467. 6-*Methoxy*-8-(ω-*piperazin*-1′-*ylalkylamino*)*quinolines*.

By P. A. Barrett, A. G. Caldwell, and L. P. Walls.

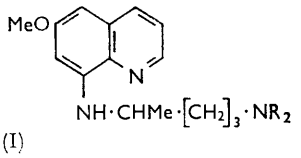
Analogues of the pamaquin-type of antimalarial but with a terminal piperazinyl group have been prepared by conventional methods, such as the condensation of 8-amino-6-methoxyquinoline with ω-piperazin-1′-ylalkyl halides. A more versatile method, involving the reduction of side-chains with one or more amide linkages by lithium aluminium hydride, has been devised which affords compounds with various piperazin-1-yl groups attached terminally to alkyl chains of 2—9 carbon atoms. Terminal *N*-substituents with carbonyl groups are simultaneously reduced. 1,2,3,4-Tetrahydroquinolines are occasional by-products. Many of the 6-methoxy-8-ω-piperazin-1′-ylalkylaminoquinolines in which the terminal N atom is basic possess high antimalarial and leishmanicidal properties.

Derivatives of 8-amino-6-methoxyquinoline with a basic side-chain show a range of chemotherapeutic activity.[1] We have now found that similar compounds in which the conventional amino-group has been replaced by 1-piperazinyl (cf. II), hitherto an almost unknown class,[2,3] not only possess very high antimalarial activity but also excel known drugs in their action on *Leishmania donovani* infections in hamsters.[4]

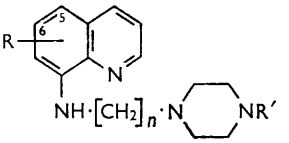
The method of condensation of 8-amino-6-methoxyquinoline with an aminoalkyl halide can be applied to piperazin-1-yl compounds, the most successful modification being that in which the aminoquinoline and the appropriate ω-piperazin-1′-ylalkyl halide (III) dihydrohalide were heated under reflux in propanol. Reaction of the aminoquinoline hydrochloride and piperazin-1-ylalkyl halide gave very similar results although one less molecular equivalent of hydrogen halide was present. The product was readily separated

[1] Schulemann, Schönhöfer, and Wingler, *Klin. Wochenschr.*, 1932, **11**, i, 381; Goble, *J. Parasitol.*, 1949, **35**, 375; Neitz, *Ondersterpoort J. Vet. Res.*, 1957, **27**, 275.
[2] Bachman and Szmant, *J. Amer. Chem. Soc.*, 1946, **68**, 32.
[3] Elderfield *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1525.
[4] Beveridge, Goodwin, and Walls, *Nature*, 1958, **182**, 316.

from unchanged aminoquinoline by distillation in a vacuum or by partition between chloroform and a citrate buffer pH 3·85.[3] The piperazin-1-ylalkylaminoquinolines were converted into trihydrochlorides (or dihydrochlorides when the terminal piperazine-N is non-basic, *e.g.*, II; R′ = CO_2Et) which crystallised from alcohols forming orange-coloured



(I)



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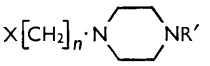


(III)

salts, readily soluble in water and, for the majority, rapidly hydrated on exposure (Table 1). The method was very satisfactory for the preparation of compounds (II) with $n = 3$ [R = 6-OMe, 6-OEt, or 5,6-$(OMe)_2$; R′ = H, Me, Et, CO_2Et, or $CH_2{\cdot}CH_2{\cdot}OH$], yields of isolated salt being ~45%. Less satisfactory results were obtained with $n = 6$, and poor yields (*ca.* 10%) with $n = 2$; and in one attempt with $n = 4$ no product was isolated. The scope of the method was evidently limited by the known propensity of aminoalkyl halides of appropriate chain-length to undergo intramolecular quaternisation-cyclisation, thus leading to poor results with tetramethylene and pentamethylene side-chains. Intermolecular quaternisation which is not dependent in the same way on chain-length is probably another yield-reducing complication. Magidson and Strukov [5] claimed to have obtained a small yield of 8-(4-diethylaminobutylamino)-6-methoxyquinoline by the condensation of 8-amino-6-methoxyquinoline with 4-diethylaminobutyl chloride, but no further examples of this condensation have been published. When the tetramethylene chain contains a substituent adjacent to a nitrogen atom, as in plasmoquine (I; R = Et), the products were obtained in rather poor yield as a mixture of position isomers. Pentamethylene compounds have been prepared by this method,[6] but experience has been limited mainly to compounds with terminal secondary amino-groups, in the preparation of which intramolecular alkylation and not quaternisation is the competing side-reaction. With these compounds and indeed with those having other chain-lengths yields vary considerably from compound to compound in a rather unpredictable way.

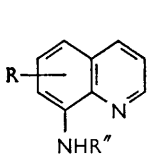
The condensation of 8-3′-chloropropylamino-6-methoxyquinoline [7] with the appropriate 1-substituted piperazines gave *ca.* 70% yields of compounds (II; $n = 3$, R′ = alkyl or hydroxyalkyl), but where R′ = H reaction at both nitrogen atoms is possible and the yield was only 27%.

Since the leishmanicidal results had pointed to the desirability of testing piperazin-1-yl compounds with tetramethylene, pentamethylene, and longer chains, particularly those with a terminal hydroxyalkyl group, we investigated the reduction of amides of the types (IV)—(VI) by lithium aluminium hydride.[8]

The method with ether as solvent gave 50—60% of crystalline trihydrochloride from amides (IV; R′ = alkyl or alkoxyalkyl) and 30—40% from amides (V). Distillation of the product was not essential but served to remove the small amount of 8-amino-6-methoxyquinoline that is sometimes formed by cleavage. Amides (IV; R′ = H or hydroxyalkyl) and diamides (VI) in tetrahydrofuran usually gave lower yields (25—35%), but exceptionally very high yields resulted, for example, of the crystalline bases (II; $n = 3$, R = 6-OMe, R′ = $[CH_2]_2CHMe{\cdot}OH$) and (II; $n = 6$, R = OMe, R′ = $CH_2{\cdot}CHMe{\cdot}OH$). The rate and course of reductions with lithium aluminium hydride probably depend on the solubility of the various complexes that are formed, and here variation in time and temperature of reaction and reverse addition of the reagents appeared to have only a

[5] Magidson and Strukov, *Arch. Pharm.*, 1933, **271**, 359.
[6] Drake *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1529.
[7] Crum and Robinson, *J.*, 1943, 561.
[8] Micovic and Mihailovic, *J. Org. Chem.*, 1953, **18**, 1190.

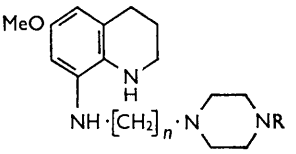
marginal influence. Reduction of the pyridine ring also occurs to a greater or smaller extent and formation of tetrahydroquinolines is certainly one circumstance responsible for the moderate yields sometimes obtained. In two reductions pure tetrahydroquinolines (VII; $n = 4$, R = Et) and (VII; $n = 5$, R = H) were isolated as their trihydrochlorides



(IV) R″ = ·CO·[CH$_2$]$_n$·N⟨ ⟩NR′

(V) R″ = ·[CH$_2$]$_2$·CO·N⟨ ⟩NR′

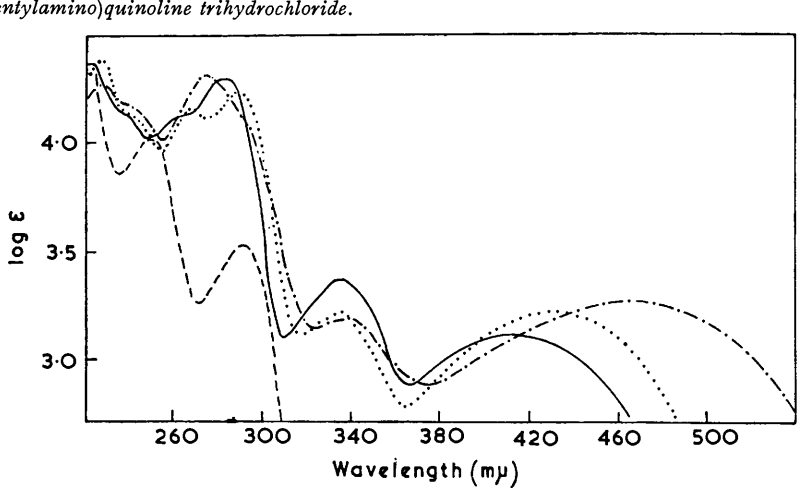
(VI) R″ = ·CO·[CH$_2$]$_2$·CO·N⟨ ⟩NR′



(VII)

which are almost colourless salts distinguished from their quinoline counterparts by absence of absorption at *ca.* 335 and 420 mμ (see Figure). Lithium aluminium hydride is known to reduce quinoline slowly to 1,2-dihydroquinoline, which absorbs at 347 mμ, and

Ultraviolet absorption of: (——) 8-*amino*-6-*methoxyquinoline hydrochloride*; (— · —) 5,6-*dimethoxy*-8-[3-(4-*methylpiperazin*-1-*yl*)*propylamino*]*quinoline trihydrochloride*; (. . .) 6-*methoxy*-8-(5-*piperazin*-1′-*ylpentylamino*)*quinoline trihydrochloride*; *and* (– – –) 1,2,3,4-*tetrahydro*-6-*methoxy*-8-(5-*piperazin*-1′-*ylpentylamino*)*quinoline trihydrochloride*.



may subsequently disproportionate to quinoline and tetrahydroquinoline.[9] Compound (VII; $n = 4$, R = Et) was also obtained by reduction of the corresponding quinoline with excess of sodium in pentyl alcohol, and identity with the lithium aluminium hydride product was established by infrared measurements.

