1139. *Quasi-steroidal Heterocycles. Part II.*[1] *The Quino*[1,2-c]*quinazoline Ring System.*

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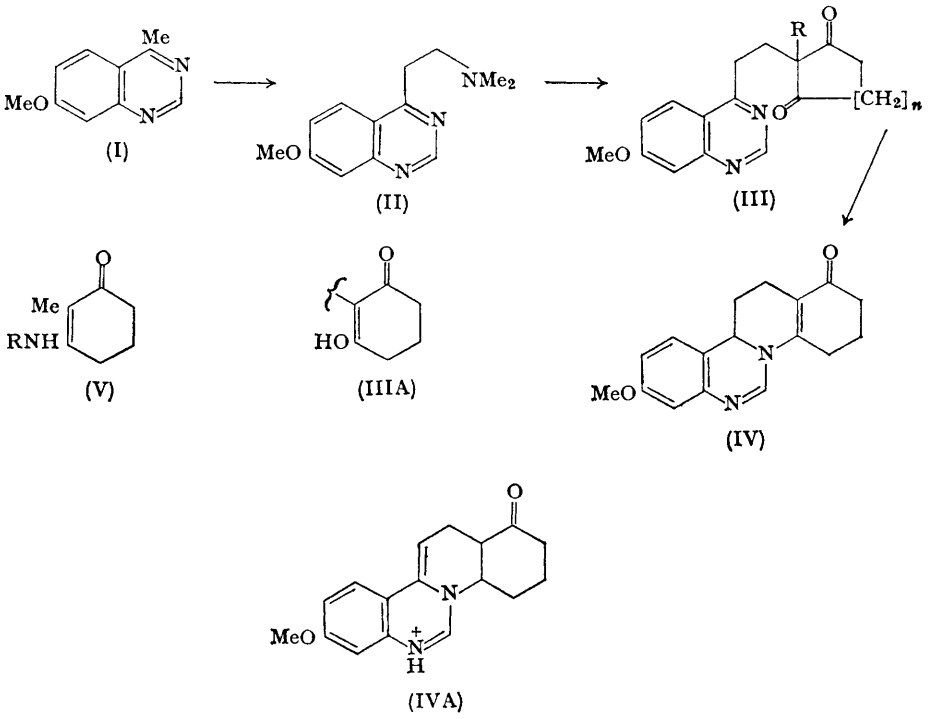
The synthesis of the new ring system quino[1,2-*c*]quinazoline, which is structurally analogous to the steroid skeleton, is described. It involves the development of a method for the reduction of 4-substituted quinazolines to their 3,4-dihydro-derivatives.

The recent synthesis of "8-azaoestrone"[2] through an isoquinoline intermediate prompted the examination of a similar synthesis involving a quinazoline intermediate (II). This was prepared from 7-methoxy-4-methylquinazoline (I) by a Mannich reaction (known[3] to occur with 4-methylquinazoline). 7-Methoxy-4-methylquinazoline was prepared from 4-methoxy-2-nitroaniline in six stages, using the Bischler quinazoline synthesis.[4] The Mannich base (II) underwent t-butoxide-catalysed Michael reactions with cyclic 1,3-diones to give (III: R = Me, $n = 1$; R = Me, $n = 2$; R = H, $n = 2$).

Reduction of quinazolines to their 3,4-dihydro-derivatives is well known.[5] However, treatment with hydrogen and palladium under the conditions previously used for this reaction failed to reduce either of the quinazolines (I) and (III; R = Me, $n = 2$). It had been

[1] Part I, preceding Paper.
[2] R. Clarkson, unpublished work.
[3] J. Siegle and B. E. Christensen, *J. Amer. Chem. Soc.*, 1951, **73**, 5778.
[4] T. A. Williamson in "Heterocyclic Compounds," ed. Elderfield, Wiley, New York, 1957, vol. VI, p. 329.
[5] Ref. 4, p. 347 *et seq.*

noted[6] that 4-alkoxyquinazolines resisted reduction under the same conditions. This stabilising effect of a 4-substituent upon the 3,4-double bond of the quinazoline nucleus has also been observed in connexion with the hydration of this bond, which occurs in the quinazolinium cation by nucleophilic attack of water on the electropositive 4-position. A 4-methyl group completely inhibits this hydration, and quinazolines possessing an electron-releasing 7-substituent (OMe, NH_2, or OH) are also resistant to hydration.[7] Both these structural features are present in the quinazolines (I) and (III), and factors similar to those affecting hydration of the 3,4-double bond may well affect its reduction.



