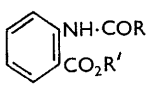
435. *The Synthesis of Some Cyclic Hydroxamic Acids from o-Aminocarboxylic Acids.*

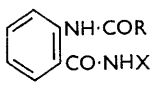
By D. Harrison and A. C. B. Smith.

Cyclic hydroxamic acids of the quinazoline and 1,3,5- and 1,3,8-triazanaphthalene series have been synthesized by two routes from esters of anthranilic acid, 2-aminonicotinic acid, and 3-aminopicolinic acid respectively. Typical compounds have been reduced by means of sodium dithionite to the cyclic amides. Two acyclic hydroxamic acids with *o*-amino-substituents have been converted into cyclic hydroxamic acids by nitrous acid.

The synthesis of substituted 4-quinazolones (4-hydroxyquinazolines) by the route (I) ⟶ (II) ⟶ (III), with or without isolation of the intermediate (II), has been extensively studied. Recent examples have been described for X = H,[1] and Heller's work [2] is concerned with compounds where X = NH_2. The present paper deals with the synthesis of cyclic hydroxamic acids (X = OH) by this route.



(I)



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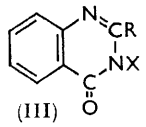


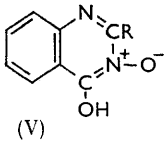
(III)

Treatment of esters of *o*-acylaminobenzoic acids with alkaline aqueous-methanolic hydroxylamine under the mild conditions used previously [3] afforded in all cases studied the cyclic hydroxamic acid (III; X = OH), not the acyclic product (II). The cyclic

[1] Stephen and Wadge, *J.*, 1956, 4420.
[2] Heller, Goring, Kloss, and Kohler, *J. prakt. Chem.*, 1925, **111**, 36.
[3] Harrison and Smith, *J.*, 1959, 3157.

hydroxamic acid structure was supported by (*a*) the dark-red colours given with aqueous-alcoholic ferric chloride, and (*b*) reduction of typical members to the corresponding 4-hydroxyquinazoline (IV) by means of sodium dithionite (hydrosulphite): an acyclic hydroxamic acid (II) would be expected to give a " permanganate " colour with ferric chloride. The reduction (*b*) probably involves the tautomeric *N*-oxide form (V) of the cyclic hydroxamic acid. Since we have no information at present as to which form predominates in the solid state, these compounds are here named as 3-oxides for brevity only. Similar routes from the esters of 2-aminonicotinic and 3-aminopicolinic acid lead to cyclic hydroxamic acids of the 1,3,8- and 1,3,5-triazanaphthalene series respectively, the structures of which were deduced in similar ways.


(IV)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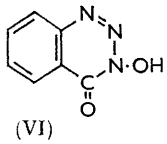
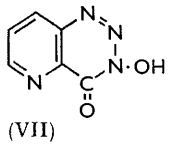

(VI)


(VII)

The reactions of the esters with hydroxylamine were normally allowed to proceed at room temperature for 7 days. However, in the case of methyl *o*-benzamidobenzoate (which is insoluble in aqueous methanol) dissolution occurred within a short time of mixing with the hydroxylamine solution, but after 8 hr. the reaction mixture was a paste; the solid is probably the sodium salt of the acyclic hydroxamic acid. A similar precipitate is formed even more rapidly in the case of ethyl 3-acetamidopicolinate.

An alternative, and in some cases more convenient, route to the cyclic hydroxamic acids is to heat the *o*-amino-hydroxamic acid with the corresponding acid anhydride $(R{\cdot}CO)_2O$, or with the acid itself when R = H. The action of acetic anhydride at room temperature on *o*-aminobenzhydroxamic acid yields a rather unstable solid, probably *o*-acetamidobenzhydroxamic acid.

The action of nitrous acid on *o*-amino-hydroxamic acids gives products which are believed to be cyclic hydroxamic acids of the triazine series, *i.e.*, (VI) and (VII) (cf. Heller and Siller [4]). These give the expected red colours with ferric chloride and the compound (VI) is degraded by concentrated sodium hydroxide solution (it is stable to dilute alkali) to *o*-azidobenzoic acid. A similar degradation has been observed with other 4-hydroxybenzo-1,2,3-triazines.[2] No cyclic hydroxamic acid was isolated after treatment of 2-aminonicotinhydroxamic acid with nitrous acid, presumably owing to the unreactive nature of the 2-amino-group.