Alternative preparative routes are available for some of the compounds of Table 1. The substituent R′ of the amides (IV—VI) may itself be a group reducible by lithium aluminium hydride. When R′ = CO_2Et the final product is a 6-methoxy-8-(4-methylpiperazin-1-ylalkylamino)quinoline, the urethane group ⩾N·CO_2Et having been reduced to the tertiary amine ⩾NMe.[10] In view of the accessibility of 1-ethoxycarbonylpiperazine this variant of the process constitutes a good route to the methylpiperazin-1-yl compounds which are produced thereby in very favourable yield. Likewise amides with R′ = CH_2·CO_2Et and COMe are reduced to 4′-hydroxyethyl- and 4′-ethyl-piperazin-1′-yl compounds respectively. Compounds (II; R′ = CO_2Et) were hydrolysed by aqueous-alcoholic alkali hydroxide with the formation of a base (II; R′ = H). Compounds (II;

[9] Bohlmann, *Chem. Ber.*, 1952, **85**, 390; Neumann, *Annalen*, 1958, **618**, 92.
[10] Dannley, Luken, and Shapiro, *J. Org. Chem.*, 1955, **20**, 92.

R′ = H) undergo reaction at the terminal cyclic NH-group, being converted back into the urethane (II; R′ = CO_2Et) by reaction with ethyl chloroformate, and into hydroxyalkyl compounds (II; R′ = $CH_2{\cdot}CH_2{\cdot}OH$ and $CH_2{\cdot}CHMe{\cdot}OH$) by reaction with alkylene oxides. Similarly reaction with DL-glycidol affords the dihydroxy-compound [II; R′ = $CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OH$]. The methods have also been applied to the preparation of compounds (II) with R = 6-OEt, 6-OPr, and 5,6-$(OMe)_2$ which are also potent leishmanicides. The 5,6-dimethoxy-compounds form brick-red trihydrochlorides which absorb at longer wavelength than the 6-methoxy-compounds (465 instead of 420 mμ, see Figure).

The amides (IV) (Table 3) were prepared by condensation of the appropriate piperazines with the halogeno-amides (VIII; X = Cl or Br). The latter (Table 2), some of which are known,[11] were prepared by conventional methods. The amides (IV) were usually crystalline for n = 1, 2, 4, and 5 and gums or low-melting solids for n = 3; several formed hydrates. The isolation of amides (IV; R′ = H), which were prepared by condensation of a halide (VIII) and anhydrous piperazine in benzene, was complicated by the simultaneous formation of the diamides (IX) (Table 4) even when an excess of piperazine was used, and by their solubility properties. The amides (IV; n = 3 and 4, R = 6-OMe, R′ = H) are highly soluble in water at room temperature, the former separating on cooling as the crystalline hydrate, which loses water on exposure to air. The lower (n = 2) and higher (n = 5 and 6) amides are less soluble in water at room temperature but otherwise behave similarly. The diamide (IX; n = 4, R = 6-OMe) was reduced by lithium aluminium hydride to the corresponding amine (CH_2 for each CO).

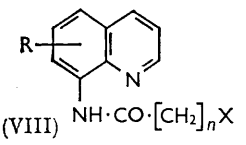
The amides (V) were prepared by condensation of the aminoquinoline with an ω-halogenoacylpiperazine (X), a reaction that is particularly favourable when the terminal nitrogen atom is also non-basic as for R′ = CO_2Et. Similar amides have been described by Neeman.[11a]

The diamides (VI) (Table 5) were prepared by condensation of the 8-aminoquinoline with the succinamic acids (XI), which need not be isolated, in the presence of *NN*′-dicyclohexylcarbodi-imide.[12] The yield of crystalline diamide (VI) varies in some cases with the solvent used. For example, preparation of (VI; R′ = $CH_2{\cdot}CH_2{\cdot}OH$) in pyridine or acetonitrile gave a very low yield, but it was satisfactory in dimethylformamide. In general, conditions giving the highest yields of diamides (VI) were not sought, but the compound (VI; R′ = $CH_2{\cdot}CO_2Et$) was readily obtained in 80% yield. The diamide (VI; R′ = Me) was also obtained by reaction of the quinolylsuccinamic acid (XII) with 4-methylpiperazine in the presence of *NN*′-dicyclohexylcarbodi-imide, but this method was less convenient and appeared to result in the formation of more by-products. Indeed, in an attempt to prepare the diamide (VI; R′ = $CH_2{\cdot}CH_2{\cdot}OH$) by this route, the major product was a compound (XIII) formed by the addition of the acid (XII) to dicyclohexylcarbodi-imide, with little or none of the desired product. This type of by-product has previously been obtained in peptide syntheses by means of *NN*′-dicyclohexylcarbodi-imide.[13]

The 1-alkylpiperazines (Pr^n, Pr^i, Bu^n) required for the preparation of certain of the compounds of Table 1 (method 2) and Table 3 were obtained by the method described by Moore, Boyle, and Thorn [14] for 1-ethylpiperazine, namely, the acid-hydrolysis of the corresponding 4-ethoxycarbonyl compounds.[15] The hydrolyses of the isopropyl [15] and butyl [16] compounds and the products have been described, and the propyl compound has been stated to have been made by the same method.[17] The most satisfactory method of

[11] (*a*) Neeman, *J.*, 1955, 2525; (*b*) Bergmann and Shapiro, *J. Org. Chem.*, 1942, **7**, 419; (*c*) Snyder and Freier, *J. Amer. Chem. Soc.*, 1946, **68**, 2485; (*d*) Hauser, Bloom, Breslow, Adams, Amore, and Weiss, *J. Amer. Chem. Soc.*, 1946, **68**, 1544.
[12] Sheehan and Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067.
[13] Khorana, *Chem. and Ind.*, 1955, 1087.
[14] Moore, Boyle, and Thorn, *J.*, 1929, 39.
[15] Stewart, Turner, and Denton, *J. Org. Chem.*, 1948, **13**, 134.
[16] Hamlin, Weston, Fischer, and Michaels, *J. Amer. Chem. Soc.*, 1949, **71**, 2732.
[17] Hromatka, Schlager, and Sauter, *Monatsh.*, 1957, **88**, 66.

preparing the 1-hydroxy- and 1-alkoxy-alkylpiperazines was reaction of two mol. of 1-ethoxycarbonylpiperazine with the appropriate halogen compound in benzene, followed by hydrolysis of the product by aqueous sodium hydroxide. One product, presumably 1-ethoxycarbonyl-4-3′-hydroxybutylpiperazine, was isolated from the reaction with



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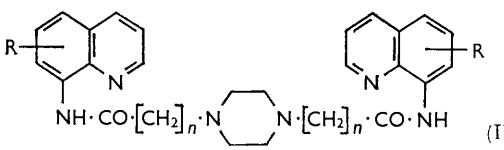
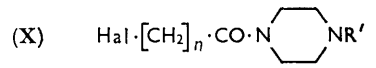


(IX)

1-chloro-3-hydroxybutane.[18] If an oxetane were formed by dehydrochlorination it could conceivably but improbably lead to an isomer. There are two references to *N*-ethoxycarbonylmethylpiperazine [14,19] but neither adequately describes the preparation and properties of this substance. Reaction of piperazine monohydrochloride and ethyl chloroacetate in alcoholic solution furnishes a good yield of the ester with little or no di-ester.



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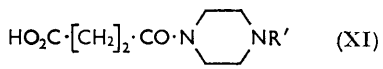

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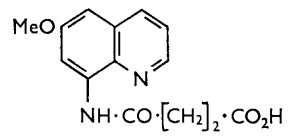
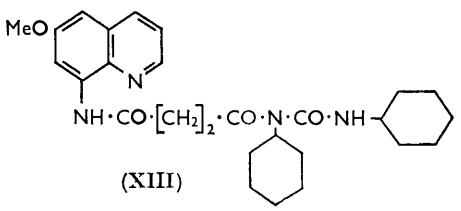


(XII)



(XIII)

Protonation of one nitrogen atom has thus effectively inhibited reaction at that centre with advantageous production of the monosubstituted compound.[20]

1-Bromo-3-chloropropane offers a simple route to the 1-3′-chloropropylpiperazines which is quite satisfactory when one nitrogen atom is non-basic as in 1-ethoxycarbonylpiperazine. With 1-methylpiperazine a yield of 50% can be obtained, but even during distillation at low temperature intramolecular quaternisation is liable to occur with a serious drop in yield. Poor results were obtained with 1-ethylpiperazine, and with 1-2′-hydroxyethylpiperazine the higher boiling point of the product favoured loss by this cause and the method has little preparative value.

The compounds of type (II) were examined for leishmanicidal properties in hamsters by Miss E. Beveridge and Dr. L. G. Goodwin of The Wellcome Laboratories of Tropical Medicine. Activity is usually present when the terminal nitrogen atom of the piperazine ring is basic, and is high when $n = 3$, 4, or 5 and less consistently so when $n = 6$.

Experimental

1-3′-*Hydroxypropylpiperazine*.—1-Ethoxycarbonylpiperazine (63·2 g.) and 1-chloro-3-hydroxypropane (18·9 g.) were heated under reflux in benzene (250 ml.) for 72 hr. The 1-ethoxycarbonylpiperazine hydrochloride (36 g.) that had separated was removed, and the filtrate was evaporated and distilled. 1-*Ethoxycarbonyl*-4-3′-*hydroxypropylpiperazine* (38 g.) distilled at 122—126°/0·05 mm., n_D^{24} 1·4823 (Found: C, 55·4; H, 8·9; N, 13·2. $C_{10}H_{20}N_2O_3$ requires C, 55·5; H, 9·3; N, 13·0%). This urethane (31 g.) was hydrolysed by heating it under reflux with 2·5N-sodium hydroxide (175 ml.) for 16 hr. An excess of sodium hydroxide

[18] Sondheimer and Woodward, *J. Amer. Chem. Soc.*, 1953, **75**, 5438.
[19] Braker and Christiansen, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1933, **22**, 951.
[20] Cymerman-Craig, Rogers, and Tate, *Austral. J. Chem.*, 1956, **9**, 399.

was added after cooling and the product was extracted with chloroform, dried, and distilled. 1-3′-Hydroxypropylpiperazine (14·2 g.) boiled at 143°/14 mm. and set to a white hygroscopic solid characterised by the dipicrate which crystallised from water in prisms, m. p. 254° (decomp.) in agreement with the literature [21] (Found: C, 37·9; H, 3·9; N, 18·4. Calc. for $C_{19}H_{22}N_8O_{15}$: C, 37·9; H, 3·7; N, 18·6%).

