929. *Oxazolopyridines and Oxazoloquinolines. Part II.* Synthesis of 2′-Hydroxyoxazolo(4′ : 5′-2 : 3)pyridine and Related Compounds.*

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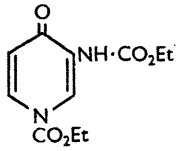
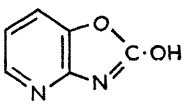
The synthesis of 2′-hydroxyoxazolo(4′ : 5′-2 : 3)pyridine (II), and attempted synthesis of 2′-hydroxyoxazolo(4′ : 5′-3 : 4)pyridine are described. Oxazolo(4′ : 5′-3 : 4)quinoline was obtained by cyclising 3-formamido-4-hydroxyquinoline with phosphoryl chloride, but this method failed to give unsubstituted oxazolopyridines.

2′-HYDROXYOXAZOLO(4′ : 5′-3 : 4)PYRIDINE could not be obtained by heating 3-amino-4-hydroxypyridine hydrochloride with urea, the only product isolated being 4-hydroxy-3-pyridylurea, a result which was similar to that observed in the quinoline series.[1] For a possible alternative route 3-amino-4-hydroxypyridine was treated in pyridine with ethyl chloroformate, readily giving the bisethoxycarbonyl derivative (I), but not the required monoethoxycarbonyl compound, even when an excess of the amine was used. The pyridone (I) was converted by cold aqueous sodium hydroxide into the urethane (IV), which was heated to 200° (cf. Groenvik [2]), but the expected hydroxyoxazole could not be isolated.



(I)



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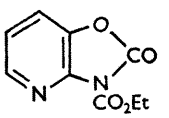
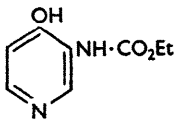


(III)



(IV)

It was of interest to ascertain whether the isomeric hydroxyoxazole (II) could be obtained by a similar series of reactions from 2-amino-3-hydroxypyridine, the hydroxyl group of which should be more phenolic [3] than that of 3-amino-4-hydroxypyridine. Ethyl chloroformate with 2-amino-3-hydroxypyridine in pyridine gave 2-ethoxycarbonylamino-3-pyridyl ethyl carbonate, which was converted by aqueous sodium hydroxide into 2-ethoxycarbonylamino-3-hydroxypyridine. The expected hydroxyoxazole (II) was obtained by heating the latter to 200° in diphenyl ether.

* Part I, *J.*, 1956, 1781.

[1] Bachman, Welton, Jenkins, and Christian, *J. Amer. Chem. Soc.*, 1947, **69**, 365.
[2] Groenvik, *Bull. Soc. chim.*, 1876, **25**, 178.
[3] Elderfield, " Chemistry of Heterocyclic Compounds," John Wiley and Sons, Inc., New York, 1950, Vol. I, p. 442.

In contrast with the behaviour of the pyridone (I), which was unchanged at 200° in inert solvents, 2-ethoxycarbonylamino-3-pyridyl ethyl carbonate on vacuum-distillation gave the ethoxycarbonyloxazolone (III) together with a little hydroxyoxazole (II), into which the oxazolone (III) was converted by cold, dilute sodium hydroxide solution.

Since 2-amino-3-hydroxypyridine with benzoic anhydride gave 2′-phenyloxazolo-(4′ : 5′-2 : 3)pyridine,[4] an attempt was made to prepare the unsubstituted oxazolopyridines by refluxing 2-formamido-3- and 3-formamido-4-hydroxypyridine with phosphoryl chloride: this failed, although oxazolo(4′ : 5′-3 : 4)quinoline was obtained in low yield by this method.

Experimental

4-Hydroxy-3-pyridylurea.—3-Amino-4-hydroxypyridine hydrochloride (2·6 g.) was fused with urea (3 g.) at 140—150° for 2 hr., allowed to cool, and triturated with water to remove urea. The product was filtered off and crystallised from water, giving the *pyridylurea* (2·3 g.), m. p. 300—302° (decomp.), sintering at 270° (Found: C, 47·0; H, 4·9; N, 27·8. $C_6H_7O_2N_3$ requires C, 47·1; H, 4·6; N, 27·4%).

