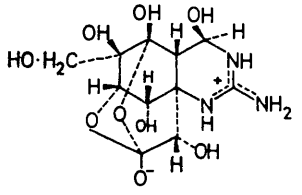
Quinazolines. Part XXI.[1] Synthesis of *cis*-2-Amino-8a-carboxymethyl-3,4,4a,5,6,7,8,8a-octahydroquinazoline and Related Compounds. Conversion of Perhydroquinazolin-2-ones into 2-Amino-3,4,4a,5,6,7,8,8a-octahydroquinazolines

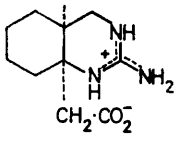
By **Wilfred L. F. Armarego** * and **Phillip A. Reece**, Medical Chemistry Group, The John Curtin School of Medical Research, The Australian National University, Canberra, A.C.T. 2600, Australia

In a study of simple analogues of tetrodotoxin (1), it was found that the halogen atom in *cis*-8a-bromomethylperhydroquinazolin-2-one (4) was readily displaced by cyanide and acetate ions to yield *cis*-8a-cyanomethyl- (5) and *cis*-8a-acetoxymethyl-perhydroquinazolin-2-one (9). Acidic hydrolysis of the cyano-group gave the corresponding 8a-carbamoylmethyl (6) and 8a-carboxymethyl (7) derivatives. A general method was found for converting *cis*-perhydroquinazolin-2-one and its 1,3-dimethyl and 8a-cyanomethyl derivatives into the respective *cis*-2-amino-3,4,4a,5,6,7,8,8a-octahydroquinazolinium salts (22), (23), and (20). From the last-named compound *cis*-2-amino-8a-carboxymethyl-3,4,4a,5,6,7,8,8a-octahydroquinazoline (2) and its methyl ester salt were obtained. 1- and 3-methyl-*trans*-perhydroquinazolin-2-one [(13) and (14)] and -2-thione [(17) and (18)] and 1-and 3-methyl-*cis*- and -*trans*-2-amino-3,4,4a,5,6,7,8,8a-octahydroquinazolinium salts were also prepared. ^{1}H N.m.r. spectra and preliminary biological evaluation (M.L.D. values in mice) of some of these compounds are briefly discussed.

ONE of the target compounds in a study of simple analogues of the puffer fish neurotoxin tetrodotoxin (1) which we required for biological evaluation is the reduced 2-aminoquinazoline (2). The synthesis of this compound is described together with those of related hydroquinazolines.



(1)



(2)

Our previous success in introducing the 8a-side-chain into a hydroquinazoline by addition of the elements of nitromethane to 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (on fusion with nitroacetic acid) [2] made *cis*-8a-nitromethylperhydroquinazolin-2-one (3) readily available and a convenient starting material. This compound was converted into the bromomethyl derivative (4) *via* the aminomethyl intermediate as before.[2] The bromomethylquinazolin-2-one readily gave the corresponding cyanomethylquinazolinone (5) in almost quantitative yield by reaction with potassium cyanide. This is a surprising result because of the known sluggish reactivity of neopentyl halides in nucleophilic displacement reactions.[3] The enhanced reactivity of the halide (4) may well be attributed to its more rigid structure, which is less sterically demanding than those of neopentyl halides. The nitrile was successfully hydrolysed to the amide (6) and to the acid (7), which yielded the methyl ester (8) with diazomethane. By analogy with the nitroacetic acid reaction mentioned earlier, 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one and cyanoacetic acid were fused with the aim of obtaining the nitrile (5) directly. The only product which was isolated (43% yield) was, unexpectedly, a 1 : 1 mixture of *cis*- and *trans*-perhydroquinazolin-2-one; we have no reasonable explanation for the course of this reaction. The halide (4) also reacted with silver acetate in acetic acid and gave *cis*-8a-acetoxymethylperhydroquinazolin-2-one (9) in high yield. Reduction of the latter with lithium aluminium hydride produced a 5 : 3 mixture of *cis*-8a-hydroxymethyl- (10) and *cis*-8a-methyl-perhydroquinazolin-2-one (11).

The next step in the sequence is the conversion of the saturated cyclic urea (5) or (9) into a cyclic guanidine. We did not find a precedent in the literature for this direct conversion, although the transformations of unsaturated cyclic ureas, *e.g.* formation of 2-aminoquinazolines from quinazolin-2(1*H*)-ones *via* 2-chloroquinazolines,[4] are well known. Preliminary reactions of the nitrile (5) with phosphorus halides followed by ammonia (or amines) under a variety of conditions were uniformly unsuccessful, and further investigations were made with the more readily available ureas (12)—(15). Also with these compounds, standard conditions (phosphorus halides and ammonia) failed, and *cis*-perhydroquinazolin-2-one was recovered unchanged after fusion with phenyl phosphorodiamidate (a reagent which converts oxo- into

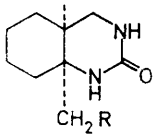
[1] Part XX, W. L. F. Armarego and P. A. Reece, *J.C.S. Perkin I*, 1974, 2313.