1-3′-*Hydroxybutylpiperazine*.—1-*Ethoxycarbonyl*-4-3′-*hydroxybutylpiperazine*, prepared by the foregoing method, by using 1-chloro-3-hydroxybutane, distilled at 120°/0·1 mm. and had n_D^{24} 1·4800 (Found: C, 56·8; H, 9·5; N, 12·5. $C_{11}H_{22}N_2O_3$ requires C, 57·4; H, 9·6; N, 12·2%). Alkaline hydrolysis converted it into the desired *product*, b. p. 138—139°/14 mm., m. p. 42—43° (Found: C, 60·0; H, 11·4; N, 18·0. $C_8H_{18}N_2O$ requires C, 60·7; H, 11·5; N, 17·8%), giving a *dipicrate* (from aqueous acetone), flat needles, m. p. 234—235° (decomp.) (Found: C, 39·1; H, 3·8; N, 18·2. $C_{20}H_{24}N_8O_{15}$ requires C, 39·0; H, 3·9; N, 18·2%).

1-4′-*Hydroxybutylpiperazine*.—This was prepared by the recorded method [21] except that the alkaline-hydrolysis method described above was advantageously substituted for acid-hydrolysis, the product being obtained in 74% yield, with b. p. 157—159°/13 mm. The *dipicrate*, crystallised from water, had m. p. 234—236° (decomp.) (Found: C, 39·0; H, 3·9; N, 18·1%).

1-2′-*Methoxyethylpiperazine*.—1-*Ethoxycarbonyl*-4-2′-*methoxyethylpiperazine* (26·9 g.) was prepared from 1-ethoxycarbonylpiperazine (50·2 g.) and 2-bromoethyl methyl ether (22·1 g.) by the method described above: it had b. p. 94—96°/0·1 mm., n_D^{25} 1·4702 (Found: C, 55·3; H, 9·0. $C_{10}H_{20}N_2O_3$ requires C, 55·5; H, 9·3%). Alkaline hydrolysis furnished 74% of 1-2′-methoxyethylpiperazine,[20] b. p. 94—95°/14 mm., of which the *dipicrate* (from water) had m. p. 232—233° (decomp.) (Found: C, 38·2; H, 3·7; N, 18·5. $C_{19}H_{22}N_8O_{15}$ requires C, 37·9; H, 3·7; N, 18·6%).

The following were similarly prepared:

1-*Ethoxycarbonyl*-4-2′-*ethoxyethylpiperazine*, b. p. 96°/0·1 mm., n_D^{25} 1·4650 (Found: C, 56·9; H, 9·6; N, 12·3. $C_{11}H_{22}N_2O_3$ requires C, 57·4; H, 9·6; N, 12·2%).

1-2′-*Ethoxyethylpiperazine*, b. p. 104—106°/14 mm., n_D^{23} 1·4677 (Found: N, 17·7. $C_8H_{18}N_2O$ requires N, 17·7%) [*dipicrate* (from water), m. p. 222—223° (decomp.) (Found: C, 38·9; H, 3·8; N, 18·4. $C_{20}H_{24}N_8O_{15}$ requires C, 39·0; H, 3·9; N, 18·2%)].

1-(2,3-*Dihydroxypropyl*)*piperazine*.—1-Ethoxycarbonylpiperazine (31·6 g.) and DL-glycidol (22·2 g.) reacted spontaneously with evolution of heat. When the temperature had subsided the mixture was heated at 100° for 2 hr. and then distilled. 1-(2,3-*Dihydroxypropyl*)-4-*ethoxycarbonylpiperazine* (33·6 g.) boiled at 165°/0·05 mm. (Found: C, 51·3; N, 8·4; N, 11·6. $C_{10}H_{20}N_2O_4$ requires C, 51·7; H, 8·7; N, 12·0%). The *picrate* (from water) had m. p. 145—146·5° (Found: C, 42·2; H, 5·0; N, 15·2. $C_{16}H_{23}N_5O_{11}$ requires C, 41·7; H, 5·0; N, 15·2%). Alkaline hydrolysis of this urethane followed by extraction of the product with chloroform and distillation yielded 1-(2,3-dihydroxypropyl)piperazine which distilled at 128—130°/0·1 mm. (9·5 g.), a viscous hygroscopic liquid which set to low-melting crystals (Found: N, 17·5. Calc. for $C_7H_{16}N_2O_2$: N, 17·5%). The *dipicrate* crystallised from water in prisms, m. p. 236—237° (decomp.) (Found: C, 37·1; H, 3·4; N, 17·9. $C_{19}H_{22}N_8O_{16}$ requires C, 36·9; H, 3·5; N, 18·1%).

1-*Ethoxycarbonylmethylpiperazine*.—To a boiling solution of piperazine hexahydrate (388 g.) and hydrogen chloride (73·0 g.) in alcohol (1 l.) was added gradually ethyl chloroacetate (122·5 g.), and the mixture was boiled for 4 hr. After cooling, piperazine dihydrochloride (166 g.) was filtered off, and the filtrate was evaporated to dryness. The residue was made alkaline with excess of potassium carbonate solution, and the mixture was extracted several times with chloroform. The residue after evaporation of the dried chloroform solution was distilled to give 1-ethoxycarbonylmethylpiperazine [19] (105 g.), b. p. 125—127°/13 mm., n_D^{15} 1·4751. Conveniently equimolar quantities of hexahydrate and dihydrochloride may be used with similar results.

6-*Alkoxy*-8-(ω-*piperazin*-1-*ylalkylamino*)*quinolines* (Table 1).

Method 1. *Condensation of* 8-*Amino*-6-*methoxyquinoline and Piperazin*-1-*ylalkyl Halides* (III).—The halides (III; $n = 2$, R′ = H, X = Cl) [22] and (III; $n = 2$, R′ = Me, X = Cl) [23]

[21] McElvain and Bannister, *J. Amer. Chem. Soc.*, 1954, **76**, 1129.
[22] Hromatka and Engel, *Ber.*, 1943, **76**, 712.
[23] Cymerman-Craig, Harrison, Tate, Thorp, and Ladd, *Austral. J. Chem.*, 1956, **9**, 89.

TABLE 1. 6-*Alkoxy*-8-(ω-*piperazin*-1′-*ylalkylamino*)*quinolines* (II).

