Quinazolines. Part XIX.[1] Reduction of 2-Amino-5,6,7,8-tetrahydroquinazoline-4-carboxylic Acid and 1,2,5,6,7,8-Hexahydro-2-oxoquinazoline-4-carboxylic Acid †

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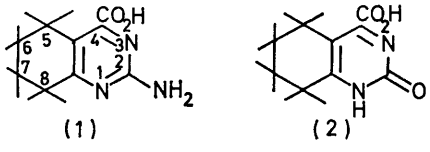
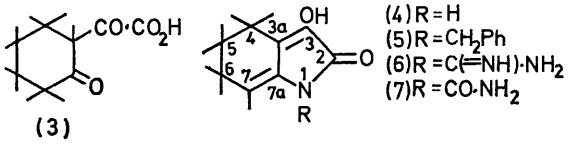
2-Oxocyclohexylglyoxylic acid condensed with guanidine carbonate and urea to yield, respectively, 2-amino-5,6,7,8-tetrahydroquinazoline-4-carboxylic acid (1) and 1,2,5,6,7,8-hexahydro-2-oxoquinazoline-4-carboxylic acid (2),† and not the isomeric indoles (6) and (7). Catalytic reduction of the carboxylic acids (and their methyl esters) gave the 3,4(or 1,4)‡-dihydro-derivatives [(8) and (12)], which rearranged to the 3,8a(or 1,8a)‡ -dihydro-isomers in the presence of acid. 1,4,5,6,7,7a-Hexahydro-3-hydroxyindol-2-one (15) and its 1-benzyl derivative (16) were prepared for spectral comparison. The former compound was further reduced with sodium borohydride to 3-hydroxy-*cis*-perhydroindol-2-one (17).

In continuing our investigation on the preparation of simple analogues of the fish poison tetrodotoxin, we studied the reduction of the quinazolinecarboxylic acids (1) and (2) with the aim of making the respective 3,4-dihydro-derivatives and then introducing the 8a-side-chain by fusion with nitroacetic acid [*cf.* 3,4,5,6,7,8-octahydroquinazolin-2(1H)-one].[3] The starting material for making these acids, 2-oxocyclohexylglyoxylic acid (3), also reacts with amines, but in a different manner, to yield isatins [*e.g.* (4) and (5)].[4-6] The properties of the acids (1) and (2) and the isatins (4) and (5), and their reduction products, are compared in this paper.





The acid (3) reacted with guanidine carbonate to give a product of elemental composition consistent with formula (1) or (6). The structure (1) is assigned from the following evidence: the compound does not give a colour with iron(III) chloride solution [the isatins, *e.g.* (4), give a blue colour]; its u.v. spectrum is similar to that of 2-amino-5,6,7,8-tetrahydroquinazoline, and it absorbs at longer wavelengths than the isatins (Table 1); its basic pK_a value (4·72) and that of its methyl ester (3·24) are comparable with that of 2-amino-5,6,7,8-tetrahydroquinazoline (4·92) and are not in accord with an acylguanidine structure [*e.g.* (6); pK_a of acetylguanidine[7] is 8·26]; and in its ^{1}H n.m.r. spectrum the 5- and 8- and the 6- and 7-protons give rise to two peaks at high field with narrow band envelopes ($W_{\frac{1}{2}}$ *ca.* 12 Hz), similar to those observed for 2-amino-5,6,7,8-tetrahydroquinazoline but different from the pattern noted from the isatins (4) and (5) (Table 2). Several attempts to decarboxylate the acid (1) directly to the known aminoquinazoline were unsuccessful, perhaps owing to the zwitterionic nature of the amino-acid. We prepared methyl 2-acetamido-5,6,7,8-tetrahydroquinazoline-4-carboxylate but careful hydrolysis, in order to obtain the acetamido-acid which might decarboxylate more readily, yielded the parent amino-acid. As an alternative, we hoped to make the acetamido-acid by hydrogenolysis of its benzyl ester, but in attempting to prepare benzyl 2-amino-5,6,7,8-tetrahydroquinazoline-4-carboxylate by a 'phase shift' esterification, in benzene containing a trace of toluene-*p*-sulphonyl chloride, we effected decarboxylation to 2-amino-5,6,7,8-tetrahydroquinazoline.