[2] W. L. F. Armarego, *J. Chem. Soc.* (*C*), 1971, 1812.

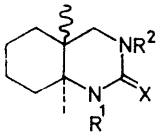
[3] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca, New York, 1969, p. 552.

[4] W. L. F. Armarego, 'Fused Pyrimidines. Part I. Quinazolines,' ed. D. J. Brown, Interscience, New York, 1967, pp. 219 and 322.

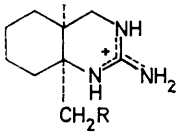
amino-heterocycles).[5] Attempts to thiate the ureas to give thioureas, *e.g.* (16) (as intermediate for guanidines) and the nitrile (5) by treatment with phosphorus pentasulphide in a number of solvents were ineffective. The authentic thioureas (17) and (18) were prepared from the corresponding aminomethylcyclohexylamines by treatment with carbon disulphide in the presence of sodium hydroxide followed by fusion of the intermediate dithiocarboxylatoaminomethylcyclohexylammonium zwitterions. We must mention here that nitroacetic acid reacted explosively with 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-thione, and when the reaction was moderated by adding nitromethane the yield of *cis*-8a-nitromethylperhydroquinazolin-2-thione was low and the product was difficult to purify. We previously reported that we were unable to isolate 2-amino-3,4,5,6,7,8-hexahydroquinazoline for fusion with nitroacetic acid in order to obtain the nitromethyl adduct (19), and that fusion of 2-amino-3,4,5,6,7,8-hexahydro-4-methoxycarbonylquinazoline caused a prototropic rearrangement to the unreactive 3,5,6,7,8,8a-hexahydroquinazoline instead of a nitromethane addition.[6]



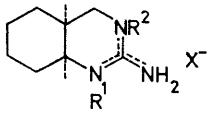
(3) R= NO
(4) R= Br
(5) R= CN
(6) R= CO·NH_2
(7) R= CO_2H
(8) R= CO_2Me
(9) R= OAc
(10) R= OH
(11) R= H



(12) $R^1=R^2=H$, X=O(*cis*)
(13) R^1=Me,R^2=H,X=O(*trans*)
(14) R^1=H,R^2=Me,X=O(*trans*)
(15) $R^1=R^2$=Me,X=O(*cis*)
(16) $R^1=R^2$=H,X=S(*trans*)
(17) R^1=Me,R^2=H,X=S(*trans*)
(18) R^1=H,R^2=Me,X=S(*trans*)

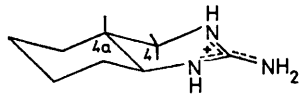


(19) R= NO_2
(20) R=CN (picrate)
(21) R=CO_2Me (picrate,Cl)

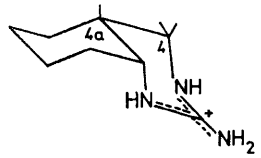


(22) $R^1=R^2$=H,X=Cl
(23) $R^1=R^2$=Me,X=picrate,Cl
(24) R^1=Me,R^2=H,X=picrate
(25) R^1=H,R^2=Me,X=picrate

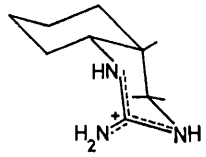
We finally succeeded in transforming *cis*-perhydroquinazolin-2-one (12) into *cis*-2-amino-3,4,4a,5,6,7,8,8a-octahydroquinazolinium chloride (22) under carefully controlled conditions (PCl_5 in $POCl_3$; then $NaNH_2$ in liquid NH_3; see Experimental section). *cis*-1,3-Dimethylperhydroquinazolin-2-one (15) was similarly converted into *cis*-2-amino-3,4,4a,5,6,7,8,8a-octahydro-1,3-dimethylquinazolinium chloride [and picrate (23)]. Attempts to prepare the latter by condensation of *N*-(*cis*-2-methylaminomethylcyclohexyl)methylamine with *S*-methylisothiouronium sulphate failed. This reaction,



(26)



(27)



(28)

however, was used to make 1- (24) and 3-methyl-*cis*-2-amino-octahydroquinazolinium salts (25) and the corresponding *trans*-isomers. The PCl_5–$NaNH_2$ method successfully converted the nitrile (5) into *cis*-2-amino-8a-cyanomethyloctahydroquinazolinium picrate (20), which on acidic hydrolysis gave the required *cis*-2-amino-8a-carboxymethyloctahydroquinazoline (2), which was esterified to the methyl ester (21).

