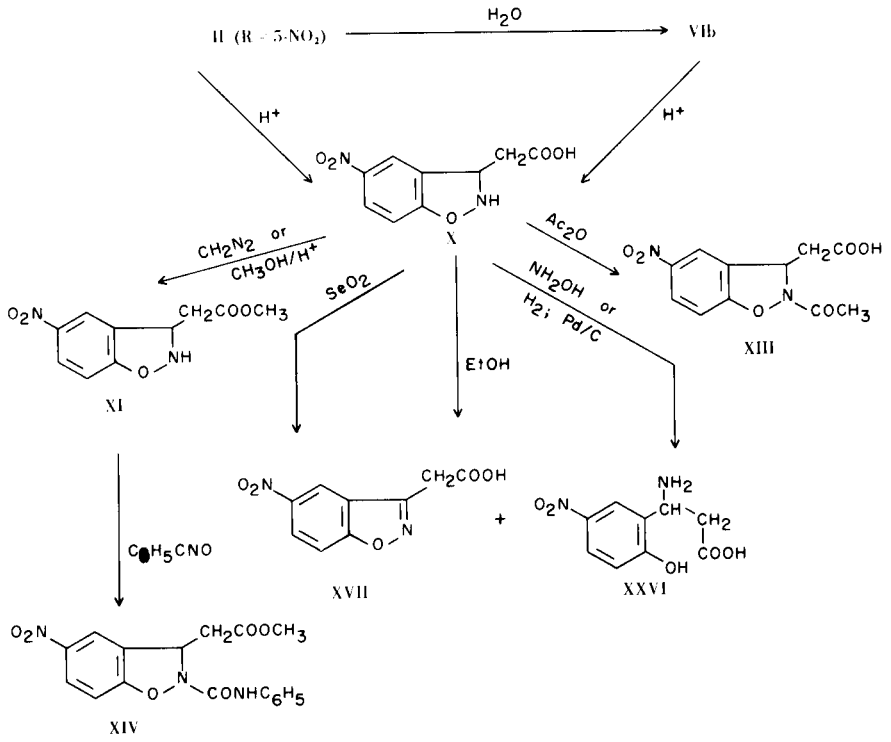
Ring Substituted β-Amino-β-2-hydroxyphenyl-propionic Acids (a)



Compound No.	R	Salt	Recryst. Solvent	M.p. °C (dec.)	% Yield (b)	Molecular Formula	Calcd., % C	H	N	Found, % C	H	N
XX	3-OCH_3		H_2O	217-219	50	$C_{10}H_{13}NO_4$	56.86	6.20	6.63	56.66	6.40	6.48
XXI	3-OCH_3	HCl	EtOH-Et_2O	196-198		$C_{10}H_{14}ClNO_4$	48.49	5.70	5.65	48.40	5.97	5.79
XXII	3-OH		(c)	>300	31	$C_9H_{11}NO_4$	54.82	5.62	7.10	54.81	5.80	6.98
XXIII	3-OH	HCl	EtOH-Et_2O	192-194		$C_9H_{12}ClNO_4$	46.26	5.18	5.99	46.35	4.90	5.88
XXIV	3-NO_2		H_2O	230-232	75	$C_9H_{10}N_2O_5$	47.79	4.46	12.39	48.00	4.53	12.50
XXV	3-NO_2	HCl	EtOH-Et_2O	211-214		$C_9H_{11}ClN_2O_5$	41.15	4.22	10.67	41.39	4.48	10.60
XXVI	5-NO_2		H_2O	228-230	65	$C_9H_{10}N_2O_5$	47.79	4.46	12.39	48.03	4.66	12.10
XXVII	5-NO_2	HCl	H_2O	244-246		$C_9H_{11}ClN_2O_5$	41.15	4.22	10.67	40.90	4.24	10.84
XXVIII	5-$NHCOCH_3$		H_2O	186-188	55	$C_{11}H_{14}N_2O_4$	55.45	5.92	11.76	55.12	6.17	11.63
XXIX (d)	5-$NHCOCH_3$	HCl	EtOH-Et_2O	154-156		$C_{11}H_{15}ClN_2O_4$	48.09	5.50	10.20	47.94	5.70	9.98
XXX	5-Cl		DMF	220-221	78	$C_9H_{10}ClNO_3$	50.13	4.67	6.50	49.98	4.47	6.34
XXXI	5-Cl	HCl	EtOH-Et_2O	236-238		$C_9H_{11}Cl_2NO_3$	42.88	4.40	5.56	42.63	4.53	5.80
XXXII	5-Br		DMF	215-217	82	$C_9H_{10}BrNO_3$	41.56	3.87	5.38	41.71	4.01	5.10
XXXIII	5-Br	HCl	EtOH-Et_2O	222-224		$C_9H_{11}BrClNO_3$	36.45	3.74	4.72	36.70	4.00	4.80
XXXIV	5-I		DMF	210-211	35	$C_9H_{10}INO_3$	35.20	3.28	4.56	35.35	3.39	4.70
XXXV	5-I	HCl	EtOH-Et_2O	202-204		$C_9H_{11}ClINO_3$	31.46	3.23	4.08	31.53	3.48	4.10