R	R′	*n*	Method	B. p./mm. (or m. p.)	HCl salt: Solvent	HCl salt: M. p.§	Formula	Found (%): C	H	Cl	N	Required (%): C	H	Cl	N
MeO	H	2	1	195—200°/0·005	MeOH	228—229°	$C_{16}H_{22}N_4O,3HCl,0{\cdot}5H_2O$	47·5	6·3	25·7	13·7	47·5	6·5	26·3	13·8
MeO	Me	2	1, 3*a*	185°/0·01	MeOH	224—225	$C_{17}H_{24}N_4O,3HCl,H_2O$	47·6	6·7	24·9	12·9	47·7	6·8	24·9	13·1
MeO	Et	2	3a	212—214°/0·4	MeOH	230—231	$C_{18}H_{26}N_4O,3HCl,1{\cdot}5H_2O$	48·2	7·2	23·3	12·6	48·0	7·2	23·6	12·4
MeO	H	3	2, 3a	218—220°/0·2	EtOH	233—234	$C_{17}H_{24}N_4O,3HCl,2H_2O$	46·0	6·8	23·5	12·4	45·8	7·0	23·9	12·6
MeO	Me	3	1, 2, 3a, b, 4	188—191°/0·08	MeOH	227—229	$C_{18}H_{26}N_4O,3HCl,1{\cdot}5H_2O$ *	48·3	7·4	23·2	12·3	48·0	7·2	23·6	12·4
MeO	Et	3	1	206—212°/0·1	MeOH	235—237	$C_{19}H_{28}N_4O,3HCl,1{\cdot}5H_2O$	49·0	7·2	23·2	12·3	49·1	7·4	23·0	12·1
MeO	Pr^n	3	2	—	MeOH	235—237	$C_{20}H_{30}N_4O,3HCl,2H_2O$	49·4	7·7	21·8	11·2	49·2	7·6	21·8	11·5
MeO	Bu	3	2	183—186°/0·01	MeOH	242—244	$C_{21}H_{32}N_4O,3HCl,2H_2O$	50·3	7·6	20·9	10·8	50·3	7·8	21·2	11·2
MeO	$[CH_2]_2$·OH	3	1	233—238°/0·05	Aq. EtOH	223—225	$C_{19}H_{28}N_4O_2,3HCl,2H_2O$	46·4	7·0	21·1	11·4	46·4	7·2	21·7	11·4
MeO	$[CH_2]_3$·OH	3	2, 3a	233—237°/0·01	Aq. EtOH	234—236	$C_{20}H_{30}N_4O_2,3HCl,2H_2O$ *	47·8	7·3	21·3	11·1	47·5	7·4	21·1	11·1
MeO	$[CH_2]_4$·OH	3	3a	284—285°/0·15	MeOH	229—230	$C_{21}H_{32}N_4O_2,3HCl,1{\cdot}5H_2O$	49·3	7·4	20·7	10·6	49·5	7·5	20·9	11·0
MeO	CH_2·CHMe·OH	3	3a	218—220°/0·02	Aq. EtOH	240—242	$C_{20}H_{30}N_4O_2,3HCl$ †	51·0	7·1	22·5	12·3	51·3	7·1	22·8	12·0
MeO	$[CH_2]_2$·CHMe·OH	3	2, 3a	M. p. 109—109·5°	MeOH	241—243	$C_{21}H_{32}N_4O_2,3HCl,2H_2O$ *	48·8	7·8	20·9	10·7	48·7	7·6	20·5	10·8
MeO	$[CH_2]_2$·OMe	3	3a	240—250°/0·1	MeOH	232—234	$C_{20}H_{30}N_4O_2,3HCl,2H_2O$ *	47·6	7·3	20·6	11·1	47·5	7·4	21·1	11·1
MeO	$[CH_2]_2$·OEt	3	3a	218—230°/0·02	Aq. EtOH	226—228	$C_{21}H_{32}N_4O_2,3HCl,H_2O$ *	50·6	7·4	21·4	10·9	50·5	7·5	21·3	11·2
MeO	CO_2Et	3	1	238—243°/0·15	EtOH	194—197	$C_{20}H_{28}N_4O_3,2HCl,2H_2O$	49·7	7·0	14·9	11·9	49·9	7·1	14·7	11·6
MeO	CO·NEt_2	3	2	—	EtOH	192—194	$C_{22}H_{33}N_5O_2,2HCl(2H_2O$ *) †	56·2	7·4	15·1	14·8	56·0	7·4	15·0	14·8
EtO	Me	3	1	—	EtOH	227—229	$C_{19}H_{28}N_4O,3HCl(1{\cdot}5H_2O$ *) †	51·7	7·1	24·6	13·0	52·1	7·1	24·3	12·8
PrO	Me	3	3a	200—201°/0·05	MeOH	237—239	$C_{20}H_{30}N_4O,3HCl,H_2O$	50·7	7·5	22·4	12·1	51·1	7·5	22·6	11·9
PrO	$[CH_2]_2$·OH	3	3a	M. p. 94—96°	Aq. EtOH	232—234	$C_{21}H_{32}N_4O_2,3HCl,0{\cdot}5H_2O$ *	51·4	7·4	21·7	11·5	51·4	7·4	21·7	11·4
5,6-$(MeO)_2$	Me	3	1, 3b	—	MeOH	227—228	$C_{19}H_{28}N_4O_2,3HCl$ ‡	50·2	6·8	23·1	12·0	50·3	6·9	23·4	12·3
MeO	H	4	3a	218—224°/0·1	Aq. EtOH	259—260	$C_{18}H_{26}N_4O,3HCl,2{\cdot}5H_2O$	46·5	7·5	22·5	11·9	46·1	7·3	22·7	11·9
MeO	Me	4	3a, b, 5	216—220°/0·01	Aq. EtOH	246—248	$C_{19}H_{28}N_4O,3HCl$ †	52·1	7·1	24·1	12·9	52·1	7·1	24·3	12·8
MeO	Pr^i	4	3a	—	MeOH	227—229	$C_{21}H_{32}N_4O,3HCl$ †	54·3	7·7	23·2	12·1	54·1	7·6	22·8	12·0
MeO	$[CH_2]_2$·OH	4	3a, b, 5	236—238°/0·02	MeOH	227—228	$C_{20}H_{30}N_4O_2,3HCl(2H_2O$ *)†	50·9	6·9	22·6	12·0	51·3	7·1	22·8	12·0
MeO	$[CH_2]_2$·CHMe·OH	4	3a	232—239°/0·05	Aq. EtOH	229—231	$C_{22}H_{34}N_4O_2,3HCl,2{\cdot}5H_2O$ *	49·1	7·9	19·6	10·3	48·9	7·8	19·7	10·4
MeO	CH_2·CH(OH)·CH_2·OH	4	3a	—	MeOH	218—220	$C_{21}H_{32}N_4O_3,3HCl,3{\cdot}5H_2O$ *	45·1	7·1	18·7	9·8	45·0	7·5	19·0	10·0
5,6-$(MeO)_2$	H	4	3a	—	Aq. EtOH	237—238	$C_{19}H_{28}N_4O_2,3HCl$	50·5	7·2	23·1	12·3	50·3	6·9	23·4	12·3
5,6-$(MeO)_2$	Me	4	5	194—198°/0·02	EtOH	218	$C_{20}H_{30}N_4O_2,3HCl,2H_2O$ *	—	—	21·1	11·0	—	—	21·1	11·1
MeO	H	5	3a	244—250°/0·1	Aq. EtOH	265	$C_{19}H_{28}N_4O,3HCl,H_2O$	50·0	7·4	22·6	—	50·0	7·3	23·4	—
MeO	Me	5	3a, b	210—214°/0·01	MeOH	236—238	$C_{20}H_{30}N_4O,3HCl,2{\cdot}5H_2O$	48·1	7·5	21·4	11·3	48·3	7·7	21·5	11·3
MeO	Pr^i	5	3a	216—219°/0·01	EtOH	226—228	$C_{22}H_{34}N_4O,3HCl(H_2O$ *) †	55·2	7·7	22·0	12·0	55·1	7·8	22·2	11·7
MeO	$[CH_2]_2$·OH	5	3a	262—264°/0·1	MeOH	219—221	$C_{21}H_{32}N_4O_2,3HCl(2H_2O$ *) †	52·6	7·2	22·1	11·6	52·3	7·3	22·1	11·6
EtO	Me	5	3a	M. p. 58·5—60°	MeOH	237—238	$C_{21}H_{32}N_4O,3HCl$ †	53·9	7·5	23·0	11·9	54·1	7·6	22·8	12·0
EtO	$[CH_2]_2$·OH	5	3a	244—252°/0·08	MeOH	228—230	$C_{22}H_{34}N_4O_2,3HCl,0{\cdot}5H_2O$ *	52·2	7·0	21·1	11·2	52·3	7·6	21·1	11·1
MeO	H	6	1, 3a	248—254°/0·1	EtOH	*ca.* 156—158	$C_{20}H_{30}N_4O,3HCl,2H_2O$	48·7	7·6	22·1	11·4	49·2	7·6	21·8	11·5
MeO	Me	6	1	218—224°/0·05	EtOH	232—233	$C_{21}H_{32}N_4O,3HCl,1{\cdot}5H_2O$	51·2	7·6	21·9	11·5	51·2	7·8	21·6	11·4
MeO	Pr^i	6	3a	250—254°/0·03	MeOH	229—231	$C_{23}H_{36}N_4O,3HCl,H_2O$ *	53·9	7·9	20·7	10·8	53·9	8·1	20·8	10·9
MeO	$[CH_2]_2$·OH	6	3a	270—278°/0·15	Aq. EtOH	219—221	$C_{22}H_{34}N_4O_2,3HCl,2H_2O$	49·6	7·6	19·8	10·4	49·7	7·8	20·0	10·5
MeO	CH_2·CHMe·OH	6	3a	M. p. 109·5°	MeOH	213—215 (maleate)	$C_{23}H_{36}N_4O_2,3HCl(2H_2O$ *) †	54·1	7·3	20·9	10·8	54·2	7·7	20·9	11·0
EtO	Me	6	1	214—222°/0·01	Aq. EtOH	166—167	$C_{22}H_{34}N_4O,2C_4H_4O_4$	59·7	7·0	—	9·3	59·8	7·0	—	9·3
MeO	H	7	3a	242—244°/0·2	Aq. EtOH	227—228	$C_{21}H_{32}N_4O,3HCl,1{\cdot}5H_2O$	51·5	7·7	22·3	11·5	51·2	7·7	21·6	11·4
MeO	Me	7	3a	206—208°/0·01	EtOH	232	$C_{22}H_{34}N_4O,3HCl$ †	—	—	22·0	11·5	—	—	22·2	11·7
MeO	Pr^i	7	3a	228—230°/0·01	EtOH	230	$C_{24}H_{38}N_4O,3HCl,2H_2O$ *	—	—	19·0	10·2	—	—	19·5	10·3
MeO	$[CH_2]_2$·OH	7	3a	244—248°/0·01	EtOH	205—207	$C_{23}H_{36}N_4O_2,3HCl,2H_2O$ *	—	—	19·9	10·2	—	—	19·5	10·3
MeO	Me	8	3a	212—216°/0·01	Pr^{i}OH	225	$C_{23}H_{36}N_4O,3HCl$ †	—	—	21·0	11·3	—	—	21·5	11·3
MeO	Me	9	3a	217—218°/0·01	Pr^{i}OH	220	$C_{24}H_{38}N_4O,3HCl$ †	—	—	20·5	11·1	—	—	20·9	11·0

* " Loss " was determined and supported the formula stated. † These compounds were analysed after drying. ‡ Found: MeO, 14·1. Required: MeO, 13·7%.
§ With decomp.

TABLE 2. *Quinoline halogeno-amides* (VIII).

R	X	*n*	Solvent for crystn.	M. p.	Formula	Found (%) C	H	Hal	N	Required (%) C	H	Hal	N
5,6-(MeO)$_2$	Cl	2	EtOH	119°	$C_{14}H_{15}ClN_2O_3$	—	—	11·9	9·5	—	—	12·0	9·5
6-PrO	Cl	2	EtOH	124—126	$C_{15}H_{17}ClN_2O_2$	61·8	5·9	12·1	9·6	61·6	5·9	12·1	9·6
6-MeO	Cl	3	Aq. EtOH	69—71	$C_{14}H_{15}ClN_2O_2$	60·7	5·4	12·8	9·9	60·3	5·4	12·7	10·1
5,6-(MeO)$_2$	Cl	4	Aq. EtOH	57—58 *	$C_{15}H_{17}ClN_2O_3$	58·1	5·8	12·2	—	58·4	5·5	11·5	—
6-MeO	Br	4	EtOH	115—116·5	$C_{15}H_{17}BrN_2O_2$	53·4	5·0	23·5	8·4	53·4	5·1	23·7	8·3
6-EtO	Br	4	Acetone	99—100	$C_{16}H_{19}BrN_2O_2$	54·9	5·2	22·8	7·8	54·7	5·4	22·8	8·0
6-MeO	Br	5	EtOH	71·5—73	$C_{16}H_{19}BrN_2O_2$	—	—	22·8	8·0	—	—	22·8	8·0
6-MeO	Br †	6	MeOH	109—111	$C_{17}H_{21}BrN_2O_2$	—	—	21·4	7·8	—	—	21·9	7·7
6-MeO	Br †	7	MeOH	63—65	$C_{18}H_{23}BrN_2O_2$	57·3	6·2	20·8	7·4	57·0	6·1	21·1	7·4
6-MeO	Cl †	8	MeOH	97—99	$C_{19}H_{25}ClN_2O_2$	65·6	7·0	10·3	8·2	65·4	7·2	10·2	8·0

* Crystallises as a hydrate which gives m. p. and analytical figures after dehydration. † The acid chlorides were obtained by heating the corresponding acids with thionyl chloride: 7-bromoheptanoyl, b. p. 134°/11 mm.; 8-bromo-octanoyl, b. p. 136°/9 mm.; 9-chlorononanoyl, b. p. 134°/10 mm.