Catalytic reduction of the amino-acid (1) gave a dihydro-derivative which could have structure (8) or (10). The reduction resulted in a large hypsochromic shift of the u.v. band at 315 to 265 nm, with a large increase in the pK_a values. The pK_a value (12·22) for the reduced amino-acid is consistent with the formation of a cyclic guanidino-compound. The ^{1}H n.m.r. spectrum supports the 3,4-dihydro-structure (8): the 4-proton gives a sharp singlet at δ 5·04 and those at positions 5—8 give two peaks with narrow band envelopes. The corresponding methyl ester hydrochloride showed little u.v. absorption above 225 nm and its ^{1}H n.m.r. spectrum did not have the two peak pattern for the ring methylene protons. The spectrum agrees with structure (11) because H-8a appears as a doublet at δ 4·95 (J 4 Hz). A model satisfying these requirements can be constructed in which H-8a is not coupled with the

† The i.r. spectra of this acid and related compounds indicate that like most 2-hydroxypyrimidines (see ref. 2) they exist predominantly in the lactam form with the hydrogen atom on N-1 or N-3. Here they will be referred to as N-1 tautomers; these are probably more favoured since they have a double bond common to two rings. The possibility, however, of the presence of even appreciable amounts of the N-3 tautomers is not excluded.

‡ In the 2-amino-compounds there is no way of knowing whether the tautomeric hydrogen atom is on N-1 or N-3, or that there is a mixture of both tautomers, but for simplicity of nomenclature these compounds will be referred to as N-3 isomers.

[1] Part XVIII, W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 3222.
[2] D. J. Brown, 'The Pyrimidines,' Interscience, New York, 1962, pp. 9, 249, 464.
[3] W. L. F. Armarego, *J. Chem. Soc.* (*C*), 1971, 1812.
[4] R. J. S. Beer and J. Hollowood, *J. Chem. Soc.*, 1964, 991.
[5] R. J. S. Beer and R. W. Turner, *J. Chem. Soc.*, 1965, 1648.
[6] L. Horowitz, *J. Amer. Chem. Soc.*, 1953, **75**, 4060.
[7] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240.

axial C-8 proton (*i.e.* torsion angle *ca.* 90°) and has a small torsion angle with reference to H-8*eq*. Catalytic reduction of methyl 2-amino-5,6,7,8-tetrahydroquinazoline-4-carboxylate in acetic acid gave a dihydro-acetate

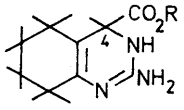
TABLE 1

U.v. spectra of quinazolines and indoles [a] at 20°

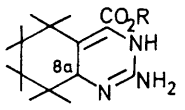
5,6,7,8-Tetrahydroquinazoline	$\lambda_{max.}$/nm	log ε	Species [b]	Solvent or pH or H_0 in H_2O
2-Amino- [c]	226, 315	4·23, 3·81	+	1·0
	228, 301	4·11, 3·65	0	7·0
2-Amino-4-carboxy- [d]	226, 330	4·10, 4·40	+	−2·0
	223, 315	4·24, 3·75	±	2·0
	226, 300	4·04, 3·63	−	7·0
	227, 305	3·81, 3·35		MeOH
2-Amino-4-methoxycarbonyl- [e]	226, 333	3·92, 3·48	+	0·10
	231, 319	4·04, 3·44	0	7·0
	233, 321	4·10, 3·60		MeOH
2-Amino-4-carboxy-3,4-dihydro- [f]	*223*, 261	*3·39*, 3·29	+	0·0
	265	3·29	±	7·0
	284	3·19	−	14·0
	264	3·18		MeOH
2-Amino-dihydro-4-methoxycarbonyl- [g]	*225*, 258	*3·59*, 3·48		MeOH
4-Carboxy-2-hydroxy- [h]	352	3·86	+	−3·0
	313	3·77	0	7·0
	305	3·77	−	12·5
	216, 318	4·22, 3·84		MeOH
4-Carboxy-2-hydroxy-3,4-dihydro-	257	4·30		MeOH
	287	3·41		MeOH [i]
1,2-Dihydro-4-methoxycarbonyl-2-oxo-	332	3·78		MeOH
1,2,3,*x*-Tetrahydro-4-methoxycarbonyl-2-oxo- [j]	262	3·32		MeOH
3-Hydroxindol-2-one				
1,4,5,6-Tetrahydro- [k]	278	4·28		EtOH
1-Benzyl-1,4,5,6-tetrahydro-	280, *290*	4·36, *4·26*		MeOH
1,4,5,6,7,7a-Hexahydro-	*240*	*3·83*		MeOH
1-Benzyl-1,4,5,6,7,7a-hexahydro-	*250*	*3·74*		MeOH

