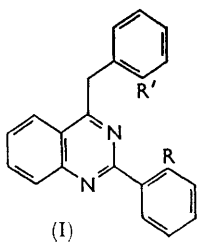
710. *Cyclic Amidines. Part XIX.*[1] *Derivatives of Triazabenzonaphthanthracene.*

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

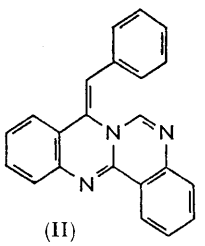
Both 7-benzylidene-7*H*-5,6a,12-triazabenz[*a*]anthracene (II) and *o*-quinazolin-4-ylaminophenyl benzyl ketone (IV; R = H) are cyclised with sodium aluminium chloride to 5,10,14c-triazabenzo[*a*]naphth[1,2,3-*de*]anthracene, the structure of which follows from its spectroscopic similarity to its unequivocally synthesised 14-methyl derivative. 10,15,15d-Triazabenzo[*qr*]naphtho[1,2,3,4-*def*]chrysene (X) results similarly from 2-*o*-benzamidophenylperimidine. The significance of the loss of carcinogenic activity in the compound (V; R = H) in tricycloquinazoline carcinogenesis is discussed.

The carcinogenic activity of tricycloquinazoline is blocked by the introduction of a single methyl substituent at the 2-position but not at the 1-, 3-, or 4-positions.[2] Accordingly, because of the symmetry of tricycloquinazoline, it may be deduced that this carcinogen reacts with a tissue receptor by a three-point union, which could involve the three peripheral nitrogen atoms of the tricycloquinazoline. Tricycloquinazoline analogues required to test this hypothesis have now been synthesised.

o-Aminophenyl benzyl ketone, which has hitherto been obtained by hydrolysis of the product of ozonolysis of 3-benzyl-2-methylindole,[3] was more conveniently prepared from *o*-aminobenzonitrile and benzylmagnesium chloride.[4] This ketone afforded an *o*-nitrobenzoyl derivative which was cyclised to the quinazoline (I; R = NO_2, R′ = H) with gaseous ammonia in molten ammonium acetate.[5] The corresponding amine (I; R = NH_2, R′ = H) yielded a triazabenzanthracene (II) with ethyl orthoformate. It has previously been shown [6] that the isomeric triazachrysenes are not formed in this type of cyclisation. Moreover, the cyclic compound (II) closely resembled the 7-oxotriazabenzanthracene (III) in spectroscopic properties and in its behaviour on hydrolysis to a formamide, in this case (I; R = NH·CHO, R′ = H).



(I)



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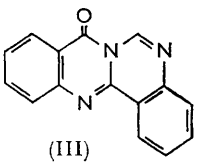


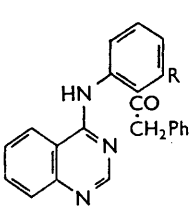
(III)

[1] Part XVIII, Partridge, Slorach, and Vipond, preceding Paper.
[2] Baldwin, Cunningham, Partridge, and Vipond, *Brit. J. Cancer*, 1962, **16**, 276.
[3] Ockenden and Schofield, *J.*, 1953, 3440.
[4] Grammaticakis, *Compt. rend.*, 1952, **235**, 546.
[5] Schofield, *J.*, 1954, 4034.
[6] Butler, Partridge, and Waite, *J.*, 1960, 4970.

This formamide (I; R = NH·CHO, R′ = H) was also formed when 4-chloroquinazoline was reacted with *o*-aminophenyl benzyl ketone in undried acetone containing a trace of concentrated hydrochloric acid, whereas in dry acetone these reagents yielded the ketone (IV). It is probable that the formation of the formamide (I; R = NH·CHO, R′ = H) from 4-chloroquinazoline involves the production of the triazabenzanthracene (II) or a hydrated derivative, which is then hydrolysed. Additional examples [1,6] of such a series of reactions have been observed with 4-anilinoquinazolines.

