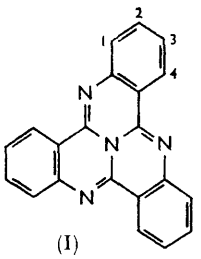
709. *Cyclic Amidines. Part XVIII.*[1] *The Synthesis of Tricycloquinazolines by Cyclodehydrogenation.*

By M. W. Partridge, S. A. Slorach, and H. J. Vipond.

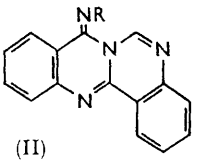
Cyclisation of 2-*o*-aminophenyl-4-arylaminoquinazolines with triethyl orthoformate yields 7-aryliminotriazabenz[*a*]anthracenes which, on cyclodehydrogenation, afford tricycloquinazolines.

Tricycloquinazoline (I) is formed in a number of pyrolyses of simple compounds.[2] We now describe the use of vigorous cyclodehydrogenation of polyaza-polycyclic compounds for the production of tricycloquinazoline and of certain derivatives, required in the study of tricycloquinazoline carcinogenesis.

7-Aryliminotriazabenzanthracenes (II) required for such cyclodehydrogenations were produced from the 2-*o*-aminophenyl-4-arylaminoquinazolines (III) formed by acid-catalysed interaction of the chloroquinazoline (IV) with an arylamine, followed by reduction of the nitro-group. Cyclisations to the triazabenzanthracenes (II) were effected with triethyl orthoformate. This cyclisation has previously been shown [3] to yield triazabenzanthracenes and not the isomeric triazachrysenes. Further support for the assigned

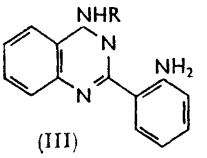


(I)

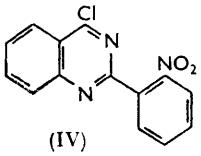


(II)

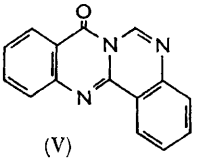
(a: R = Ph)
(b: R = *o*-C_6H_4OH)
(c: R = *p*-C_6H_4Br)
(d: R = 2-$C_{10}H_7$)



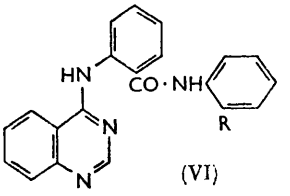
(III)



(IV)



(V)



(VI)

structures was provided by the close resemblance of the 7-phenylimino-derivative (IIa) to the 7-oxo-derivative (V) [3] in absorption spectrum and ease of hydrolysis. Thus, in hot aqueous butanol or cold 2N-hydrochloric acid, the imino-derivative (IIa) gave 4-anilino-2-*o*-formamidophenylquinazoline, whereas, with hot acid or alkali, the product was the 4-anilinoquinazoline (IIIa).

The anilide (VI; R = H), formed by treatment of 4-chloroquinazoline with *o*-aminobenzanilide, afforded, with 100% phosphoric acid, not the triazabenzanthracene (IIa), but 2-*o*-aminophenyl-4-hydroxyquinazoline. Treatment of this anilide (VI; R = H) with aqueous alkali furnished the same product. Since the 4-anilinoquinazoline (IIIa) is not readily hydrolysed, it is unlikely to be an intermediate in either of the reactions leading to 2-*o*-aminophenyl-4-hydroxyquinazoline. Evidently, in each case elimination of aniline from the anilide (VI; R = H) gives the 7-oxotriazabenzanthracene (V), which is then hydrolysed either when its solution in phosphoric acid is poured into water, or directly

[1] Part XVII, Partridge and Stevens, preceding Paper.
[2] Baldwin, Butler, Cooper, Partridge, and Cunningham, *Nature*, 1958, **181**, 838.
[3] Butler, Partridge, and Waite, *J.*, 1960, 4970.

by alkali. The *o*-chloroanilide (VI; R = Cl) behaved likewise with aqueous alkali. A similar reaction sequence has been observed with analogous 4-anilinoquinazolines.[3]