^1H *N.m.r. Spectra.*—The splitting patterns, the coupling constants of the two C-4 protons, and the $W_{\frac{1}{2}}$ values of the carbocyclic H band envelope of 1- and 3-methyl-*trans*-amino-3,4,4a,5,6,7,8,8a-octahydroquinazoline cations are similar to those of the unmethylated amine [7] and are consistent with the rigid structure (26). The *cis*-2-amino-octahydroquinazolinium cations behaved like the *cis*-perhydroquinazolinium cations and the *cis*-perhydroquinazolin-2-ones [1] in solution. The spectra clearly indicated that the 3-methyl derivative (25) is entirely in the conformation (27) and that the 1-methyl (24) and 1,3-dimethyl derivative (23) are in the preferred conformation (28). The last two compounds are further examples of this unusual conformation in hydroquinazolines (for discussion see ref. 1). All the *cis*-8a-substituted hydroquinazolines described above which gave clearly resolved patterns of signals for the C-4 protons [*i.e.* (2), (6)—(10), (20), and (21)] are almost entirely in the more common conformation (27).

Biological Evaluation.—In a preliminary study, the

[5] E. A. Arutyunyan, V. I. Gunar, E. P. Gracheva and S. I. Zavyalov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1969, 587; A. Rosowsky and N. Papathanasopoulos, *J. Heterocyclic Chem.*, 1972, **9**, 1235.

[6] W. L. F. Armarego and B. A. Milloy, *J.C.S. Perkin I*, 1973, 2814.

[7] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 238.

M.L.D. values (minimum lethal dose) for mice of a number of hydroquinazolines were determined and are

Minimum lethal doses for male mice (intraperitoneal)

2-Amino-3,4,4a,5,6,7,8,8a-octahydroquinazoline	M.L.D. (mg per kg mouse) †
cis-(hydrochloride)	100
trans-(hydrochloride)	110
cis-1-Methyl-(sulphate)	100
cis-3-Methyl-(sulphate)	90
trans-1-Methyl-(sulphate)	110
trans-3-Methyl-(sulphate)	150
cis-8a-Carboxymethyl-	>500
cis-8a-Methoxycarbonylmethyl-(hydrochloride)	210
cis-8a-Cyanomethyl-(hydrochloride)	100—500
cis-3-Methylperhydroquinazolin-2-one	75
Tetrodotoxin	0.013

† Injected in sterile saline 0.9N-solution to *ca.* 40 g mice (*ca.* 10 weeks old); error *ca.* 10—20 mg kg^{-1}.

listed in the Table. Death occurred within 1—6 min by apparent paralysis of the limbs and inhibition of respiration. Mice that survived this period recovered completely without apparent resistance or sensitisation to these compounds. Although the most active aminoquinazoline was much less toxic than tetrodotoxin, it was nevertheless comparable with the most active cyclic guanidines known.[8,9] The oxo-compound (14) was the most toxic compound tested but it killed the animals by affecting the central nervous system, causing severe convulsions. Further evaluation of these compounds is in progress.

EXPERIMENTAL

Elemental analyses were determined by the Australian National University Analytical Services Unit. I.r. spectra (KBr discs for solids and films for liquids) were measured on a Perkin-Elmer 21 spectrometer and assignments are tentative; the C–H stretching vibrations near 3 000 cm^{-1} are not included. ^1H N.m.r. spectra were measured on a Varian T60A spectrometer unless otherwise stated; J and $W_{\frac{1}{2}}$ values are in Hz. All extracts were dried over Na_2SO_4 and evaporations were carried out below 30 °C at *ca.* 18 mmHg.

cis-8a-*Cyanomethylperhydroquinazolin*-2-*one* (5).—The bromomethyl compound (4) [2] (1.08 g) in ethanol (60 ml) was added to a solution of potassium cyanide (315 mg, 1.1 mol. equiv.) in water (2 ml); the mixture was refluxed for 6 h and evaporated. The residue was dissolved in 7N-ammonia saturated with NaCl and extracted with chloroform. The dried extract gave the *cyanomethylquinazolinone* (835 mg, 98%), m.p. 226—227° (from ethyl acetate) (Found: C, 62.1; H, 7.8; N, 21.6. $C_{10}H_{15}N_3O$ requires C, 62.15; H, 7.8; N, 21.75%), $\nu_{max.}$ 3 260, 3 125 (NH), 2 250 (CN), and 1688 cm^{-1} (amide) δ [100 MHz; $(CD_3)_2SO$] 6.36br (s, NH), 6.25br (s, NH), 3.39 (q, H-4eq, $J_{4,4'}$ 13, $J_{4,4a}$ 4), 2.80 (q, H-4*ax*, $J_{4,4'}$ 13, $J_{4',4a}$ 2), 2.73 (s, CH_2·CN), and 2.0—1.0 (carbocyclic H, $W_{\frac{1}{2}}$ 14).

