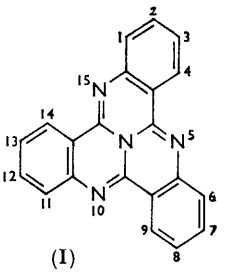
492. *Cyclic Amidines. Part XV.*[1] *Derivatives of Tricycloquinazoline.*

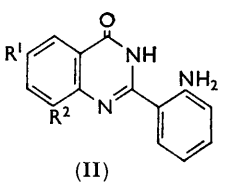
By M. W. PARTRIDGE, H. J. VIPOND, and J. A. WAITE.

Unsymmetrically substituted tricycloquinazolines, required for examination of the relevance of the symmetry of tricycloquinazoline to its carcinogenic activity, have been synthesised by a number of routes.

THE inapplicability of the K-region hypothesis [2] to the interpretation of the carcinogenic activity of tricycloquinazoline [3] (I) has led to a search for other possibilities. The feasibility of a tissue receptor–carcinogen union involving multiple symmetrical bonding could be established by a significant change in carcinogenic activity in unsymmetrically substituted tricycloquinazolines. Such derivatives have now been prepared for examination of their carcinogenic activity.



(I)



(II)

	R^1	R^2
a:	H	H
b:	H	Me
c:	Me	H
d:	Br	H
e:	F	H

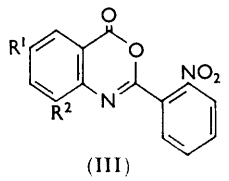
o-Cyanoaniline and methyl anthranilate toluene-*p*-sulphonate at 210° yielded tricycloquinazoline. The quinazolinone (IIa) is suggested as an intermediate since, with *o*-cyanoaniline toluene-*p*-sulphonate, this quinazolinone readily gave tricycloquinazoline; with toluene-*p*-sulphonic acid alone, this quinazolinone, even under more vigorous conditions, yielded only 0·75% of tricycloquinazoline. The quinazolinone (IIa) with toluene-*p*-sulphonic acid and 2-cyano-5-, - , and -3-methyl-, 4-bromo-2-cyano-, and 2-cyano-4-fluoroaniline readily furnished 2-, 3- and 4-methyl-, 3-bromo-, and 3-fluoro-tricycloquinazoline

[1] Part XIV, Butler, Partridge, and Waite, *J.*, 1960, 4970.
[2] Pullman and Pullman, " Advnnces in Cancer Research," Academic Press, New York, 1955, Vol. III, p. 117.
[3] Butler and Partridge, *J.*, 1959, 2396.

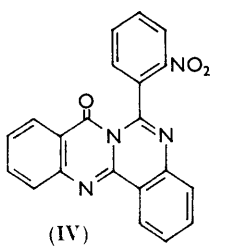
respectively. Likewise the substituted quinazolinones (IIb, c, and d) with *o*-cyanoaniline and toluene-*p*-sulphonic acid gave 1-methyl-, 3-methyl-, and 3-bromo-tricycloquinazoline. 3,8-Dimethyl-, 3,8-dibromo-, and 3,8-difluoro-tricycloquinazolines were similarly obtained from the quinazolinones (IIc—e) and appropriately substituted cyanoanilines.

Nitro-compounds required for reduction to the foregoing quinazolinones (II) were prepared in high yield either by treatment of substituted *N*-(*o*-cyanophenyl)-*o*-nitrobenzamides with alkaline hydrogen peroxide [4] or by heating the corresponding benzoxazines (IIIa—e) in an excess of urea at 180—190°. Clark and Wagner [5] have described an analogous formation of 2,4-dihydroxyquinazoline from isatoic anhydride and urea (0·5 mol.).

The formation of tricycloquinazoline by cyclisation of the *o*-nitrobenzoyl derivative of the quinazolinone (IIa) to the triazabenz[*a*]anthracene (IV), followed by reduction and



(III)



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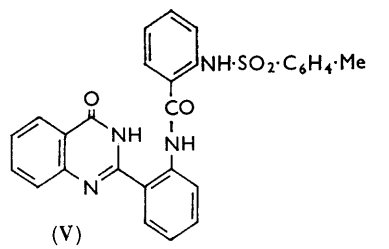
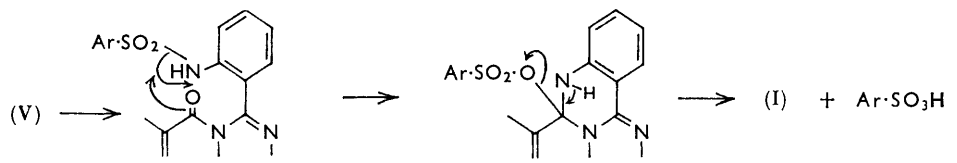


(V)