[a] Inflections in italics. [b] + = cation, 0 = neutral species, − = anion, ± = zwitterion. [c] pK_a 4·89 ± 0·05 ($\lambda_{analyt.}$ 315 nm; 1·69 × 10^{-4}M). [d] pK_a 0·61 ± 0·05 and 4·72 ± 0·05 ($\lambda_{analyt.}$ 315 nm; 3·5 × 10^{-5}M). [e] pK_a 3·24 ± 0·04 ($\lambda_{analyt.}$ 335 nm; 5·4 × 10^{-5}M). [f] pK_a 2·71 ± 0·03 and 12·22 ± 0·03 ($\lambda_{analyt.}$ 290 nm; saturated solution *ca.* 10^{-4}M). [g] Contains a mixture of compounds (8) and (11) in the ratio of 2·5 : 1. [h] pK_a − 0·82 ± 0·05 ($\lambda_{analyt.}$ 360 nm; 3·0 × 10^{-5}M), 3·36 ± 0·05 ($\lambda_{analyt.}$ 260 nm; 1·4 × 10^{-4}M), and 10·38 ± 0·04 ($\lambda_{analyt.}$ 335 nm; 1·4 × 10^{-4}M). [i] Spectrum in methanol containing 0·014% of dry hydrogen chloride after 24 h. [j] Contains a mixture of the 3,4- and 3,8a-dihydro-derivatives in the ratio of 2·3 : 1. [k] Values from ref. 4.

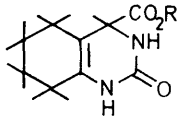
which, like the dihydro-amino-acid, has $\lambda_{max.}$ 261 nm (pH 7, in water). The n.m.r. spectrum indicated that it was a mixture. A singlet and a doublet near δ 5·0 corresponded to the salts of compounds (9) and (11) in the ratio 2·5 : 1, respectively; this ratio was confirmed by the ratio of the sharp methyl ester resonances. When the dihydro-amino-acid (8) and the preceding ester mixture were kept at 20° in the presence of acid, the u.v. absorption around 260 nm decreased, owing to prototropic rearrangement to the isomers (10) and (11). The $t_{\frac{1}{2}}$ values in dry methanolic 1·38N-hydrogen chloride at 275 nm and 20° are, respectively, 47·2 and 53·5 min. The u.v. spectrum of the acid (8) after 48 h retained a weak maximum at 264 nm implying that small amounts of the 4-H tautomer (8) are still present at equilibrium, but the ester lost all its u.v. absorption at 261 nm. These changes are confirmed by the n.m.r. spectra. Thus the primary products from reduction are the 4-H compounds, which isomerise to the thermodynamically more stable 8a-H compounds in acidic medium. The



(8) R = H
(9) R = Me



(10) R = H
(11) R = Me



(12) R = H
(13) R = Me

neutral species probably have the second double bond between N-1 and C-2 (see footnote p. 2814), but in these salts the 'double bond' is shared amongst the three nitrogen atoms in a guanidinium resonance structure.