cis-8a-*Acetoxymethylperhydroquinazolin*-2-*one* (9).—The bromomethyl compound (4) (460 mg) in acetic acid (5 ml) was added to a solution of silver acetate (372 mg, 1.2 mol. equiv.) in hot acetic acid (180 ml). After boiling for 15 min precipitation of silver bromide was complete and the solution was filtered through Celite and evaporated. The residue was added to saturated aqueous potassium carbonate (5 ml) and extracted with chloroform. The extract was evaporated to a small volume, diluted with benzene (5 vol.) and evaporated until the *acetoxymethylquinazolin*-2-*one* (90%) separated as needles, m.p. 168—170°. Recrystallisation from $CHCl_3$–C_6H_6 followed by sublimation at 170° and 0.1 mmHg raised the m.p. to 175° (Found: C, 58.2; H, 8.0; N, 12.1. $C_{11}H_{18}N_2O$ requires C, 58.4; H, 8.0; N, 12.4%), $\nu_{max.}$ 3 240 and 3 100 (NH), 1 740 (ester CO), and 1 680 cm^{-1} (amide); δ ($CDCl_3$) 6.40br (s, NH), 5.85br (s. NH), 4.05 (q, CH_2O, J_{gem} 11), 3.58 (q, H-4eq, $J_{4,4'}$ 12, $J_{4,4a}$ 2), 2.95 (q, H-4*ax*, $J_{4,4'}$ 12, $J_{4',4a}$ 4), 2.10 (s, CH_3), and 2.0—1.0 (carbocyclic H, $W_{\frac{1}{2}}$ 10).

cis-8a-*Hydroxymethylperhydroquinazolin*-2-*one* (10).—The preceding acetoxy-compound (820 mg) in tetrahydrofuran (50 ml) was added to lithium aluminium hydride (2 g) suspended in tetrahydrofuran (100 ml) and the mixture was refluxed with stirring for 24 h. The cooled solution was treated with saturated aqueous potassium carbonate (20 ml), refluxed for 20 min, and filtered, and the filtrate was evaporated. The residue was dissolved in chloroform (100 ml), the solution was evaporated, and the process was repeated. The residue (546 mg) was triturated with chloroform (10 ml); this left cis-8a-*hydroxymethylquinazolin*-2-*one* (250 mg), m.p. 199—201°, undissolved. A further quantity (100 mg, total yield 52%) of hydroxy-compound was obtained on concentrating the chloroform extract to 1.5 ml. After sublimation at 190° and 0.5 mmHg it had m.p. 201—202° (Found: C, 58.4; H, 8.8; N, 15.0. $C_9H_{16}N_2O_3$ requires C, 58.7; H, 8.75; N, 15.2%), $\nu_{max.}$ 3 285sh (OH), 3 255 and 3 100 (NH), and 1 687 and 1 644 cm^{-1} (amide); δ (D_2O), 3.53 (q, H-4eq, $J_{4,4'}$ 13.4, $J_{4,4a}$ 4.2), 3.51 (q, CH_2O, J_{gem} 12), 2.93 (q, H-4*ax*, $J_{4,4'}$ 13.4, $J_{4',4a}$ 2), and 2.0—1.0 (carbocyclic H, $W_{\frac{1}{2}}$ 8) (HOD signal as marker at δ 4.72).

The filtrate gave *cis*-8a-methylperhydroquinazolin-2-one (11) (190 mg, 30%), m.p. 225—226°, identical with an authentic sample.[2]

cis-8a-*Carbamoylmethylperhydroquinazolin*-2-*one* (6).—The cyanomethyl compound (5) (198 mg) in concentrated sulphuric acid (10 ml) was heated on a steam-bath for 30 min. The solution was cooled, diluted with water (20 ml), neutralised with aqueous 4N-sodium hydroxide, and passed through a Dowex 50W (H^+) column which was washed extensively with water. Elution with aqueous 6N-ammonia and evaporation gave cis-8a-*carbamoylmethylperhydroquinazolin*-2-*one* (89 mg, 42%), m.p. 259° (from MeOH) (Found: C, 57.1; H, 8.2; N, 19.9. $C_{10}H_{17}N_3O_2$ requires C, 56.9; H, 8.1; N, 19.9%), $\nu_{max.}$ 3 297 (NH) and 1 680 cm^{-1} (amide and urea).