1-Ethoxycarbonyl-3-ethoxycarbonylamino-4-pyridone (I).—A solution of 3-amino-4-hydroxypyridine (2·2 g., 0·02 mole) in pyridine (8 c.c.) was cooled to 0° and ethyl chloroformate (4·3 g., 0·04 mole) was added dropwise with stirring. The mixture was kept overnight at room temperature, then 5N-hydrochloric acid was added to give a pH of 4. After 30 min. at 0° the precipitate was collected and washed with a little water. Crystallisation from aqueous alcohol gave the *pyridone* (3·4 g.), m. p. 83·5—84·5° (Found: C, 52·0; H, 5·5; N, 11·1. $C_{11}H_{14}O_5N_2$ requires C, 52·0; H, 5·5; N, 11·0%).

3-Ethoxycarbonylamino-4-hydroxypyridine (IV).—1-Ethoxycarbonyl-3-ethoxycarbonylamino-4-pyridone (1 g.) was dissolved in N-sodium hydroxide (6 c.c.), and after 2 min. at room temperature the solution was neutralised with N-hydrochloric acid (vigorous evolution of carbon dioxide). The mixture was evaporated to dryness under reduced pressure and the residue was extracted with hot chloroform. Concentration of the filtered extract gave *3-ethoxycarbonylamino-4-hydroxypyridine* as needles, m. p. 148—149° (Found: C, 52·6; H, 5·7; N, 15·6. $C_8H_{10}O_3N_2$ requires C, 52·7; H, 5·5; N, 15·4%).

2-Amino-3-hydroxypyridine.[5]—A mixture of 3-hydroxy-2-nitropyridine (10 g.), methanol (100 c.c.), and 10% palladised charcoal (1 g.) was shaken with hydrogen at 1 atm. until absorption ceased. Removal of the catalyst and evaporation under reduced pressure in an atmosphere of nitrogen gave the brown product (6·9 g.) which was used without further purification. A specimen for analysis (m. p. 163—165°) was obtained by crystallisation (charcoal) from acetone–chloroform (Found: C, 54·3; H, 5·1; N, 25·8. Calc. for $C_5H_6ON_2$: C, 54·5; H, 5·5; N, 25·5%).

2-Ethoxycarbonylamino-3-pyridyl Ethyl Carbonate.—A solution of 2-amino-3-hydroxypyridine (1·6 g.) in dry pyridine (4 c.c.) was stirred at 0° while ethyl chloroformate (3·2 g.) was added dropwise. The mixture was kept at room temperature for 3 hr. and the pH was adjusted to 4 with hydrochloric acid. Extraction of the mixture with ether, evaporation of the dried (Na_2SO_4) extract, and keeping the residue in a vacuum-desiccator over concentrated sulphuric acid for several hours gave crude 2-ethoxycarbonylamino-3-pyridyl ethyl carbonate as a brown viscous oil (3·1 g.).

2-Ethoxycarbonylamino-3-hydroxypyridine.—Crude 2-ethoxycarbonylamino-3-pyridyl ethyl carbonate (3 g.) was warmed on a steam-bath with N-sodium hydroxide (20 c.c.) for 5 min. and allowed to cool, and the excess of oil was removed by extraction with ether. After a further 10 min. at room temperature the mixture was neutralised with dilute hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with hot chloroform, evaporation of which gave the crude urethane as a sticky solid (1 g.). This was recrystallised several times from chloroform–ether, affording *2-ethoxycarbonylamino-3-hydroxypyridine* as light yellow prisms, m. p. 104—105° (Found: N, 15·6. $C_8H_{10}O_3N_2$ requires N, 15·4%).

2′-Hydroxyoxazolo(4′ : 5′-2 : 3)pyridine (II).—2-Ethoxycarbonylamino-3-hydroxypyridine (0·4 g.) was heated in diphenyl ether (3 c.c.) at 200° for 1 min. and, after cooling, treated with

[4] Fraser and Tittensor, *J.*, 1956, 1781.
[5] B.P. 360,188/1931; Bray, Neale, and Thorpe, *Biochem. J.*, 1950, **46**, 506.

light petroleum (b. p. 60—80°; 3 c.c.). The solid was collected and dissolved in acetone–chloroform (1 : 1), and the solution was clarified by filtration through kieselguhr. Concentration of the filtrate gave the *oxazolopyridine* (0·1 g.), m. p. 211—212° (Found: C, 53·1; H, 3·0; N, 20·9. $C_6H_4O_2N_2$ requires C, 52·9; H, 2·9; N, 20·6%). The *picrate* formed yellow prisms, m. p. 154—155°, from benzene (Found: C, 39·0; H, 1·9. $C_6H_4O_2N_2,C_6H_3O_7N_3$ requires C, 39·5; H, 1·9%).