As model experiments for the synthesis of the quinazoline (I; R = NO_2, R′ = CO_2Et) having an ester group available for a later cyclisation, the reactions of 4-chloro-2-*o*-nitrophenylquinazoline with diethyl sodiomalonate were examined. In benzene, the product was diethyl 2-*o*-nitrophenylquinazolin-4-ylmalonate, which was hydrolysable to 4-methyl-2-*o*-nitrophenylquinazoline, and in ethanol the product was ethyl 2-*o*-nitrophenylquinazolin-4-ylacetate. However, 4-chloro-2-*o*-nitrophenylquinazoline did not react with either diethyl sodiohomophthalate or ethyl sodiophenylacetate.

Cyclodehydrogenation of the triazabenzanthracene (II) to the triazabenzonaphthanthracene (V; R = H) proved difficult. No product was isolated using sulphur in dimethylformamide, aluminium chloride in benzene, or palladium–charcoal, whereas with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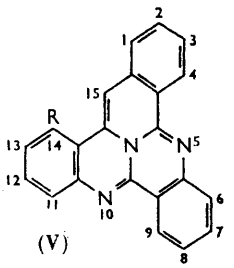
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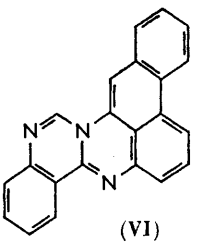
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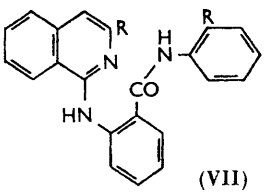
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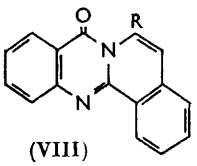
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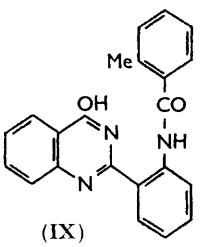
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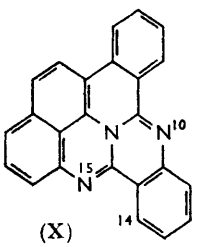
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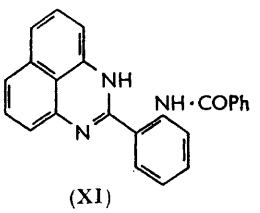
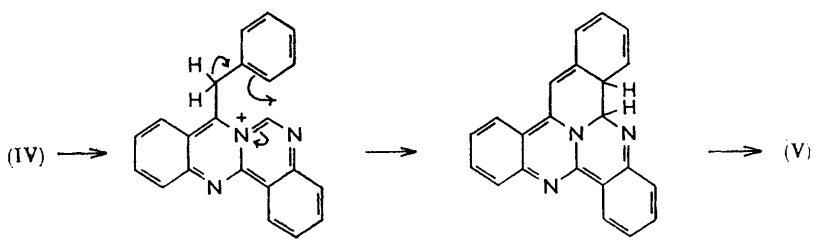

(XI)

sodium aluminium chloride an optimum yield of only 10% was obtained. In contrast, the last reagent converted the ketone (IV; R = H) directly into the hexacyclic compound (V; R = H) in 48% yield. It is therefore improbable that the triazabenzanthracene (II) is an intermediate in the cyclisation of this ketone (IV; R = H). Significant steps in the process may be as follows:

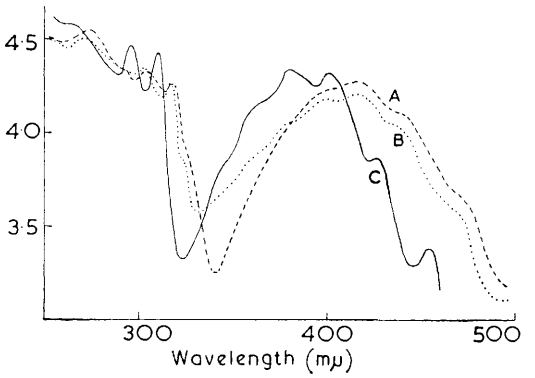


Although this triazabenzonaphthanthracene showed some similarity in its absorption spectrum to tricycloquinazoline (see Figure), the bathochromic shifts, especially in the $n \longrightarrow \pi^*$ band, associated with the replacement of N by CH, were contrary to some

previously reported observations [7] on the effect of aza-substitution in polycyclic compounds. However, the absorption spectra of benzo[*a*]-[3,6]phenanthroline [8] and of 1,3,5-triazine,[9] compared with benzo[*c*]phenanthrene and pyrimidine, respectively, provide examples of similar bathochromic shifts. Nevertheless, spectroscopic comparison of the triazabenzonaphthanthracene with tricycloquinazoline is inadequate to exclude the alternative structure (VI).

The structure of the triazabenzonaphthanthracene (V; R = H) was established by the close spectroscopic similarity of its methyl derivative (V; R = Me) (see Figure). This compound was synthesised unequivocally from the ketone (IV; R = Me) in which the alternative cyclisation is blocked by the methyl group. The ketone (IV; R = Me) was prepared from 2-amino-6-methylbenzonitrile and benzylmagnesium chloride, followed by treatment of the resulting benzyl *o*-tolyl ketone with 4-chloroquinazoline.

The anilide (VII; R = H), prepared by condensation of 1-chloroisoquinoline and *o*-aminobenzanilide in acetone, could not be cyclised to the triazabenzonaphthanthracene (V; R = H) with sodium aluminium chloride. This failure may be ascribed to the elimination of aniline during the initial cyclisation of the anilide (VII; R = H), since 1-chloroisoquinoline and *o*-aminobenzanilide, when heated together at 130°, yielded the diazabenzanthracene (VIII; R = H), identical with that formed from 1-chloroisoquinoline



Absorption spectra of 14-methyl-5,10,14c-triazabenzo[*a*]naphth[1,2,3-*de*]anthracene (A), 5,10,14c-triazabenzo[*a*]naphth[1,2,3-*de*]anthracene (B), and tricycloquinazoline (C) in chloroform.

and methyl anthranilate. In contrast, the dichloro-derivative (VII; R = Cl), produced from 1,3-dichloroisoquinoline and 2-amino-2′-chlorobenzanilide was stable at 180°, but underwent an analogous elimination when treated with phosphoric oxide in xylene; the product was the chlorodiazabenzanthracene (VIII; R = Cl).

2-*o*-Aminophenyl-4-hydroxyquinazoline formed an alkali-soluble *o*-toluoyl derivative (IX). Attempts to effect its cyclisation to the hexacyclic compound (V; R = H) were unsuccessful, a trace of tricycloquinazoline being the only recognisable product.

Isosteric replacement of N of tricycloquinazoline by CH in the triazabenzonaphthanthracene (V; R = H) may result in the latter becoming sensitive to metabolic change at position 15. Accordingly the heptacyclic compound (X), in which this position is protected by annellation, was synthesised by cyclodehydrogenation of the perimidine (XI). Compound (X) is, moreover, structurally related to carcinogenic phenanthrene derivatives, such as benzo[*a*]pyrene. The similarity in the longer-wavelength absorption spectra of the compounds (V; R = H) and (X) is evidently a manifestation of similarities in their $n \longrightarrow \pi^*$ transitions.

Biological tests by Dr. R. W. Baldwin showed that, after 10 months, the triazabenzonaphthanthracene (V; R = H) produced no tumours by skin-painting in mice, whereas the corresponding tumour incidence with tricycloquinazoline was 78%. This loss of

[7] Badger, Pearce, and Pettit, *J.*, 1951, 3199.
[8] Partridge and Vipond, *J.*, 1962, 632.
[9] Mason, *J.*, 1959, 1240.

activity resulting from the replacement of a peripheral N in tricycloquinazoline by CH is in agreement with the suggestion that the bonding of all three peripheral nitrogen atoms to a tissue receptor is involved in tricycloquinazoline carcinogenesis.