(a) Ir and uv spectra of the compounds in the table are in agreement with the proposed structures. (b) Based on pure compound. (c) Not crystallized because of its insolubility. (d) Hygroscopic.

CHART IV



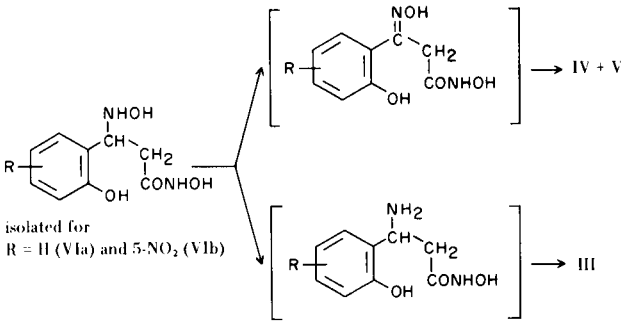
isoxazole-3-acetic acid (XVII) in a 1:1 ratio. Similarly when X was boiled in ethanol with an excess of hydroxylamine, it was almost completely reduced to XXVI and only traces of XVII were found. Compound X was quantitatively oxidized to XVII by selenium dioxide; the ready loss of two hydrogen atoms from X was confirmed by its mass spectrum which shows a very strong peak at P-2 in addition to the parent peak at 238 m/e.

Conclusions.

In accord with Posner (2,3), reduction of the intermediate adducts 1:3 or 1:2 by hydroxylamine leads to the corresponding β-aminoacid. However this does not explain the simultaneous formation of the 1,2-benzisoxazole-3-acetic acid which clearly requires oxidation of the same intermediate adducts. Nevertheless, on the basis of our findings, the course of the reaction can be rationalized by assuming a disproportionation reaction of the intermediate and a simultaneous reduction by hydroxylamine.

One can speculate whether the disproportionation reaction takes place on an intermediate like VI or like X; however since *o*-hydroxyacetophenone oximes (V) are always present as by-products, VI is preferred. In any event, hydrolysis of the intermediate hydroxamic acid occurs and IV and V are eventually obtained (see Chart V).

CHART V



When an excess of hydroxylamine is present (8) the reduction reaction is favored and 1,2-benzisoxazole-3-acetic acid will be obtained only in small quantities; with a smaller excess of hydroxylamine the contribution of the disproportionation reaction will be larger, as shown from the increasing yield in 1,2-benzisoxazole-3-acetic acid going from the 1:3 to the 1:2 adducts. When no hydroxylamine is present, the reaction follows the course of a simple disproportionation, giving the oxidized and the reduced products in an equimolecular amount.

As further evidence it can be pointed out that the same intermediate gives the 1,2-benzisoxazole-3-acetic acid under

oxidizing conditions (selenium dioxide) in nearly quantitative yield whereas, under reducing conditions, a quantitative yield of aminoacid is obtained.

Biological Activity.

Substituted 1,2-benzisoxazole-3-acetic acids were tested for auxin-like activity according to Went (9). They proved to be less active than the parent compound (1).

EXPERIMENTAL (10)

Reaction between Coumarins and Hydroxylamine.

The appropriate coumarin (11-16) (0.1 mole) was dissolved in a solution of free hydroxylamine obtained from sodium (0.3 mole) and hydroxylamine hydrochloride (0.3 mole) in ethanol (200 ml.). The precipitate which appeared after 6-8 hours refluxing was separated by filtration of the hot solution and washed with hot ethanol. The products obtained, the ring substituted β-amino-β-(2-hydroxyphenyl)propionic acids, are shown in Table II.

