349. *Oxazolopyridines and Oxazoloquinolines. Part I. 2′-Alkyl and 2′-Aryl Derivatives of Oxazolo*(4′ : 5′-3 : 4)*pyridine and Oxazolo*(4′ : 5′-3 : 4)*quinoline.*

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The synthesis and some reactions of oxazolo(4′ : 5′-3 : 4)pyridines and oxazolo(4′ : 5′-3 : 4)quinolines are described.

In an attempt to synthesise 2′-substituted oxazolo(4′ : 5′-3 : 4)pyridines and oxazolo-(4′ : 5′-3 : 4)quinolines the standard methods used in the benzoxazole series, *viz.*, heating *o*-hydroxy-amines with amides, nitriles, carboxylic acids, esters, or acid chlorides, proved of no value. Equally unsuccessful were attempts at cyclodehydration of hydroxy-acylamino-compounds by phosphoryl chloride, the yields being extremely poor. Extension of the method generally used for 2-methylbenzoxazoles, 2′-methyloxazolo(5′ : 4′-2 : 3)pyridines,[1, 2] and 2′-methyloxazolo(4′ : 5′-3 : 4)quinolines,[3] namely, refluxing *o*-hydroxy-amines in acetic anhydride, to the use of a variety of aliphatic and aromatic acid anhydrides, gave moderately good yields of the desired oxazolopyridines and oxazoloquinolines. It has not been possible to prepare the parent compounds, for although 3-amino-4-hydroxy-pyridine and -quinoline both yield formamido-derivatives in refluxing formic acid, these have not yet been cyclised. The oxazolo(4′ : 5′-3 : 4)-pyridines and -quinolines are solids, the 2′-alkyl derivatives having a characteristic odour. They readily form crystalline monomethiodides. At room temperature 2′-methyloxazolo(4′ : 5′-3 : 4)pyridine is hydrolysed rapidly by N-hydrochloric acid but it is stable to water and aqueous sodium hydroxide. Unlike 2-methylbenzoxazole it is also stable to boiling water and in this resembles 2-methyl-5- and 2-methyl-7-nitro-benzoxazole which according to Phillips [4] can be recrystallised from hot water containing a little acetic acid.

[1] Saikachi, *J. Pharm. Soc. Japan*, 1944, **64**, 201.
[2] Yamamoto and Takahashi, *ibid.*, 1951. **71**, 169.
[3] Bachman, Welton, Jenkins, and Christian, *J. Amer. Chem. Soc.*, 1947, **69**, 370.
[4] Philips, *J.*, 1930, 2685.

Skraup *et al.*[5, 6] observed that 2-methylbenzoxazole condensed with benzaldehyde although they did not characterise the product. They also found that it did not react with dimethyl-*p*-nitrosoaniline, nitrous acid, or diazonium salts, and that it was oxidised by aqueous potassium permanganate to benzoxazole-2-carboxylic acid. 2′-Methyloxazolo(4′ : 5′-3 : 4)pyridine condenses with benzaldehyde to give a styryl derivative. It is decomposed by aqueous potassium permanganate and does not react with the other reagents mentioned. Attempts to oxidise the 2′-methyl group by means of selenium dioxide or to convert it into a bromomethyl group by means of *N*-bromosuccinimide failed.

Improved syntheses of 3-amino-4-hydroxy-pyridine and -quinoline, in which reduction was best accomplished by hydrogenation of the corresponding nitro-compounds by palladised charcoal, are described.

EXPERIMENTAL

3-*Amino*-4-*hydroxyquinoline*.—A suspension of 4-hydroxy-3-nitroquinoline (3 g.) and 10% palladised charcoal (1 g.) in methanol (100 c.c.) was shaken with hydrogen at atmospheric pressure until absorption ceased. Removal of the catalyst and evaporation under reduced pressure in an atmosphere of nitrogen gave the light-brown product (2·4 g.) which was used without further purification. The acetyl derivative had m. p. 283—284° (Ochiai and Ogura[7] give m. p. 285°).

3-*Amino*-4-*hydroxypyridine*.—4-Hydroxy-3-nitropyridine (10 g.) was reduced as above in methanol (100 c.c.), with 10% palladised charcoal (1 g.). The product was obtained as colourless or pale purple prisms (7·4 g.) which oxidised in air. The *monoacetyl derivative*, m. p. 213—214°, formed colourless needles from aqueous acetone (Found: C, 49·7; H, 6·1; N, 16·8. $C_7H_8O_2N_2,H_2O$ requires C, 49·4; H, 5·9; N, 16·5%).

Preparation of 2′-*Alkyloxazolo*(4′ : 5′-3 : 4)-*pyridines and -quinolines*.—A mixture of 3-amino-4-hydroxy-pyridine or -quinoline (0·04 mole) and the acid anhydride (0·2—0·3 mole) was refluxed for 24 hr., cooled, and stirred with ice-water (300 c.c.). The solution was basified by aqueous sodium hydroxide with cooling, and extracted with benzene (6 × 50 c.c.). The combined extracts were washed with saturated aqueous sodium chloride (20 c.c.) and dried (Na_2SO_4). Evaporation under reduced pressure gave a coloured product which was crystallised (charcoal) from light petroleum (b. p. 40—60°). The *products* are tabulated.