Experimental

o-*Aminophenyl Benzyl Ketone.*—*o*-Aminobenzonitrile (9·4 g.) in dry ether (100 ml.) was added dropwise with stirring to a boiling solution of benzylmagnesium chloride, prepared from benzyl chloride (81 g., 8 mol.) and magnesium (15·4 g.) in ether (700 ml.). The ether was replaced by toluene (700 ml.) and the mixture was refluxed for 12 hr. After distillation of toluene (500 ml.), the cooled mixture was acidified with hydrochloric acid (1 l.), adjusted to pH 8 with ammonia, extracted with ether (4 × 250 ml.), and the ether distilled. The resulting toluene solution was refluxed with concentrated hydrochloric acid (500 ml.) for 1 hr., separated, and extracted with further acid (2 × 200 ml.). The combined acid extracts yielded the amino-ketone (8·2 g., 49%), m. p. 97—99° (lit.,[3] 103—104°) after basification with ammonia, ether extraction, and crystallisation from 60% methanol.

Interaction of the Grignard reagent and nitrile in ether and in benzene gave 9 and 22%, respectively, of the amino-ketone.

2-*Amino*-6-*methylphenyl benzyl ketone*, prepared analogously (37%) from 2-amino-6-methylbenzonitrile [10] and benzylmagnesium chloride, crystallised from light petroleum as prisms, m. p. 40—42° (Found: C, 79·5; H, 6·6; N, 6·3. $C_{15}H_{15}NO$ requires C, 80·0; H, 6·7; N, 6·2%).

2-o-*Nitrobenzamidophenyl Benzyl Ketone.*—*o*-Aminophenyl benzyl ketone (20 g.) was heated for 2 hr. on a steam-bath with *o*-nitrobenzoyl chloride (20 g.) in pyridine (200 ml.) and benzene (60 ml.), and poured into water (1 l.). A benzene extract of the mixture afforded the *amide* (25 g.) which crystallised from benzene–light petroleum as plates, m. p. 127—128° (Found: N, 7·8. $C_{21}H_{16}N_2O_4$ requires N, 7·8%).

4-*Benzyl*-2-o-*nitrophenylquinazoline* (I; R = NO_2, R′ = H).—A rapid stream of dry ammonia was passed for 3 hr. through a solution of the foregoing ketone (10 g.) in ammonium acetate (100 g.) at 160°. The water-insoluble material was dissolved in benzene, dried, concentrated, and chromatographed on alumina. Addition of light petroleum to the concentrated benzene eluate gave an oil which slowly crystallised to give the *quinazoline* (7·8 g.), prisms, m. p. 91·5—92·5° (from benzene–light petroleum) (Found: N, 12·2. $C_{21}H_{15}N_3O_2$ requires N, 12·3%).

2-o-*Aminophenyl*-4-*benzylquinazoline* (97%), formed when the foregoing nitro-compound (8 g.) was reduced in ethanol (500 ml.) at 65° with hydrazine hydrate (16 ml.) and Raney nickel, crystallised from aqueous ethanol as yellow needles m. p. 98—99° (Found: C, 81·2; N, 5·9; N, 13·5. $C_{21}H_{17}N_3$ requires C, 81·0; H, 5·5; N, 13·5%).

7-*Benzylidene*-7H-5,6a,12-*triazabenz*[a]*anthracene* (II).—On being refluxed in triethyl orthoformate (70 ml.) for 3 hr., the above quinazoline (5 g.) yielded the *triazabenzanthracene* (4·1 g.), orange needles, m. p. 216—217° (from butanol), $\lambda_{max.}$ (in EtOH) 246, 290, 364 mμ (log ε 4·57, 4·06, 4·29) (Found: C, 82·0; H, 4·7; N, 12·7. $C_{22}H_{15}N_3$ requires C, 82·2; H, 4·7; N, 13·1%).

