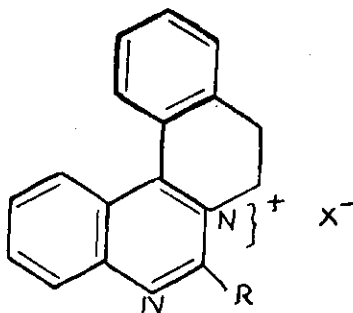


Chapter II

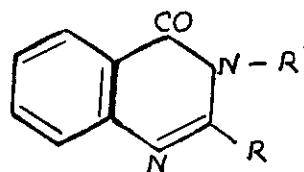
a) Object of the Investigation

(1) Quinazoline-isoquinolinium salts (CII)

Craig⁸⁰ in his review article on 'Curariform Activity and Chemical Structure' has catalogued a vast array of quaternary ammonium salts of various types displaying varying degrees of Curariform activity. Naturally, then, it suggests itself that quinazolino-isoquinolinium salts (CII) should be of interest as curare-active compounds. With a view to building such quinazoline-isoquinolinium salts (CII) the present investigations on 3-substituted-4(3)quinazolones (CIII) were undertaken.

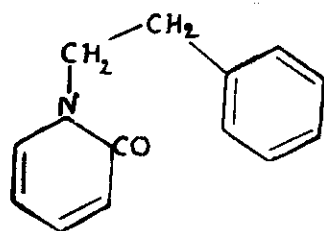


CII

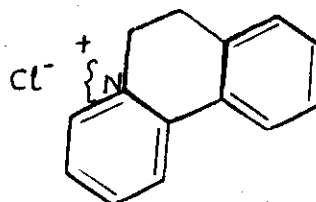
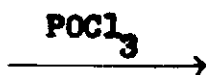


CIII

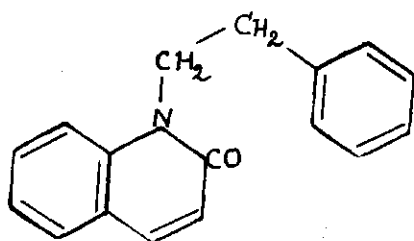
Sugasawa^{81,82} and co-workers have shown that N- β -phenylethyl-2-pyridones (CIV) and N- β -phenylethyl-2-quinolones (CV) cyclise with ease in presence of phosphorus-oxy-chloride to yield benzquinolizinium (CVI) and dibenzquinolizinium (CVII) salts respectively.



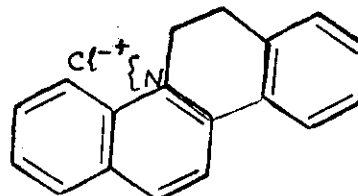
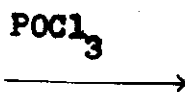
CIV



CVI



CV

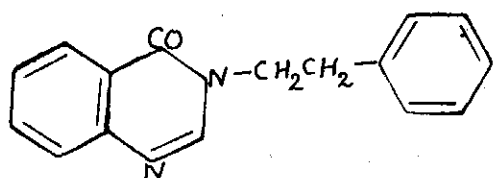


CVII

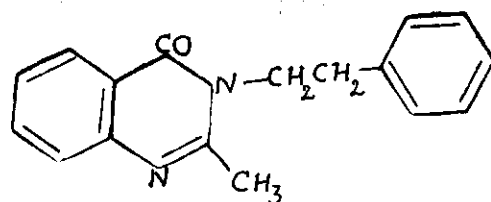
The 3- β -phenylethylquinazolones [CIII where R' = Phenylethyl] resemble the β -phenylethylquinolones (CV) closely, but for an extra nitrogen in the nucleus. The following 4(3)quinazolones were, therefore, prepared:

3- β -phenylethylquinazolone-4 (CVIII), 2-methyl-3- β -phenylethylquinazolone-4 (CIX), 2-methyl-3 β -3',4'-dimethoxyphenylethylquinazolone-4 (CX), 2-ethyl-3 β -phenylethylquinazolone-4 (CXI), and

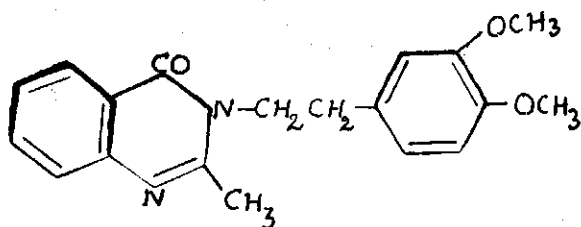
3 β -3'-methoxyphenylethylquinazolone-4 (CXII). Attempts at ring closure of these quinazolones (CXII excluded) with phosphorus oxychloride have yielded only their hydrochlorides — instead of quinazolino-isoquinolinium salts of the type (CII).