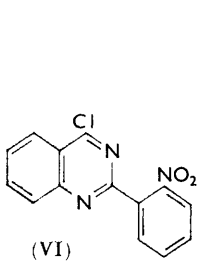
dehydration, was unsuccessfully tried [3] before the instability of 7-oxo-7*H*-5,6*a*,12-triazabenz[*a*]anthracenes had been demonstrated.[1] We now find that a synthesis essentially of this type may be effected by dehydration of the *o*-aminobenzoyl derivatives of the quinazolinones (IIa and c). A similar example is provided by the conversion of the sulphonamide (V) into tricycloquinazoline; dehydration and an elimination of toluene-*p*-sulphonic acid (V ⟶ I), formally analogous to the degradation of sulphonylcarboximides,[6] may be involved. The required *o*-aminobenzoyl derivatives of the quinazolinones (IIa and c) resulted from reduction of their *o*-nitrobenzoyl derivatives. A synthesis of the *o*-nitrobenzoyl derivative of compound (IIa) by cyclisation of the possible product from the benzoxazine (IIIa) and *o*-cyanoaniline failed because these two compounds failed to react at temperatures up to 250°.



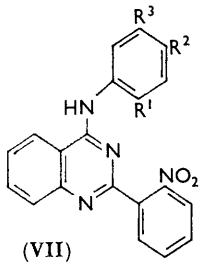
The conversion of 4-hydroxy-2-*o*-nitrophenylquinazoline into the 4-chloro-derivative (VI) made available the most flexible synthetical method for the production of tricycloquinazolines. Acid-catalysed reaction of this chloro-compound with suitably substituted arylamines in acetone readily furnished the hydrochlorides of 4-aminoquinazolines (VIIa—g). After reduction of the nitro-group, the conditions for the final cyclisation were examined. With phosphoric oxide in xylene, both the reduced acid (VIIIb) and its ester (VIIIa) gave only 15% of tricycloquinazoline, whereas in 100% phosphoric acid at 160° this ester gave a 77%, and the acid a 48% yield. Similar results were obtained in the cyclisation of other esters by 100% phosphoric acid to 2- and 3-methyltricycloquinazoline. The cyanides (VIIIf and g) underwent thermal cyclisation to give satisfactory yields of 2-methyl- and 2-methoxy-tricycloquinazoline. Elementary analyses of these

[4] Bogert and Hand, *J. Amer. Chem. Soc.*, 1902, **24**, 1031; McKee, McKee, and Bost, *ibid.*, 1946, **68**, 1902.
[5] Clark and Wagner, *J. Org. Chem.*, 1944, **9**, 55.
[6] Oxley, Partridge, Robson, and Short, *J.*, 1946, 763.

amino-cyanides were inconclusive but the tricycloquinazolines derived from them, like all other examples we have prepared by the several methods, were fully characterised by their eight light-absorption maxima between 250 and 460 mμ.

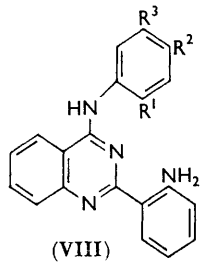


(VI)



(VII)

	R¹	R²	R³
a :	CO_2Me	H	H
b :	CO_2H	H	H
c :	CN	H	H
d :	CO_2Me	Me	H
e :	CO_2Me	H	Me
f :	CN	H	Me
g :	CN	H	OMe



(VIII)

Demethylation of 2-methoxytricycloquinazoline afforded the 2-hydroxy-derivative. 3,8,13-Trimethyltricycloquinazoline resulted from the pyrolysis of 2-cyano-4-methylaniline toluene-*p*-sulphonate.

From preliminary observations of biological tests by Dr. R. W. Baldwin, the most significant indication is that 2-methyltricycloquinazoline is almost non-carcinogenic, whereas 1-methyl-, 3-methyl-, and 4-methyl-tricycloquinazoline are carcinogenic.

Experimental

2-Amino-5-fluorobenzoic Acid.—A solution of 5-fluoroisatin [7] (15 g.) in 2·5N-sodium hydroxide (150 ml.) was treated dropwise with 30% hydrogen peroxide (27 ml.), warmed to 80—90° for 15 min., and filtered through charcoal. The *acid*, precipitated by concentrated hydrochloric acid, crystallised from xylene as needles (7 g.), m. p. 182—183° (Found: C, 54·3; H, 4·1; N, 8·6. $C_7H_6FNO_2$ requires C, 54·2; H, 3·9; N, 9·0%).

N-(o-*Cyanophenyl*)-o-*nitrobenzamide.*—2-Cyanoaniline (11·8 g.) in dry benzene (40 ml.) and pyridine (20 ml.) was shaken for 1 hr. with *o*-nitrobenzoyl chloride (20 g.) in benzene (70 ml.). The benzene was distilled and the residue was treated with water (300 ml.) to precipitate the *amide* (16·4 g.); on recrystallisation from ethanol it afforded needles, m. p. 205—206° (Found: C, 62·6; H, 3·2; N, 15·9. $C_{14}H_9N_3O_3$ requires C, 62·9; H, 3·4; N, 15·7%).