With sulphur at 280° or in boiling dimethylformamide, the triazabenzanthracene (IIa) did not evolve hydrogen sulphide. Cyclodehydrogenation with palladium charcoal was inefficient, only 3% of tricycloquinazoline (I) being obtained, whereas with sodium aluminium chloride at 320°, the yield was 45%. Experience with other aryliminotriazabenzanthracenes (IIb, c, d) showed that the latter reaction was not entirely a cyclodehydrogenation, because tricycloquinazoline was formed in addition to the expected 1-hydroxy-, 3-bromo-,[4] and benzo[*c*]-derivatives. It is probable that tricycloquinazoline results in these cases from extensive pyrolysis of the triazabenzanthracenes. 1-Hydroxytricycloquinazoline, which is a probable tissue metabolite of tricycloquinazoline, was conveniently prepared by this method, since it is easily separable from tricycloquinazoline.

The enhanced reactivity of the 1-position of the naphthyl group in the naphthyliminoderivative (IId) augmented the efficiency of palladium–charcoal cyclodehydrogenation in the production of benzo[*c*]tricycloquinazoline. For comparison, benzo[*c*]- and benzo[*b*]-tricycloquinazoline were synthesised unequivocally by a previously described procedure.[4] This established that no rearrangement occurred during these vigorous cyclisations.

Experimental

2-o-*Aminophenyl*-4-*anilinoquinazoline* (IIIa).—4-Anilino-2-*o*-nitrophenylquinazoline (2 g.), dissolved in ethanol (150 ml.) and hydrazine hydrate (3 ml.), underwent reduction on the gradual addition of Raney nickel to maintain the temperature at 60—70° until gas evolution ceased. The *amine* (1·7 g.), which separated from the concentrated filtrate, had m. p. 203—204° (from ethanol) (Found: C, 76·7; H, 5·1; N, 17·4. $C_{20}H_{16}N_4$ requires C, 76·9; H, 5·2; N, 17·9%).

7-*Phenylimino*-7H-5,6a,12-*triazabenz*[a]*anthracene* (IIa).—The foregoing amine (IIIa) (8 g.) was refluxed in triethyl orthoformate (100 ml.) for 2 hr. Crystallisation of the resulting solid from butanol furnished the *triazabenzanthracene* (6·3 g.) as yellow needles, m. p. 236—237°, and subliming at 215—220°/0·2 mm. $\lambda_{max.}$ (in EtOH) 243, 321, 364 mμ (log ε 4·58, 4·07, 4·09) (Found: C, 77·8; H, 3·8; N, 17·2. $C_{21}H_{14}N_4$ requires C, 78·2; H, 4·4; N, 17·4%).

This triazabenzanthracene (1 g.), when refluxed in butanol (30 ml.) and water (10 ml.) for 4 hr. and kept overnight, gave 4-*anilino*-2-o-*formamidophenylquinazoline* (0·62 g.), needles, m. p. 220—222° (from ethanol) (Found: C, 74·4; H, 4·5; N, 16·2. $C_{21}H_{16}N_4O$ requires C, 74·1; H, 4·7; N, 16·5%). When shaken for 2 hr. with cold 2N-hydrochloric acid, the triazabenzanthracene furnished the same amide (32%), m. p. and mixed m. p. 220—222°. In refluxing N-hydrochloric acid, it gave, after 1 hr., orange needles which, when basified in ethanolic ammonia, yielded the 4-anilinoquinazoline (IIIa) (72%), m. p. and mixed m. p. 203—204°. The same amine (IIIa) (99%) resulted from hydrolysis in refluxing 2·5N-sodium hydroxide in aqueous ethanol.

2-(*Quinazolin*-4-*ylamino*)*benzanilide* (VI; R = H).—4-Chloroquinazoline (9·9 g.) and *o*-aminobenzanilide (12·7 g.) were boiled together in dry acetone (150 ml.) for 1 hr. Next day, the solid product was dissolved in aqueous methanol and basified with ammonia to yield the *secondary amine* (13·2 g.), needles, m. p. 231—232° (from benzene) (Found: C, 74·4; H, 4·9. $C_{21}H_{16}N_4O$ requires C, 74·1; H, 4·7%).