The filtrate was evaporated and the residue partitioned between ether and a saturated aqueous sodium bicarbonate solution. From the organic layer about 5-10% of the corresponding 2-hydroxyacetophenone oxime was obtained.

The alkaline solution, when acidified with dilute hydrochloric acid, gave the substituted 1,2-benzisoxazole-3-acetic acid. New compounds are reported in Table I; known compounds were identical to those synthesized by other methods (1).

No 1,2-benzisoxazole-3-acetic acid was obtained in the reaction with 6-chloro-, 6-bromo-, and 8-hydroxycoumarin.

The β-aminoacids (III; R = 3-OCH_3, 3-OH, 3-NO_2, 5-NO_2, 5-$NHCOCH_3$, 5-Cl, 5-Br, and 5-I) were characterized as their hydrochlorides; their nmr spectra are in agreement with the proposed structure showing the A_2X/ABX system of a β,β-disubstituted propionic acid. The spectrum of XXXIII is reported as an example. Signals (DMSO) at δ 2.90 (2H, AB part, αCH_2), 4.64 (1H, t-X part, βCH), 6.80-7.70 (3H, m, aromatic protons), 8.00-10.00 (5H, very broad, OH, NH_3^+, and COOH).

β-Amino-β-(2-hydroxy-5-nitrophenyl)propionic Acid, Methyl Ester (XXXVI).

A solution of XXVI in methanol was treated with anhydrous hydrogen chloride. After standing at room temperature for a few hours the solution was evaporated, treated with sodium bicarbonate and extracted with ethyl acetate. The yellow solid was crystallized from methanol, m.p. 151-152° dec.; ir cm^{-1} 1740 (CO), 3250 (NH_2); uv λ max (log ε) 235 (3.74), 390 mμ (3.79).

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 50.07; H, 5.07; N, 11.48.

β-Amino-β-(2-hydroxy-5-nitrophenyl)propionic Acid, Ethyl Ester (XXXVII).

The ethyl ester XXXVII was obtained as described above for the methyl ester and crystallized from ethanol, m.p. 164-166° dec.; ir cm^{-1} 1715 (CO), 3180 (NH_2); uv λ max (log ε) 233.5 (3.69), 388 mμ (3.83); nmr (DMSO) δ 1.06 (3H, t, CH_3), 2.85 (2H, d, αCH_2), 3.99 (2H, q, OCH_2), 4.46 (1H, t, βCH), 6.35 (1H, d, aromatic), 7.22 (3H, s, NH_2 and OH), 7.70-8.00 (2H, m, aromatic).

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 51.70; H, 5.78; N, 11.10.

β-Hydroxylamino-β-(2-hydroxyphenyl)propionhydroxamic Acid, Hydroxylamine Salt (II; R = H).

The above was prepared according to Posner (2) and purified by washing the crude material with ethyl acetate, before crystallization from absolute ethanol (the solution should be quickly cooled to avoid decomposition). It gave a purple color with ferric chloride and reduced the Fehling and Tollens reagents, m.p. 118° dec. [Posner (2) 123°; (3) 120-122°]; ir cm^{-1} 1650 (broad) (CO), 3500-2500 (broad) (NH, OH); uv λ max (log ε) 276 mμ (3.41).

Anal. Calcd. for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.17; N, 17.14. Found: C, 44.30; H, 6.00; N, 17.04.

The other adducts (II; R = 5-NO_2, 5-Br, 5-$NHCOCH_3$) were isolated in the same way but could not be purified to give an analytical sample; they were too hygroscopic and contaminated by sodium chloride.

When compounds II were refluxed for 4-5 hours in ethanol and the mixture worked up as previously described, the yields were: 14% for 1,2-benzisoxazole-3-acetic acid (1:0.25 ratio with the corresponding β-aminopropionic acid), 20% for 5-nitro-1,2-benzisoxazole-3-acetic acid (1:0.3), 25% for 5-bromo-1,2-benzisoxazole-3-acetic acid (1:0.6), and 35% for 5-acetamido-1,2-benzisoxazole-3-acetic acid (1:0.7).

β-Hydroxylamino-β-(2-hydroxyphenyl)propionhydroxamic Acid (VIa).