Attempts to obtain an 8a-nitromethyl derivative by fusing any of the foregoing reduction products with nitroacetic acid failed. The resulting materials showed little u.v. absorption above 225 nm. It is possible that the strong acid isomerises the 4a,8a-double bond to the unreactive 4,4a-position. In order to investigate this further we examined the condensation of 2-oxocyclohexylglyoxylic acid with urea. The product was identified as the keto-acid (2) because it liberated carbon dioxide from aqueous sodium hydrogen carbonate, did not give a blue colour with iron(III) chloride solution, and showed u.v. and n.m.r. spectra similar to those of the amino acid (1) and different from those of the isatins (4) and (5); the indole structure (7) is thus ruled out. The i.r. band at 1748 cm^{-1} is assigned to an unionised carboxy-group. Reduction of the acid, catalytically or with sodium borohydride, gave the hexahydroquinazoline (12) (see u.v. and n.m.r. data in Tables). Methyl 1,2,5,6,7,8-hexahydro-2-oxoquinazoline-4-carboxylate was also reduced to a dihydro-derivative. Its n.m.r. spectrum showed that it was a mixture of the ester (13) and its 8a-H tautomer in the ratio 2·3 : 1, respectively, as measured from the intensities of the two methyl ester signals (δ 4·02 and 4·06). Like the dihydro-amino-compounds (8) and (9), the acid (12) and the mixture of dihydro-esters lose their u.v. peak near 260 nm in dry methanolic 1·38N-hydrogen chloride, but the reactions were too fast for accurate measurement. The reactions of the acid and esters at 20° in very dilute methanolic hydrogen chloride (0·014%) were, however, slower: $t_{\frac{1}{2}}$ 6·6 min (275 nm) and 15·1 min (280 nm), respectively. Also, when the dihydro-acid (12) was fused with nitroacetic acid no addition reaction occurred and the acid was recovered in the isomerised form.

3-Hydroxyindol-2-ones.—Chemical and i.r. evidence [4-6,8]

[8] D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 1959, 876.

TABLE 2

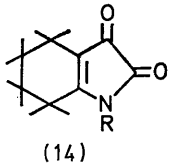
^{1}H N.m.r. spectra of quinazolines and indoles (δ values) [a]

5,6,7,8-Tetrahydroquinazoline	H-5,8	H-6,7	H-4	H-8a	NH or OH [b]	OCH_3	Field (MHz)	Solvent
2-Amino-	2·52(m,$W_{\frac{1}{2}}$ 9) [c]	1·75(m,$W_{\frac{1}{2}}$ 12)	7·97(s)		3·32br(s)		60	$(CD_3)_2SO$ [d,e]
2-Amino-4-carboxy-	2·55(m,$W_{\frac{1}{2}}$ 9) [c]	1·76(m,$W_{\frac{1}{2}}$ 12)			3·60br		60	$(CD_3)_2SO$ [d,f]
2-Amino-4-methoxycarbonyl-	2·76(m,$W_{\frac{1}{2}}$ 18)	1·85(m,$W_{\frac{1}{2}}$ 12)			5·45br	3·95(s)	60	$CDCl_3$
2-Amino-4-carboxy-3,4-dihydro-	2·62(m,$W_{\frac{1}{2}}$ 14)	2·17(m,$W_{\frac{1}{2}}$ 12)	5·04(s)	*g*			100 [h]	2NDCl–D_2O
2-Amino-3,8a-dihydro-4-methoxycarbonyl-(hydrochloride)	← 1·5—3·0br(m) →			4·95(d,*J* 4)		4·36(s)	100 [h]	2NDCl–D_2O
4-Carboxy-1,2-dihydro-2-oxo-	2·50(m,$W_{\frac{1}{2}}$ 12)	1·60(m,$W_{\frac{1}{2}}$ 13)					60	$(CD_3)_2SO$ [d,i]
1,2-Dihydro-4-methoxycarbonyl-2-oxo-	2·76(m,$W_{\frac{1}{2}}$ 18)	1·85(m,$W_{\frac{1}{2}}$ 12)				3·95(s)	60	$CDCl_3$
4-Carboxy-1,2,3,4-tetrahydro-2-oxo-	1·95(m,$W_{\frac{1}{2}}$ 12)	1·49(m,$W_{\frac{1}{2}}$ 12)	4·04(s)		6·76(s,NH), 8·00(s, NH), 13·50br (s,CO_2H)		100 [h]	$(CD_3)_2SO$