N-(2-*Cyano*-4-*methylphenyl*)-o-*nitrobenzamide*, prepared analogously (61%), separated from ethanol as needles, m. p. 185—186° (Found: C, 64·0; H, 3·9; N, 14·6. $C_{15}H_{11}N_3O_3$ requires C, 64·05; H, 3·9; N, 14·9%).

N-(4-*Bromo*-2-*cyanophenyl*)-o-*nitrobenzamide*, similarly prepared (58%), crystallised from acetic acid or butanol as prisms, m. p. 196—197° (Found: C, 48·7; H, 2·3; N, 12·2. $C_{14}H_8BrN_3O_3$ requires C, 48·6; H, 2·3; N, 12·1%).

5-*Methyl*-2-o-*nitrobenzamidobenzoic Acid.*—*o*-Nitrobenzoyl chloride (65 g.) in benzene (200 ml.) was added during 10 min. to a stirred solution of 2-amino-5-methylbenzoic acid (49 g.) in 0·8N-sodium hydroxide (500 ml.), and stirring was continued for a further 30 min. The *amide*, completely precipitated when the solution was adjusted to pH 4 by addition of acetic acid, crystallised from butanol as prisms, m. p. 229·5—231° (69 g.) (Found: C, 59·7; H, 3·8; N, 9·3. $C_{15}H_{12}N_2O_5$ requires C, 60·0; H, 4·0; N, 9·3%).

The same procedure was employed for the preparation of the following 2-o-*nitrobenzamidobenzoic acids*: 3-*methyl*- (88%), needles, m. p. 209—210° (from ethanol) (Found: C, 60·2; H, 4·3; N, 9·25. $C_{15}H_{12}N_2O_5$ requires C, 60·0; H, 4·0; N, 9·3%), 5-*bromo*- (75%), prisms, m. p. 251—252° (from butanol) (Found: Br, 21·6; N, 7·7. $C_{14}H_9BrN_2O_5$ requires Br, 21·9; N, 7·7%), and 5-*fluoro*- (70%), prisms, m. p. 252—253° (from ethanol) (Found: C, 55·7; H, 3·2; N, 9·1. $C_{14}H_9FN_2O_5$ requires C, 55·3; H, 3·0; N, 9·2%).

6-*Methyl*-2-o-*nitrophenyl*-4-*oxo*-3,1-*benzoxazine.*—5-Methyl-2-*o*-nitrobenzamidobenzoic acid (68 g.), when boiled for 1 hr. with acetic anhydride [8] (200 ml.), gave the *benzoxazine* (58 g.) which crystallised from acetic acid as needles, m. p. 186·5—188° (Found: C, 63·6; H, 3·2; N, 10·2. $C_{15}H_{10}N_2O_4$ requires C, 63·8; H, 3·6; N, 9·9%).

[7] Yen, Buu-Hoï, and Xuong, *J. Org. Chem.*, 1958, **23**, 1858.
[8] Zentmyer and Wagner, *J. Org. Chem.*, 1949, **14**, 967.

The following 2-o-*nitrophenyl*-4-*oxo*-3,1-*benzoxazines* were similarly prepared: 8-*methyl*- (86%), needles, m. p. 186—187°, from acetic acid (Found: C, 63·6; H, 3·7; N, 9·5. $C_{15}H_{10}N_2O_4$ requires C, 63·8; H, 3·6; N, 9·9%); 6-*bromo*- (86%), needles, m. p. 145—146°, from ethanol (Found: C, 48·4; H, 1·9; N, 8·3. $C_{14}H_7BrN_2O_4$ requires C, 48·4; H, 2·0; N, 8·1%); and 6-*fluoro*- (92%), prisms, m. p. 170—171°, from acetic acid (Found: C, 58·6; H, 2·4; N, 9·6. $C_{14}H_7FN_2O_4$ requires C, 58·7; H, 2·4; N, 9·8%).

4-*Hydroxy*-2-o-*nitrophenylquinazoline*.—(i) *N*-(*o*-Cyanophenyl)-*o*-nitrobenzamide (5 g.) in dioxan (15 ml.) and 20% aqueous sodium hydroxide (100 ml.) was refluxed for 1 hr. with 30% hydrogen peroxide (60 ml.); further hydrogen peroxide (25 ml.) was added and refluxing was continued for 30 min. Water (500 ml.) was added, and the solution was neutralised with acetic acid and made alkaline with aqueous ammonia. The precipitated quinazoline (4·35 g., 87%) had m. p. and mixed [3] m. p. 227—228° after crystallisation from toluene.