TABLE 3. *6-Alkoxy-8-(ω-piperazin-1'-ylacylamino)quinolines* (IV).

R	R'	*n*	Method	Derivative	Solvent for crystn.‡	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
MeO	Me	1	A	—	MeOH	113°	$C_{17}H_{22}N_4O_2$	65·2	6·9	17·5	64·9	7·0	17·8
MeO	Et	1	A	—	Pet	103·5	$C_{18}H_{24}N_4O_2$	66·1	7·3	17·1	65·8	7·4	17·1
MeO	H	2	D	—	EtOAc	130	$C_{17}H_{22}N_4O_2$	64·9	6·6	17·7	64·9	7·0	17·8
MeO	Me	2	A	—	EtOAc	95—96 *	$C_{18}H_{24}N_4O_2$	66·1	7·3	16·9	65·8	7·4	17·1
MeO	$[CH_2]_3$·OH	2	A	—	C_6H_6–Ch	132—133	$C_{20}H_{28}N_4O_3$	64·6	7·5	15·0	64·5	7·6	15·0
MeO	$[CH_2]_4$·OH	2	A	—	EtOAc	123—124	$C_{21}H_{30}N_4O_3$	65·2	7·7	14·2	65·3	7·8	14·5
MeO	CH_2·CHMe·OH	2	A	—	Ch	117·5—118·5	$C_{20}H_{28}N_4O_3$	64·4	7·6	15·1	64·5	7·6	15·0
MeO	$[CH_2]_2$·CHMe·OH	2	A	—	EtOH	160—162	$C_{21}H_{30}N_4O_3$	65·3	7·5	14·3	65·3	7·8	14·5
MeO	$[CH_2]_2$·OMe	2	A	Di-(H maleate)	EtOH	175	$C_{20}H_{28}N_4O_3,2C_4H_4O_4$	55·6	6·0	9·2	55·6	6·0	9·2
MeO	$[CH_2]_2$·OEt	2	A	—	Et_2O–Pet	82—83	$C_{21}H_{30}N_4O_3$	65·3	7·7	14·3	65·3	7·8	14·5
PrO	Me	2	A	—	Ch	101—102	$C_{20}H_{28}N_4O_2$	67·3	7·8	15·7	67·4	7·9	15·7
PrO	$[CH_2]_2$·OH	2	A	—	EtOAc	126—127	$C_{21}H_{30}N_4O_3$	65·5	7·6	14·7	65·3	7·8	14·5
5,6-$(MeO)_2$	CO_2Et	2	B	—	Ch	121—122	$C_{21}H_{28}N_4O_5$	60·3	6·7	13·3	60·6	6·8	13·4
MeO	H	3	D	—	Pet	113 *	$C_{18}H_{24}N_4O_2$	66·1	7·2	16·9	65·8	7·4	17·1
MeO	Me	3	B	Di-(H maleate)	MeOH	190—191	$C_{19}H_{26}N_4O_2,2C_4H_4O_4$	56·1	6·0	9·5	56·4	6·0	9·7
MeO	CO_2Et	3	B	—	Pet	76—77	$C_{21}H_{28}N_4O_4$	62·9	6·7	14·0	63·0	7·0	14·0
MeO	Pr^i	3	B	Di-(H maleate)	MeOH	186—187	$C_{21}H_{30}N_4O_2,2C_4H_4O_4$	57·7	6·0	9·1	57·8	6·4	9·3
MeO	$[CH_2]_2$·OH	3	A, B, C	Di-(H maleate)	MeOH	166—167	$C_{20}H_{28}N_4O_3,2C_4H_4O_4$	55·9	6·0	9·1	55·6	6·0	9·2
MeO	CH_2·CO_2Et	3	C	Di-(H maleate)	EtOH	151	$C_{22}H_{30}N_4O_4,2C_4H_4O_4$	55·2	6·1	8·7	55·7	5·9	8·7
MeO	$[CH_2]_2$·CHMe·OH	3	B	Di-(H maleate)	EtOH	181·5	$C_{22}H_{32}N_4O_3,2C_4H_4O_4$	56·9	6·5	8·9	57·0	6·4	8·9
MeO	CH_2·CH(OH)·CH_2·OH	3	A	Dipicrate	H_2O	230° (decomp.)	$C_{21}H_{30}N_4O_4,2C_6H_3N_3O_7$	45·8	4·2	15·8	46·0	4·3	16·3
5,6-$(MeO)_2$	H	3	D	—	EtOAc	105—106	$C_{19}H_{26}N_4O_3$	63·9	7·0	15·5	63·7	7·3	15·6
MeO	H	4	D	—	Pet	104—106	$C_{19}H_{26}N_4O_2$	66·6	7·5	16·4	66·6	7·6	16·4
MeO	Me	4	C	—	Ch	81·5—83·5	$C_{20}H_{28}N_4O_2$	67·1	7·9	15·7	67·4	7·9	15·7
MeO	CO_2Et	4	A	—	EtOAc	113—114	$C_{22}H_{30}N_4O_4$	63·6	7·2	13·3	63·7	7·3	13·5
MeO	Pr^i	4	B	Di-(H maleate)	EtOH	180·5	$C_{22}H_{32}N_4O_2,2C_4H_4O_4$	58·3	6·4	8·9	58·4	6·5	9·1
MeO	$[CH_2]_2$·OH	4	B	—	C_6H_6	70—71	$C_{21}H_{30}N_4O_3$	65·4	7·5	14·2	65·3	7·8	14·5
EtO	Me	4	B	Di-(H maleate)	EtOH	184	$C_{21}H_{30}N_4O_2,2C_4H_4O_4$	57·5	6·6	9·1	57·8	6·4	9·3
EtO	$[CH_2]_2$·OH	4	A	Di-(H maleate)	EtOH	151·5	$C_{22}H_{32}N_4O_3,2C_4H_4O_4$	57·3	6·2	8·8	57·0	6·4	8·9
MeO	H	5	D	—	Ether	102	$C_{20}H_{28}N_4O_2$	67·6	7·6	15·6	67·4	7·9	15·7
MeO	Pr^i	5	B	Di-(H maleate)	EtOH	181—182	$C_{23}H_{34}N_4O_2,2C_4H_4O_4$	58·9	6·8	8·8	59·0	6·7	8·9
MeO	$[CH_2]_2$·OH	5	B	—	C_6H_6	97·5—98·5	$C_{22}H_{32}N_4O_3$	66·0	7·7	13·8	66·0	8·0	14·0
MeO	CH_2·CHMe·OH	5	B	—	C_6H_6	126—127·5	$C_{23}H_{34}N_4O_3$	66·8	8·4	13·5	66·6	8·3	13·5
MeO	H	6	D	—	Ether	98	$C_{21}H_{30}N_4O_2$	67·9	7·9	14·5	68·1	8·2	15·1
MeO	Me	6	B	—	Ether	81—82	$C_{22}H_{32}N_4O_2$	68·6	8·2	14·2	68·7	8·4	14·6
MeO	Pr^i	6	B	—	Pet	65—66	$C_{24}H_{36}N_4O_2$	70·3	8·9	13·6	69·9	8·8	13·6
MeO	$[CH_2]_2$·OH	6	B	Di-(HCl)		193—195	$C_{23}H_{34}N_4O_3,2HCl$	—	—	11·3	—	—	11·5
MeO	Me	7	B	—	Pet	64—66	$C_{23}H_{34}N_4O_2$	69·6	8·2	14·1	69·3	8·6	14·1
MeO	Me	8	B	—	Pet	67—79	$C_{24}H_{36}N_4O_2$	70·1	8·9	13·8	69·9	8·8	13·6

* M. p. after crystalline hydrate had lost water on exposure. † The base crystallised from water as a hydrate which lost water on exposure and became gummy. ‡ Pet = light petroleum (b. p. 60—80°); Ch = cyclohexane.

were prepared by the recorded methods. The preparation of the other halides and the condensation with the aminoquinoline were as follows:

1-3′-*Chloropropyl*-4-*methylpiperazine* (III; n = 3, R′ = Me, X = Cl). 1-Methylpiperazine (70 g.), 1-chloro-3-bromopropane (52·5 g.), and dry benzene were heated under reflux for 4 hr. After cooling, the benzene solution was separated from solid and extracted with 3N-hydrochloric acid (3 × 75 ml.). The extract was made strongly alkaline with solid sodium hydroxide, and the liberated *base* was removed with ether, dried, and distilled at 98—100°/8 mm. (28·5 g.) (Found: Cl, 19·5; N, 16·3. $C_8H_{17}ClN_2$ requires Cl, 20·1; N, 15·9%). The dihydrochloride has been described.[24]

1-3′-*Chloropropyl*-4-*ethoxycarbonylpiperazine*, b. p. 109°/0·1 mm. (Found: C, 51·1; H, 8·0; Cl, 15·1; N, 12·0. $C_{10}H_{19}ClN_2O_2$ requires C, 51·2; H, 8·2; Cl, 15·1; N, 11·9%), and 1-3′-*chloropropyl*-4-2′-*hydroxyethylpiperazine*, b. p. 95—96°/0·01 mm. (Found: C, 52·0; H, 9·2; Cl, 17·4; N, 13·6. $C_9H_{19}ClN_2O$ requires C, 52·3; H, 9·3; Cl, 17·2; N, 13·6%), were similarly prepared, the yield of the latter being very poor.

TABLE 4. *The bisquinoline amides* (IX).