Indol-2-one	H-4, 5, and 6	H-7	H-7a	Other H	NH or OH [b]	Field (MHz)	Solvent
1,4,5,6-tetrahydro-3-hydroxy-	1·50—1·90 (q,H-5,5) [j] 1·99—2·22 (m,H-4,4,6,6) [j]	5·38(t,*J* 5)			9·58(s)	60	$(CD_3)_2SO$
1-Benzyl-1,4,5,6-tetrahydro-3-hydroxy-	2·18(t,H-4,4) [j] 2·56(t,H-6,6) [j] 1·77(q,H-5,5) [j]	5·50(t,*J* 4)		4·80(s,CH_2Ph), 7·28(s,Ph)	8·26br(s)	60	$CDCl_3$
3-Acetoxy-1-benzyl-1,4,5,6-tetrahydro-	2·65—2·05 (m,H-4,4,6,6) 1·50—2·00(m,H-5,5)	5·63(t,*J* 4)		4·97(s,CH_2Ph), 7·31(s, Ph), 2·30(s,Me)		60	$CDCl_3$
1-Benzyl-1,4,5,6,7,7a-hexahydro-3-hydroxy-	← 0·9—3·2br(m) →		3·47(q,*J* 6 and 11)	5·05(d), 4·25(d) (*J* 16, CH_2Ph), 7·37(s,Ph)		60	$CDCl_3$
1,4,5,6,7,7a-hexahydro-3-hydroxy-	← 0·7—3·0br(m) →		3·55(q,*J* 6 and 12)		8·16br(s), 8·82br(s)	60	$(CD_3)_2SO$
3-Hydroxy-*cis*-perhydro-	← 1·1—2·7br(m) →		4·15(q,*J* 4·5 and 7·5m $W_{\frac{1}{2}}$ 8)	3·00(m,$W_{\frac{1}{2}}$ 35, H-3a), 4·94 (d,*J* 6·5,H-3)		100	D_2O

[a] Me_4Si as internal standard; *J* and $W_{\frac{1}{2}}$ values in Hz. [b] Protons exchanged by D_2O or DCl. [c] Signal on top of dimethyl sulphoxide peak. [d] Material sparingly soluble. [e] 45 scans. [f] 69 scans. [g] Weak doublet at δ 4·87 (*J*4). [h] Me_4Si external standard. [i] 111 scans. [j] Apparent multiplicity; *J* values not given because these signals are complex.

clearly demonstrated that in the 4,5,6,7-tetrahydroisatins the dienol tautomer [*e.g.* (4) and (5)] predominates over the enone tautomer (14). The present n.m.r. data



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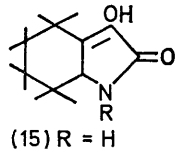
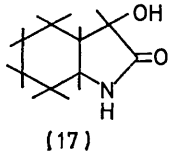


(15) R = H
(16) R = CH_2Ph



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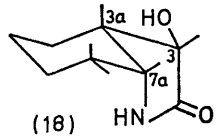

(18)

(Table 2) substantiate this and show that in the indoles (4) and (5) the enone concentration is so small that it is not detected under the conditions of measurement. The 3-OH signal is absent and the vinylic 7-proton signal integrates for one hydrogen atom. The dienols absorb one molecule of hydrogen on catalytic reduction and yield the enols (15) and (16). These give blue colours with aqueous iron(III) chloride, like the parent compounds (4) and (5), and i.r. and n.m.r. spectroscopy show clearly that the enol structure predominates. Unlike the dihydroquinazolines (8) and (12), these reduced indoles have no u.v. maximum above 220 nm. The indole (15) can be reduced further with sodium borohydride, most probably *via* the diketo-tautomer, to 3-hydroxy-*cis*-perhydroindol-2-one (17). The perhydroindole has no u.v. absorption and does not give a colour with iron(III) chloride. It has a sharp m.p. and behaves as a single substance on t.l.c., and its mass spectrum is consistent with structure (17) (see Experimental section). The coupling constants of the 7a-proton (Table 2) are small and rule out a *trans*-diaxial coupling, implying that H-7a is equatorial with respect to the carbocyclic ring and that the *cis*-structure (18) is the major conformer. The 3-hydroxy-group is probably (quasi) equatorial. In structure (18) the torsion angle between H-3 and H-3a is about 25°, in agreement with the small coupling constant (*J* 6·5 Hz) of the observed H-3 doublet.