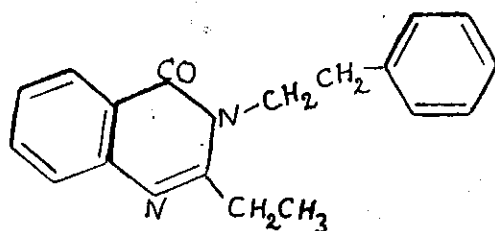
CVIII



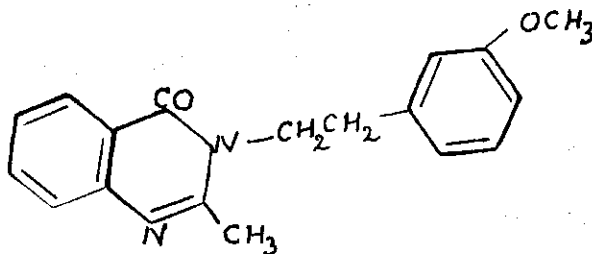
CIX



CX



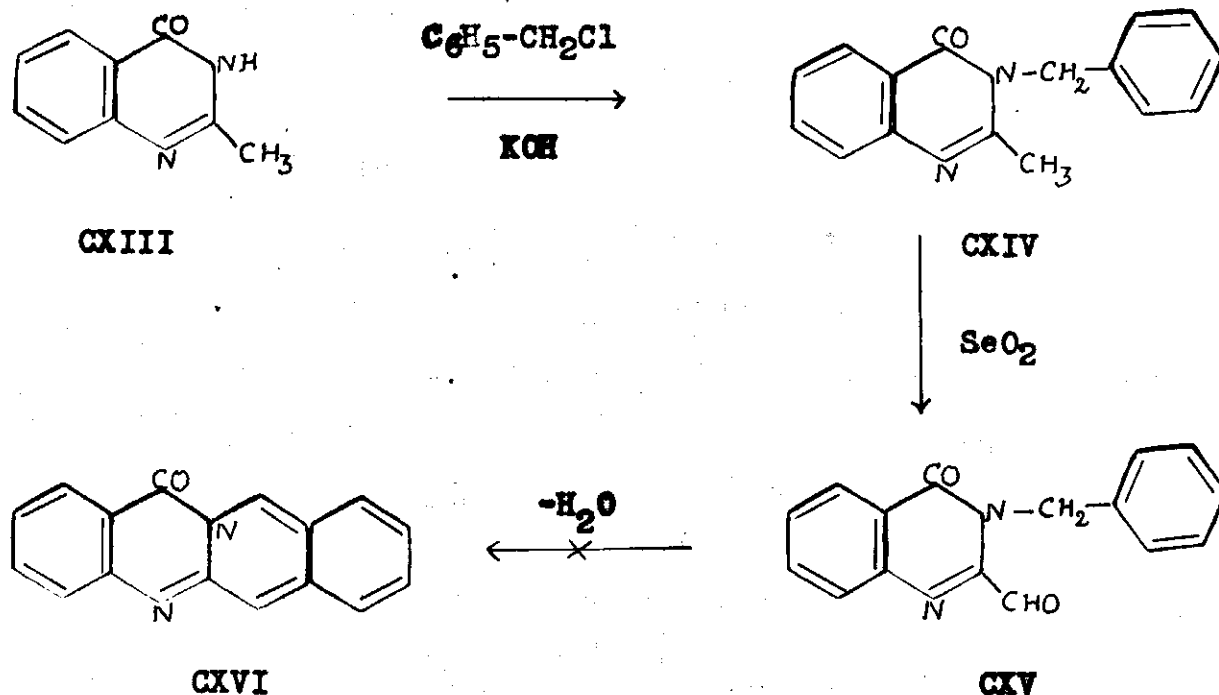
CXI



CXII

(11) Isoquinolino(2,3:3',2')quinazolinone-4' (CXVI)

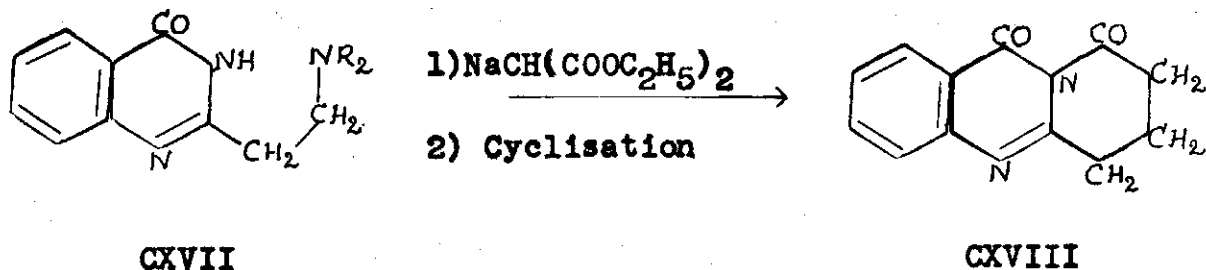
An attempt was made to synthesise isoquinolino(2,3:3',2')quinazolinone-4' (CXVI) following the scheme shown below.



Polyphosphoric acid, hydrobromic acid and glacial acetic acid, and concentrated sulphuric acid were tried to effect cyclisation of CXV to CXVI without success. Some high-melting coloured solids could be isolated, none of which could be proved to have the structure CXVI.

(111) Mannich Condensations with 2-Methyl-quinazolone-4 (CXIII)

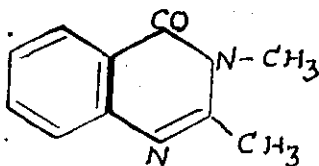
The methyl group in 2-methyl-quinazolone-4 nucleus, as in quinaldine^{83,84} and α -picoline^{83,85}, is quite reactive. It can be oxidised to the formyl group with selenium dioxide, and it can be brominated with N-bromosuccinimide. It was therefore presumed that when 2-methyl-quinazolone-4^{86,87} (CXIII) is condensed with paraformaldehyde and hydrochlorides of secondary amines (NHR₂) Mannich bases of the type (CXVII) would be formed, which could be used for building the interesting tri-cyclic system (CXVIII).



A search of literature on the subject showed that Monti^{88,89} and co-workers had conducted some experiments on Mannich bases of 2-methyl-quinazolone-4. Duplicating part of Monti's work on Mannich bases⁸⁹ of 2-methyl-quinazolone-4, certain results have been obtained from which certain conclusions have been drawn, which are not in agreement with those drawn by her.

(iv) Dearylalkylation and dealkylation in the hydrochlorides of substituted quinazolones

During the course of the above investigations, the phenomenon of dealkylation (or dearylalkylation) was observed in the hydrochlorides of 2-methyl-3-benzyl-quinazolone-4 (CXIV) and 2,3-dimethyl-quinazolone-4 (CXIX) at high temperatures (ca. 250°C). This has been proved to be due to water of crystallisation in the molecules.