cis-8a-*Carboxymethylperhydroquinazolin*-2-*one* (7).—The cyanomethyl compound (5) (250 mg) in concentrated sulphuric acid (3.5 ml) and water (5 ml) was refluxed for 2 h. The solution was cooled, diluted with water, saturated with Na_2SO_4, and extracted with chloroform (6 × 100 ml). Evaporation of the extract gave the *carboxymethyl compound* (232 mg, 87%), m.p. 255° (decomp.) (from H_2O) (Found: C, 56.7; H, 7.8; N, 13.1. $C_{10}H_{16}N_2O_3$ requires C, 56.6; H, 7.6; N, 13.2%), $\nu_{max.}$ 3 305 (NH) and 1 692 cm^{-1} (carboxy and urea); δ [$(CD_3)_2SO$] 6.20br (s, NH), 5.98br (s, NH), 3.44 (q, H-4eq, $J_{4,4'}$ 13, $J_{4,4a}$ 4), 2.78 (q, H-4*ax*, $J_{4,4'}$ 12, $J_{4',4a}$ 2), 2.42 (s, CH_2·CO_2H), and 2.0—1.0 (carbocyclic H, $W_{\frac{1}{2}}$ 20).

cis-8a-*Methoxycarbonylmethylperhydroquinazolin*-2-*one* (8).—The preceding acid (100 mg) in methanol (5 ml) was

[8] B. K. Ranney, F. A. Fuhrman, J. L. Schmiegel, and H. S. Mosher, *Arch. Int. Pharmacodyn.*, 1968, **175**, 1.

[9] P. B. Goldberg and C. Y. Kao, *J. Pharm. Exp. Ther.*, 1973, **186**, 569.

treated dropwise with a solution of diazomethane in ether at 0 °C until the yellow colour persisted. Evaporation of the solvent left the *methyl ester* (110 mg, 99%), m.p. 184° (from MeOH–H_2O, 1 : 1) (Found: C, 58.4; H, 8.0; N, 12.4. $C_{11}H_{18}N_2O_3$ requires C, 58.2; H, 8.3; N, 12.0%), $\nu_{max.}$ 3 240 (NH), 1 721 (ester), and 1 691 cm^{-1} (amide); δ ($CDCl_3$) 5.73br (s, NH), 5.35br (s, NH), 3.71 (s, CH_3·O·CO), 3.64 (q, H-4*eq*, $J_{4,4'}$ 12, $J_{4,4a}$ 2.5), 3.02 (q, H-4*ax*, $J_{4,4'}$ 12, $J_{4',4a}$ 1), 2.62 (s, CH_2CO), and 2.1—1.2 (carbocyclic H, $W_{\frac{1}{2}}$ 15).

cis-2-*Amino*-3,4,4a,5,6,7,8,8a-*octahydroquinazolinium Chloride* (22).—*cis*-Perhydroquinazolin-2-one (154 mg) and phosphorus pentachloride (208 mg, 1 mol. equiv.) in phosphoryl chloride (10 ml) were heated in a sealed tube at 130 °C for 3 h. The volatile components were removed and the residue was dissolved in liquid ammonia (30 ml) containing sodamide (39 mg, 1 mol. equiv.). The ammonia was allowed to evaporate and the residue was extracted with chloroform and evaporated. The residue was dissolved in ethanol and passed through a Dowex-1 (OH^-) column. The ethanolic eluate was acidified with hydrochloric acid and evaporated to give *cis*-2-amino-octahydroquinazolinium chloride (157 mg, 83%), identical with an authentic sample.[6]

cis-2-*Amino*-3,4,4a,5,6,7,8,8a-*octahydro*-1,3-*dimethylquinazolinium Picrate* (23).—*cis*-1,3-Dimethylperhydroquinazolin-2-one [1] was treated as above at 130 °C and 1 h; the residue from the chloroform extract was a gum but gave the crystalline *picrate* (50 mg, 49%), m.p. 135.5—137° (from C_6H_6) (Found: C, 47.1; H, 5.5; N, 20.5. $C_{18}H_{22}N_6O_7$ requires C, 46.8; H, 5.4; N, 20.5%), $\nu_{max.}$ 1 668 and 1 631 cm^{-1} (guanidino); δ [$(CD_3)_2SO$] 8.70 (s, picrate H), 7.12br (s, NH_2), 3.3br (H-8a), 3.28 (t, H-4*ax*, $J_{4,4'}$ 12, $J_{4,4a}$ 12.1), and 3.11 (q, H-4*eq*, $J_{4,4'}$ 12, $J_{4',4a}$ 6.0).