EXPERIMENTAL

Microanalyses were performed by Dr. J. E. Fildes and her staff. The instruments used are given in ref. 9, and ionization constants were measured at ionic strength 0·01 and at 20° as before.[10] All i.r. spectral assignments (KBr discs) are tentative and the C–H stretching bands near 3000 cm^{-1} are not included. Evaporations were carried out at $<30°$ and *ca.* 18 mmHg.

2-Amino-5,6,7,8-tetrahydroquinazoline-4-carboxylic Acid (1).—2-Oxocyclohexylglyoxylic acid[11] (8·5 g) was added slowly to a warm solution of guanidine carbonate (9·9 g, 1·1 mol. equiv.) in aqueous methanol (50 ml; 1 : 1); the mixture was refluxed for 2 h and evaporated. The residue was washed with dilute hydrochloric acid (pH 2) and recrystallised from hot water to give the *amino-acid* (68%), m.p. 237° (effervescence) (Found: C, 55·5; H, 5·7; N, 21·6. $C_9H_{11}N_3O_2$ requires C, 55·95; H, 5·7; N, 21·75%), $\nu_{max.}$ 3000br (NH_3^+ hydrogen bonded), 1670 (CO_2^-), and 1605br (NH bend) cm^{-1}. The amino-acid was also obtained in 32% yield when 2,4,5,6-tetrahydro-2-oxobenzofuran-5-yl acetate[12] and guanidine carbonate were boiled for 2 h.

2-Amino-3,4,5,6,7,8-hexahydroquinazoline-4-carboxylic Acid (8).—The amino-acid (1) (2·4 g) in glacial acetic acid (600 ml) containing platinum oxide (600 mg) was hydrogenated at 20° and 720 mmHg. The mixture was filtered and evaporated. The residue was washed with water and recrystallised from hot water (100 parts) to give the hexahydroquinazoline (1·5 g, 62%), m.p. 327—328° (decomp.) (Found: C, 55·6; H, 6·8; N, 21·4%; M^+, 195. $C_9H_{13}N_3O_2$ requires C, 55·4; H, 6·7; N, 21·5%; *M*, 195), $\nu_{max.}$ 3300, 3000, 1680, and 1600 cm^{-1}.

Methyl 2-amino-5,6,7,8-tetrahydroquinazoline-4-carboxylate, m.p. 154—155°, was obtained in 77% yield when the amino-acid (1) (1·8 g) in dry saturated methanolic hydrogen chloride (25 ml) was refluxed for 3 h. The mixture was evaporated and the residue basified with aqueous 5N-ammonia and extracted with chloroform; evaporation of the extract gave a residue which was recrystallised from benzene, benzene–light petroleum (b.p. 40—60°), or ether, and sublimed at 140° and 3 mmHg (Found: C, 58·0; H, 6·4; N, 20·5. $C_{10}H_{13}N_3O_2$ requires C, 58·0; H, 6·3; N, 20·3%), $\nu_{max.}$ 3410, 3340, 1720, and 1220 (ester) cm^{-1}.

Methyl 2-Amino-3,5,6,7,8,8a-hexahydroquinazoline-4-carboxylate Hydrochloride.—The acid (8) (100 mg) in dry saturated methanolic hydrogen chloride (30 ml) was refluxed for 3 h; the mixture was evaporated, and the residue kept *in vacuo* (over KOH) until free from hydrogen chloride. The *ester hydrochloride* (111 mg, 84%) had m.p. 194—195° (decomp.) (from methanol–ether) (Found: C, 46·5; H, 6·9; Cl, 14·1; N, 16·4. $C_{10}H_{16}ClN_3O_2,0{\cdot}67H_2O$ requires C, 46·6; H, 6·8; Cl, 13·8; N, 16·3%), $\nu_{max.}$ 1720 (ester) and 1680 and 1620 (guanidine salt) cm^{-1}.