On being boiled for 1 hr. with 2N-sodium hydroxide, this compound afforded aniline and 2-*o*-aminophenyl-4-hydroxyquinazoline (72%), needles, m. p. 238—240° (from ethanol), undepressed by an authentic specimen.[5] The secondary amine (0·5 g.) was heated in 100% phosphoric acid (25 g.) at 220° for 3 hr., cooled, poured into water, and adjusted to pH 7. The precipitate yielded 2-*o*-aminophenyl-4-hydroxyquinazoline (0·05 g.), m. p. and mixed m. p. 238—240° (from benzene).

2′-*Chloro*-2-(*quinazolin*-4-*ylamino*)*benzanilide* (VI; R = Cl).—4-Chloroquinazoline (1·65 g.) and 2-amino-2′-chlorobenzanilide (2·5 g.), when refluxed together in dry acetone (30 ml.) containing concentrated hydrochloric acid (0·5 ml.) and basified, furnished the *secondary amine*

[4] Partridge, Vipond, and Waite, *J.*, 1962, 2549.
[5] Butler and Partridge, *J.*, 1959, 2396.

(3 g.), m. p. 209—211° (from benzene) (Found: C, 67·3; H, 3·6. $C_{21}H_{15}ClN_4O$ requires C, 67·3; H, 4·0%).

The secondary amine (1 g.) was refluxed with 2N-sodium hydroxide (30 ml.) for 1 hr. Benzoylation of the product after steam-distillation gave 2′-chlorobenzanilide (0·54 g.), m. p. and mixed m. p. 101—103°. The non-volatile product was precipitated with acetic acid and crystallised from ethanol, to give 2-*o*-aminophenyl-4-hydroxyquinazoline (0·29 g.), m. p. and mixed m. p. 238—239°.

Tricycloquinazoline (I).—(*a*) The triazabenzanthracene (IIa) (0·5 g.) and sodium aluminium chloride (1·2 g.) were heated together at 320° for 4 hr., cooled, and ground with water. A benzene extract of the dried product furnished tricycloquinazoline (0·22 g.), m. p. and mixed m. p. 317—319°, as a yellow fluorescent band, eluted from alumina by benzene. Dehydrogenation with 30% palladium–charcoal at 320° for 3 hr. similarly gave 3% of tricycloquinazoline.

(*b*) *o*-Quinazolin-4-ylaminobenzanilide (1 g.) and sodium aluminium chloride (2·4 g.) at 320° for 3 hr. likewise furnished tricycloquinazoline (0·042 g.), m. p. and mixed m. p. 317—319°.

2-*o*-Nitrophenyl-4-arylaminoquinazolines, prepared from 4-chloro-2-*o*-nitrophenylquinazoline and an arylamine, and the corresponding amines obtained on reduction of the nitro-group,[4] are given in the Table.

2,4-Disubstituted quinazolines.

R	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
2-o-*Nitrophenylquinazolines* (III; NO_2 for NH_2).								
o-C_6H_4·OH	238—239°	67·2	4·0	15·5	$C_{20}H_{14}N_4O_3$	67·0	3·9	15·6
p-C_6H_4Br	198—200	57·0	3·2	12·9	$C_{20}H_{13}BrN_4O_2$	57·0	3·1	13·3
2-Naphthyl	191	73·0	4·0	14·7	$C_{24}H_{16}N_4O_2$	73·5	4·1	14·3
1-Methoxycarbonyl-2-naphthyl	204—205	69·1	3·8	12·0	$C_{26}H_{18}N_4O_4$	69·3	4·0	12·4
3-Methoxycarbonyl-2-naphthyl	239—240	69·3	3·8	12·2				
2-o-*Aminophenylquinazolines* (III).								
o-C_6H_4OH	209—211	73·2	5·0	17·0	$C_{20}H_{16}N_4O$	73·2	4·9	17·1
p-C_6H_4Br	245—246	61·1	3·7		$C_{20}H_{15}BrN_4$	61·4	3·8	
2-Naphthyl	211—212			15·7	$C_{24}H_{18}N_4$			15·5
1-Methoxycarbonyl-2-naphthyl	180—181	74·7	4·5	13·7	$C_{26}H_{20}N_4O_2$	74·3	4·8	13·3
3-Methoxycarbonyl-2-naphthyl	223—224	74·4	4·9	12·9				