The 1:3 adduct (II; R = H) (0.5 g.) was treated with water (5 ml.); the material dissolved and after a few minutes a white solid precipitated. The precipitation was hastened by the addition of a small quantity of dilute acetic acid. The product was crystallized from absolute ethanol with the same precautions used for II. It gave a purple color with ferric chloride reduced the Fehling and Tollens reagents and was soluble in dilute alkali, m.p. 133-134° dec. [Posner (3) 110-112°; 120-135°]; ir cm^{-1} 1640 (CO), 3250 (broad) (NH, OH); uv λ max (log ε) 274 mμ (3.53); nmr (DMSO) δ 2.40 (2H, d, αCH_2), 4.45 (1H, t, βCH), 6.60-7.30 (4H, m, aromatic), 7.50-9.00 (5H, broad, OH and NH).

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.91; H, 5.95; N, 12.97.

Compound VIa (3.0 g.), refluxed for 35 hours in absolute ethanol (50 ml.), gave 1.2 g. of β-amino-β-(2-hydroxyphenyl)propionic acid (47%), 0.6 g. of 1,2-benzisoxazole-3-acetic acid (24%), 0.14 g. of 2-hydroxyacetophenone oxime (6%), and 0.1 g. of coumarin (5%). The ratio between reduced (XXXVIII) and oxidized products (XXXIX and V: R = H) was 1:0.65.

β-Hydroxylamino-β-(2-hydroxy-5-nitrophenyl)propionhydroxamic Acid (VIb).

The 1:3 adduct (II; R = 5-NO_2) (0.5 g.) was dissolved in water, and after a few minutes VIb began to precipitate. It was crystallized from *N,N*-dimethylformamide-water, m.p. 126-129° dec. It gave a purple color with ferric chloride and reduced the Fehling and Tollens reagents; it was soluble in sodium bicarbonate but the acidification of the solution provided only the cyclized compound X; the same transformation occurred by action of heat; ir cm^{-1} 1650 (CO), 3200-3080 (OH and NH); uv λ max (log ε) 230 (3.85), 320 mμ (3.87).

Anal. Calcd. for $C_9H_{11}N_3O_6$: C, 42.03; H, 4.31; N, 16.34. Found: C, 42.24; H, 4.51; N, 16.52.

Compound VIb (0.5 g.), boiled for 50 hours in absolute ethanol, gave 0.25 g. (57%) of XXVI and 0.15 g. (35%) of XVII, the ratio XXVI:XVII being 1:0.6.

3-(2-Hydroxyphenyl)isoxazolidine-5-one (VII).

Adduct VIa (2.5 g.) was slowly treated with dilute acetic acid (25 ml.) under stirring and cooling, and the mixture left for 4 hours at room temperature. The white solid obtained (1.3 g.) was crystallized from ethyl acetate-ligroine, m.p. 110-111° dec. Compound VII gave a light red color with ferric chloride, was insoluble in sodium bicarbonate and slowly decomposed with water and ethanol; ir cm^{-1} 1780 (CO), 3200-3000 (OH), 3240 (NH); uv λ max (log ε) 274 mμ (3.41); nmr (DMSO) δ 2.90 (2H, AB part, $4CH_2$), 5.00 (1H, q-X part, 3CH), 6.60-7.60 (4H, m, aromatic), 8.60 (1H, d, NH), 9.75 (1H, s, OH).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.33; H, 4.95; N, 8.01.

An ethanolic solution of VII (1.0 g.) was hydrogenated at room temperature and atmospheric pressure, using 0.2 g. of 10% palladium on charcoal, to give 0.9 g. of XXXVIII.

Compound VII, boiled for several hours in ethanol (10 ml.), gave equal amounts of XXXVIII and XXXIX.

When VII (0.7 g.) was boiled for several hours in a solution of hydroxylamine in ethanol (40 ml.) gave 0.4 g. of XXXVIII and 0.1 g. of XXXIX.

The product VII, kept at room temperature overnight with a slight excess of phenylisocyanate, gave an unstable solid which crystallized from ethyl acetate-ligroine, m.p. 159-160° dec.; ir cm^{-1} 1660 (CO), 1805 (CO), 3360, 3300 (NH and OH).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.26; H, 4.85; N, 9.40.

2-Acetyl-3-(2-hydroxyphenyl)isoxazolidine-5-one (IX).

When VII (1.0 g.) was dissolved at room temperature in acetic anhydride (4 ml.) a white solid precipitated in a few minutes. It was filtered, washed with anhydrous ether and crystallized from ethyl acetate-cyclohexane, m.p. 118-120°; it gave a purple color with ferric chloride; ir cm^{-1} 1625 (CO), 1820 (CO), 3260 (broad) (OH); uv λ max (log ε) 270 (3.36), 277 mμ (3.39); nmr (DMSO), δ 2.03 (3H, s, CH_3), 3.08 (2H, AB part, 4-CH_2), 5.87 (1H, X part, 3-CH), 7.00-7.81 (4H, m, aromatic), 10.16 (1H, s, OH).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.73; H, 5.11; N, 6.40.