Reduction of Methyl 2-Amino-5,6,7,8-tetrahydroquinazoline-4-carboxylate.—The ester (207 mg) in glacial acetic acid (10 ml) containing platinum oxide was reduced as before. The residue was recrystallised from methanol–ether to give a 2·5 : 1 mixture (by n.m.r.) of 2-amino-4-methoxycarbonyl-3,4,5,6,7,8-hexahydro- and 2-amino-4-methoxycarbonyl-3,5,6,7,8,8a-hexahydroquinazoline acetates (230 mg, 85%), m.p. 182—183° (Found: C, 53·3; H, 7·3; N, 15·4. Calc. for $C_{10}H_{15}N_3O_2,CH_3CO_2H$ requires C, 53·5; H, 7·1; N, 15·6%), $\nu_{max.}$ 3000br (NH), 1748 (ester), 1690, 1600, and 1205 cm^{-1}.

1,2,5,6,7,8-Hexahydro-2-oxoquinazoline-4-carboxylic Acid (2).—2-Oxocyclohexylglyoxylic acid (3·4 g) was added to a solution of urea (2·4 g, 2 mol. equiv.) in 50% methanol (10 ml) and the mixture was refluxed for 1·5 h. The crystals that separated were freed from colour with methanol and recrystallised from a large volume of methanol to give the *oxoquinazoline* (82%), m.p. 186° (decomp.) (Found: C, 56·0; H, 5·3; N, 14·6. $C_9H_{10}N_2O_3$ requires C, 55·7; H, 5·2; N, 14·4%), $\nu_{max.}$ 2650br (hydrogen-bonded OH), 1748 (CO_2H), 1627, and 1600 (amide) cm^{-1}. This condensation was successful in acetic acid and acetonitrile but larger amounts of coloured impurities were formed.

The *methyl ester*, decomp. $>140°$ (from chloroform–cyclohexane), was prepared in 86% yield by refluxing the acid in 25% (v/v) methanolic sulphuric acid for 18 h (low yields were obtained with saturated methanolic hydrogen chloride) (Found: C, 57·8; H, 5·8; N, 13·3. $C_{10}H_{12}N_2O_3$ requires C, 57·7; H, 5·8; N, 13·5%); $\nu_{max.}$ 2900br (hydrogen-bonded NH), 1735 (ester), 1646, and 1605 (amide) cm^{-1}. Catalytic reduction of this ester over platinum oxide in methanol gave a mixture (91% yield) of the 3,4- and 3,8a-dihydro-derivatives in the ratio 2·3 : 1, respectively. It did not recrystallise readily, but gave crystals from chloroform–cyclohexane which effervesced at 175—182° (Found: C, 55·0; H, 6·3; N, 12·5%; M^+, 210. $C_{10}H_{14}N_2O_3,0{\cdot}1CHCl_3$ requires C, 54·6; H, 6·4; N, 12·6%; *M*, 210), $\nu_{max.}$ 3250, 3100 (NH), 1725 (ester), and 1683 (amide) cm^{-1}; δ (100 MHz; Me_4Si external standard) 4·02 (s, $CO_2{\cdot}CH_3$), 4·54 (s, H-4), and 7·18, and 8·42 (s, NH) (3,4-dihydro-isomer); 4·06 (s, $CO_2{\cdot}CH_3$), 4·59 (d, *J* 5 Hz, H-8a), and 6·00 and 6·56 (s, NH) (3,8a-dihydro-isomer); after addition of concentrated DCl the spectrum was altered to δ 4·12 (s, CO_2CH_3) and 4·17 (s, H-4) (3,4-isomer), and 4·20 (s, $CO_2{\cdot}CH_3$) and 4·93 (d, *J* 5 Hz, H-8a) (3,8a-isomer), in the ratio 1·5 : 1, respectively.