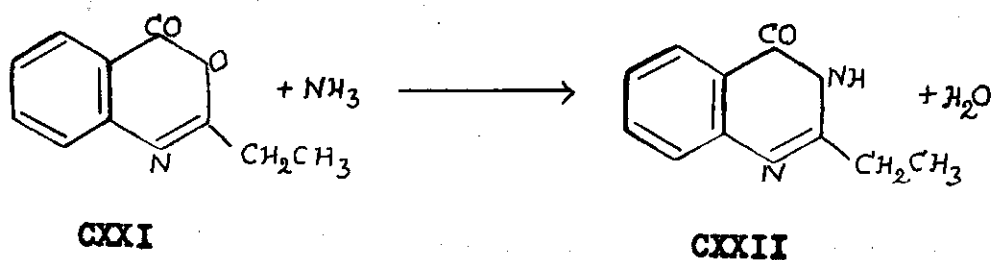
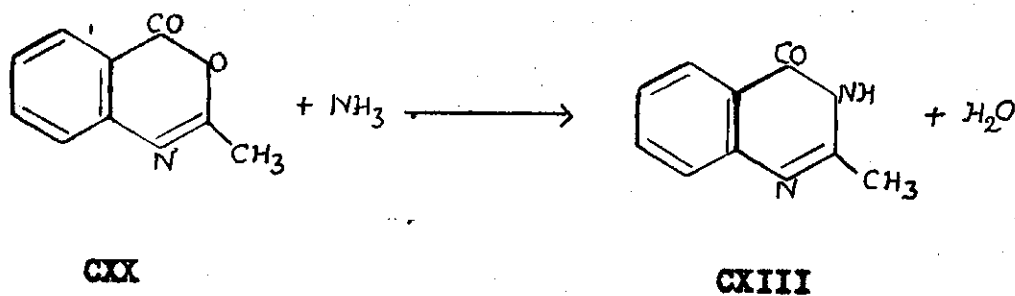
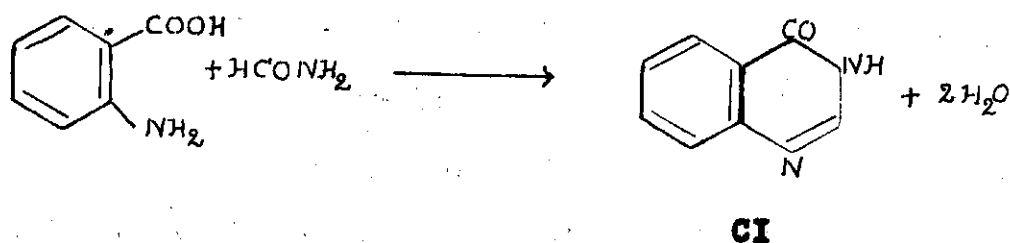


CXIX

b) Discussion of the Experimental Data

(1) (Vide Experimental 1-24 inclusive)

Quinazolone-4⁷⁶ (CI) was prepared by condensing anthranilic acid with formamide following the procedure outlined by Niementowski. 2-Methylquinazolone-4⁸⁷ (CXIII) was prepared by condensing acetyl-anthranil⁸⁶ (CXX) with ammonia. Similarly, by condensing propionyl-anthranil (CXXI) with ammonia 2-ethyl-quinazolone-4⁹⁰ (CXXII) was prepared.

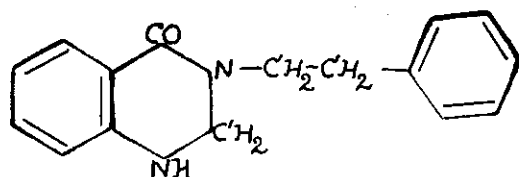


The phenylethylation of CI was later investigated. With β -phenylethylbromide⁹¹ and alcoholic potassium hydroxide, quinazolinone-4(CI) gave very poor yields of 3 β -phenylethylquinazolinone-4 (CVIII).

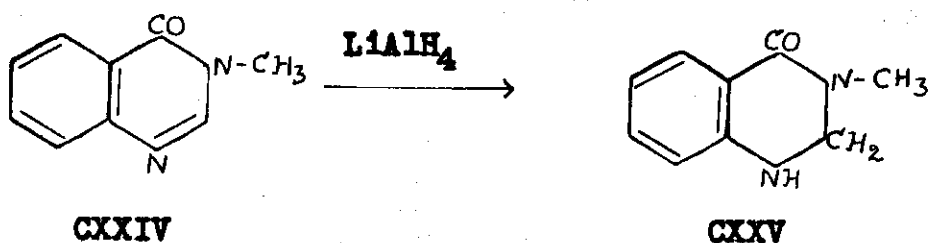
The yields of CVIII were quite good when the procedure of Pachter and Kloetzel⁹² for the N-methylation of p-nitroacetanilide was tried for the introduction of phenylethyl group to the quinazolone-4 system. The method is simple; it consists in just refluxing a mixture of quinazolone-4 (CI), powdered potassium hydroxide, and β -phenylethylbromide. The phenylethylation of both 2-methylquinazolone-4 (CXIII) and 2-ethyl-quinazolone-4 (CXXII) was similarly effected. Following the same procedure, but from β -meta-methoxyphenylethyl bromide, 3 β -3'-methoxy-phenylethyl-quinazolone-4 (CXII) could be synthesised, but the yields were discouragingly low. 2-Methyl-3 β -3',4'-dimethoxyphenylethylquinazolone-4 (CX) could, however, be prepared in very good yields by condensing homoveratrylamine⁹³ with acetylanthranil⁸⁶ (CXX).

The cyclisation of the above bases was then taken up. On refluxing 3 β -phenyl-ethyl-quinazolone-4 (CVIII) with different quantities of phosphorus oxychloride — both in presence and ⁱⁿ absence of solvents like dry toluene or benzene — for 1-2 hours, it was found that a crystalline solid generally separated out on cooling the reaction mixture. The solid, after crystallisation from a large quantity of benzene, was found to be identical in solubility, melting-point, etc., with the hydrochloride of 3- β -phenylethylquinazolone-4. Mixed melting-point of the two compounds showed no depression affirming their identity with each other. 3 β -phenyl-ethyl-quinazolone-4 (CVIII)

could be regenerated from the reaction product on treatment with alkali, just as it could be done from the hydrochloride of the base (CVIII). Both the reaction product and the hydrochloride of CVIII gave rise to 1,2-dihydro-3 β -phenyl-ethylquinazolone-4 (CXXIII) when they were subjected to lithium-aluminiumhydride reduction. This behaviour of the quinazolone nucleus with lithium-aluminium hydride, though curious, was not unique, for Mirza⁹⁴ had observed that 3-methyl-quinazolone-4 (CXXIV) when reduced with lithium-aluminium hydride yielded 1,2-dihydro-3-methyl-quinazolone-4 (CXXV). Again, their behaviour was similar when they were catalytically hydrogenated with 10% Pd-C. Both of them yielded very small quantities of a high-melting solid which could not be characterised, besides unchanged 3 β -phenylethyl-quinazolone-4 (CVIII).