(ii) 2-*o*-Nitrophenyl-4-oxo-3,1-benzoxazine [9] (30 g.) and urea (150 g.) were heated together at 180—190° for 30 min. and then poured into water (1·25 l.) with vigorous stirring. The precipitated quinazoline (26 g., 87%) had m. p. 224—227° after thorough washing with water. A specimen recrystallised from butanol had m. p. and mixed m. p. 227—229°.

The foregoing methods were used in the preparation of the following 2-o-*nitrophenylquinazolines*: 4-*hydroxy*-6-*methyl*-, method (i) 88%, (ii) 92%, prisms, m. p. 271—273°, from butanol (Found: C, 63·8; H, 4·0; N, 15·1. $C_{15}H_{11}N_3O_3$ requires C, 64·05; H, 3·9; N, 14·9%); 4-*hydroxy*-8-*methyl*-, method (ii) 74%, prisms, m. p. 286—288°, from acetic acid (Found: C, 64·3; H, 4·0; N, 14·7. $C_{15}H_{11}N_3O_3$ requires C, 64·05; H, 3·9; N, 14·9%); 6-*bromo*-4-*hydroxy*-, method (i) 90%, (ii) 79%, prisms, m. p. 279—280°, from acetic acid (Found: Br, 23·0; N, 12·0. $C_{14}H_8BrN_3O_3$ requires Br, 23·1; N, 12·1%); and 6-*fluoro*-4-*hydroxy*-, method (ii) 68%, needles, m. p. 248—249°, from aqueous 2-methoxyethanol (Found: C, 59·4; H, 2·9. $C_{14}H_8FN_3O_3$ requires C, 59·0; H, 2·8%).

2-o-*Aminophenyl*-4-*hydroxyquinazoline*.—(i) Sodium dithionite (10·5 g.) was added gradually to 4-hydroxy-2-*o*-nitrophenylquinazoline (2·7 g.) in 2N-sodium hydroxide (20 ml.) at 80°, the solution being kept more alkaline than pH 9 by the addition of further 2N-sodium hydroxide. After 30 min., the solution was cooled and neutralised with acetic acid. The precipitated amine (1·4 g., 57%) had m. p. and mixed [3] m. p. 239—241°.

(ii) Raney nickel was added in portions to the nitro-compound (2·7 g.) and 80% hydrazine hydrate (4 ml.) in ethanol (80 ml.), maintained at 60—65° until effervescence subsided. The amine (1·56 g., 64%), m. p. and mixed m. p. 240—241°, crystallised from the filtered reaction mixture.

With *o*-nitrobenzoyl chloride, this compound afforded 4-hydroxy-2-(*o*-*o*′-nitrobenzamidophenyl)quinazoline [3] (63%), m. p. and mixed m. p. 272—273°.

Reduction with Raney nickel and hydrazine in ethanol or butanol was used for the preparation of the following *quinazolines* from the corresponding nitro-compounds: 2-o-*aminophenyl*-4-*hydroxy*-6-*methyl*- (76%), needles, m. p. 223—224°, from propan-2-ol (Found: C, 71·8; H, 5·2; N, 16·2. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2; N, 16·7%) [its *hydrochloride* separated from 2N-hydrochloric acid as pale yellow needles, m. p. 279—281° (Found: Cl, 12·8; N, 14·6. $C_{15}H_{13}N_3O$,HCl requires Cl, 12·4; N, 14·6%)]; 2-o-*aminophenyl*-4-*hydroxy*-8-*methyl*- (78%), needles, m. p. 259—260°, from butanol (Found: C, 72·0; H, 5·3. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2%); 2-o-*aminophenyl*-6-*bromo*-4-*hydroxy*- (67%), needles, m. p. 264—265°, from butanol (Found: Br, 24·9; N, 12·7. $C_{14}H_{10}BrN_3O$ requires Br, 25·3; N, 13·3%); and 2-o-*aminophenyl*-6-*fluoro*-4-*hydroxy*- (68%), needles, m. p. 266—267°, from ethanol (Found: C, 65·6; H, 3·4. $C_{14}H_{10}FN_3O$ requires C, 65·9; H, 3·9%).

4-*Hydroxy*-2-(o-o′-*phthalimidobenzamidophenyl*)*quinazoline*.—2-*o*-Aminophenyl-4-hydroxyquinazoline (1 g.) was refluxed for 90 min. in pyridine (25 ml.) with *o*-phthalimidobenzoyl chloride (1·4 g.). The alkali-soluble fraction of the material precipitated by water furnished the *phthalimido-derivative* (1·1 g., 57%), m. p. 316—318° (from toluene) (Found: C, 71·2; H, 3·8; N, 11·9. $C_{29}H_{18}N_4O_4$ requires C, 71·6; H, 3·7; N, 11·5%).