1,2,3,4,5,6,7,8-Octahydro-2-oxoquinazoline-4-carboxylic Acid (12).—The preceding acid (4 g) in ethanol (500 ml) containing platinum oxide (560 mg) was reduced as above. The residue was washed with ethanol and recrystallised from water to give the *octahydroquinazoline* (2·27 g, 56%), m.p. 202—203° (decomp.) [Found (after drying at 100° overnight): C, 54·8; H, 6·4; N, 14·4. $C_9H_{12}N_2O_3$ requires C, 55·1; H, 6·2; N, 14·4%], $\nu_{max.}$ 3250br (OH), 1702 (CO_2H), and 1640 (amide) cm^{-1}.

1,4,5,6,7,7a-Hexahydro-3-hydroxyindol-2-one (15).—1,4,5,6-Tetrahydro-3-hydroxyindol-2-one (1·5 g), m.p. 228—230° (decomp.) (in a sealed tube) (Found: C, 63·5; H, 6·2; N, 9·2. Calc. for $C_8H_9NO_2$: C, 63·6; H, 6·0; N, 9·3%) (lit.,[4] m.p. 204—206° in a sealed tube) in ethanol (80 ml) containing platinum oxide (50 mg) was reduced as above. The *hexahydroindol-2-one* (1·4 g, 92%) had m.p. 226—228° (from acetone) (Found: C, 63·1; H, 7·3; N, 9·2. $C_8H_{11}NO_2$ requires C, 62·7; H, 7·2; N, 9·1%), $\nu_{max.}$ 3260br (NH and OH) and 1672br (C=O and C=C) cm^{-1}.

1-Benzyl-1,4,5,6,7,7a-hexahydro-3-hydroxyindol-2-one (16).—Catalytic reduction of 1-benzyl-1,4,5,6-tetrahydroindol-2-one,[6] m.p. 175—176° (Found: C, 74·7; H, 6·6; N, 5·8. Calc. for $C_{15}H_{15}NO_2$: C, 74·7; H, 6·3; N, 5·8%) (lit.,[6] m.p. 163—164°) [*acetate*, m.p. 97—98° (Found: 72·5; H, 6·1; N, 5·0. $C_{17}H_{17}NO_3$ requires C, 72·1; H, 6·1; N, 5·0%)] as

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above gave the 1-*benzylhexahydroindol*-2-*one* (70%), m.p. 159—160° [from benzene–light petroleum (b.p. 40—60°) with sublimation at 140° and 0·5 mmHg] (Found: C, 74·2; H, 7·1; N, 5·9. $C_{15}H_{17}NO_2$ requires C, 74·1; H, 7·0; N, 5·8%), $\nu_{max.}$ 3240br (OH) and 1675 (amide) cm^{-1}.

3-*Hydroxy*-cis-*perhydroindol*-2-*one* (17).—To 1,4,5,6,7,7a-hexahydro-3-hydroxyindole-2-one (1·1 g) in warm ethanol (45 ml) was added sodium borohydride (0·82 g). The mixture was stirred for 3 h at 20°, acidified to pH 2, and evaporated to dryness, and the residue was extracted (Soxhlet) with benzene (3 × 300 ml; 6 h each). The extract was evaporated to half its volume and cooled; the *perhydroindol*-2-*one* (650 mg, 59%) crystallised in glistening plates, m.p. 195·5—196° (from benzene) (Found: C, 61·7; H, 8·6; N, 9·2. $C_8H_{13}NO_2$ requires C, 61·9; H, 8·4; N, 9·0%), $\nu_{max.}$ 3395 (OH), 3260 (NH), and 1675 (amide) cm^{-1}; *m/e* 155 (M^+, 77%), 137 ($M^+ - H_2O$, 6), 127 ($M^+ - CO$, 30), 113 ($M^+ - NCO$, 58), 96 ($C_7H_{12}^+$, 100), 82 (46), and 81 (88).

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