Lott and Shaw [5] obtained small yields of cyclic hydroxamic acids by the action of perbenzoic acid on 2-hydroxy-pyridine or -quinoline. Attempts to perform the parallel conversion (IV) ⟶ (V) (R = Me) by using monoperphthalic acid in ether–chloroform or 100-vol. hydrogen peroxide in acetic acid were unsuccessful; some reaction occurred, possibly at the nitrogen atom remote from the hydroxyl group, but the products appear to be unstable. Under more drastic conditions, the only product isolated was *o*-nitrobenzamide, formed by breakdown of the pyrimidine ring. Unexpectedly, the 3-oxides (V; R = H or Me) also gave *o*-nitrobenzamide under these conditions, the peracid appearing to bring about loss of an oxygen atom from $N_{(3)}$ since this atom appears in an amino-group in the product.

In view of the antibacterial action of some cyclic hydroxamic acids, a few of the simpler compounds were subjected to biological screening by Messrs. Boots Pure Drug Co. Results were negative except that the cyclic hydroxamic acids (V; R = H, Me, and Ph) had slight schistasomacidal activity *in vitro*. The compounds were inactive *in vivo*. The compound (V; R = Me) has previously been tested.[6]

[4] Heller and Siller, *J. prakt. Chem.*, 1927, **116**, 9.
[5] Lott and Shaw, *J. Amer. Chem. Soc.*, 1949 ,**71**, 70.
[6] Newbold and Spring, *J.*, 1948, 1864.

Experimental

The hydroxylamine solution used was prepared as previously described.[3] Where a compound was prepared by two different routes, identities of products were confirmed by mixed m. p.s. Percentage yields and m. p. of cyclic hydroxamic acids are given in the Table.

Ethyl 3-Acetamidopicolinate.—Ethyl 3-aminopicolinate (1·1 g.) was heated with acetic anhydride (4 ml.) at 100° for 45 min. Evaporation gave the *ester* (0·72 g.) (needles from methanol), m. p. 140—142° (Found: C, 58·2; H, 5·6; N, 13·2. $C_{10}H_{12}N_2O_3$ requires C, 57·7; H, 5·8; N, 13·4%).

Cyclization of o-Aminohydroxamic Acids (Method A).—(a) *By acetic anhydride.* *o*-Aminobenzhydroxamic acid (1 g.) was heated under reflux with acetic anhydride (6 ml.) for 20 min., excess of water and charcoal were added, and boiling was continued for a further 5 min. From the filtrate, on cooling, the crude *4-hydroxy-2-methylquinazoline 3-oxide* (see Table) (0·78 g.)

3-Oxides	M. p.	Yield (%) by method A	Yield (%) by method B	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
4-Hydroxyquinazoline	242—244° [a]	94	24	59·7	3·8	17·1	$C_8H_6N_2O_2$	59·3	3·7	17·3
4-Hydroxy-2-methylquinazoline	214—215 [a] (lit.,[7] 214°)	67	76	61·3	4·5	15·8	$C_9H_8N_2O_2$	61·3	4·5	15·9
4-Hydroxy-2-phenylquinazoline	176—177 [a]	52	55	70·6	4·1	11·8	$C_{14}H_{10}N_2O_2$	70·6	4·2	11·8
4-Hydroxy-2-methyl-1,3,5-triazanaphthalene	254—256 [b]	25	45	54·4	3·6	23·8	$C_8H_7N_3O_2$	54·2	4·0	23·7
4-Hydroxy-2-methyl-1,3,8-triazanaphthalene	245—247 [b]	50	36	53·9	3·9	23·2	$C_8H_7N_3O_2$	54·2	4·0	23·7
4-Hydroxybenzo-1,2,3-triazine	180—181 [a] (decomp.)	86		52·2	3·2	25·6	$C_7H_5N_3O_2$	51·5	3·1	25·7
4-Hydroxy-1,2,3,5-tetra-azanaphthalene	195 [a] (explodes)	32		43·8	2·7	33·9	$C_6H_4N_4O_2$	43·9	2·5	34·1

[a] From ethanol. [b] From water.

separated. 2-Aminonicotinhydroxamic acid was converted similarly into a cyclic product, but 3-aminopicolinhydroxamic acid afforded a crude product which was a mixture. By gentle warming with a little water the latter was separated into a less-soluble fraction, m. p. 216—218° (probably 3-acetamidopicolinic acid, but not further investigated), and the required cyclic hydroxamic acid, which was difficult to purify.