CXXIII



The above-mentioned empirical evidences went to prove that, under the experimental conditions adopted, 3 β -phenylethylquinazolone-4 (CVIII) was not cyclised to the desired quinazolino-isoquinolinium-chloride, but was always converted to its hydrochloride.

The behaviour of 2-methyl-3 β -phenylethylquinazolone-4 (CIX) when subjected to phosphorus oxychloride treatment was not in any way different from that of 3 β -phenyl-ethyl-quinazolone-4 (CVIII). The crystalline reaction product was, however, pale-yellow in colour, which, after purification, was found to be identical with the hydrochloride of the base (CIX).

The behaviour of 2-methyl-3 β -3',4'-dimethoxyphenylethylquinazolone-4 (CX) with phosphorus-oxychloride was reminiscent of that of both the bases CVIII and CIX. At the end of the reaction, the solvent and the excess of phosphorusoxychloride were distilled off at low pressure and the residual solid, on crystallisation from absolute ethanol, yielded a crystalline solid whose identity with the hydrochloride of the base (CX) could be easily established.

The behaviour of 2-ethyl-3 β -phenylethylquinazolone-4 (CXI) with phosphorus oxychloride merely endorsed the behaviour of the earlier quinazolones - CVIII, CIX, and CX - with phosphorus-oxychloride.

In view of the failure of the above quinazolones - CVIII, CIX, CX, and CXI - to yield the desired tetracyclic compounds with POCl₃, no attempt was made to cyclise 3 β -3'-methoxy-phenylethylquinazolone-4 (CXII).

(11) (Vide Experimental 25-36 inclusive)

The procedure of Pachter and Kloetzel⁹² for the N-methylation of p-nitroacetanilide was followed for the N-benylation of 2-methylquinazolone-4 (CXIII). 2-Methyl-3-benzylquinazolone-4 (CXIV) was obtained in good yields; its melting-point (70°C) was, however, far too low compared with the melting-point (123°C) that had already been reported for it by Bogert⁹⁵. Bogert had obtained it by condensing acetylanthranil (CXX) with benzylamine. His experiment was repeated; only once, a product having the melting-point reported by Bogert could be obtained; on subsequent repetitions only the 70°C-melting compound could be obtained. Naturally, it was thought that they were the polymorphic modifications of the same compound. Attempts at interconversion of each other, however, completely failed.

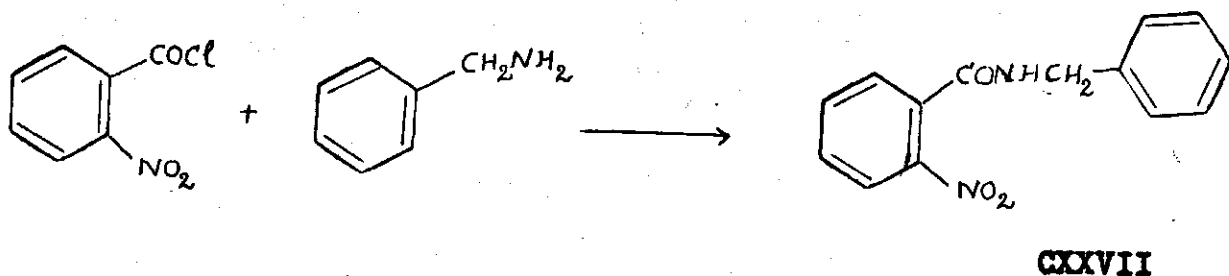
Considerable differences in their properties were also observed. Bogert's compound could not be oxidised with selenium dioxide⁹⁶ to 2-formyl-3-benzyl-quinazolone-4 (CXV); moreover, it formed a

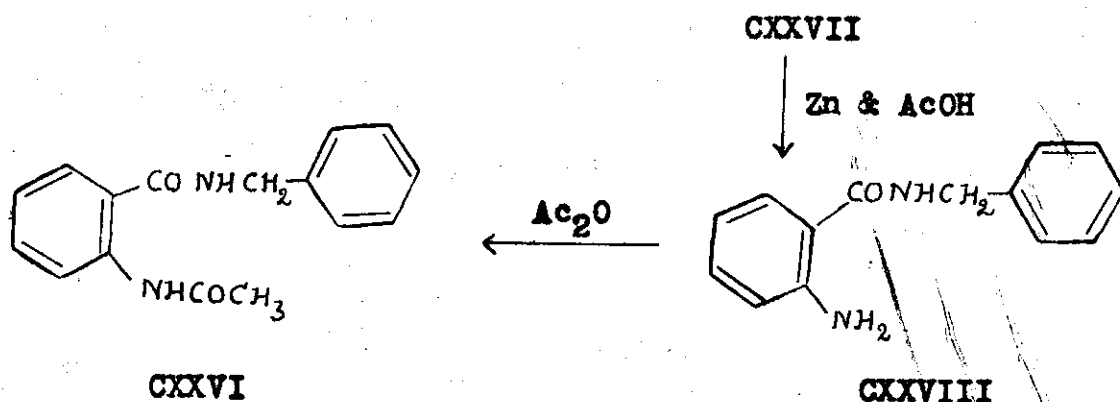
water-soluble hydrochloride. On the other hand, the 70°C-melting compound could be easily oxidised to CXV with SeO₂; besides, it readily formed a hydrochloride sparingly soluble in water. The curious thing about the two hydrochlorides was that they had the same melting-point, and the mixed melting-point was also suggestive of their identity with each other.

From the above-mentioned evidences no positive conclusion regarding the nature of Bogert's compound could be drawn. A remote possibility that it might be o-acetylamino-N-benzyl-benzamide (CXXVI) was there. The formation of such a compound during the condensation of acetylanthranil (CXX) with benzylamine would not be surprising. The synthesis of CXXVI was therefore undertaken. o-Nitro-benzoyl-chloride was condensed with benzylamine to yield o-nitro-N-benzyl-benzamide (CXXVII). CXXVII was then reduced with zinc and acetic acid to o-amino-N-benzyl-benzamide (CXXVIII) which was later acetylated to CXXVI. The synthesis of o-acetylamino-N-benzyl-benzamide (CXXVI) (m.p. 147-8°C), however, did not contribute to the elucidation of the structure of Bogert's compound. The limited availability of Bogert's compound forbade further investigations into its nature.