A sample, shaken with N-hydrochloric acid for 3 hr., yielded 4-*benzyl*-2-o-*formamidophenylquinazoline* (I; R = NH·CHO, R′ = H), m. p. 141—142° (from methanol), $\lambda_{max.}$ (in EtOH) 240, 270 mμ (log ε 4·51, 4·41) (Found: C, 77·9; H, 5·0; N, 11·9. $C_{22}H_{17}N_3O$ requires C, 77·9; H, 5·1; N, 12·4%).

o-*Quinazolin*-4-*ylaminophenyl Benzyl Ketone* (IV; R = H).—4-Chloroquinazoline (3·3 g.) and *o*-aminophenyl benzyl ketone (4·2 g.) were refluxed together in dry acetone (60 ml.) and concentrated hydrochloric acid (0·5 ml.) for 1 hr. A hot aqueous ethanolic solution of the solid which separated deposited the *secondary amine* (4·4 g.), m. p. 167—170°, when basified with aqueous ammonia, $\lambda_{max.}$ (in EtOH) 239, 277, 287, 352, 367, 386 mμ (log ε 4·17, 4·11, 4·11, 4·18, 4·13, 3·78) (Found: N, 12·4; $C_{22}H_{17}N_3O$ requires N, 12·4%).

When undried acetone was used in the foregoing experiment, the product was 4-benzyl-2-*o*-formamidophenylquinazoline (I; R = NH·CHO, R′ = H) (61%), m. p. and mixed m. p. 141—142°.

Diethyl 2-o-*Nitrophenylquinazolin*-4-*ylmalonate.*—Diethyl malonate (2·4 ml.) was stirred in benzene (100 ml.) for 10 min. with sodium hydride (0·36 g. dispersed in oil) under anhydrous conditions. 4-Chloro-2-*o*-nitrophenylquinazoline (4·3 g.) was added and the mixture was stirred

[10] Gabriel and Thieme, *Ber.*, 1919, **52**, 1079.

and refluxed for 12 hr. After being shaken with water, the dried benzene solution afforded a gum, the ether-soluble fraction of which gave the *ester*, needles, m. p. 112—114° (from light petroleum) (Found: C, 61·7; H, 4·8; N, 10·3. $C_{21}H_{19}N_3O_6$ requires C, 61·6; H, 4·7; N, 10·3%).

This ester (1 g.), when boiled for 3 hr. with potassium hydroxide (1 g.) in methanol (20 ml.), diluted with water, and neutralised, gave 4-*methyl*-2-o-*nitrophenylquinazoline* (0·55 g.) as yellow needles, m. p. 152—154° (from aqueous ethanol) (Found: N, 15·6. $C_{15}H_{11}N_3O_2$ requires N, 15·8%).

Diethyl sodiomalonate [from the ester (20 g.) and sodium (2·76 g.) in ethanol (50 ml.)] when refluxed with the chloroquinazoline (22·8 g.) for 18 hr. afforded a water-insoluble gum from which *ethyl* 2-o-*nitrophenylquinazolin*-4-*ylacetate* (11·3 g.) was isolated, yellow needles, m. p. 122—123° (from aqueous ethanol then light petroleum) (Found: C, 64·4; H, 4·6; N, 12·1. $C_{18}H_{15}N_3O_4$ requires C, 64·1; H, 4·5; N, 12·5%).

5,10,14c-*Triazabenzo*[a]*naphth*[1,2,3-de]*anthracene* (V; R = H).—(*a*) The melt obtained by heating the ketone (IV; R = H) (1 g.) with sodium aluminium chloride (2·4 g.) at 320° for 1 hr. was ground with water and dried. A benzene extract of its chloroform-soluble fraction was chromatographed on alumina, first in benzene and then in benzene–light petroleum; the weakly fluorescent yellow fraction gave the *triazabenzonaphthanthracene* (0·45 g.), orange needles, m. p. 300—301° (from light petroleum) (Found: C, 82·9; H, 4·3; N, 13·5. $C_{22}H_{13}N_3$ requires C, 82·7; H, 4·1; N, 13·2%).