5-Nitro-1,2-benzisoxazoline-3-acetic Acid (X).

Compound VIb was dissolved in sodium bicarbonate solution and the solution carefully acidified with dilute hydrochloric acid; the yellow solid obtained was crystallized from absolute ethanol, m.p. 178-179° dec. It dissolved in sodium bicarbonate solution and precipitated unaltered after acidification. The same compound was obtained by acidification of a water solution of II (R = 5-NO_2). Ir cm^{-1} 1705 (CO), 3100-2800 (OH), 3230 (NH); uv λ max (log ε) 232 (4.06), 309 mμ (3.87); nmr (DMSO) δ 2.88 (2H, d, αCH_2), 5.28 (1H, t, βCH), 7.28 (1H, d, aromatic), 8.20-8.70 (2H, m, aromatic), 9.13 (2H, broad, NH and OH).

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.41; H, 3.75; N, 12.70.

An ethanolic solution of X (1.0 g.) was hydrogenated at room temperature and atmospheric pressure, using 0.2 g. of 10% palladium on charcoal. When one mole of hydrogen was absorbed, the reaction was terminated and the mixture worked up to give 0.7 g. of XXVI.

Compound X, suspended in concentrated hydrochloric acid and stirred for a few hours at room temperature, gave the hydrochloride (XV) as a white solid that was crystallized from methanol-ether, m.p. 156°; ir cm^{-1} 1725 (CO), 3100-2500 (NH and OH); uv λ max (log ε) 230 (3.93), 318 mμ (3.93); nmr (deuteriomethanol) δ 3.10 (2H, AB part, αCH_2), 5.55 (1H, t-X part, βCH), 7.18 (1H, dd, aromatic), 8.10-8.30 (2H, m, aromatic).

Anal. Calcd. for $C_9H_9ClN_2O_5$: C, 41.47; H, 3.48; N, 10.75. Found: C, 41.64; H, 3.64; N, 10.81.

Compound X, boiled for 60 hours in absolute ethanol, gave equimolecular amounts of XXVI and XVII.

The acid X (0.5 g.) was boiled for 7 hours with selenium dioxide (0.26 g.) in dioxane (30 ml.) to give, after elimination of selenium and evaporation of the solvent, a residue that was partitioned between ether and a saturated sodium bicarbonate solution. The organic layer gave 0.05 g. of 5-nitro-2-hydroxyacetophenone oxime and the alkaline solution, acidified with dilute hydrochloric acid, gave 0.3 g. of XVII.

Compound X (0.5 g.) was boiled for 6 hours with a solution of hydroxylamine in ethanol; after evaporation of the solvent the residue, worked up as reported above, yielded 0.4 g. of XXVI and traces of XVII.

5-Nitro-1,2-benzisoxazoline-3-acetic Acid, Methyl Ester (XI).

The above was obtained as a yellow solid by treating X with diazomethane or with methanol and anhydrous hydrogen chloride. It crystallized from methanol, m.p. 125-126° dec.; ir cm^{-1} 1715 (CO), 3200 (NH); uv λ max (log ε) 231 (3.93), 320 mμ (3.99); nmr (deuteriochloroform) δ 2.85 (2H, AB part, αCH_2), 3.78 (3H, s, OCH_3), 5.20 (1H, X part, βCH), 6.90 (1H, dd, aromatic), 8.10-8.30 (2H, m, aromatic).

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.61; H, 3.98; N, 11.54.

Compound XI (0.35 g.) was treated with an excess of phenylisocyanate, and the product slowly dissolved. After a few hours at room temperature carbon tetrachloride was added and the yellow solid obtained (XIV) was crystallized from methylene chloride-ligroine, m.p. 133-134°; ir cm^{-1} 1695 (CO), 1735 (CO), 3340 (NH); uv λ max (log ε) 236 (4.33), 308 mμ (4.00); nmr (deuteriochloroform) δ 3.00 (2H, AB part, αCH_2), 3.80 (3H, s, OCH_3), 6.10 (1H, t-X part, βCH), 7.00-8.25 (8H, m, aromatic).