2-(o-o′-*Aminobenzamidophenyl*)-4-*hydroxyquinazoline* was produced (24%) by reduction of the corresponding nitro-compound [3] with Raney nickel and hydrazine in ethanol and crystallised from butanol as needles, m. p. 314—316° (Found: C, 70·8; H, 4·55; N, 15·6. $C_{21}H_{16}N_4O_2$ requires C, 70·8; H, 4·5; N, 15·7%).

The same compound (0·11 g., 50%) resulted when the foregoing phthalimido-derivative

[9] Schroeter and Eisleb, *Annalen*, 1909, **367**, 101.

(0·3 g.) in 2-methoxyethanol (20 ml.) was refluxed for 2 hr. with 80% hydrazine hydrate (0·5 ml.) and the solution was neutralised with hydrochloric acid.

4-Hydroxy-6-methyl-2-(o-o′-nitrobenzamidophenyl)quinazoline.—2-*o*-Aminophenyl-4-hydroxy-6-methylquinazoline (0·75 g.) and *o*-nitrobenzoyl chloride (0·6 g.) were refluxed together in dry benzene (16 ml.) and pyridine (25 ml.) for 90 min. The solid obtained by removal of the benzene and dilution with water gave the *amide* (0·87 g.), m. p. 272—273° (from butanol) (Found: C, 65·6; H, 4·1; N, 13·7. $C_{22}H_{16}N_4O_4$ requires C, 66·0; H, 4·0; N, 14·0%). The mother-liquors deposited a second *compound* (0·045 g.), m. p. 249—250°, which was probably the secondary amide (Found: C, 63·8; H, 3·8; N, 12·7. $C_{29}H_{19}N_5O_7$ requires C, 63·5; H, 3·5; N, 12·75%).

2-(o-o′-*Aminobenzamidophenyl*)-4-*hydroxy*-6-*methylquinazoline* was prepared (58%) by reduction of the corresponding nitro-compound with hydrazine and Raney nickel and formed needles, m. p. 317—320°, from butanol (Found: N, 15·2. $C_{22}H_{18}N_4O_2$ requires N, 15·1%). Its *acetyl derivative* (prisms from butanol) had m. p. 295—297° (Found: N, 13·7. $C_{24}H_{20}N_4O_3$ requires N, 13·6%).

When the reduction was effected with hydrogen and Adams catalyst in acetic acid, the yield was 52%.

4-Hydroxy-2-(o-o′-toluene-p-sulphonamidobenzamidophenyl)quinazoline.—Prepared in 61% yield from 2-*o*-aminophenyl-4-hydroxyquinazoline and 2-toluene-*p*-sulphonamidobenzoyl chloride,[9] this *amide* crystallised from butanol as needles, m. p. 266—267° (Found: C, 65·8; H, 4·3; N, 10·9. $C_{28}H_{22}N_4O_4S$ requires C, 65·9; H, 4·3; N, 11·0%).

4-Chloro-2-o-nitrophenylquinazoline.—(i) 4-Hydroxy-2-*o*-nitrophenylquinazoline (2·7 g.), dimethylformamide (0·73 g.), and thionyl chloride (15 ml.) were boiled together for 75 min. and cooled. The oil precipitated by pouring the suspension on to stirred, crushed ice (100 g.) rapidly solidified, and, after being washed with ice–water and vacuum-dried over phosphoric oxide, had m. p. 177—179° (2·7 g., 96%); crystallisation from dry acetone gave the *chloro-derivative* as pale yellow needles, m. p. 179—181° (Found: C, 58·5; H, 2·9; N, 14·4. $C_{14}H_8ClN_3O_2$ requires C, 58·8; H, 2·8; N, 14·7%).

(ii) The 4-hydroxyquinazoline (40 g.) and freshly redistilled phosphoryl chloride (160 ml.) were heated together at 140° for 2½ hr., filtered whilst hot, and kept at 0°. Next day, the crystalline chloroquinazoline (20·6 g.; m. p. 179—181°) was washed with dry acetone. The mother-liquor gave a further quantity (9·3 g.), m. p. 178—180°.

4-o-Methoxycarbonylanilino-2-o-nitrophenylquinazoline (VIIa).—4-Chloro-2-*o*-nitrophenylquinazoline (2·85 g.), methyl anthranilate (1·51 g.), and concentrated hydrochloric acid (0·2 ml.), when refluxed together in acetone (150 ml.) for 1 hr., furnished the *4-anilinoquinazoline hydrochloride* (4 g.) which crystallised from methanol as yellow needles, m. p. 232—233° (Found: N, 13·1. $C_{22}H_{17}ClN_4O_4$ requires N, 12·8%). The *base*, precipitated from methanol with ammonia, yielded pale yellow needles, m. p. 187—188°, from acetic acid (Found: C, 65·7; H, 3·9; N, 13·6. $C_{22}H_{16}N_4O_4$ requires C, 66·0; H, 4·0; N, 14·0%).