TABLE 1. *Products.*

No.	2′-Subst.	Yield (%)	M. p.	Formula	Found (%)			Required (%)		
					C	H	N	C	H	N
			Oxazolo(4′ : 5′-3 : 4)*pyridines.*							
1	Me [a]	27	57·5—59°	$C_7H_6ON_2$	62·7	4·7	20·6	62·7	4·5	20·9
2	Et [a]	32	46—7	$C_8H_8ON_2$	64·8	5·6	18·9	64·9	5·4	18·9
3	Pr^n [a]	42	72·5—73·5	$C_9H_{10}ON_2$	66·8	6·3	17·5	66·7	6·2	17·3
4	Ph [b]	45	123·5—4·5	$C_{12}H_8ON_2$	73·4	4·1	14·4	73·4	4·1	14·3
5	*p*-C_6H_4Me [b]	57	179·5—180	$C_{13}H_{10}ON_2$	74·5	4·7	13·5	74·3	4·8	13·3
6	*p*-MeO·C_6H_4 [b]	53	177—178	$C_{13}H_{10}O_2N_2$	69·1	4·4	12·5	69·0	4·4	12·4
7	*p*-C_6H_4Cl [b]	32	157—158	$C_{12}H_7ON_2Cl$	62·8	3·0	12·3	62·5	3·0	12·1
			Oxazolo(4′ : 5′-3 : 4)*quinolines.*							
8	Me [a]	75	90—91	$C_{11}H_8ON_2$	—	—	15·3	—	—	15·2
9	Et [a]	72	72·5—73·5	$C_{12}H_{10}ON_2$	72·6	5·2	14·1	72·8	5·1	14·1
10	Pr^n [b]	45	69—70	$C_{13}H_{12}ON_2$	73·3	5·8	13·1	73·6	5·7	13·2
11	Ph [a]	63	168—169	$C_{16}H_{10}ON_2$	78·0	4·1	13·4	77·8	4·1	11·4
12	*p*-C_6H_4Me [b]	42	216—218	$C_{17}H_{12}ON_2$	78·7	4·7	10·8	78·5	4·6	10·8
13	*p*-MeO·C_6H_4 [b]	40	188—189	$C_{17}H_{12}O_2N_2$	73·7	3·9	10·3	73·9	4·3	10·1
14	*p*-C_6H_4Cl [b]	86	219·5—220·5	$C_{16}H_9ON_2Cl$	68·6	3·2	9·8	68·4	3·2	10·0

[a] Needles. [b] Prisms.

Preparation of 2′-*Aryloxazolo*(4′ : 5′-3 : 4)-*pyridines and -quinolines*.—A mixture of 3-amino-4-hydroxy-pyridine or -quinoline (0·01 mole) and the acid anhydride (0·03 mole) was heated rapidly to 300° in a flask fitted with a wide air-condenser and the temperature kept thereat for

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[5] Skraup and Böhm, *Ber.*, 1926, **59**, 1007.

[6] Skraup and Moser, *Ber.*, 1922, **55**, 1080.

[7] Ochiai and Ogura, *J. Pharm. Soc. Japan*, 1952, **72**, 767.

15 min. The cooled melt was dissolved in benzene (200 c.c.) and extracted with ice-cold 2N-hydrochloric acid (3 × 20 c.c.). The combined extracts were filtered and basified with aqueous sodium hydroxide. The white precipitate was collected and crystallised from acetone. *Products* are tabulated.

TABLE 2. *Derivatives.*

Methiodide of No.	M. p.	Solvent	Formula	Found (%)			Required (%)		
				C	H	N	C	H	N
1	147—148° [b]	A	$C_8H_9ON_2I$	35·1	3·4	10·2	34·8	3·3	10·1
2	146—147 [a]	A	$C_9H_{11}ON_2I$	37·3	4·0	9·6	37·2	3·8	9·7
3	94—96·5 [a]	A	$C_{10}H_{13}ON_2I$	—	—	—	—	—	—
4	279—280 [b]	B	$C_{13}H_{12}ON_2I$	46·5	3·4	8·3	46·2	3·3	8·3
5	226—227·5 [b]	B	$C_{14}H_{13}ON_2I$	47·3	3·6	7·7	47·7	3·7	8·0
6	234—235·5 [b]	B	$C_{14}H_{13}O_2N_2I$	—	—	—	—	—	—
7	267·5—268·5 [b]	B	$C_{13}H_{10}ON_2ClI$	42·4	2·6	7·6	41·9	2·7	7·5
8	252·5—253·5 [a]	B	$C_{12}H_{11}ON_2I$	44·3	3·5	8·8	44·2	3·4	8·6
9	216—217 [a]	B	$C_{12}H_{13}ON_2I$	46·3	3·9	8·3	45·9	3·8	8·2
10	193—194 [a]	B	$C_{14}H_{15}ON_2I$	47·6	4·1	7·5	47·5	4·2	7·9
11	260—261 [b]	C	$C_{17}H_{13}ON_2I$	52·2	3·2	7·5	52·5	3·4	7·2
12	238—240 [b]	C	$C_{13}H_{15}ON_2I$	53·9	3·6	7·1	53·7	3·7	7·0
13	251—252 [b]	C	$C_{18}H_{15}O_2N_2I$	51·9	3·4	6·7	51·7	3·6	6·7
14	250—251 [b]	C	$C_{17}H_{12}ONClI$	48·2	2·8	6·7	48·3	2·8	6·6
Picrate of No.									
3	130—131 [a]	B	$C_9H_{10}ON_2,C_6H_3O_7N_3$	46·3	3·4	17·8	46·0	3·3	17·9
6	251—252 [a]	B	$C_{13}H_{10}O_2N_2,C_6H_3O_7N_3$	50·3	3·1	15·3	50·1	2·9	15·4