Anal. Calcd. for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76. Found: C, 57.07; H, 4.25; N, 11.53.

5-Nitro-1,2-benzisoxazoline-3-acetic Acid, Ethyl Ester (XII).

Compound XII was obtained by treatment of X with ethanol and anhydrous hydrogen chloride; it crystallized from ethyl acetate, m.p. 75-76°; ir cm^{-1} 1720 (CO), 3250 (NH); uv λ max (log ε) 232 (3.86), 318.5 mμ (3.92).

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.58; H, 5.00; N, 11.20.

2-Acetyl-5-nitro-1,2-benzisoxazoline-3-acetic Acid (XIII).

The product X (0.5 g.) was heated in acetic anhydride (4 ml.) until dissolution. After a few hours at room temperature, the acetic anhydride was evaporated and the residue crystallized from water; the product was soluble in sodium bicarbonate solution from which it could be precipitated by acidification, m.p. 189-190°; ir cm^{-1} 1625 (CO), 1720 (CO), 3100-2500 (OH); uv λ max (log ε) 233.5 (4.18), 302 mμ (3.92); nmr (DMSO) δ 2.23 (3H, s, CH_3), 3.03 (2H, AB-part, αCH_2), 6.10 (1H, t-X part, βCH), 7.56 (1H, d, aromatic), 8.40-8.79 (2H, m, aromatic).

Anal. Calcd. for $C_{11}H_{10}N_2O_6$: C, 49.63; H, 3.79; N, 10.52. Found: C, 49.40; H, 4.02; N, 10.60.

REFERENCES

(1) M. Giannella, F. Gualtieri and C. Melchiorre, *Phytochemistry*, **10** (3), 539-544 (1970).

(2) T. Posner, *Ber.*, 42, 2523 (1909).

(3) T. Posner and R. Hess, *ibid.*, 46, 3816 (1913).

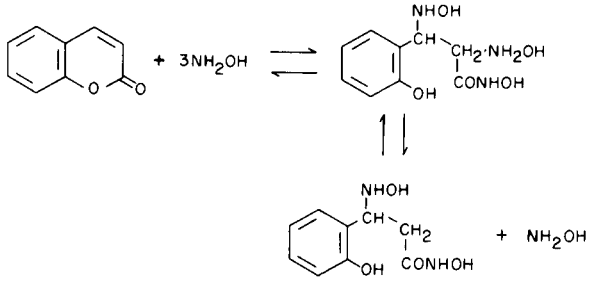
(4) G. Casini, F. Gualtieri and M. L. Stein, *J. Heterocyclic Chem.*, 6, 279 (1969).

(5) R. Scarpati, D. Sica and C. Santacroce, *Gazz. Chim. Ital.*, 96, 375 (1966).

(6) R. Huisgen, R. Groshey, H. Seidl and H. Hanck, *Chem. Ber.*, 101, 2559 (1968).

(7) H. Seidl, R. Huisgen and R. Knorr, *ibid.*, 102, 904 (1969).

(8) The excess of free hydroxylamine is due to the following equilibrium that exists in solution and has been verified for R = H:



In fact, coumarin was present in the solution of 1:3 and 1:2 adducts previously purified, as evidenced by thin layer chromatography. Furthermore, by treating the same compounds with strong acid, coumarin was obtained in quantitative yields.

(9) F. W. Went, *Amer. Sci.*, 31, 189 (1943).

(10) 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; the uv spectra were taken in ethanol with an UNICAM SP-800 spectrometer. The proton magnetic resonance spectra were measured on a JEOL JNH-MH-60 spectrometer, using tetramethylsilane as internal standard. In reporting nmr data the following abbreviations are used: s = singlet, d = doublet, q = quartet and m = multiplet. The authors wish to thank Dr. Giuseppa Valentini for the microanalyses.

(11) A. Clayton, *J. Chem. Soc.*, 97, 2102 (1910).

(12) L. Gattermann, *Ber.*, 27, 1927 (1894).

(13) B. B. Dey and H. Dalal, *J. Chem. Soc.*, 123, 3384 (1923).

(14) E. Cingolani, *Gazz. Chim. Ital.*, 84, 843 (1954).

(15) E. N. Marvell, B. Richardson, R. Anderson, J. L. Stephenson and T. Crandall, *J. Org. Chem.*, 30, 1032 (1965).

(16) W. Miller and F. Kinkelin, *Ber.*, 22, 1705 (1889).