As mentioned previously, 2-methyl-3-benzyl-quinazolone-4 (CXIV) was oxidised with selenium dioxide to 2-formyl-3-benzyl-quinazolone-4 (CXV) in good yields. Cyclisation of CXV to CXVI was first attempted with concentrated sulphuric acid. It generally gave rise to two products: a rose-red powder, very soluble in chloroform,

sintering above 270°C and melting with profound decomposition around 340-50°C; and a deep-red solid, sparingly soluble in chloroform, melting with deep decomposition around 300°C. Both of them refused to yield picrates. Neither of them analysed all right. With polyphosphoric acid as cyclising agent a rose-red powder, sintering above 270°C and melting around 350°C, and closely resembling one of the sulphuric-acid-cyclisation products, was obtained. The analytical results on it were in no way encouraging. With 48% hydrobromic acid and glacial acetic acid, the cyclisation was very incomplete, and only traces of a reddish powder melting around 230°C could be obtained. Further attempts at cyclising 2-formyl-N-benzyl-quinazolone-4 (CXV) to CXVI were not made.



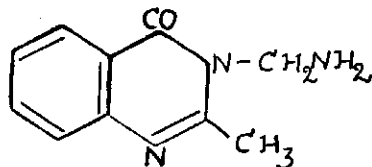


(iii) (Vide Experimental 37-42 inclusive)

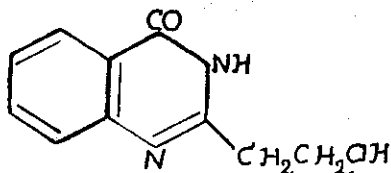
Monti⁸⁹ had condensed 2-methyl-quinazolone-4 (CXIII) with p-formaldehyde and ammonium chloride to obtain a pale-brown solid supposed to be having the structure CXXIX. When the experiment was repeated here, a product having all the properties reported by Monti for CXXIX was obtained. It was, however, soluble in alkali. Its solubility in alkali could not be reconciled with Monti's structure for it.

A possible structure for the product which would account for its solubility in alkali was CXVII, where $-NR_2 = NH_2$. On the basis of this structure neither its high-melting-point nor its great stability could be explained for the Mannich bases of quinaldine⁹⁷ (which bears a close resemblance to 2-methyl-quinazolone-4) have been reported to be highly unstable. Hence a tentative structure CXXX was assigned to it which would at once account for

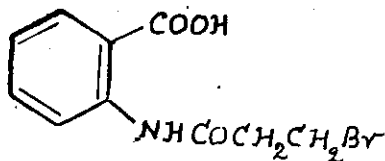
its solubility in bases and its high stability. The nitrogen analysis of the product completely endorsed such an assignment. Incidentally it may be pointed out that Baker⁹⁸ and co-workers have opined that Monti and her colleagues could not have isolated Mannich bases as illustrated by CXXIX in view of the great instability of the N-C-N linkage to acids. Working on the lines of Monti and co-workers with quinazolone-4, secondary amine hydrochlorides and formaldehyde, Baker⁹⁸ and his colleagues have shown that the only isolable product under the experimental conditions is the hydrochloride of quinazolone-4.



CXXIX

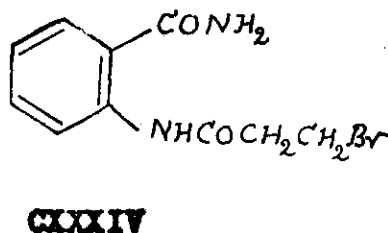
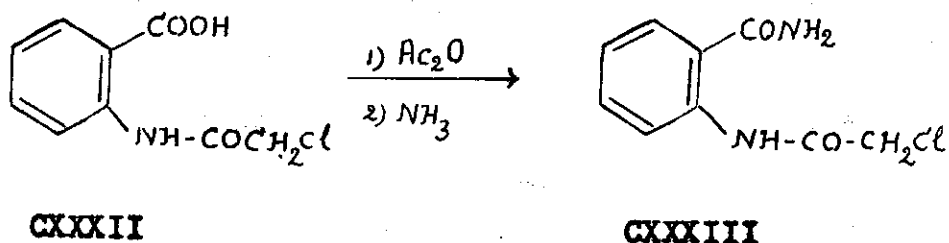


CXXX

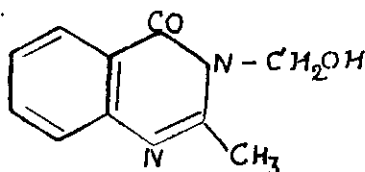


CXXXI

Attempts at synthesising CXXX from *o*- ω -bromo-propionamide-benzoic acid (CXXXI) with acetic anhydride and ammonia and from the ammonium salt of CXXXI yielded bromine-free products which could not be characterised. This behaviour of CXXXI with acetic anhydride and ammonia was in disagreement with that of *o*-chloroacetamido-benzoic acid (CXXXII), for the latter yielded under similar conditions *o*-chloroacetamido-benzamide (CXXXIII). Brown intractable semi-solids were the result when attempts were made to condense *o*-amino-benzamide with β -bromo-propionyl-chloride to obtain *o*- ω -bromo-propionamidobenzamide (CXXXIV). Further attempts at synthesising CXXX were not made.



2-Methyl-quinazolone-4 (CXIII), when condensed with p-formaldehyde and piperidine acetate, gave a high-melting solid as one of the condensation products, which might presumably have the structure CXXXV.