cis-2-*Amino*-3,4,4a,5,6,7,8,8a-*octahydro*-3-*methylquinazolinium Picrate* (25).—*cis*-1-Amino-2-methylaminomethylcyclohexane [1] (142 mg; b.p. 58° at 0.7 mmHg) in water (0.5 ml) was added to *S*-methylisothiouronium sulphate (135 mg, 0.5 mol. equiv.) and the mixture was refluxed for 1.5 h. Evaporation gave the crude sulphate (215 mg) as a hygroscopic gum which was passed through an Amberlite IR-400 (OH^-) column in ethanol; the eluates were acidified with ethanolic hydrogen chloride and evaporated to give the hydrochloride, also as a gum. This gave a crystalline *picrate* (354 mg, 92%), m.p. 181° (from MeOH) (Found: C, 45.8; H, 4.9; N, 21.3. $C_{15}H_{20}N_6O_7$ requires C, 45.5; H, 5.1; N, 21.2%), $\nu_{max.}$ 1 662 and 1 621 cm^{-1} (guanidino); δ [$(CD_3)_2SO$] 8.70 (s, picrate H), 7.47br (s, NH), 6.89 (s, NH_2), 3.5br (H-8a), 3.45 (q, H-4*eq*, $J_{4,4'}$ 11.2, $J_{4,4a}$ 5.5), 3.16 (q, H-4*ax*, $J_{4,4'}$ 11.2, $J_{4',4a}$ 4.6), 3.00 (s, NCH_3), 2.08 (m, H-4a), and 1.1—1.8 (carbocyclic H, $W_{\frac{1}{2}}$ 14).

cis-2-*Amino*-3,4,4a,5,6,7,8,8a-*octahydro*-1-*methylquinazolinium Picrate* (24).—To *cis*-1-aminomethyl-2-methylaminocyclohexane [1] (142 mg; b.p. 40—42° at 2.5 mmHg) in water (0.5 ml) was added *S*-methylisothiouronium sulphate (135 mg, 0.5 mol. equiv.) and the mixture was refluxed for 12 h. The residue left after evaporation gave the *picrate* (365 mg, 95%), m.p. 193° (from MeOH) (Found: C, 45.0; H, 5.3; N, 20.4. $C_{15}H_{20}N_6O_7$ requires C, 45.0; H, 5.4; N, 20.1%), $\nu_{max.}$ 1 659 and 1 632 cm^{-1} (guanidino); δ [$(CD_3)_2SO$], 8.68 (s, picrate H), 7.42br (NH), 6.91 (s, NH_2), 3.3br (H-8a), 3.37 (t, H-4*ax*, $J_{4,4'}$ 12.3, $J_{4,4a}$ 12.2), 3.14 (q, H-4*eq*, $J_{4,4'}$ 12.3, $J_{4',4a}$ 4.5), and 1.8—1.0 (carbocyclic H, $W_{\frac{1}{2}}$ 22).

Similarly *trans*-1-aminomethyl-2-methylaminocyclohexane [10] (b.p. 42° at 0.5 mmHg) gave trans-2-*amino*-3,4,4a,5,6,7,8,8a-*octahydro*-1-*methylquinazolinium picrate* (95%), m.p. 211° (from MeOH) (Found: 45.5; H, 5.1; N, 20.9. $C_{15}H_{20}N_6O_7$ requires C, 45.4; H, 5.1; N, 21.2%), $\nu_{max.}$ 1 660 and 1 620 cm^{-1} (guanidino); δ [$(CD_3)_2SO$] 8.60 (s, picrate H), 7.61br (NH), 7.02 (s, NH_2), 3.93 (q, H-4*eq* $J_{4,4'}$ 11.6, $J_{4,4a}$ unclear), 3.23 (q, H-4*ax*, $J_{4,4'}$ 11.6, $J_{4',4a}$ 3.0?), *ca.* 3.2br (H-8a), 2.93 (s, NCH_3), and 2.3—0.9br (carbocyclic H, $W_{\frac{1}{2}}$ 48); and *trans*-1-amino-2-methylaminomethylcyclohexane (b.p. 52° at 1 mmHg) gave trans-2-*amino*-4,4a,5,6,7,8,8a-*octahydro*-3-*methylquinazolinium picrate* (92%), m.p. 218° (from MeOH) (Found: C, 45.1; H, 4.9; N, 21.2. $C_{15}H_{20}N_6O_7$ requires C, 45.4; H, 5.1; N, 21.2%), $\nu_{max.}$ 1 661 and 1 620 cm^{-1} (guanidino); δ [$(CD_3)_2SO$] 8.60 (s, picrate H), 7.54 (s, NH), 6.90br (NH_2), *ca.* 3.2br (H-8a), 3.18 (q, H-4*eq*, $J_{4,4'}$ 11, $J_{4,4a}$ 5), 3.04 (t, H-4*ax*, $J_{4,4'}$ 11, $J_{4',4a}$ 10.9), 2.96 (s, NCH_3), and 2.2—0.9 (carbocyclic H, $W_{\frac{1}{2}}$ 48), after 2.5 h boiling.