R	n	Solvent for crystn.	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
6-MeO	2	2-Ethoxyethanol	230°	$C_{30}H_{34}N_6O_4$	66·1	6·1	15·3	66·4	6·3	15·5
6-MeO	3	EtOH	144—146	$C_{32}H_{38}N_6O_4$	67·3	6·6	14·6	67·4	6·7	14·7
5,6-$(MeO)_2$	3	Pet	134—135	$C_{34}H_{42}N_6O_6$	64·2	6·9	12·8	64·8	6·7	13·3
6-MeO	4	EtOH	149—150	$C_{34}H_{42}N_6O_4$	67·8	7·0	14·1	68·3	7·0	14·0
6-MeO	5	EtOH	168	$C_{36}H_{46}N_6O_4$	68·8	7·2	—	69·0	7·4	—

TABLE 5. *The diamides* (VI).

R	R′	Solvent for prep.	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
6-MeO	Me *	$CHCl_3$	164—165°	$C_{19}H_{24}N_4O_3$	64·0	6·8	15·8	64·0	6·8	15·7
6-MeO	CO_2Et *	$CHCl_3$	137—138	$C_{21}H_{26}N_4O_5$	60·9	6·3	13·6	60·9	6·3	13·5
6-MeO	$[CH_2]_2$·OH †	H·CO·NMe_2	143—145	$C_{20}H_{26}N_4O_4$	62·1	7·2	14·1	62·2	6·8	14·5
6-MeO	CH_2·CO_2Et †	$CHCl_3$	92—93	$C_{22}H_{28}N_4O_5$	61·3	6·5	12·7	61·7	6·6	12·7
5,6-$(MeO)_2$	CO_2Et	$CHCl_3$	155—156	$C_{22}H_{28}N_4O_6$	59·6	6·3	12·4	59·4	6·3	12·6

*† These diamides on reduction gave the same product: Table 1, * R′ = Me, † R′ = $[CH_2]_2$·OH)

By essentially the methods of Cowan and Marvel [25] the following were obtained: 1-*Ethyl*-4-3′-*phenoxypropylpiperazine*, b. p. 135—137°/0·4 mm. (Found: C, 72·7; H, 9·7; N, 11·2. $C_{15}H_{24}N_2O$ requires C, 72·5; H, 9·7; N, 11·3%), 1-3′-*bromopropyl*-4-*ethylpiperazine dihydrobromide*, colourless plates (from ethanol), m. p. 234° (effervescence) (Found: C, 27·4; H, 5·3; Br, 60·3; N, 7·1. $C_9H_{21}Br_3N_2$ requires C, 27·2; H, 5·3; Br, 60·4; N, 7·1%), 1-6′-*methoxyhexyl*-4-*methylpiperazine*, b. p. 122—124°/4·5 mm., n_D^{22} 1·4659 (Found: C, 67·1; H, 12·5; N, 13·0. $C_{12}H_{26}N_2O$ requires C, 67·2; H, 12·2; N, 13·0%), and 1-6′-*bromohexyl*-4-*methylpiperazine dihydrobromide*, soft needles (from ethanol), m. p. 242—244° (Found: C, 31·1; H, 5·8; Br, 56·2; N, 6·7. $C_{11}H_{25}Br_3N_2$ requires C, 31·1; H, 5·9; Br, 56·4; N, 6·6%).

6-*Methoxy*-8-[3-(4-*methylpiperazin*-1-*yl*)*propylamino*]*quinoline trihydrochloride*. 8-Amino-6-methoxyquinoline hydrochloride (25·6 g.), 1-3′-chloropropyl-4-methylpiperazine (20·2 g.), and propan-1-ol (120 ml.) were heated under reflux for 72 hr. An excess of aqueous sodium hydroxide was added and the basic product was extracted with ether. After evaporation of ether the residue was shaken with chloroform–citrate buffer (pH 3·85) (30 ml. of each). The chloroform layer contained unchanged aminoquinoline. The citrate layer was made alkaline and the basic product was isolated with ether and dissolved in 3 equivalents of N-hydrochloric acid. The solution was evaporated to dryness under reduced pressure and the residue was crystallised twice from methanol, forming orange needles which rapidly became hydrated (22·5 g.).

6-*Ethoxy*-8-[6-(4-*methylpiperazin*-1-*yl*)*hexylamino*]*quinoline trihydrochloride*. 8-Amino-6-ethoxyquinoline (36 g., 3 equiv.), 1-6′-bromohexyl-4-methylpiperazine dihydrobromide (22·2 g., 1 equiv.) and propan-1-ol (20 ml.) were heated under reflux for 72 hr. The base was liberated

[24] Hromatka, Grass, and Sauter, *Monatsh.*, 1956, **87**, 706.
[25] Cowan and Marvel, *J. Amer. Chem. Soc.*, 1936, **58**, 1537.

by alkali, isolated with ether, and distilled. A fraction (17·2 g.) boiling at 120—135°/0·01 mm. consisted of 8-amino-6-ethoxyquinoline, and the product (7 g.) distilled at 214—222°/0·01 mm. The *dimaleate* (Table 1) was obtained by reaction of the constituents in hot ethyl acetate. The pale yellow crystals were recrystallised from aqueous alcohol (10% water) forming cream-coloured clumps of needles, m. p. 166—167° with effervescence.

Method 2. *Condensation of* 8-3′-*Chloropropylamino*-6-*methoxyquinoline and Piperazines.*— 8-[3-(4-3′-*Hydroxybutylpiperazin*-1-*yl*)*propylamino*]-6-*methoxyquinoline*. 8-3′-Chloropropylamino-6-methoxyquinoline hydrochloride (2·9 g.) and 1-3′-hydroxybutylpiperazine (4·75 g., 3 equiv.) were heated at 130° for 6 hr. The dark red melt was dissolved in 2N-hydrochloric acid, and the solution was made alkaline. The base was extracted with ether, a small amount of tar being left undissolved. The ether extract was dried (Na_2SO_4) and evaporated, leaving the *base*, m. p. 101—104°. Recrystallisation from ethyl acetate furnished cream-coloured needles, m. p. 109—109·5° (Found: C, 67·4; H, 8·9; N, 14·9. $C_{21}H_{32}N_4O_2$ requires C, 67·7; H, 8·7; N, 15·0%).

Method 3a. *Reduction of* 8-ω-*piperazin*-1′-*ylacylaminoquinolines* (IV). The quinoline halogeno-amides (VIII) (Table 2) were prepared by the following method.

8-γ′-*Chlorobutyramido*-6-*methoxyquinoline*. A solution of 8-amino-6-methoxyquinoline (78 g.) in acetone (600 ml.) was stirred with anhydrous sodium carbonate (72 g.) while a solution of γ-chlorobutyryl chloride [26] (67 g.) in acetone (150 ml.) was slowly added. The mixture was heated under reflux for 4 hr. and then filtered hot. Acetone was distilled from the filtrate, leaving a residue which crystallised from aqueous alcohol (10%) as white prisms (104 g.), m. p. 69—71°.

8-ω-*Piperazin*-1′-*ylacylaminoquinolines* (IV) (Table 3) were prepared by condensation of the foregoing halogeno-amides with piperazines, four methods being used.

(A) 8-[3-(4-2′-*Hydroxypropylpiperazin*-1-*yl*)*propionamido*]-6-*methoxyquinoline*. A solution of 8-β-chloropropionamido-6-methoxyquinoline (13·3 g.) and 1-3′-hydroxypropylpiperazine (10·8 g., 1·5 equiv.) in benzene (75 ml.) was heated under reflux for 18 hr. When cold the mixture was extracted with 2N-acetic acid. The extract (charcoal) was made alkaline and the basic amide (14 g.) thus liberated was collected, washed, dried, and recrystallised from benzene–cyclohexane forming almost white leaflets, m. p. 132—133°.

(B) 8-[δ-(4-*Isopropylpiperazin*-1-*yl*)*valeramido*]-6-*methoxyquinoline*. A mixture of 8-δ-bromovaleramido-6-methoxyquinoline (13·5 g.) and 1-isopropylpiperazine (7·7 g., 1·5 equiv.) was kept at 100° for 6 hr. The melt was then dissolved in 2N-acetic acid, and the solution was made alkaline and extracted with benzene, some amorphous material remaining undissolved. The extract was dried (Na_2SO_4) and evaporated, leaving the amide as a gum which was used for reduction. It was characterised as the di(hydrogen maleate), formed by mixing ethyl acetate solutions of the components, and crystallised from ethanol as white leaflets, m. p. 181—182°.

(C) This was essentially method A except that one equivalent only of the piperazine was used and 1·1 equivalents of triethylamine.

(D) 6-*Methoxy*-8-(ω-*piperazin*-1′-*ylacylamino*)*quinolines* (IV; R′ = H). The 6-methoxy-8-(ω-chloro- or -bromo-acylamino)quinoline (VIII; X = Cl or Br) (0·1 mol.) and anhydrous piperazine (34·4 g., 0·4 mol.) in dry benzene (300 ml.) were boiled under reflux for 4—6 hr. and left overnight. The mixture was filtered from piperazine hydrohalide and 1,4-di-[ω-*N*-(6-methoxy-8-quinolyl)carbamoylalkyl]piperazine (IX; Table 4). The diamine (IX) was separated from the piperazine hydrohalide by washing with water. To isolate the amide (IV; $n = 3$, R′ = H) the benzene filtrate was extracted with water (3 × 100 ml.). When the aqueous extracts cooled, the amide (IV; $n = 3$, R′ = H) separated as colourless needles of the hydrate. The latter lost water on exposure, or by azeotropic distillation with benzene, to give the anhydrous compound, which was initially oily but later solidified and was recrystallised from light petroleum (b. p. 60—80°). The anhydrous amide is readily soluble in cold water, but separates as an oil on warming. On storage the aqueous solution deposits the crystalline hydrate. To isolate the amides (IV; $n = 2$, 4, 5, and 6; R′ = H) the benzene filtrate was evaporated to dryness and the residue dissolved in water. The solution was filtered from further diamide (IX) and extracted several times with chloroform. The residue left after removal of the chloroform was recrystallised to give the pure amide.