(*b*) The triazabenzanthracene (II) (0·5 g.), cyclised with sodium aluminium chloride (1·2 g.) at 320° for 1 hr., gave the hexacyclic compound (10%), m. p. and mixed m. p. 300—301°, and having the same absorption and fluorescence spectra and behaviour on thin-layer chromatography (Found, on a sublimed sample: C, 83·0; H, 4·6; N, 13·4%). Increase in the scale or variation in the reaction time reduced the yield.

6-*Methyl*-2-*quinazolin*-4-*ylaminophenyl benzyl ketone* (IV; R = Me), prepared similarly to the parent compound from 4-chloroquinazoline and 2-amino-6-methylphenyl benzyl ketone, had m. p. 174—176° (decomp.) (from methanol), $\lambda_{max.}$ (in EtOH) 240, 277, 286, 353, 369, 387 mμ (log ε 4·13, 4·08, 4·11, 4·18, 4·13, 3·77) (Found: N, 11·8. $C_{23}H_{19}N_3O$ requires N, 11·9%).

14-*Methyl*-5,10,14c-*triazabenzo*[a]*naphth*[1,2,3-de]*anthracene* (V; R = Me), orange needles (0·075 g.), m. p. 203—204° (from light petroleum), was obtained when 6-methyl-2-quinazolin-4-ylaminophenyl benzyl ketone (0·5 g.) was dehydrogenated with sodium aluminium chloride (1·2 g.) at 320° for 1 hr. and the mixed product was chromatographically fractionated as described for the parent compound (Found: C, 82·6; H, 4·6; N, 12·4. $C_{23}H_{15}N_3$ requires C, 82·9; H, 4·5; N, 12·6%).

o-*Isoquinolin*-1-*ylaminobenzanilide* (VII; R = H).—1-Chloroisoquinoline [11] (16·4 g.) and *o*-aminobenzanilide (21·5 g.) were refluxed together in dry acetone (250 ml.) for 2 hr. The solid which separated from the cooled solution, after being basified with aqueous ammonia in methanol, gave the *isoquinoline derivative* (23·4 g.), m. p. 248—249° (decomp.) (from ethanol) (Found: N, 10·9. $C_{22}H_{17}N_3O,C_2H_6O$ requires N, 10·9%).

7-*Oxo*-7H-6a,12-*diazabenz*[a]*anthracene* (VIII; R = H).—(*a*) 1-Chloroisoquinoline (0·8 g.) and methyl anthranilate (0·75 ml.) were heated together at 130° for 15 min. A solution of the melt in aqueous ethanolic ammonia deposited the *diazabenzanthracene* (1·12 g.), m. p. 170—171°, $\lambda_{max.}$ (in EtOH) 239, 273, 282, 302, 342, 360, 379 mμ (log ε 4·39, 4·44, 4·60, 4·06, 4·10, 4·26, 4·24) (Found: C, 77·95; H, 3·7. $C_{16}H_{10}N_2O$ requires C, 78·0; H, 4·1%).

(*b*) 1-Chloroisoquinoline (1·6 g.) and *o*-aminobenzanilide (2·25 g.), brought into reaction in the same way, furnished the same compound (1·2 g.), m. p. and mixed m. p. 169—171°.

2-*Amino*-2′-*chlorobenzanilide*, prepared (91%) by reduction of 2′-chloro-2-nitrobenzanilide [12] with hydrazine and Raney nickel in ethanol at 65°, had m. p. 101—102° (from light petroleum) (Found: C, 63·3; H, 4·6. $C_{13}H_{11}ClN_2O$ requires C, 63·3; H, 4·5%).