cis-2-*Amino*-8a-*cyanomethyl*-3,4,4a,5,6,7,8,8a-*octahydroquinazolinium Picrate* (20).—The cyanomethyl compound (5) (300 mg) and phosphorus pentachloride (1 mol. equiv.) in phosphoryl chloride (15 ml) were heated in a sealed tube at 130 °C for 2.5 h. The solution was evaporated, the residue was added to liquid ammonia (150 ml) containing sodamide (60 mg, 1 mol. equiv.), and the ammonia was evaporated off. The residue was extracted with chloroform; the extract was then in turn extracted with aqueous N-hydrochloric acid and the acidic extract was evaporated, leaving cis-2-*amino*-8a-*cyanomethyloctahydroquinazolinium chloride* (220 mg, 64%) as a hygroscopic solid, $\nu_{max.}$ 3 360 (NH), 2 260 (CN), and 1 666 and 1 624 cm^{-1} (guanidino); δ (D_2O) 3.58 (q, H-4*eq*, $J_{4,4'}$ 13, $J_{4,4a}$ 5), 3.31 (q, H-4*ax*, $J_{4,4'}$ 13, $J_{4',4a}$ 1), 2.92 (s, CH_2CN), and 2.3—1.1 (carbocyclic H, $W_{\frac{1}{2}}$ 20) (HOD signal at δ 4.70 taken as standard). The *picrate* had m.p. 180° (Found: C, 45.2; H, 4.5; N, 23.5. $C_{16}H_{19}N_7O_7$ requires C, 45.5; H, 4.5; N, 23.4%), $\nu_{max.}$ 3 455 and 3 320 (NH), 2 260 (CN), and 1 672 and 1 609 cm^{-1} (guanidino).

cis-2-*Amino*-8a-*carboxymethyl*-3,4,4a,5,6,7,8,8a-*octahydroquinazoline* (2) *and its Methyl Ester Hydrochloride and Picrate* (21).—The preceding chloride (114 mg) in water (2.3 ml) and concentrated sulphuric acid (1.7 ml) was refluxed for 2 h. The mixture was cooled, neutralised, and evaporated. The residue was extracted with cold ethanol and the extracts were evaporated to give cis-2-*amino*-8a-*carboxymethyloctahydroquinazoline* as a hygroscopic solid (120 mg, 97%), $\nu_{max.}$ 3 260 (NH) and 1 663 and 1 625br cm^{-1} (guanidino and carboxy); δ (D_2O) 3.58 (q, H-4*eq*, $J_{4,4'}$ 13, $J_{4,4a}$ 4.5), 3.07 (q, H-4*ax*, $J_{4,4'}$ 13, $J_{4',4a}$ 2), 2.56 (s, CH_2CO_2), and 2.2—1.1 (carbocyclic H, $W_{\frac{1}{2}}$ 18) (HOD at δ 4.70 as standard). The acid (60 mg) was refluxed overnight in methanolic 36% hydrogen chloride (5 ml) and the solution was evaporated leaving cis-2-*amino*-8a-*methoxycarbonylmethyloctahydroquinazolinium chloride* as a hygroscopic solid (64 mg, quant.), $\nu_{max.}$ 3 260 (NH), 1 728 (ester), and 1 663 and 1 630 cm^{-1} (guanidino); δ ($CDCl_3$) 3.73 (s, CH_3·O·CO), 3.62 (q, H-4*eq*, $J_{4,4'}$ 15, $J_{4,4a}$ 4.5), 3.04 (q, H-4*ax*, $J_{4,4'}$ 15, $J_{4',4a}$ 1), 2.62 (s, CH_2·CO_2), and 2.2—1.2 (carbocyclic H, $W_{\frac{1}{2}}$ 15). The *picrate* had m.p. 157—158° (Found: C, 45.1; H, 5.0; N, 18.5. $C_{17}H_{22}N_6O_9$ requires C, 44.9; H, 4.9; N, 18.5%), $\nu_{max.}$ 3 420 and 3 230 (NH), 1 730 (ester), and 1 672 and 1 650 cm^{-1} (guanidino).

trans-1-*Methylperhydroquinazolin*-2-*one* (13).—To *trans*-1-aminomethyl-2-methylaminocyclohexane (426 mg) suspended in water (1.5 ml) were added dropwise, simultaneously, a 12.5% solution of phosgene in toluene (1.95 ml, 2 mol. equiv.) and aqueous 2N-sodium hydroxide (2.1 ml,

[10] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 2502.