In Table 1 are recorded analogous *4-anilinoquinazolines* similarly prepared from appropriately substituted arylamines.

TABLE 1.

4-Anilino-2-*o*-nitrophenylquinazolines.

Compound (VII)		Yield (%)	Found (%) M. p.	C	H	N	Formula	Required (%) C	H	N
b		70	309—311°	65·2	4·1	14·5	$C_{21}H_{14}N_4O_4$	65·3	3·7	14·5
	hydrochloride		253—255			12·9	$C_{21}H_{15}ClN_4O_4$ †			13·2
c		74	186—187	68·7	3·6		$C_{21}H_{13}N_5O_2$	68·7	3·6	
d		74	196—197	66·3	4·2	13·2	$C_{23}H_{18}N_4O_4$	66·7	4·4	13·5
	hydrochloride		173—175 *			10·9	$C_{25}H_{25}ClN_4O_5$ ‡			11·3
e		69	214—215	66·7	4·2	14·0	$C_{23}H_{18}N_4O_4$	66·7	4·4	13·5
	hydrochloride		217—219 *			12·7	$C_{23}H_{19}ClN_4O_4$			12·4
f		83	197—199	69·2	4·0		$C_{22}H_{15}N_5O_2$	69·3	4·0	
	hydrochloride		192—193 *			15·0	$C_{24}H_{20}ClN_5O_4$ §			14·7
g		76	197—198	66·3	3·6	17·4	$C_{22}H_{15}N_5O_3$	66·5	3·8	17·6
	hydrochloride		161—162			15·8	$C_{22}H_{16}ClN_5O_3$			16·1

* With decomp. † Found: Cl, 8·6. $C_{21}H_{15}ClN_4O_4$ requires Cl, 8·4%. ‡ With ethanol of crystallisation (Found: Cl, 7·1. $C_{25}H_{25}ClN_4O_5$ requires Cl, 7·1%). § With acetic acid of crystallisation (Found: Cl, 7·2. $C_{24}H_{20}ClN_5O_4$ requires Cl, 7·4%).

2-o-*Aminophenyl*-4-o-*methoxycarbonylanilinoquinazoline* (VIIIa).—(i) The nitrophenylquinazoline (VIIa) (2·2 g.) in acetic acid (150 ml.) gradually became orange on being shaken with hydrogen and Adams catalyst (0·01 g.). The acid-soluble fraction of the residue obtained by evaporation of the filtrate furnished, on basification, the *amine* (1·3 g., 63%), which crystallised from butanol as needles, m. p. 192—193° (Found: C, 70·9; H, 5·0; N, 14·8. $C_{22}H_{18}N_4O_2$ requires C, 71·3; H, 4·9; N, 15·1%); its *hydrochloride* separated as needles, m. p. 176—178°, from 2N-hydrochloric acid (Found: Cl, 8·9; N, 13·4. $C_{22}H_{19}ClN_4O_2$ requires Cl, 8·7; N, 13·8%), and its *acetyl derivative* crystallised from acetic acid as needles, m. p. 212—213° (Found: C, 69·6; H, 5·0; N, 13·2. $C_{24}H_{20}N_4O_3$ requires C, 69·9; H, 4·9; N, 13·6%).

(ii) Reduction with Raney nickel and hydrazine in butanol as described for 2-*o*-aminophenyl-4-hydroxyquinazoline gave 76% of the amine, m. p. and mixed m. p. 191—193°.

The foregoing method (ii) gave the following 2-o-*aminophenylquinazolines*: 4-(2-*methoxycarbonyl*-4-*methylanilino*)- (VIIId) (75%), needles (from methanol), m. p. 152—153° (Found: C, 71·9; H, 5·4; N, 14·0. $C_{23}H_{20}N_4O_2$ requires C, 71·9; H, 5·2; N, 14·6%); 4-(2-*methoxycarbonyl*-5-*methylanilino*)- (VIIIe) (90%), needles (from butanol), m. p. 182—183° (Found: C, 71·8; H, 5·1; N, 14·0. $C_{23}H_{20}N_4O_2$ requires C, 71·9; H, 5·2; N, 14·6%); 4-(2-*cyano*-5-*methylanilino*)- (VIIIf) (59%), needles (from toluene), m. p. 195—196° (decomp.) (Found: N, 21·4. $C_{22}H_{17}N_5$ requires N, 19·9%); and 4-(2-*cyano*-5-*methoxyanilino*)- (VIIIg) (60%), yellow needles (from butanol), m. p. 201—203° (decomp.) (Found: N, 20·1. $C_{22}H_{17}N_5O$ requires N, 19·1%).