[26] Reppe, *Annalen*, 1955, **596**, 190.

The amides were reduced to 6-alkoxy-8-(ω-piperazin-1′-ylalkylamino)quinolines (Table 1) by essentially the following method. In some examples the yield of trihydrochloride was substantially below that expected from the distilled base used in its preparation. We attribute this disparity at least partly to the presence of tetrahydroquinolines in the distillate. The boiling ranges given in the Table are only approximate.

A solution of 6-methoxy-8-[5-(4-methylpiperazin-1-yl)pentanoylamino]quinoline (Table 3) (27·5 g.) in ether (412 ml.) was added to a stirred solution of lithium aluminium hydride (5·4 g., 2 mol.) in ether (108 ml.). The mixture was stirred under reflux for 2 hr., then cooled in ice and treated successively with water (5·4 ml.), 15% aqueous sodium hydroxide (5·4 ml.), and water (16·2 ml.) to decompose the complexes. Filtration was rapidly effected and the ethereal solution was dried, evaporated, and distilled. The product (22·4 g.) was collected at *ca.* 210—214°/0·01 mm. and was converted into the trihydrochloride which crystallised from methanol in deep yellow needles (22 g.), rapidly hydrated on exposure and then having m. p. 236—238°.

Some of the bases crystallised before and some after distillation and the following were obtained pure. 8-[3-(4-2′-*Hydroxyethylpiperazin*-1-*yl*)*propylamino*]-6-*propoxyquinoline* crystallised from cyclohexane in white needles, m. p. 97·5° (Found: C, 67·6; H, 9·3; N, 14·9. $C_{21}H_{32}N_4O_2$ requires C, 67·7; H, 8·7; N, 15·0%).

6-*Ethoxy*-8-[5-(4-*methylpiperazin*-1-*yl*)*pentylamino*]*quinoline* crystallised from light petroleum (b. p. 60—80°) in pale yellow prisms, m. p. 58·5—60° (Found: C, 70·5; H, 9·0; N, 15·4. $C_{21}H_{32}N_4O$ requires C, 70·7; H, 9·0; N, 15·7%).

8-[6-(4-2′-*Hydroxypropylpiperazin*-1-*yl*)*hexylamino*]-6-*methoxyquinoline* crystallised from ethyl acetate in cream-coloured prisms, m. p. 108—109·5° (Found: C, 68·8; H, 9·1; N, 13·7. $C_{23}H_{36}N_4O_2$ requires C, 69·0; H, 9·1; N, 14·0%).

Method 3b. *Reduction of Amides* (IV) *with Ethoxycarbonyl Groups*. Essentially the same method as 3a except that 2·5 mol. of lithium aluminium hydride were used. *N*-Ethoxycarbonyl groups were converted into *N*-methyl, and *N*-ethoxycarbonylmethyl groups into *N*-hydroxyethyl.

Method 4. *Reduction of* 8-(3-*Oxo*-3-*piperazin*-1′-*ylpropylamino*)*quinolines* (V).—(i) 1-β-*Chloropropionyl*-4-*methylpiperazine hydrochloride*. A suspension of anhydrous sodium carbonate (12·7 g.) in 1-methylpiperazine (10 g.) and dry acetone (100 ml.) was mechanically stirred and cooled in ice. β-Chloropropionyl chloride (14 g.) was added dropwise at such a rate that the temperature of the mixture remained between 20° and 25°. Then the mixture was stirred in the ice-bath for a further 3 hr. The solid was filtered off and washed with dry acetone, and to the filtrate was added an excess of ethereal hydrogen chloride. More dry ether was added to complete the precipitation of the cream-coloured solid, which was collected, washed with ether, and dried in a vacuum-desiccator (19·3 g.). The *hydrochloride* crystallised from alcohol in colourless plates, m. p. 189° (effervescence) (Found: C, 42·6; H, 6·7; N, 12·4. $C_8H_{16}Cl_2N_2O$ requires C, 42·3; H, 7·1; N, 12·4%).

(ii) 1-β-*Chloropropionyl*-4-*ethoxycarbonylpiperazine*. 1-Ethoxycarbonylpiperazine (15·8 g.) was treated with β-chloropropionyl chloride (12·7 g.) in the presence of anhydrous sodium carbonate (10·6 g.) under conditions similar to those described above. The filtered acetone solution was evaporated to dryness and the residue was distilled to give a pale yellow oil boiling at 164—166°/0·5 mm., with some decomposition. Analyses for this material were somewhat high in carbon and low in chlorine.

(iii) 8-[3-(4-*Methylpiperazin*-1-*yl*)-3-*oxopropylamino*]-6-*methoxyquinoline*. A solution of 8-amino-6-methoxyquinoline (8·7 g.) and 1-β-chloropropionyl-4-methylpiperazine hydrochloride (11·35 g.) in propan-1-ol (50 ml.) was refluxed for 93 hr. The orange solid which had separated towards the end of this time was filtered from the cooled solution. It was 8-[3-(4-*methylpiperazin*-1-*yl*)-3-*oxopropylamino*]-6-*methoxyquinoline dihydrochloride* (10·0 g.), crystallising from aqueous ethanol in yellow needles, m. p. 232° (effervescence) (Found: Cl, 16·9; N, 13·5; loss at 110°/vac., 4·0. $C_{18}H_{26}Cl_2N_4O_2,H_2O$ requires Cl, 16·9; N, 13·4; H_2O, 4·3%).

The base crystallised from aqueous methanol as needles of the *dihydrate*, m. p. unsharp 68—78° (Found: C, 59·7; H, 7·7; N, 15·4. $C_{18}H_{24}N_4O_2,2H_2O$ requires C, 59·3; H, 7·7; N, 15·4%).

(iv) 8-[3-(4-*Ethoxycarbonylpiperazin*-1-*yl*)-3-*oxopropylamino*]-6-*methoxyquinoline*. A mixture of the 8-aminoquinoline (17·4 g.) and 1-β-chloropropionyl-4-ethoxycarbonylpiperazine (12·4 g.) was heated at 130° (bath-temperature) for 6 hr. The mass was extracted with chloroform

(*ca.* 100 ml.) and the insoluble hydrochloride of the starting quinoline was filtered off. The chloroform solution was evaporated to dryness and the residual viscous oil was boiled with ether and then cooled. The pale yellow solid (13·9 g.) was collected and recrystallised from aqueous methanol, to give pale yellow prisms, m. p. 133—134°, of 8-[3-(4-*ethoxycarbonylpiperazin*-1-*yl*)-3-*oxopropylamino*]-6-*methoxyquinoline* (Found: C, 62·3; H, 6·7; N, 14·5. $C_{20}H_{26}N_4O_4$ requires C, 62·2; H, 6·8; N, 14·5%). The *hydrochloride* crystallised from methanol–ethyl acetate in yellow needles, m. p. 192—194° (effervescence) (Found: Cl, 8·6; N, 13·3. $C_{20}H_{27}ClN_4O_4$ requires Cl, 8·4; N, 13·3%).

The foregoing amides, when reduced with lithium aluminium hydride in ether by the general method described above, both gave, in yields of 30% and 38% respectively, pure 6-*methoxy*-8-[3-(4-*methylpiperazin*-1-*yl*)*propylamino*]*quinoline trihydrochloride*, identical with the material described in Table 1.

Method 5. *Reduction of the Quinoline Diamides* (VI).—1-β-*Carboxypropionyl*-4-*methylpiperazine*. Succinic anhydride (10 g.) was added cautiously to a solution of 1-methylpiperazine (10 g.) in chloroform (25 ml.). The mixture was heated on the steam-bath for 1 hr., and then evaporated to dryness. The residue crystallised from slightly aqueous acetone to give 1-β-*carboxypropionyl*-4-*methylpiperazine* as prisms, m. p. 95—96° (Found: C, 49·7; H, 8·1; N, 12·6; loss at 80°/vac., 8·3. $C_9H_{16}N_2O_3,H_2O$ requires C, 49·5; H, 8·3; N, 12·8; H_2O, 8·3%). The *hydrochloride*, prepared in alcohol, crystallised from alcohol in prisms, m. p. 177—178° (Found: C, 45·6; H, 7·3; Cl, 15·2; N, 11·9. $C_9H_{17}ClN_2O_3$ requires C, 45·7; H, 7·2; Cl, 15·0; N, 11·8%).

6-*Methoxy*-8-[4-(4-*methylpiperazin*-1-*yl*)-1,4-*dioxobutylamino*]*quinoline*. (*a*) To a mixture of 8-amino-6-methoxyquinoline (1 g.) and the preceding piperazine derivative (1·3 g.) in methylene dichloride (20 ml.) was added *NN'*-dicyclohexylcarbodi-imide (1·2 g.), and the whole was left at room temperature for 17 hr. The solid was collected and shown to be *NN'*-dicyclohexylurea (m. p. 232—233°). The filtrate was evaporated to dryness, and the residue was shaken with dilute hydrochloric acid (5 ml. of 2N-acid + 25 ml. of water). The filtered solution was basified, and the resulting suspension was shaken with ether. The white solid was collected and recrystallised from ethyl acetate, to give the *diamide* (see Table 5) (800 mg.). It formed a *hydrochloride*, crystallising from alcohol as colourless needles, m. p. 227—228° (Found: Cl, 9·0; N, 14·4. $C_{19}H_{25}ClN_4O_3$ requires Cl, 9·0; N, 14·3%).

(*b*) To a solution of *N*-(6-methoxy-8-quinolyl)succinamic acid [21] (2·74 g.) and 1-methylpiperazine (1 g.) in dioxan (25 ml.), was added *NN'*-dicyclohexylcarbodi-imide (2·04 g.). After 20 hr. the insoluble *NN'*-dicyclohexylurea (1·25 g.) was collected, and the filtrate was evaporated to dryness. The residue was shaken with N-acetic acid (50 ml.) and chloroform (25 ml.), and the aqueous solution was separated and made alkaline. The precipitated solid (1·05 g.) was shown to be identical (m. p. and mixed m. p.) with the diamide described above.