4 mol. equiv.). The mixture was stirred vigorously for 1 day, a further quantity of phosgene in toluene (0.97 ml, 1 mol. equiv.) was added, and stirring was continued for 1 day. The solution was diluted with chloroform (50 ml) and extracted with aqueous 0.1N-hydrochloric acid (2 × 10 ml). The chloroform layer was dried and evaporated leaving a glassy solid which was sublimed at 180° and 0.2 mmHg yielding trans-1-*methylperhydroquinazolin*-2-*one* (290 mg, 58%), m.p. 128° (Found: C, 64.3; H, 9.7; N, 16.2. $C_9H_{16}N_2O$ requires C, 64.3; H, 9.6; N, 16.6%), $\nu_{max.}$ 3 320 and 3 240 (NH), and 1 656 cm^{-1} (amide); δ ($CDCl_3$) *ca.* 5.3br (NH), *ca.* 3.0br (H-8a), 2.88 (s, NCH_3), *ca.* 3.0 (m, H-4*eq* and H-4*ax*), and 2.0—0.8 (carbocyclic H, $W_{\frac{1}{2}}$ 46).

Similarly *trans*-1-amino-2-methylaminomethylcyclohexane gave trans-3-*methylperhydroquinazolin*-2-*one* (47%), 167—168° after sublimation at 180° and 0.03 mmHg (Found: C, 64.3; H, 9.7; N, 16.5. $C_9H_{16}N_2O$ requires C, 64.3; H, 9.6; N, 16.6%), $\nu_{max.}$ 3 320 and 3 240 (NH) and 1 655 cm^{-1} (amide), δ ($CDCl_3$) 4.58br (NH), *ca.* 3.0br (H-8a), *ca.* 3.0 m (H-4*eq* and H-4*ax*), 2.97 (s, NCH_2), and 2.1—0.8 (carbocyclic H, $W_{\frac{1}{2}}$ 48).

trans-1-*Methylperhydroquinazoline*-2-*thione* (17).—To a 50% aqueous ethanolic solution of *trans*-1-methylamino-2-methylaminocyclohexane (256 mg) carbon disulphide (0.5 ml) was added dropwise, and the mixture was refluxed for 1 h and then set aside for 1 h. The precipitate (270 mg) was the dithio-zwitterion ($\nu_{max.}$ 3 255, 2 970, 2 890, 1 589, 1 474, 1 451, 1 306, 1 260, 1 220, 959, and 900 cm^{-1}) which on heating at its m.p. for 30 s (effervescence with loss of H_2S) afforded a residue which crystallised from benzene–light petroleum (b.p. 40—60°) (9 : 1) to give the trans-1-*methyl*-2-*thione* (122 mg, 70%), m.p. 182—183° (Found: C, 58.2; H, 9.1; N, 15.0. $C_9H_{16}N_2S$ requires C, 58.2; H, 8.8; N, 15.2%), $\nu_{max.}$ 3 255 (NH) and 1 089 cm^{-1} (CS); δ ($CDCl_3$) 6.93br (NH), 3.51 (s, NCH_3), 3.23 (t, H-4*eq*, $J_{4.4'}$ 10.4, $J_{4.4a}$ 11), 3.12 (q, H-4*ax*, $J_{4,4'}$ 10.4, $J_{4',4a}$ 5), *ca.* 3.0br (H-8a), and 2.2—0.9 (carbocyclic H, $W_{\frac{1}{2}}$ 46).

Similarly *trans*-1-amino-2-methylaminomethylcyclohexane gave a zwitterion ($\nu_{max.}$ 2 940, 2 875, 1 606, 1 475, 1 262, 1 212, 1 109, and 970 cm^{-1}) which after heating at 200 °C for 30 s and recrystallisation from benzene gave trans-3-*methylperhydroquinazoline*-2-*thione* (61%), m.p. 238.5—239.5° (Found: C, 58.5; H, 8.9; N, 15.2. $C_9H_{16}N_2S$ requires C, 58.6; H, 8.8; N, 15.2%), $\nu_{max.}$ 3 265 (NH) and 1 082 cm^{-1} (CS); δ ($CDCl_3$) 6.2br (NH), 3.38 (s, NCH_3), 3.15 (not clearly resolved multiplet for H-4 and -4′), *ca.* 3.0br (H-8a), and 2.2—0.9 (carbocyclic H, $W_{\frac{1}{2}}$ 46).

We thank Dr D. J. Brown for discussions and encouragement, and one of us (P.A.R.) acknowledges a Commonwealth Postgraduate Scholarship award.

[5/191 *Received*, 28*th January*, 1975]