When *o*-aminobenzhydroxamic acid (2·17 g.) was stirred at room temperature with acetic anhydride (4·5 ml.), heat was evolved and a pasty solid formed. After cooling for 30 min., ether was added, and the solid collected, washed with ether, and dried at room temperature *in vacuo*. The product was too unstable for purification, but is probably *o-acetamidobenzhydroxamic acid* (2·57 g., 93%), m. p. 127—130° (incomplete) (Found: C, 56·3; H, 5·3; N, 13·7. $C_9H_{10}N_2O_3$ requires C, 55·7; H, 5·2; N, 14·4%); it gave an intense "permanganate" colour with aqueous ferric chloride (all the *cyclic* hydroxamic acids prepared gave red colours with this reagent) and was converted into 4-hydroxy-2-methylquinazoline 3-oxide by (*a*) boiling it with water for 10 min., or (*b*) dissolving it in cold dilute hydrochloric acid and neutralizing after 4 hr.

(b) *By formic acid.* *o*-Aminobenzhydroxamic acid (1·47 g.) and 98% formic acid (3 ml.) were heated under reflux for 15 min. Addition of water (10 ml.), further boiling, and cooling gave crude 4-hydroxyquinazoline 3-oxide (1·44 g.).

(c) *By benzoic anhydride.* *o*-Aminobenzhydroxamic acid (0·60 g.) and benzoic anhydride (1·30 g.) were heated together at 130—140° for 3 hr. The residue was extracted with ether, and the insoluble material crystallized from ethanol to give *4-hydroxy-2-phenylquinazoline 3-oxide* (0·49 g.).

Formation of Cyclic Hydroxamic Acids from o-Formamido-, o-Acetamido-, and o-Benzamidocarboxylic Esters (Method B).—Methyl *o*-acetamidobenzoate (5·8 g.), methanol (25 ml.), and hydroxylamine solution (30 ml.) (see above) were mixed at room temperature and left for 7 days. The methanol and most of the water were removed (reduced pressure) and the residue dissolved in water (25 ml.). Addition of 4N-hydrochloric acid (15 ml.) gave the crude 4-hydroxy-2-methylquinazoline 3-oxide (6·13 g.). The cyclic product was obtained similarly from methyl 2-acetamidonicotinate and from methyl *o*-formamidobenzoate, methanol being replaced by

[7] Anschutz, Schmidt, and Greiffenberg, *Ber.*, 1902, **35**, 3480.

water in the latter case. For methyl *o*-benzamidobenzoate initial dissolution was followed within about 4 hr. by formation of a paste. The solid was filtered off after 24 hr., dissolved in water, and then treated as above. A similar preparation left for 7 days gave the required product even if acidified with acetic acid, though after shorter reaction times mineral acid was necessary. Ethyl 3-acetamidopicolinate also formed a paste (*ca.* 3 min.) in this reaction, the cyclic product being isolated after 2 days by using hydrochloric acid.

Reduction of Cyclic Hydroxamic Acids.—Sodium dithionite (16 g.) was added in small portions during 3 hr. to a refluxing mixture of 4-hydroxy-2-methylquinazoline 3-oxide (1·35 g.), water (32 ml.), and ethanol (16 ml.). The solution was then adjusted to pH 6—7 by 4N-sodium hydroxide and evaporated under reduced pressure. Extraction of the dried residue with boiling ethanol (2 × 50 ml.), filtration, and concentration of the extract gave 4-hydroxy-2-methylquinazoline (0·5 g.), m. p. 237—238° (lit.,[8] 238—239°) not depressed by a sample prepared from acetamide and anthranilic acid.[8]

4-Hydroxy-2-phenylquinazoline 3-oxide was reduced similarly, except that addition of excess of aqueous sodium hydroxide was desirable. The product (47%) had m. p. 237—238° (lit.,[1] 236°) not depressed by a sample from *o*-benzamidobenzamide.[1]

