111. *New Therapeutic Agents of the Quinoline Series. Part VI. Quinolyl-thiazoles, -amidines, and -pyrroles.*

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Seven cyanoquinolines have been prepared and converted into thioamides; these in turn were condensed with bromoacetone (in one case, with bromoacetal) to yield thiazoles. Several of the nitriles were converted into amidines, but attempts to condense these with acetylacetone in order to obtain quinolylpyrimidines were unsuccessful. A number of *N*-pyrrylquinolines, obtained by condensing aminoquinolines with 1 : 4-dicarbonyl compounds, are also described.

As the spasmolytic activity of simple pyridylquinolines appeared also in comparable lutidylquinolines, it was thought advisable to prepare compounds containing a quinoline system linked to other simple heterocyclic nuclei. Recalling the similar biological activities of sulphapyridine and various sulphathiazoles, we selected the thiazylquinoline system for examination.

2-, 3-, 4-, and 5-Cyanoquinoline were prepared by slight modifications of the literature methods. As neither fusion of potassium quinoline-6-sulphonate with potassium cyanide (Fischer and Willmack, *Ber.*, 1884, **17**, 449) nor distillation of the diquinolylthiourea with paraffin and copper bronze (D.R.-P. 259,363) appeared convenient for the preparation of 6-cyanoquinoline, we obtained this compound in rather poor yield by a Sandmeyer reaction on 6-aminoquinoline. The same method afforded 8-cyano-6-methoxyquinoline; in this case the instability of the diazonium salt obtained from 8-amino-6-methoxyquinoline seemed to make neutralisation of acid as was done by Strukow (*Chem. pharmaz. Ind. Russ.*, 1934, **3**, 13; *Chem. Zentr.*, 1935, I, 2371) inadvisable. The usefulness of *Bz*-aminoquinolines in such reactions is surprisingly variable and we were, for example, unable to convert 6-amino-8-methoxyquinoline into the nitrile either by direct diazotisation or by using the nitrosoacetamido-compound. 8-Cyanoquinoline was obtained by distilling 8-chloroquinoline in presence of cuprous cyanide; a considerable quantity of the 8-amide was formed.

Each of these nitriles was converted into the corresponding thioamide by heating with alcoholic hydrogen sulphide, and thence by condensation with bromoacetone into the 5′-methyl-2-thiazylquinoline.

It appeared possible that the spamolytic activity of compounds of the pyridylquinoline type might be traced to the common feature of a basic residue separated from the quinoline nucleus by at least one carbon atom. Opportunity was therefore taken to convert some of the nitriles prepared above into iminoethers and thence into the corresponding amidines, which, however, as reported in Part I, proved to be inactive. Attempts to condense the amidines with acetylacetone in order to obtain quinolylpyrimidines were unsuccessful because of the unusually ready fission of the amidines into amides.

Of pyrrylquinolines, the 2 : 2′-representative had been prepared and Lions and his co-workers (*J. Proc. Roy. Soc. N.S. Wales*, 1936, **70**, 43; 1937, **71**, 92; 1940, **74**, 443) have described the preparation of *N*-5′-quinolyl-, -8′-quinolyl-, and -3′-quinaldyl-2 : 5-dimethylpyrrole by condensing appropriate aminoquinolines with acetonylacetone. In the present work this synthetic method was extended to the preparation of *N*-3′-quinolyl-, -6′-quinolyl-, -6′-methoxy-8′-quinolyl-, and -8′-methoxy-6′-quinolyl-2 : 5-dimethylpyrrole. In similar manner, by substituting diacetylsuccinic ester for acetonylacetone, a variety of quinolyldicarbethoxydimethylpyrroles was obtained. None of these new pyrrylquinolines had any appreciable spasmolytic activity.

Experimental.

2-5′-*Methyl*-2′-*thiazylquinoline*.—A solution of 2-cyanoquinoline (Hamer, J., 1939, 1011) (2 g.) in ethanol (15 c.c.) and concentrated aqueous ammonia (15 c.c.) was saturated with hydrogen sulphide and heated in a sealed tube at 150° for 4 hours. The *quinoline*-2-*thioamide* (1·3 g.) obtained crystallised from methanol in needles which were converted into prisms on standing, m. p. 168—169° (Found: N, 14·6. $C_{10}H_8N_2S$ requires N, 14·9%). A mixture of the thioamide (1·3 g.) and bromoacetone (1·5 c.c.) in ethanol (5 c.c.) was heated on the steam-bath for 1 hour and after removal of solvent the residue was treated with water (20 c.c.) and concentrated hydrochloric acid (10 c.c.), filtered, and neutralised. 2-5′-*Methyl*-2′-*thiazylquinoline*, recrystallised from aqueous ethanol, had m. p. 121·5—122·5°; yield, quantitative (Found: N, 12·5. $C_{13}H_{10}N_2S$ requires N, 12·4%).