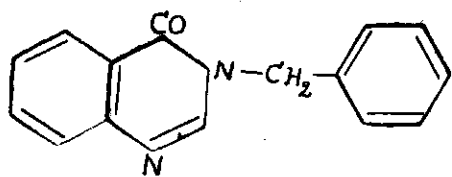
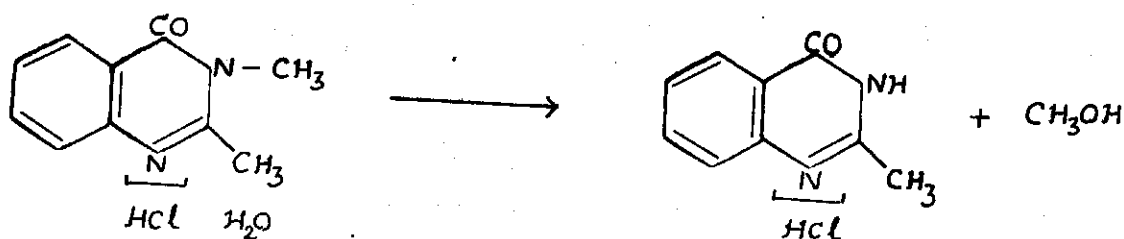
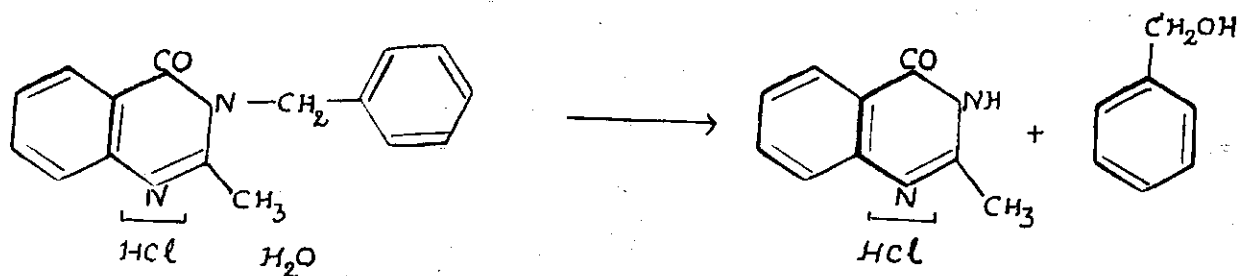


CXXXV

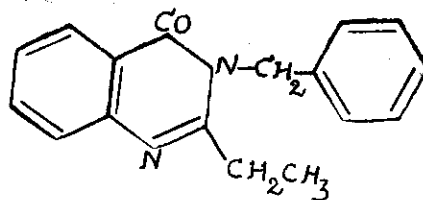
(iv) (Vide Experimental 43-53 inclusive)

The phenomenon of debenylation was observed in the hydrochloride of 2-methyl-3-benzyl-quinazolone-4 (CXIV). At its melting-point, debenylation occurred yielding the hydrochloride of 2-methyl-quinazolone-4 (CXIII). This was attributed to water of crystallisation in the molecule, as debenylation could not be observed in the hydrochlorides of 3-benzyl-quinazolone-4 (CXXXVI) and 2-ethyl-3-benzyl-quinazolone-4 (CXXXVII) [both having no water of crystallisation] under similar conditions. The truth of the above statement was verified by anticipating and observing demethylation in the hydrochloride of 2,3-dimethylquinazolone-4 which, like the hydrochloride of 2-methyl-3 benzyl-quinazolone-4, contained one

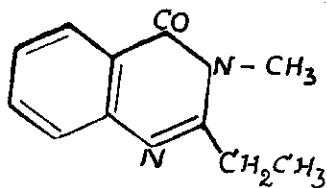
molecule of water of crystallisation. Again, as anticipated, no demethylation could be observed in the hydrochloride of 2-ethyl-3-methyl-quinazolone-4 (CXXXVIII) as it carried no water of crystallisation.



CXXXVI



CXXXVII



CXXXVIII

c) Experimental

(1) Preparation of Quinazolone-4⁷⁶ (CI)

Anthranilic acid (65 g) and formamide (50 g) were heated together for three hours at 120-30°C. As the reaction proceeded, quinazolone-4 separated out. At the end of the reaction, the solid reaction product was triturated with ethanol (50 ml) and then crystallised from hot water in long slender needles (m.p. 210-3°C; yield 45 g).

(2) Preparation of 2-Methyl-quinazolone-4⁸⁶⁻⁸⁷ (CXIII)

Anthranilic acid (20 g) and acetic anhydride (45 ml) were refluxed for thirty minutes. Acetic acid and the excess of acetic anhydride were then removed by distillation. The residue (crude acetylanthranil) was gradually added into liquor ammonia (30 ml). The precipitate thus obtained was dissolved in 50% potassium hydroxide solution (30 ml) and boiled for 5 minutes. It was then acidified with concentrated hydrochloric acid (40 ml). The precipitate (hydrochloride of 2-methyl-quinazolone-4) was thoroughly washed with water, sodium bicarbonate solution, and then with water to obtain 2-methyl-quinazolone-4 (CXIII). (m.p. 230-4°C; 10 g).

(3) Preparation of 2-Ethyl-quinazolone-4⁹⁰ (CXXII)

Anthranilic acid (5 g) and propionic acid anhydride (10 ml) were boiled for 15 minutes, and the excess of propionic acid anhydride was then distilled off. The residue, which solidified on standing, was added to liquor ammonia (30 ml) and warmed on a water-bath

for thirty minutes. The solid thus formed was dissolved in potassium hydroxide solution (KOH = 5g) and boiled for ten minutes. It was subsequently acidified with acetic acid to obtain 2-ethyl-quinazolone-4 (CXXII), (m.p. 225-7°C; yield 3.5 g).

(4) Preparation of β -Phenyl-ethyl-bromide⁹¹

Phosphorus tribromide (76.3 g) was added drop by drop over thirty minutes to β -phenylethyl alcohol (69 g) cooled in ice. After the addition, the contents of the flask were warmed on a water-bath the temperature of which was gradually raised to 90°C, and held at that temperature for one hour. Then they were cooled and taken up in ether; the ether solution of β -phenylethyl-bromide was washed with ice-cold water, sodium bicarbonate solution, and then with water. The ether solution was subsequently dried over anhydrous sodium sulphate and distilled. The distillate coming over between 93°C and 95°C at 12 mm. was collected (yield - 87 g).

(5) Synthesis of 3 β -phenylethylquinazolone-4 (CVIII)

To a refluxing mixture of quinazolone-4 (10 g) and powdered potassium hydroxide (14 g) in acetone (500 ml) was added β -phenylethylbromide (15 g) in acetone (100 ml) over thirty minutes. After refluxing for three hours, acetone was distilled off; the residue was treated with water and extracted with chloroform. From the chloroform extract 3 β -phenylethyl-quinazolone-4 (7.5 g) was obtained after distilling off chloroform and triturating the residue with petrol ether (m.p. 92-5°C). It was crystallised from aqueous alcohol (m.p. 100° C).

The quinazolone (CVIII) was very soluble in alcohol, benzene and toluene. It was insoluble in alkali; with aqueous hydrochloric acid it formed a crystalline monohydrochloride. Its alcoholic solution fluoresced blue.