Tricycloquinazolines.—(i) *o*-Cyanoaniline (3 g.) and methyl anthranilate toluene-*p*-sulphonate (8 g.) reacted exothermically when heated together at 210° for 40 min. The neutral fraction of the product obtained by extraction of an amphoteric compound with hot acid and alkali was tricycloquinazoline (1·02 g., 27%), m. p. and mixed m. p. 317—320°, having the characteristic eight light-absorption bands between 245 and 455 mμ. 5-*Amino*-11-*hydroxyphenhomazine* (0·4 g.), recovered by neutralisation of the acidic and alkaline extracts, crystallised from methanol as yellow prisms, m. p. 213—215°, depressed to about 196° by its isomer, 2-*o*-aminophenyl-4-hydroxyquinazoline (Found: C, 71·0; H, 4·4. $C_{14}H_{11}N_3O$ requires C, 70·9; H, 4·7%). Its *diacetyl derivative*, prisms from acetic acid, had m. p. 238—239° (Found: C, 67·8; H, 4·7; N, 13·2. $C_{18}H_{15}N_3O_3$ requires C, 67·3; H, 4·7; N, 13·1%).

(ii) 2-*o*-Aminophenyl-4-hydroxyquinazoline (0·6 g.), *o*-cyanoaniline (0·3 g.), and toluene-*p*-sulphonic acid (0·1 g.) were heated together at 210° for 45 min. The powdered product was washed with warm 2N-hydrochloric acid and with 2N-sodium hydroxide; the residue, on extraction with benzene, gave tricycloquinazoline (0·49 g.), m. p. and mixed m. p. 318—320°.

Substituted *tricycloquinazolines*, prepared analogously, are given in Table 2.

TABLE 2.

Substituted tricycloquinazolines.

No. in text	Subst.	Yield (%)	Found (%) M. p.	C	H	N	Formula	Required (%) C	H	N
1	1-Me	31	292—294°	78·8	4·1	16·8				
2	2-Me	31	278—279	78·6	4·3	17·2				
3a	3-Me	31	266—267	78·7	4·5	16·3	$C_{22}H_{14}N_4$	79·0	4·2	16·8
3b	3-Me	33	266—267							
4	4-Me	20	246—248	78·8	4·0	16·5				
5a	3-Br	34	290—291			13·6	$C_{21}H_{11}BrN_4$			14·0
5b	3-Br	35	290—291							
6	3-F	30	322—323	74·3	3·5	16·5	$C_{21}H_{11}FN_4$	74·5	3·3	16·6
7	3,8-Me_2	42	273—275	79·5	5·0	16·2	$C_{23}H_{16}N_4$	79·3	4·6	16·1
8	3,8-Br_2	18	325—326			11·3	$C_{21}H_{10}Br_2N_4$			11·7
9	3,8-F_2	29	336—338	70·6	2·7	15·0	$C_{21}H_{10}F_2N_4$	70·7	2·8	15·7

The foregoing tricycloquinazolines crystallised from toluene or xylene as yellow needles.

(1) From (IIb) and *o*-cyanoaniline.

(2) From (IIa) and 2-cyano-5-methylaniline. The cyanide (VIIIf), when heated at 210° for 1 hr., furnished this tricycloquinazoline (30%), m. p. and mixed m. p. 278—280°.

(3a) From (IIa) and 2-cyano-4-methylaniline. The cyanide resulted (47%) from the pyrolysis of 5-methylisatin 3-oxime.[10]

[10] Bedford and Partridge, *J.*, 1959, 1633.

(3b) From (IIc) and *o*-cyanoaniline.

(4) From (IIa) and 2-cyano-3-methylaniline.

(5a) From (IIa) and 4-bromo-2-cyanoaniline (Found: Br, 19·7. $C_{21}H_{11}BrN_4$ requires Br, 20·0%).

(5b) From (IId) and *o*-cyanoaniline.

(6) From (IIa) and 2-*cyano*-4-*fluoroaniline* which was prepared by the pyrolysis of 5-fluoroisatin 3-oxime [7] and had b. p. 130°/15 mm., m. p. 94—95° (from water) (Found: C, 61·6; H, 3·9; N, 20·5. $C_7H_5FN_2$ requires C, 61·8; H, 3·7; N, 20·6%).

(7) From (IIc) and 2-cyano-4-methylaniline at 255° for 45 min.; the crude product was purified by elution as a yellow band from an alumina column with benzene.

(8) From (IId) and 4-bromo-2-cyanoaniline (Found: Br, 33·1. $C_{21}H_{10}Br_2N_4$ requires Br, 33·4%).

(9) From (IIe) and 2-cyano-4-fluoroaniline.

(iii) 2-(*o*-*o*'-Aminobenzamidophenyl)-4-hydroxyquinazoline (0·1 g.) and phosphoric oxide (0·4 g.), when boiled together in xylene (15 ml.) for 90 min. and subsequently treated with water, furnished tricycloquinazoline (20 mg.), m. p. and mixed m. p. 317—320°. The corresponding 6-methylquinazoline similarly gave 3-methyltricycloquinazoline (23%) m. p. and mixed m. p. 264—266°.