3'-Ethoxycarbonyl-2'-oxo-oxazolo(4' : 5'-2 : 3)*pyridine* (III).—Crude 2-ethoxycarbonylamino-3-pyridyl ethyl carbonate (2·4 g.) was distilled at 2 mm. The distillate solidified and was recrystallised from ether–light petroleum (b. p. 40—60°), giving *3'-ethoxycarbonyl-2'-oxo-oxazolo*(4' : 5'-2 : 3)*pyridine* (0·79 g.) as needles, m. p. 105—106·5° (Found: C, 51·7; H, 3·9; N, 13·6. $C_9H_8O_4N_2$ requires C, 51·9; H, 3·8; N, 13·5%).

The tarry distillation residue was extracted with acetone–benzene (1 : 1), and the solution was treated with charcoal and filtered through kieselguhr. The filtrate on concentration gave colourless needles (0·05 g.), m. p. alone or mixed with 2'-hydroxyoxazolo(4' : 5'-2 : 3)pyridine 211—212°.

Decomposition of the Oxazolone (III) *in Alkaline Solution.*—The oxazolone (0·1 g.) was stirred with N-sodium hydroxide (0·6 c.c.) until dissolution was complete (5 min.). After a further 2 min. the solution was neutralised with N-sulphuric acid (0·6 c.c.) (evolution of carbon dioxide). The solution gradually deposited a colourless solid which was collected and recrystallised from acetone–benzene, giving 2'-hydroxyoxazolo(4' : 5'-2 : 3)pyridine, m. p. and mixed m. p. 211—212°.

Attempted Cyclisation of 1-Ethoxycarbonyl-3-ethoxycarbonylamino-4-pyridone (I).—Liquid paraffin (2 c.c.) was heated to 200° and the pyridone (0·1 g.) was added. Heating was continued for 3 min. and the mixture was cooled and treated with light petroleum (b. p. 40—60°; 5 c.c.). A colourless precipitate was obtained, together with a small amount of a red resin. The precipitate was collected and washed with light petroleum. It (0·05 g.) had m. p., alone or mixed with starting material, 83·5—84·5°.

2'-Phenyloxazolo(4' : 5'-2 : 3)*pyridine.*—2-Amino-3-hydroxypyridine (1 g.) was refluxed with benzoic anhydride (6 g.) for 10 min. The cooled mixture was dissolved in benzene (200 c.c.) and extracted with ice-cold 3N-hydrochloric acid (3 × 20 c.c.). The combined extracts were filtered and basified with aqueous sodium hydroxide. The precipitate was collected and crystallised from aqueous acetone, giving the *2'-phenyl derivative* as needles, m. p. 127—127·5° (Found: C, 73·2; H, 4·0; N, 14·5. $C_{12}H_8ON_2$ requires C, 73·4; H, 4·1; N, 14·3%).

Oxazolo(4' : 5'-3 : 4)*quinoline.*—Crude, dry 3-formamido-4-hydroxyquinoline (0·5 g.), obtained from 3-amino-4-hydroxyquinoline and formic acid, was refluxed with phosphoryl chloride (2 c.c.) for 1 hr. Crushed ice (20 g.) and ammonia (*d* 0·880; 25 c.c.) were added and the mixture was immediately extracted with benzene (3 × 20 c.c.). The dried (Na_2SO_4) extract was distilled to remove benzene, and the residue was crystallised from light petroleum (b. p. 40—60°). The *oxazole* formed pale yellow needles (0·05 g.), m. p. 105—105·5° (Found: C, 70·0; H, 3·8; N, 16·5. $C_{10}H_6ON_2$ requires C, 70·6; H, 3·5; N, 16·5%).

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