Analysis: Found - C=76.13, H=5.29, N=11.11%;

$C_{16}H_{14}ON_2$ requires C=76.81, H=5.6, N=11.2%.

(6) Picrate of CVIII

Boiling solutions of CVIII (0.5 g) in alcohol (5 ml) and picric acid (1 g) in alcohol (10 ml) were mixed and allowed to cool. The picrate thus obtained was crystallised from alcohol in long narrow plates, m.p. 169-71°C.

Analysis: Found - N = 14.68%;

$C_{22}H_{17}O_8N$ requires N = 14.68%.

(7) Methosulphate of CVIII

Dimethylsulphate (1 ml) was added to 3 β -phenylethylquinazolone-4 (1 g) in dry toluene (10 ml). The mixture was refluxed for fifteen minutes when the methosulphate of CVIII separated out as a crystalline solid (1.35 g). It was very soluble in water. It was crystallised from alcohol, m.p. 185-7°C.

Analysis: Found - N = 7.75%;

$C_{18}H_{20}O_5N_2S$ requires N = 7.45%.

(8) Methiodide of CVIII

Methyl iodide (1.5 ml) was added to 3 β -phenylethylquinazolone-4 (0.5 g) in dry benzene (5 ml). The mixture was refluxed for two hours and allowed to cool when the crystalline methiodide of CVIII separated out (150 mg). It was crystallised from alcohol in fine needles; m.p. 212°C.

Analysis: Found - N = 6.93%;

C₁₇H₁₇ON₂ requires N = 7.14%.

(9) Hydrochloride of CVIII

(a) 3 β -Phenylethylquinazolone-4 (0.5 g) was refluxed with dilute hydrochloric acid (50 ml)[Conc. HCl = 3 ml] for thirty minutes, filtered, and the filtrate allowed to cool when the hydrochloride crystallised out in fine needles (0.4 g ; m.p. 225°C). For analysis it was crystallised from dilute hydrochloric acid, m.p. 227-30°C.

Analysis: Found - N = 9.77%;

C₁₆H₁₅ON₂Cl requires N = 9.77%.

(b) Phosphorus oxychloride (1 ml) was added to 3 β -phenylethylquinazolone-4 (0.5 g) in dry toluene (10 ml). The mixture was refluxed for one hour and allowed to cool. The crystalline solid thus obtained (0.14 g) was crystallised from a large volume of dry benzene (m.p. 225-8°C).

Analysis: Found - N = 9.7%;

C₁₆H₁₅ON₂Cl requires N = 9.77%.

(10) Preparation of 1,2-dihydro-3 β -phenylethylquinazolone-4 (CXXIII)
by reducing the hydrochloride of CVIII (obtained by both methods)
with lithiumaluminiumhydride

To the hydrochloride of CVIII (0.7 g) in dry ether (100 ml) in a 3-necked flask fitted with an efficient stirrer, was added lithiumaluminiumhydride (0.14 g). The mixture was stirred at 16°C for ninety minutes. It was stirred and refluxed for ninety minutes more. The complex was then cooled and decomposed with dilute ice-cold sulphuric acid. The mixture, after being rendered alkaline with concentrated sodiumhydroxide solution, was extracted with ether. From the ether extract, after distilling off ether, a pale-brown liquid which solidified on standing was obtained. It was crystallised from aqueous alcohol (m.p. 84-7°C; 0.33 g). The dihydroquinazolone (CXXIII) was very soluble in alcohol, benzene, toluene, and acetone. Its alcoholic solution had an intense blue fluorescence.

Analysis: Found - N = 11.05%;

$C_{16}H_{16}ON_2$ requires N = 11.11%.

(11) Picrate of CXXIII

This was prepared by following the procedure for the picrate of CVIII. The picrate was crystallised from alcohol in needles, m.p. 166-8°C.

Analysis: Found - N = 14.25%;

$C_{22}H_{19}O_3N_5$ requires N = 14.55%.

(12) Catalytic reduction of the hydrochloride of CVIII (by both methods) with 10% Pd-C

The hydrochloride of CVIII (0.5 g) in dioxane (40 ml) was subjected to catalytic hydrogenation with 10% Pd-C (0.1 g). The total volume of hydrogen absorbed at the end of six hours was 31 ml. at N.T.P. The catalyst was filtered off; the washings of the catalyst were added to the main filtrate. Dioxane was distilled off from the total filtrate. The residue was triturated with alcohol when a greenish-yellow solid (15 mg ; m.p. 319-21°C) was obtained. From the alcohol filtrate 3 β -phenylethylquinazolone-4 (CVIII) was recovered.

(13) Synthesis of 2-methyl-3 β -phenylethyl-quinazolone-4 (CIX)

To a refluxing mixture of 2-methyl-quinazolone-4 (2 g) and powdered potassium hydroxide (3 g) in acetone (100 ml) was added β -phenylethylbromide (2.3 g) in acetone (20 ml) over ten minutes. After refluxing the mixture for three hours, acetone was distilled off; the residue was extracted with chloroform after diluting it with water. Chloroform was distilled off from the chloroform extract to obtain 2-methyl-3 β -phenylethyl-quinazolone-4 (0.6 g; m.p. 90°C). The quinazolone (CIX) was very soluble in alcohol, benzene, and toluene. It was insoluble in alkali. With aqueous hydrochloric acid it formed a crystalline monohydrochloride. Its alcoholic solution had a blue fluorescence. For analysis it was crystallised from aqueous alcohol, m.p. 100°C.

Analysis: Found - C = 77.61, H = 6.088, N = 10.35%;

$C_{17}H_{16}ON_2$ requires C = 77.27, H = 6.06, N = 10.6%.

(14) Picrate of CIX

This was prepared just as the picrate of CVIII was prepared. It was crystallised from alcohol in needles, m.p. 218-9°C.

Analysis: Found - N = 14.12%;

$C_{23}H_{19}O_8N_5$ requires N = 14.2%.

(15) Hydrochloride of CIX

(a) 2-Methyl-3 β -phenylethyl-quinazolone-4 (0.5 g) was refluxed with dilute hydrochloric acid (50 ml) (Conc. HCl = 3 ml) for thirty minutes and allowed to cool when the hydrochloride of CIX separated out in clusters of fragile needles (0.4 g ; m.p. 221-4°C). Crystallisation from dilute hydrochloric acid did not improve the melting-point.