2′-*Chloro*-2-(3-*chloroisoquinolin*-1-*ylamino*)*benzanilide* (VII; R = Cl).—1,3-Dichloroisoquinoline (4 g.), 2-amino-2′-chlorobenzanilide (5 g.) and copper-bronze (3 g.) were stirred together at 185° for 6 hr. The benzene-soluble fraction of a chloroform extract of the product was chromatographed on alumina (50 g.) in light petroleum–benzene. Concentration of the colourless eluate gave the *isoquinolinyl derivative* (2·3 g.), m. p. 186—187° (from light petroleum) (Found: C, 64·4; H, 4·2; N, 10·0. $C_{22}H_{15}Cl_2N_3O$ requires C, 64·6; H, 3·7; N, 10·3%).

[11] Haworth and Robinson, *J.*, 1948, 777.
[12] Heacock and Hey, *J.*, 1952, 4059.

6-*Chloro*-7-*oxo*-7H-6a,12-*diazabenz*[a]*anthracene* (VIII; R = Cl).—The foregoing isoquinolinyl derivative (0·5 g.) was refluxed with phosphorus pentoxide (2 g.) in dry xylene (10 ml.) for 4 hr. After treatment with water, the xylene layer was fractionated on alumina to give a yellow benzene eluate which was rechromatographed to give the *diazabenzanthracene* (0·12 g.), yellow needles, m. p. 147—148° (from light petroleum), $\lambda_{max.}$ (in hexane) 240, 282, 287, 310, 352, 369, 389 mμ (log ε 4·39, 4·46, 4·50, 3·85, 4·10, 4·15, 4·00) (Found: C, 67·9; H, 3·1; N, 9·9. $C_{16}H_9ClN_2O$ requires C, 68·4; H, 3·2; N, 10·0%).

2′-(4-*Hydroxyquinazolin*-2-*yl*)-2-*methylbenzanilide* (IX).—*o*-Toluoyl chloride, prepared from *o*-toluic acid (6·8 g.) and thionyl chloride (8·2 g.) in benzene (50 ml.), was refluxed with 2-*o*-aminophenyl-4-hydroxyquinazoline (11·3 g.) in pyridine (200 ml.) for 1·5 hr. and the solvent (150 ml.) was distilled off. The *amide* (15·3 g.), precipitated by ice–water, had m. p. 275—277° (from 2-methoxyethanol) (Found: N, 11·8. $C_{22}H_{17}N_3O_2$ requires N, 11·8%). This compound was soluble in aqueous sodium hydroxide.

2-o-*Benzamidophenylperimidine* (XI) separated (1·36 g.) when a solution of 2-*o*-aminophenylperimidine [13] (1 g.) and benzoyl chloride (2 ml.) in dry benzene (15 ml.) was refluxed for 45 min., and crystallised from benzene–light petroleum as orange needles, m. p. 260° (decomp.) (Found: C, 79·0; H, 4·5; N, 11·2. $C_{24}H_{17}N_3O$ requires C, 79·3; H, 4·7; N, 11·6%).

10,15,15d-*Triazabenzo*[qr]*naphtho*[1,2,3,4-def]*chrysene* (X).—The foregoing perimidine (1 g.) and sodium aluminium chloride (2·4 g.) were stirred at 320° for 1 hr. Chromatography of a benzene extract of the chloroform-soluble fraction on alumina (50 g.) furnished a yellow solution which deposited the *chrysene* (0·2 g., 21%) as orange needles, m. p. 322—324°, on being concentrated, $\lambda_{max.}$ (in $CHCl_3$) 265, 305, 319, 385, 404, 422, 429, 480 mμ (log ε 4·82, 4·21, 4·04, 4·12, 4·18, 4·09, 3·98, 3·56) (Found: C, 84·2; H, 3·2; N, 12·2. $C_{24}H_{13}N_3$ requires C, 83·9; H, 3·8; N, 12·2%).

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[13] Sachs and Steiner, *Ber.*, 1909, **42**, 3674.