3-5′-*Methyl*-2′-*thiazylquinoline*.—A mixture of 3-bromoquinoline (47 g.) and cuprous cyanide (29 g.) was heated gently until reaction commenced. From the reaction mixture, 3-cyanoquinoline was sublimed in a vacuum; recrystallised from benzene–light petroleum, it had m. p. 104° (yield, 10 g.). The nitrile was treated at 130° for 3 hours with ethanol and ammonium sulphide as above. *Quinoline*-3-*thioamide* formed pale yellow crystals from ethanol, m. p. 197—198° (decomp.) (Found: N, 14·9; S, 16·6. $C_{10}H_8N_2S$ requires N, 14·9; S, 17·0%). On heating with bromoacetone and ethanol as in the above example, 3-5′-*methyl*-2′-*thiazylquinoline* was obtained (yield, 0·8 g. from 2 g. of thioamide); it separated from benzene–light petroleum in rosettes of needles, m. p. 118—118·5° (Found: N, 12·3%).

4-5′-*Methyl*-2′-*thiazylquinoline*.—4-Cyanoquinoline (Kaufmann, *Ber.*, 1918, **51**, 121) (4 g.) in ethanol (25 c.c.) and

15% alcoholic ammonia (35 c.c.) saturated at 0° with hydrogen sulphide was heated at 120° for 3 hours. After removal of solvent and crystallisation of the residue from ethanol–light petroleum, *quinoline-4-thioamide* separated in pale yellow plates (2·3 g.), m. p. 223° (decomp.) (Found : N, 14·8%). A mixture of the thioamide (1·5 g.) and bromoacetone (1·5 g.) was warmed gently, and reaction completed with ethanol (6 c.c.) and bromoacetone (0·5 g.). The residue was dissolved in dilute hydrochloric acid, the filtered solution basified, and the solid distilled at 100—110° in a high vacuum. *4-5′-Methyl-2′-thiazylquinoline* (1·4 g.) was further purified by chromatography on alumina in benzene solution and finally crystallised from aqueous ethanol or benzene–light petroleum; it formed almost colourless prisms, m. p. 82·5—83·5° (Found : N, 12·4%).

5-5′-Methyl-2′-thiazylquinoline.—5-Cyanoquinoline (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1940, **62**, 1640) (2·0 g.) was dissolved in 20% alcoholic ammonia (45 c.c.) and aqueous ammonia (*d* 0·88, 5 c.c.), and the solution saturated with hydrogen sulphide at 0°. Heating at 120° for 3 hours and removal of solvent gave *quinoline-5-thioamide*, which separated from methanol in yellow prisms (1·2 g.), m. p. 187—188° (decomp.) (Found : S, 16·7%). The thioamide (1 g.) was condensed with bromoacetone (1 g.) in ethanol (5 c.c.) on the steam-bath. After removal of solvent, the residue was extracted with 15% hydrochloric acid, the solution made alkaline, and the precipitate chromatographed in benzene on alumina. *5-5′-Methyl-2′-thiazylquinoline*, recrystallised from aqueous methanol, formed fine colourless needles, m. p. 97—98° (Found : N, 12·4%).

6-5′-Methyl-2′-thiazylquinoline.—6-Aminoquinoline (19 g.), dissolved in concentrated sulphuric acid (41·5 c.c.) and water (76 c.c.), was diazotised at 0° with 15% sodium nitrite solution (64 c.c.). After 1 hour, the solution was added with vigorous stirring to excess of cuprous cyanide solution, and the reaction completed by keeping for 1 hour at 60°. Extraction of the red solid with benzene and crystallisation of extracted material from light petroleum gave 6-cyanoquinoline (5 g.), m. p. 131° (lit., 131—135°). The nitrile (1·1 g.) was dissolved in dry ethanol (10 c.c.), ethanol saturated with ammonia (20 c.c.) added, and the whole saturated with hydrogen sulphide at 0°. The semi-solid mass was heated for 1·5 hours under pressure at 100°, and solvent removed. The residual *quinoline-6-thioamide* crystallised from much water in buff needles, m. p. 184—185° (decomp.) (Found : N, 14·7%). The thioamide (0·5 g.) was condensed with bromoacetone (0·75 g.) in ethanol (3 c.c.), solvent removed, the product dissolved in dilute hydrochloric acid, and the solution basified. The brown oily deposit soon solidified and was purified by distillation at 90—100° in a high vacuum. *6-5′-Methyl-2′-thiazylquinoline* formed pale yellow clusters of prisms, m. p. 90·5—91·5°, from benzene–light petroleum (Found : N, 12·3%).