(iv) The sulphonamide (V), treated in the same way as the foregoing amides, gave 17% of tricycloquinazoline, m. p. and mixed m. p. 318—320°.

(v) After similar treatment, the anilinoquinazoline (VIIIa) was recovered (30%) as the acid-soluble fraction; the acid-insoluble fraction was tricycloquinazoline (14%), m. p. and mixed m. p. 319—320°.

(vi) The same compound (VIIIa) (0·5 g.) was heated in 100% phosphoric acid (25 g.) at 160° for 3 hr. and poured into water (70 ml.). The precipitated tricycloquinazoline had m. p. and mixed m. p. 319—320° after crystallisation from toluene (yield 0·34 g., 77%). The yield fell to 63% at 135° and to 70% at temperatures up to 250°; the optimum time at 160° was 2—3 hr. The homologue (VIIIe) similarly afforded 80% of 2-methyltricycloquinazoline, m. p. and mixed m. p. 278—279°, and its isomer (VIIId) gave 70% of 3-methyltricycloquinazoline, m. p. and mixed m. p. 266—267°.

3,8,13-*Trimethyltricycloquinazoline* was obtained (11%) when 2-cyano-4-methylaniline toluene-*p*-sulphonate was heated at 210° for 45 min. and the solid formed was crystallised from xylene; it formed yellow needles, m. p. 388—390° (Found: C, 80·0; H, 5·0; N, 15·7. $C_{24}H_{18}N_4$ requires C, 79·5; H, 5·0; N, 15·5%).

TABLE 3.

Light absorption (λ in mμ) of tricycloquinazolines.

Subst.											
None	$\lambda_{max.}$	252		284	296	310		379	400	425	453
	log ε	4·61		4·38	4·48	4·44		4·34	4·34	3·90	3·40
1-Me	$\lambda_{max.}$	254		288	298	311		381	402	428	455
	log ε	4·68		4·40	4·50	4·44		4·42	4·40	3·94	3·45
2-Me	$\lambda_{max.}$	254		285	296	310		380	400	424	451
	log ε	4·71		4·43	4·55	4·48		4·39	4·38	3·94	3·45
3-Me	$\lambda_{max.}$	252		286	297	311		382	402	427	455
	log ε	4·67		4·39	4·50	4·45		4·38	4·37	3·91	3·42
4-Me	$\lambda_{max.}$	252		288	297	310		378	400	427	454
	log ε	4·64		4·36	4·48	4·42		4·40	4·35	3·86	3·42
3-Br	$\lambda_{max.}$	250		287	298	312		383	404	429	456
	log ε	4·71		4·40	4·51	4·45		4·39	4·37	3·95	3·47
3-F	$\lambda_{max.}$	250		285	296	310		381	402	428	455
	log ε	4·63		4·34	4·43	4·37		4·36	4·33	3·86	3·38
3,8-Me_2	$\lambda_{max.}$	252		288	299	313		384	404	430	457
	log ε	4·63		4·37	4·48	4·42		4·38	4·35	3·92	3·41
3,8-Br_2	$\lambda_{max.}$	251	265	290	300	315		386	408	433	461
	log ε	4·72	4·65	4·46	4·54	4·46		4·42	4·41	3·97	3·48
3,8-F_2	$\lambda_{max.}$	257		285	295	310		383	404	432	460
	log ε	4·60		4·34	4·41	4·34		4·35	4·31	3·82	3·34
3,8,13-Me_3	$\lambda_{max.}$	253		289	301	315		386	406	431	459
	log ε	4·63		4·39	4·50	4·48		4·40	4·39	3·96	3·44
2-OMe	$\lambda_{max.}$		263		296	309	321	382	397	421 *	448
	log ε		4·70		4·56	4·43	3·96	4·36	4·34	3·97	3·43

* Inflexion.

2-*Methoxytricycloquinazoline* was obtained (0·73 g.) when the anilinoquinazoline (VIIIg) (1 g.) was heated at 255° for 2 hr. and the product was crystallised from toluene; it had m. p. 250—251° (Found: C, 75·2; H, 4·1; N, 16·0. $C_{22}H_{14}N_4O$ requires C, 75·4; H, 4·0; N, 16·0%). Demethylation by boiling (1 hr.) hydrobromic acid afforded 2-*hydroxytricycloquinazoline* (92%) which, crystallised from aqueous pyridine, had m. p. 367—369° (Found C, 75·0; H, 3·8. $C_{21}H_{12}N_4O$ requires C, 75·0; H, 3·6%).

Spectra.—Light absorptions, determined for chloroform solutions, are recorded in Table 3.

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