A, alcohol–ether; B, absolute alcohol; C, aq. alcohol. [a] Needles. [b] Prisms.

Hydrolysis of 2′-Methyloxazolo(4′ : 5′-3 : 4)*pyridine.*—A solution of the oxazole (0·3 g.) in N-hydrochloric acid (4·0 c.c.) was kept at 25° for 2 hr. On basification with aqueous sodium hydroxide and extraction with ether unchanged oxazole (0·01 g.) was recovered. The aqueous layer was neutralised with acetic acid and cooled in ice, giving 3-acetamido-4-pyridone (needles; 0·1 g.), m. p. and mixed m. p. 213—214°.

The oxazole was recovered from refluxing aqueous solution after 30 min.

2′-Styryloxazolo(4′ : 5′-3 : 4)*pyridine.*—2′-Methyloxazolo(4′ : 5′-3 : 4)pyridine (0·5 g.), freshly distilled benzaldehyde (3 c.c.), and zinc chloride (0·3 g.) were refluxed for 5 hr. (bath at 170°). The mixture was diluted with benzene (20 c.c.) and extracted with 2N-hydrochloric acid (2 × 10 c.c.), and the combined acid layers were basified with sodium hydroxide. The resulting yellow precipitate was recrystallised from aqueous acetone, to give colourless needles (0·06 g.), m. p. 122—123° (Found: C, 76·0; H, 4·7; N, 12·9. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%).

Cyclisation of 3-Benzamido-4-hydroxyquinoline by Phosphoryl Chloride.—3-Benzamido-4-hydroxyquinoline[8] (0·56 g.) was refluxed with phosphoryl chloride (10 c.c.) for 2 hr. The excess of chloride was evaporated under reduced pressure, and the residue, a very viscous liquid, was treated with ice-water and basified with aqueous sodium hydroxide. The mass gradually solidified, and after 3 hr. was collected. Crystallisation from acetone gave 2′-phenyloxazolo(4′ : 5′-3 : 4)quinoline (0·1 g.), m. p. 168—169°.

3-Amino-4-hydroxy-2 : 8-dimethylquinoline Hydrochloride.—4-Hydroxy-2 : 8-dimethylquinoline (10 g.) was dissolved in warm 5N-sodium hydroxide (100 c.c.), and the solution diluted with water (20 c.c.) and cooled to 5°. A solution of benzenediazonium chloride, made from aniline (6 g.), was added slowly and with stirring, the temperature being kept below 5°; the mixture was then made neutral by addition of ice-cold 5N-hydrochloric acid. The resulting copious red precipitate was collected, washed with water, and dried in a vacuum-desiccator. The crude dry phenylazo-derivative was heated for 2 hr. on a steam-bath with concentrated hydrochloric acid (200 c.c.) and stannous chloride (26 g.). After cooling, the yellow precipitate was collected, dissolved in hot water, and freed from tin by treatment with hydrogen sulphide and filtration. Evaporation of the filtrate to about 300 c.c. and keeping at 0° gave colourless needles of 3-amino-4-hydroxy-2 : 8-dimethylquinoline hydrochloride (7·0 g.). The *acetyl derivative*, prepared by adding acetic anhydride followed by sodium acetate to an aqueous solution of the hydrochloride, crystallised from aqueous ethanol as needles, m. p. 313·5—314° (Found: C, 62·7; H, 6·3; N, 11·4. $C_{13}H_{14}O_2N_2,H_2O$ requires C, 62·9; H, 6·5; N, 11·3%).

2′ : 2 : 8-Trimethyloxazolo(4′ : 5′-3 : 4)*quinoline.*—3-Amino-4-hydroxy-2 : 8-dimethylquinoline hydrochloride (1·89 g.) was refluxed with acetic anhydride (30 c.c.) and anhydrous sodium

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[8] Musajo, *Gazzetta*, 1937, **67**, 222.

acetate (1·2 g.) for 4 hr. By using the general method of isolation described above for 2'-alkyloxazolo-derivatives, 2' : 2 : 8-*trimethyloxazoloquinoline* was obtained as pale-yellow needles (**1·6** g.), m. p. 83—84° (Found: C, 74·0; H, 5·7; N, 13·0. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7; N, 13·2%).

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