8-2′-Thiazylquinoline.—*o*-Chloroaniline (85 g.), sulphuric acid (*d* 1·56, 435 c.c.), sodium *m*-nitrobenzenesulphonate (192 g.), and glycerol (128 g.) were refluxed for 9 hours. The cooled solution was made alkaline with ammonia and distilled in steam. The distillate (18 l.) was extracted with benzene, and the extract dried and distilled, eventually in a vacuum. 8-Chloroquinoline (75 g.) was collected at 174°/25 mm. The chloro-compound was converted into 8-cyanoquinoline by Fieser and Hershberg's method (*loc. cit.*), quinoline-8-amide being obtained in considerable quantity as a by-product. *Quinoline-8-thioamide*, prepared as in previous similar reactions, separated from methanol–ether in yellow needles, m. p. 112—112·5° (decomp.); yield, 3 g. from 4 g. of nitrile (Found : N, 14·7%). A mixture of quinoline-2-thioamide (1 g.), bromoacetal (10 c.c.), and dilute sulphuric acid (3 c.c.) was heated on the steam-bath with intermittent shaking for 15 minutes in a closed flask. After being kept overnight, the product was extracted with 15% hydrochloric acid, the solution filtered and made alkaline, and the precipitate chromatographed on alumina from benzene. The material recovered from the filtrate was crystallised from benzene–light petroleum (yield, 0·7 g.). *8-2′-Thiazylquinoline* had m. p. 69—70° (Found : N, 13·3. $C_{12}H_8N_2S$ requires N, 13·2%).

Quinoline-2-amidine.—Dry hydrogen chloride was passed into a solution of 2-cyanoquinoline (2 g.) in dry ethanol (5 c.c.) and benzene (25 c.c.) cooled in ice. The precipitate which first appeared redissolved and the whole was kept for several days at 0°. The precipitate of quinoline-2-iminoether hydrochloride was ground with dry ether and with ethanol, added immediately to 15% alcoholic ammonia (40 c.c.), and shaken at room temperature for 4 days. Ammonium chloride was removed, the filtrate concentrated to small bulk, and the amidine hydrochloride precipitated with ether as an extremely hygroscopic solid. Its *picrate*, prepared from an alcoholic solution of the hydrochloride and picric acid, separated from acetone in yellow prisms, m. p. 258—259° (decomp.) (Found : N, 20·8. $C_{10}H_9N_3,C_6H_3O_7N_3$ requires N, 21·0%).

Quinoline-3-amidine.—Quinoline-3-iminoether hydrochloride was prepared from 3-cyanoquinoline as above. The precipitated hydrochloride was washed with dry ether and shaken with 15% alcoholic ammonia (50 c.c.) for 24 hours. Ammonium chloride was removed, the filtrate concentrated, and *quinoline-3-amidine hydrochloride* precipitated with dry ether; it separated from ethanol–ether in colourless prisms (3·5 g.), m. p. 168—169° (decomp.) after drying at 140—150° for 20 hrs. (Found : N, 20·0. $C_{10}H_9N_3$,HCl requires N, 20·1%).

Quinoline-6-amidine.—6-Cyanoquinoline (2·2 g.) was converted into the corresponding amidine as in the foregoing reaction. *Quinoline-6-amidine hydrochloride* separated from ethanol–ether in colourless prisms (1 g.), m. p. 242° (decomp.) (Found : N, 19·8%).

Quinolyldicarbethoxydimethylpyrroles.—Ethyl diacetylsuccinate (4·5 g.) and the appropriate aminoquinoline (2·5 g.) were dissolved in ethanol (9 c.c.) and acetic acid (1 c.c.) and the whole boiled under reflux for 24 hours. The product was made alkaline with ammonia, water (50 c.c.) added, and the pyrrole extracted with benzene (20, 10 c.c.).

The combined extract was dried and filtered through a short column of alumina. On evaporating the filtrate, the pyrrole remaining slowly crystallised. *Ethyl 1-5′-quinolyl-2 : 5-dimethylpyrrole-3 : 4-dicarboxylate* separated from ether in stout prisms, m. p. 99° (yield, 50%) (Found : N, 7·7. $C_{21}H_{22}O_4N_2$ requires N, 7·7%). The corresponding *6′-quinolyl* compound had m. p. 115° (Found : N, 7·7%) and the corresponding *6′-methoxy-8′-quinolyl* and *8′-methoxy-6′-quinolyl* compounds separated from benzene–light petroleum in prisms, m. p. 141 and 117° respectively (Found : N, 7·3, 7·2 respectively. $C_{22}H_{24}O_5N_2$ requires N, 7·1%).

Quinolyldimethylpyrroles.—Acetonylacetone (2·0 g.) and the appropriate aminoquinoline (0·5 g.) were refluxed in ethanol (9 c.c.) and acetic acid (1 c.c.) for 24 hours, the solution poured into water (100 c.c.) containing ammonia in excess, and the precipitate collected and extracted with boiling light petroleum. When the extracts were concentrated and cooled, the pure quinolyldimethylpyrroles were obtained. The following were prepared : *1-3′-Quinolyl-2 : 5-dimethylpyrrole*, m. p. 167° (yield, 30%) (Found : N, 12·6. $C_{15}H_{14}N_2$ requires N, 12·6%); *1-6′-methoxy-8′-quinolyl-2 : 5-dimethylpyrrole*, m. p. 147° (yield, 23%) (Found : N, 11·0. $C_{16}H_{16}ON_2$ requires N, 11·1%).

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