The reduction of 7-methoxy-4-methylquinazoline with hydrogen was therefore studied in detail. No reduction took place at room temperature under one atmosphere of hydrogen, using palladium, platinum, ruthenium, and rhodium catalysts (all 5% on carbon; 5% palladium on calcium carbonate and Adams platinum oxide were also used) in ethanol, ethanolic hydrogen chloride, or acetic acid. When the reaction temperature was raised until reduction took place (50—100°, depending on the catalyst used) and reduction was carried out under 100 atm. of hydrogen, a mixture of products was obtained. The use of water as the reaction medium caused reduction to occur at room temperature and 1 atm. of hydrogen with all the above catalysts, but severe catalyst poisoning occurred. The addition of acid eliminated this difficulty, and optimum reduction conditions were found using either palladium or platinum catalysts in aqueous hydrochloric or aqueous acetic acid. This result is comparable with that obtained by Rylander and his co-workers,[8,9] who found that the rate of catalytic reduction of ketones and oximes was greatly affected by the solvent used. Water gave the highest rate in all cases. Using these optimum conditions, 7-methoxy-4-methylquinazoline (I) was reduced to its 3,4-dihydro-derivative. That the 1,2-double bond

[6] R. C. Elderfield, T. A. Williamson, W. J. Gensler, and C. B. Kremer, *J. Org. Chem.*, 1947, **12**, 405.
[7] A. Albert in "Physical Methods in Heterocyclic Chemistry," ed. Katritzky, Academic Press, New York and London, 1962, vol. I, pp. 24, 27.
[8] E. Breitner, E. Roginski, and P. N. Rylander, *J. Org. Chem.*, 1959, **24**, 1855.
[9] E. Breitner, E. Roginski, and P. N. Rylander, *J.*, 1959, 2918.

was still present was shown by the small hypsochromic shift of the major peak (229 mμ, ε 23,800) in the ultraviolet spectrum of the 3,4-dihydro-compound (as oxalate) relative to the major peak (236 mμ, ε 49,600) in the spectrum of 7-methoxy-4-methylquinazoline oxalate. This comparatively small difference between the ultraviolet spectra of quinazolines and 3,4-dihydroquinazolines had been recorded previously.[6]

Application of the same reduction conditions (using a palladium catalyst) to the dione (III; R = Me, $n = 2$) gave a product which was extractable from aqueous solution only to the extent of 25%. This extract contained several substances, chromatography yielding neither a fraction which could be crystallised nor one from which crystalline derivatives could be obtained. Failure to obtain a 3,4-dihydro-derivative in this case may have been due to hydrolysis of the 2,2-disubstituted 1,3-dione to give an amino-acid. When the analogous quinazoline (III; R = H, $n = 2$), lacking the 2-methyl group and hence more resistant to hydrolysis because of its existence in the enol form (IIIA), was reduced under the above conditions, reduction of the 3,4-double bond in the quinazoline nucleus was followed by cyclisation to the quino[1,2-*c*]quinazoline (IV). This compound could only be isolated in a pure crystalline state as its dihydrate. However, its structure was established by (*a*) an infrared band at 1665 cm.$^{-1}$ assigned to the vinylogous amide carbonyl (the infrared spectrum of its keto–enol precursor has no band between 2800 and 1630 cm.$^{-1}$) and (*b*) a band in its ultraviolet spectrum (289 mμ, ε 21,300) due to the same grouping and comparable with one in the ultraviolet spectra of simple aminocyclohexenones (V) (305 mμ, ε 37,200, when R = cyclohexyl).[10]

The n.m.r. spectrum of the quino[1,2-*c*]quinazoline (IV) in trifluoroacetic acid was compatible with the structure assigned to it (see Experimental section) except for a one-proton signal at 4·86 τ. This is probably due to the isomerisation of (IV) in a strongly protonating environment to give a structure such as (IVA) which has one olefinic proton. The ultraviolet spectrum of (IV) in methanol containing hydrochloric acid confirmed this explanation, since the band at 289 mμ assigned to the vinylogous amide group (see above) was absent under these conditions.

Experimental

Ultraviolet spectra were determined in 0·001% methanolic solution using a Perkin-Elmer 137 instrument, infrared spectra in Nujol using a Perkin-Elmer Infracord 137, and n.m.r. spectra with a Varian A60 spectrometer at 60 Mc./sec. with tetramethylsilane as an internal standard (τ = 10·00). Organic solvent extracts were dried over magnesium sulphate.