Reduction of 4-hydroxy-2-methyl-1,3,8-triazanaphthalene (0·55 g.) yielded the required product (0·03 g.), m. p. 260—262°, only after repeated fractional crystallisation to remove inorganic matter. Since there is only one previous reference to the preparation of this compound,[9] and other work in the same paper has been disputed,[10] we prepared a sample of the reduction product for comparison as follows: 2-Aminonicotinic acid (2·03 g.) was mixed with acetamide (8·43 g.) and heated at 200—220° for 10 hr. The residue was extracted with hot ethanol (charcoal) and furnished a crude product (0·52 g.) which after crystallisation from ethanol had m. p. 260—262° (lit.,[9] 258°) (Found: C, 60·0; H, 4·1; N, 26·1. Calc. for $C_8H_7N_3O$: C, 59·6; H, 4·4; N, 26·1%).

Oxidation of 4-*Hydroxyquinazolines and their* 3-*Oxides.*—A solution of 4-hydroxy-2-methylquinazoline (4·28 g.) in acetic acid (25 ml.) and 100-vol. hydrogen peroxide (20 ml.) was kept at 70—80° for 40 hr. Partial evaporation (reduced pressure), addition of more water, and further evaporation left a yellow-brown gum. This dissolved in hot water (10 ml.) and, on cooling, the solution deposited a red solid which became yellow on addition of 20% aqueous sodium hydroxide (4 ml.). The crude product (1·38 g.) was collected and crystallized from water, giving *o*-nitrobenzamide as pale green needles, m. p. 174—176° (lit.,[11] 176°) not depressed on admixture with a sample prepared from *o*-nitrobenzoyl chloride and ammonia.

Similar treatment of 4-hydroxy- and 4-hydroxy-2-methyl-quinazoline 3-oxide gave *o*-nitrobenzamide (23% and 28%).

Action of Nitrous Acid on o-*Amino-hydroxamic Acids.*—(a) o-*Aminobenzhydroxamic acid.* To a solution of the hydroxamic acid (2·3 g.) in water (70 ml.) and concentrated hydrochloric acid (4 ml.) was added 1·5M-sodium nitrite (1·1 equiv.), 4-*hydroxybenzo*-1,2,3-*triazine* 3-*oxide* (2·12 g.) separating at once.

(b) 3-*Aminopicolinhydroxamic acid.* The hydroxamic acid (0·5 g.), dissolved in water (5 ml.) and concentrated hydrochloric acid (0·6 ml.) by stirring at 0° for 5 min., was treated with 2·5M-sodium nitrite (1·5 equiv.). After 1·5 hr. the solid was collected, washed with small volumes of cold water, and dried at room temperature *in vacuo*, affording 4-*hydroxy*-1,2,3,5-*tetra-azanaphthalene* 3-*oxide* (0·21 g.) as a yellow powder.

Alkaline Degradation of 4-*Hydroxybenzo*-1,2,3-*triazine* 3-*Oxide.*—The oxide (0·4 g.) in water (5 ml.) and 20% aqueous sodium hydroxide (5 ml.) was refluxed for 1 hr. Cooling and addition of 2·5N-hydrochloric acid (12 ml.) afforded a flesh-coloured precipitate (0·33 g.), m. p. 142—143° (decomp.) (lit.,[12] 144·5—146°), which did not depress the m. p. of a sample of *o*-azidobenzoic acid prepared from anthranilic acid.[12] A similar solution, left for 24 hr. at room temperature, also furnished *o*-azidobenzoic acid (0·29 g.), but a solution in 0·1N-sodium hydroxide gave 80% recovery of starting material.

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[8] Bogert and Gotthelf, *J. Amer. Chem. Soc.*, 1900, **22**, 522.
[9] Klisiecki and Sucharda, *Roczniki Chem.*, 1923, **3**, 251.
[10] Robbins and Hitchings, *J. Amer. Chem. Soc.*, 1955, **77**, 2256.
[11] Bischoff and Siebert, *Annalen*, 1887, **239**, 92.
[12] Bamberger and Demuth, *Ber.*, 1901, **34**, 1309.