7-*Arylamino*-7H-5,6a,12-*triazabenz*[a]*anthracenes* were prepared as described for the phenyl derivative (IIa): o-*hydroxyphenyl* (IIb), red prisms, m. p. 243—244° (Found: C, 74·6; H, 4·2; N, 16·4. $C_{21}H_{14}N_4O$ requires C, 74·5; H, 4·2; N, 16·6%); p-*bromophenyl* (IIc), yellow needles, m. p. 285—286° (Found: C, 62·4; H, 3·1. $C_{21}H_{13}BrN_4$ requires C, 62·8; H, 3·2%); 2-*naphthyl* (IId), orange needles, m. p. 241—242° (Found: C, 81·0; H, 4·4; N, 15·1. $C_{25}H_{16}N_4$ requires C, 80·6; H, 4·3; N, 15·1%).

Substituted *tricycloquinazolines* were obtained in the yields given by the method (*a*) described for tricycloquinazoline or by the condensation of the esters (III; R = 1- or 3-methoxycarbonyl-2-naphthyl) with 100% phosphoric acid.[4] 1-*Hydroxytricycloquinazoline* (sodium aluminium chloride dehydrogenation) (17%) was eluted from an alumina column by 10% formic acid in acetone, after elution of simultaneously formed tricycloquinazoline with benzene, and had m. p. 317—319°, $\lambda_{max.}$ (in $CHCl_3$) 254, 287, 299, 333, 382, 402, 430, 457 mμ (log ε 4·58, 4·33, 4·37, 4·24, 4·36, 4·34, 3·90, 3·43) (Found: C, 75·2; H, 3·7; N, 16·5. $C_{21}H_{12}N_4O$ requires C, 75·0; H, 3·6; N, 16·7%). 3-Bromotricycloquinazoline (sodium aluminium chloride dehydrogenation) (12%) was separated from simultaneously formed tricycloquinazoline by thin-layer chromatography on silica gel and shown to be identical with authentic material[4] by fluorescence and fluorescence activation spectra. *Benzo*[c]*tricycloquinazoline* (sodium aluminium chloride, palladium charcoal dehydrogenation, condensation) (5, 10, 92%, respectively), obtained together with tricycloquinazoline when formed by the sodium aluminium chloride dehydrogenation, formed orange needles, m. p. 268—269°, $\lambda_{max.}$ (in $CHCl_3$) 273, 298, 323, 339, 383, 397, 401, 419, 450, 479 mμ (log ε 4·61, 4·46, 4·32, 4·48, 4·29, 4·35, 4·34, 4·21, 3·73, 3·44) (Found: C, 81·5; H, 3·7; N, 15·2. $C_{25}H_{14}N_4$ requires C, 81·1; H, 3·8; N, 15·1%). *Benzo*[b]*tricycloquinazoline* (condensation) (82%) had m. p. 285—286°, $\lambda_{max.}$ (in $CHCl_3$) 255, 270, 279, 290, 303, 344, 355, 370, 394, 420, 445 mμ (log ε 4·67, 4·68, 4·73, 4·63, 4·57, 4·27, 4·30,

4·30, 4·29, 4·21, 4·12) (Found: C, 81·3; H, 3·6; N, 14·9. $C_{25}H_{14}N_4$ requires C, 81·1; H, 3·8; N, 15·1%).

We are grateful to the British Empire Cancer Campaign for the award of a maintenance grant (to S. A. S.), and to the Fleming Memorial Fund for a grant to purchase an Aminco-Bowman spectrophotofluorometer.

THE UNIVERSITY, NOTTINGHAM. [*Received, December 23rd*, 1963.]