4-Methoxy-2-nitroacetophenone.—This was prepared by a modification of the method due to Osborne and Schofield.[11] A tetrahydrofuran solution of 4-methoxy-2-nitrobenzoyl chloride was prepared by boiling the corresponding acid[12] (80 g.) and thionyl chloride (200 ml.) under reflux for 2 hr., removing the excess of thionyl chloride *in vacuo* (the last traces by co-distillation with benzene), and dissolving the residual acid chloride in dry tetrahydrofuran (200 ml.). This solution was added rapidly, with stirring, at room temperature, to a solution of diethyl sodiomalonate prepared from diethyl malonate (128 ml.) in dry tetrahydrofuran (400 ml.) by the gradual addition, with stirring, of a 50% dispersion in oil of sodium hydride (38·6 g.), followed by stirring of the mixture at room temperature for 0·5 hr., then under reflux for 2 hr. After the addition of the acid chloride solution, the mixture was stirred at room temperature for 0·5 hr., then under reflux for 0·5 hr. To the cooled mixture was added concentrated sulphuric acid (80 ml.) in water (800 ml.), and after stirring for 5 min. the whole was poured into water (1200 ml.) and extracted with chloroform (2 × 800 ml.). The dried extract was evaporated, and to the residual crude benzoylmalonic ester was added acetic acid (120 ml.), water (80 ml.), and concentrated sulphuric acid (20 ml.). The mixture was boiled under reflux for 4 hr., cooled, basified with aqueous sodium carbonate, and extracted with ether (2 × 400 ml.). Evaporation of the dried extract gave an upper layer of oil (from the sodium hydride dispersion) which was separated from the lower layer of crude product (73·5 g.). The latter could be distilled, b. p. 167—170°/5 mm., but was usually used directly for

[10] R. Clarkson, personal communication.
[11] A. R. Osborne and K. Schofield, *J.*, 1955, 2100.
[12] N. B. Chapman, G. M. Gibson, and F. G. Mann, *J.*, 1947, 890.

reduction to the corresponding amine, since the use of this crude product caused no decrease in yield of the amine.

2-Amino-4-methoxyacetophenone.—This was prepared according to Osborne and Schofield.[11] Use of 10 g. of distilled nitro-compound gave 7 g. of amine, m. p. 113—117°; use of 108 g. of crude nitro-compound gave 88 g. of amine, m. p. 108—112° (lit., 120—121°). The reduction was more conveniently carried out on the larger scale by hydrogenation of the nitro-compound in ethanolic solution at room temperature and 100 atm., using a 5% palladium–charcoal catalyst. The *N-formyl derivative*, m. p. 114—117° (from ethanol) (Found: C, 62·4; H, 5·5; N, 7·2. $C_{10}H_{11}NO_3$ requires C, 62·2; H, 5·7; N, 7·3%), was prepared by boiling the amine with an equal weight of 98% formic acid for 2 hr., and pouring the mixture into water; 86 g. of amine gave 65 g. of formyl derivative.

7-Methoxy-4-methylquinazoline (I).—The above *N*-formyl derivative (34 g.) and saturated ethanolic ammonia (340 ml.) were heated at 140° for 13 hr. The mixture was evaporated to dryness and crystallised from light petroleum (b. p. 60—80°) to give the *product*, m. p. 92—94° (21 g., 69%). Further crystallisation raised the m. p. to 100—102° (Found: C, 68·7; H, 5·9; N, 15·9. $C_{10}H_{10}N_2O$ requires C, 68·9; H, 5·7; N, 16·1%). The *oxalate*, m. p. 193° (effervescence), was crystallised from water (Found: C, 54·7; H, 4·4; N, 10·6. $C_{12}H_{12}N_2O_5$ requires C, 54·6; H, 4·5; N, 10·6%), $\lambda_{max.}$ 236, 311 mμ (ε 48,600, 4100). The picrate had m. p. 210° (decomp.).

7-Methoxy-4-(2-dimethylaminoethyl)quinazoline (II) *Hydrochloride.*—7-Methoxy-4-methylquinazoline (20 g.; m. p. 92—94°), dimethylamine hydrochloride (14 g.), ethanol (200 ml.), and 37% formalin (10 ml.) were mixed, and the resulting orange solution was allowed to stand overnight at room temperature. The solvents were evaporated at 40° or below, and acetone was added to the oily residue (a few drops of ethanol aided crystallisation) to give the required *hydrochloride*, m. p. 153—154° (effervescence) (18·7 g., 61%). It could not be recrystallised satisfactorily (Found: C, 58·1; H, 6·9; N, 15·9; ionic Cl, 13·0. $C_{13}H_{18}ClN_3O$ requires C, 58·4; H, 6·7; N, 15·7; ionic Cl, 13·3%).