The preparations of all the diamides in Table 5 were carried out by the general method exemplified by the following:

8-[4-(4-*Ethoxycarbonylmethylpiperazin*-1-*yl*)-1,4-*dioxobutylamino*]-6-*methoxyquinoline*. A solution of succinic anhydride (40 g.) and 1-ethoxycarbonylmethylpiperazine (68·8 g.) in chloroform (400 ml.) was refluxed for 1 hr. 8-Amino-6-methoxyquinoline (69·6 g.) was added, and the solution was cooled. *NN'*-Dicyclohexylcarbodi-imide (90·6 g.) was added gradually with shaking and cooling, and then the mixture was left overnight. The *NN'*-dicyclohexylurea (82 g.) was filtered off and washed with chloroform, and the filtrate was evaporated to dryness. The residue was warmed with N-hydrochloric acid (500 ml.), the solution was filtered, and the filtrate was made alkaline with cooling and stirring. Ether (400 ml.) was added and the mixture was stirred vigorously for 1 hr., during which the suspended oil was replaced by a white solid. This required *diamide* (140 g.) (Table 5) was collected and washed with water and ether.

The reductions of the diamides were carried out by methods similar to the general method described above for the monoamides, tetrahydrofuran being used as solvent. For diamides with no other reducible groups, 3 mol. of lithium aluminium hydride were used, and for diamides having also a CO_2Et group, 4 mol.

Attempted reaction of N-(6-*methoxy*-8-*quinolyl*)*succinamic acid with* 1-2′-*hydroxyethylpiperazine*. To a solution of the succinamic acid (2·5 g.) and 1′-2-hydroxyethylpiperazine (1·2 g.) in chloroform (50 ml.) was added *NN'*-dicyclohexylcarbodi-imide (2 g.). After 48 hr., the solution had deposited only a little solid which was removed by filtration. The filtrate was evaporated to dryness, and the residue was extracted with warm N-acetic acid, from which

only a trace of material was deposited on basification. The acid-insoluble material (2·9 g.) crystallised from methanol as fine needles, m. p. 130—132°, of NN′-*dicyclohexyl*-N-[4-(6-*methoxy*-8-*quinolylamino*)-1,4-*dioxobutyl*]*urea* (XIII) (Found: C, 67·7; H, 7·7; N, 11·7. $C_{27}H_{36}N_4O_4$ requires C, 67·5; H, 7·6; N, 11·7%).

1,2,3,4-*Tetrahydro*-6-*methoxy*-8-(5-*piperazin*-1′-*ylpentylamino*)*quinoline*. 6-Methoxy-8-(5-piperazin-1′-ylpentanoylamino)quinoline (IV; $n = 4$, R′ = H) (17 g.) in tetrahydrofuran (160 ml.) was reduced with lithium aluminium hydride (6 g.) in ether (200 ml.). The crude base was distilled (b. p. 244—250°/0·1 mm.) and converted into the trihydrochloride, which, crystallised from ethanol containing a few drops of water, gave orange 6-methoxy-8-(5-piperazin-1′-ylpentylamino)quinoline trihydrochloride (II; $n = 5$, R = 6-MeO, R′ = H) (7 g.), m. p. 265° (decomp.). The filtrate, on dilution with ether, gave a yellow solid which was freed from tar by washing it with a little hot ethanol and recrystallised from ethanol containing a very little water, to give 1,2,3,4-*tetrahydro*-6-*methoxy*-8-(5-*piperazin*-1′-*ylpentylamino*)*quinoline trihydrochloride* (4 g.), yellow prisms, m. p. 235° (decomp.) (Found: C, 50·5; H, 7·9; N, 12·4. $C_{19}H_{35}Cl_3N_4O,\frac{1}{2}H_2O$ requires C, 50·6; H, 8·0; N, 12·4%).

8-[3-(4-*Ethylpiperazin*-1-*yl*)*propylamino*-1,2,3,4-*tetrahydro*-6-*methoxyquinoline*. A mixture of 6-methoxy-8-(β-piperazin-1-ylpropionamido)quinoline (10 g.), acetic anhydride (20 ml.), and dry benzene (50 ml.) was heated under reflux for ½ hr. After removal of solvent *in vacuo*, the residual gum was dissolved in water and cautiously basified with sodium hydroxide, and the precipitated solid was filtered off, washed with water, and dried. It was recrystallised from benzene to give 8-[β-(4-*acetylpiperazin*-1-*yl*)*propionamido*]-6-*methoxyquinoline* (9·0 g.) as colourless crystals, m. p. 136° (Found: C, 64·3; H, 7·1; Ac, 12·2. $C_{19}H_{24}N_4O_3$ requires C, 64·0; H, 6·8; Ac, 12·1%). The acetyl compound was reduced with lithium aluminium hydride and the crude base was converted into its trihydrochloride. The latter crystallised from aqueous ethanol, to give 8-[3-(4-ethylpiperazin-1-yl)propylamino]-6-methoxyquinoline trihydrochloride (6·2 g.) as deep yellow needles, m. p. 239° (decomp.) unchanged on crystallisation from methanol, or on admixture with the product obtained by method 1.

The filtrate from the first crystallisation gradually deposited light coloured solid (4·0 g.), m. p. 235—236° (decomp.), which after crystallisation from ethanol gave 8-[3-(4-*ethylpiperazin*-1-*yl*)*propylamino*]-1,2,3,4-*tetrahydro*-6-*methoxyquinoline trihydrochloride* as fawn needles (3·2 g.), m. p. 240° (decomp.), depressed on admixture with the foregoing material to 224—228° (decomp.) (Found: C, 49·8; H, 8·3; N, 11·9; Cl, 23·1; loss, 4·5. $C_{19}H_{35}ClN_4O,H_2O$ requires C, 49·6; H, 8·1; N, 12·2; Cl, 23·1; H_2O, 3·9%).

The same compound was obtained by reduction of the corresponding quinoline with an excess of sodium and pentyl alcohol by the method of Barber and Wragg.[27]

6-*Methoxy*-8-(3-*piperazin*-1′-*ylpropylamino*)*quinoline Trihydrochloride* (II; $n = 3$, R = 6-OMe, R′ = H): *Alternative Preparation*.—A solution of potassium hydroxide (6 g.) in water (6 ml.) was added to a solution of 8-[3-(4-ethoxycarbonylpiperazin-1-yl)propylamino]-6-methoxyquinoline (2·8 g.; Table 1) in methanol (56 ml.), and the mixture was heated under reflux for 16 hr. The solution was decanted from inorganic salt and evaporated to small bulk. Water was added and the basic product was isolated with ether and converted into the trihydrochloride (Table 1).

8-[2-(4-*Ethoxycarbonylpiperazin*-1-*ylethyl*)*amino*]-6-*methoxyquinoline Dihydrochloride* (II; $n = 2$, R = 6-OMe, R′ = CO_2Et).—6-Methoxy-8-(2-piperazin-1′-ylethylamino)quinoline (5 g.; Table 1) was dissolved in ethyl acetate and stirred with 0·5N-sodium hydroxide (38·5 ml.) with ice-cooling. Ethyl chloroformate (2·1 g.) in ethyl acetate (10 ml.) was added. After 2 hr. an excess of alkali was added and the ethyl acetate layer was separated and dried (Na_2SO_4). The residue left after evaporation of solvent was converted into the *dihydrochloride* which crystallised from ethanol. The salt (4·6 g.) separated at first as deep yellow prisms, but rapid cooling gave leaflets only, m. p. 199—200° (effervescence) (Found after drying: C, 53·1; H, 6·6; Cl, 16·1; N, 12·9. $C_{19}H_{28}Cl_2N_4O_3$ requires C, 52·9; H, 6·6; Cl, 16·4; N, 13·0%).

8-[4-(4-2′-*Hydroxyethylpiperazin*-1-*yl*)*butylamino*]-6-*methoxyquinoline* (II; $n = 4$, R = 6-OMe, R′ = $CH_2{\cdot}CH_2{\cdot}OH$): *Alternative Preparation*.—A solution of 6-methoxy-8-(4-piperazin-1′-ylbutylamino)quinoline (2·5 g.; Table 1) in methanol (25 ml.) was cooled in ice and treated with ethylene oxide (0·52 g.). The solution was left for several days and then evaporated and distilled. The distillate was converted into the trihydrochloride (Table 1).

[27] Barber and Wragg, *J.*, 1946, 613.

8-{3-[4-(2,3-*Dihydroxypropyl*)*piperazin*-1-*yl*]*propylamino*}-6-*methoxyquinoline Trihydrochloride* [II; $n = 3$, R = 6-OMe, R′ = CH_2·CH(OH)·CH_2·OH].—6-Methoxy-8-(3-piperazin-1′-ylpropylamino)quinoline (3 g.; Table 1) in ethanol (30 ml.) was treated with DL-glycidol (0·8 g.) and left for 4 days. Evaporation of ethanol left a base that was insoluble in ether. It was purified by conversion into the *trihydrochloride* and crystallised first from aqueous ethanol and then from a large volume of methanol, forming yellow prisms (2·3 g.), m. p. 228—230° (decomp.) (Found: C, 47·0; H, 7·1; Cl, 20·4; N, 10·7. $C_{20}H_{32}Cl_2N_4O_3,2H_2O$ requires C, 46·2; H, 7·2; Cl, 20·5; N, 10·8%).

NN′-Di-[4-(6-*methoxy*-8-*quinolylamino*)*butyl*]*piperazine* (IX; $n = 3$, R = 6-OMe, CH_2 for CO).—The diamide (IX; $n = 3$) (11·3 g.) in tetrahydrofuran (150 ml.) was reduced with lithium aluminium hydride (3 g.) in tetrahydrofuran (150 ml.). The crude product solidified. Several crystallisations from light petroleum (b. p. 60—80°) gave the *compound* (3·4 g.) as pale yellow prisms, m. p. 110—111° (Found: C, 71·0; H, 8·0; N, 15·1. $C_{32}H_{42}N_6O_2$ requires C, 70·9; H, 7·8; N, 15·5%).

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