Michael Reactions with 7-Methoxy-4-(2-dimethylaminoethyl)quinazoline (II).—(*a*) *With 2-methylcyclohexane-1,3-dione.* The above Mannich base hydrochloride (7·0 g.) and 2-methylcyclohexane-1,3-dione (3·5 g.) were added to dry t-butyl alcohol (70 ml.) containing potassium (1·26 g.). The mixture was boiled under reflux in a stream of nitrogen, the effluent gas being passed through a water trap and titrated against N-hydrochloric acid. Nearly 80% of the theoretical amount of dimethylamine was evolved in 8½ hr. After a further 3 hr., the mixture was filtered hot and the filtrate concentrated to half its volume, to give, on cooling, the product (4·8 g.), m. p. 125—130°. Evaporation of the mother liquor to dryness and crystallisation of the residue from methanol gave a further 0·4 g., m. p. 122—126° (total yield 64%). Crystallisation from ethanol gave *2-methyl-2-[2-(7-methoxyquinazolin-4-yl)ethyl]cyclohexane-1,3-dione* (III; R = Me, $n = 2$), m. p. 126—127° (Found: C, 69·4; H, 6·5; N, 9·1. $C_{18}H_{20}N_2O_3$ requires C, 69·2; H, 6·4; N, 9·0%), $\nu_{max.}$ 1735, 1690 cm.$^{-1}$. Repetition of the experiment, using a 15 hr. reaction time, gave a 70% yield. The use of pyridine as catalyst (in benzene) or of sodium hydride (in tetrahydrofuran or xylene) gave low yields. The *hydrochloride*, precipitated from acetone solution by concentrated hydrochloric acid, had m. p. 172° (effervescence) (from ethanol) (Found: N, 8·0. $C_{18}H_{21}ClN_2O_3$ requires N, 8·0%).

(*b*) *With 2-methylcyclopentane-1,3-dione.* The Mannich base hydrochloride (1·0 g.) and 2-methylcyclopentane-1,3-dione (0·42 g.) were added to t-butyl alcohol (20 ml.) containing potassium (0·18 g.), and the mixture was boiled under reflux in a stream of nitrogen for 24 hr., poured into water, and extracted with chloroform. The dried extract was evaporated and the residue was extracted with boiling light petroleum (b. p. 60—80°), and, on standing, deposited *2-methyl-2-[2-(7-methoxyquinazolin-4-yl)ethyl]cyclopentane-1,3-dione* (III; R = Me, $n = 1$), m. p. 130—131°, in low yield (Found: C, 68·3; H, 6·0; N, 9·2. $C_{17}H_{18}N_2O_3$ requires C, 68·5; H, 6·0; N, 9·4%), $\nu_{max.}$ 1750, 1720 cm.$^{-1}$.

(*c*) *With cyclohexane-1,3-dione.* The reaction was carried out as described above, using the Mannich base (13·4 g.), cyclohexane-1,3-dione (5·6 g.), t-butyl alcohol (270 ml.), and potassium (2·4 g.), and a reaction time of 20 hr. The product was worked up as described in (a), above, to give *2-[2-(7-methoxyquinazolin-4-yl)ethyl]cyclohexane-1,3-dione* (III; R = H, $n = 2$), m. p. 204—206° (8·1 g., 54%), m. p. 206—207° (from ethanol) (Found: C, 68·3; H, 6·1; N 9·6. $C_{17}H_{18}N_2O_3$ requires C, 68·5; H, 6·0; N, 9·4%). The infrared spectrum showed no band between 2800 and 1630 cm.$^{-1}$, $\lambda_{max.}$ 214 (infl., ε 19,700), 235 (42,900), 262 (15,300), 287 (infl. 9800), and 311 mμ (infl., 5700).

Reduction of the Quinazolines.—(a) *7-Methoxy-4-methylquinazoline* (I). This quinazoline (500

mg.) was dissolved in water (25 ml.) containing concentrated hydrochloric acid (1 ml.); 5% platinum–carbon (500 mg.) was added and the mixture was shaken under 1 atm. hydrogen. One molecular proportion (68 ml., theory 64 ml.) of hydrogen was absorbed in 2 hr. The mixture was filtered, the filtrate was basified with aqueous sodium hydroxide and extracted with ethyl acetate, and the dried extract was evaporated to give an oil. Thin-layer chromatography on alumina in 25% ethyl acetate in benzene showed the absence of starting material. An *oxalate* which had m. p. 188—190° (effervescence), resolidifying and remelting at 248—250° (effervescence) (from water) (Found: C, 54·1; H, 5·4; N, 10·3. $C_{12}H_{14}N_2O_5$ requires C, 54·1; H, 5·3; N, 10·5%), $\lambda_{max.}$ 229 (ε 23,800), 278 (infl. 3100), 284 (3200), and 302 mμ (2800), and a *picrate hemihydrate*, m. p. 196—198° (decomp.) (from ethanol) (Found: C, 46·4; H, 4·0; N, 16·7. $C_{16}H_{15}N_5O_8,\frac{1}{2}H_2O$ requires C, 46·4; H, 3·9; N, 16·9%), proved to be salts of 3,4-dihydro-7-methoxy-4-methylquinazoline. A mixture of this picrate and the picrate of the starting material had m. p. 165—185°. Omission of hydrochloric acid from the reaction medium led to catalyst poisoning with all catalysts tried (Pd, Pt, Rh, and Ru, all 5% on carbon, and Adams PtO_2). It could, however, be replaced successfully by a larger amount of acetic acid. No reduction took place at room temperature in solvents (ethanol, ethanol–HCl, acetic acid) other than water. The 5% platinum–carbon catalyst used could be replaced either by Adams platinum oxide or by 5% palladium–carbon; other catalysts were not tried.

(b) 2-*Methyl*-2-[2-(7-*methoxyquinazolin*-4-*yl*)*ethyl*]*cyclohexane*-1,3-*dione* (III; R = Me, $n = 2$). This dione (1·283 g.) was dissolved in acetic acid (4 ml.), and the solution was diluted with water (100 ml.). A 5% palladium–carbon catalyst (1·00 g.) was added, and the mixture was shaken under 1 atm. hydrogen at room temperature. An uptake of 188 ml. of hydrogen was observed during 21 hr. (theory for 2 mol. H_2 is 184 ml.). The reaction mixture was filtered from catalyst, basified with aqueous sodium hydroxide, and continuously extracted (24 hr.) with ethyl acetate. Evaporation of the dried extract gave a gum (350 mg.) which contained three major (R_F 0·00, 0·82, 0·95) and two minor (R_F 0·08, 0·14) constituents, revealed by thin-layer chromatography on alumina in 25% ethyl acetate in benzene. Chromatography on neutral alumina in the same solvent gave 110 mg. of a fraction containing the two fast-running components. This was a gum which could not be crystallised and which gave no crystalline salts or a dinitrophenylhydrazone.

(c) 2-[2-(7-*Methoxyquinazolin*-4-*yl*)*ethyl*]*cyclohexane*-1,3-*dione* (III; R = H, $n = 2$). This compound (1·50 g.), 5% palladium–carbon (4·5 g.), acetic acid (150 ml.), and water (150 ml.) were shaken under hydrogen (1 atm.) at room temperature until absorption of hydrogen had stopped (19 hr.). The mixture was filtered and the residual catalyst washed with acetic acid. The combined filtrates were then evaporated to dryness *in vacuo*, and the residual oil was chromatographed on silica gel (Hopkin and Williams M.F.C.; 150 g.), collecting 200-ml. fractions. After development with 2% methanol–chloroform (fractions 1—3), then with 5% (fractions 4 and 5), and finally 10% methanol–chloroform (fractions 6—17), the major product was found in fractions 8—14, all of which showed a single spot, R_F 0·50, on thin-layer chromatography on silica gel in 50% methanol–chloroform (cf. starting material, R_F 0·65 in the same system). Fractions 9—12 solidified and were crystallised from methanol, to give 1,2,3,4,12,13-*hexahydro*-9-*methoxy*-1-*oxo*-11b*H*-*quino*-[1,2-c]*quinazoline* (IV) *dihydrate*, m. p. 198—200° (289 mg.) (Found: C, 64·7; H, 6·8; N, 9·2. $C_{17}H_{18}N_2O_2,2H_2O$ requires C, 64·2; H, 6·9; N, 8·8%); second crop (33 mg.), m. p. 192—194° (total yield 20%); mixed m. p. with starting material 187—190°. $\lambda_{max.}$ 227 (ε 22,300) and 289 mμ (21,300); $\lambda_{max.}$ (HCl–MeOH) 228 (ε 24,800), 263 (16,200), and 300 mμ (infl., 3200); $\nu_{max.}$ 1665 cm.$^{-1}$; τ (trifluoroacetic acid) 2·7—3·2 (3 aromatic H), 4·86 (1 olefinic H), 6·01 (CH_3O), 6·8—8·2 (10 aliphatic H). Thorough drying (100°/0·1 mm./24 hr.) of the dihydrate gave an exceedingly hygroscopic material; elemental analysis showed between one and two molecules of water (Found: C, 66·3; H, 6·2; N, 8·9%).

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