Analysis: Found - N = 9.14%;

$C_{17}H_{17}ON_2Cl$ requires N = 9.32%.

(b) Phosphorusoxychloride (1 ml) was added to 2-methyl-3 β -phenylethylquinazolone-4 (0.5 g) in dry toluene (10 ml). The mixture was then refluxed for one hour and allowed to cool. The pale-yellow solid (0.4 g) thus obtained was crystallised from a large volume of toluene, m.p. 220-3°C.

Analysis: Found - N = 9.024%;

$C_{17}H_{17}ON_2Cl$ requires N = 9.32%.

(16) Preparation of homoveratrylamine

Starting from veratraldehyde, hippuric acid, anhydrous sodium acetate and acetic anhydride the azalactone of α -benzoylamino- β -(3,4-dimethoxy-phenyl)acrylic acid⁹⁹ was prepared. The azalactone was hydrolysed to sodium-3,4-dimethoxy-phenyl-pyruvate¹⁰⁰ by refluxing it with 10% sodium hydroxide solution for 6-7 hours. The sodium salt of 3,4-dimethoxy-phenyl-pyruvic acid was directly allowed to react with hydroxylamine hydrochloride. By rendering the reaction mixture acidic, the oxime of dimethoxyphenylpyruvic acid was obtained. This was straightaway dehydrated and decarboxylated to homoveratronic nitrile by refluxing it with acetic anhydride¹⁰¹ [From 20 g. of veratraldehyde 9.5 g. of homoveratronic nitrile (b.p._{3.5} = 150-60°C) were obtained].

With Adam's catalyst¹⁰² homoveratronic nitrile in glacial acetic acid was hydrogenated to homoveratrylamine⁹³. The yield of homoveratrylamine (b.p.₃ = 135-40°C) was poor (32%).

(17) Synthesis of 2-methyl-3 β -3',4', dimethoxy-phenyl-ethyl-quinazolone-4 (CX)

Homoveratrylamine (1.1 g) in dry toluene (10 ml) was added to acetylanthranil (1.5 g) (obtained as in the preparation of 2-methyl-quinazolone-4, but crystallised from petrol ether). The mixture was then refluxed for thirty minutes. The solvent was removed in vacuo, and the residue, after being washed with sodium hydroxide solution, was crystallised from aqueous alcohol to yield CX (1.2 g). It was soluble in hot alcohol, benzene and toluene. It was soluble in dilute

hydrochloric acid, but insoluble in alkali. Its alcoholic solution fluoresced blue. For analysis it was crystallised from alcohol (m.p. 133-4°C).

Analysis: Found - C = 70.51, H = 5.84, N = 8.87%;
 $C_{19}H_{20}O_3N_2$ requires C = 70.37, H = 6.17, N = 8.64%.

(18) Picrate of CX

It was prepared by adopting the procedure for the preparation of the picrate of CVIII. It was crystallised from alcohol in short needles, m.p. 205-6°C.

Analysis: Found - N = 12.59%;
 $C_{25}H_{23}O_5N_5$ requires N = 12.66%.

(19) Hydrochloride of CX

(a) 2-Methyl-3 β -3',4'-dimethoxyquinazolone-4 (0.3 g) was taken in dry toluene (20 ml); dry hydrogen chloride was passed into ^{it} when a pale-yellow powder separated out. It was crystallised from absolute ethanal, m.p. 200-02°C.

Analysis: Found - N = 7.85%;
 $C_{19}H_{21}O_3N_2Cl$ requires N = 7.77%.

(b) Phosphorusoxychloride (2 ml) was added to CX (0.3 g) in dry toluene (5 ml). The mixture was refluxed for two hours. The solvent and the excess of phosphorus-oxychloride were removed in vacuo, and the residue was crystallised from absolute ethanal, m.p. 203-05°C.

(20) Synthesis of 2-ethyl-3 β -phenyl-ethyl-quinazolone-4 CXI

To a refluxing mixture of 2-ethyl-quinazolone-4 (4 g) and powdered

potassium hydroxide (10 g) in acetone (400 ml) was added β -phenylethyl-bromide (8 g) in acetone (100 ml) over fifteen minutes. After refluxing it for six hours, acetone was distilled off; the residue, after diluting it with water, was extracted with benzene. Benzene was distilled off, and the residue was treated with concentrated hydrochloric acid. The hydrochloride of the base (CXI) was evaporated to dryness, and the residue, after being thoroughly washed with benzene, was rendered alkaline to obtain 2-ethyl-3 β -phenylethyl-quinoxaline-4 (1.2 g). CXI was soluble in alcohol, benzene and toluene. It was insoluble in alkali, but soluble in dilute hydrochloric acid. Its alcoholic solution had a blue fluorescence. For analysis, the base (CXI) was crystallised from aqueous alcohol m.p. 99-100°C.

Analysis: Found - C = 77.45, H = 6.48, N = 10.19%;

$C_{18}H_{18}ON_2$ requires C = 77.7, H = 6.47, N = 10.07%.

(21) Picrate of CXI

This was obtained by following the procedure for the preparation of the picrate of CVIII. It was crystallised from aqueous alcohol in needles, m.p. 194°C.

Analysis: Found - N = 13.2%; the monohydrate of the picrate -

$C_{24}H_{23}O_9N_5$ requires N = 13.33%.

(22) Hydrochloride of CXI

(a) 2-Ethyl-3 β -phenylethyl-quinoxaline-4 (0.5 g) was dissolved in dilute hydrochloric acid. The solution was evaporated to dryness, and the residue was crystallised from alcohol (m.p. 194-6°C). The

hydrochloride rapidly dehydrochlorinated at 80°C and 2 mm. pressure.

Analysis: Found - N = 9.02%;

$C_{18}H_{19}ON_2Cl$ requires N = 8.9%.

(b) Phosphorusoxychloride (1 ml) was added to a solution of CXI (0.5 g) in dry benzene (5 ml). The mixture was refluxed for one hour. The solvent and the excess of phosphorus-oxy-chloride were removed in vacuo. The residue was crystallised from alcohol, m.p. 193-5°C. [This product also rapidly dehydrochlorinated at 80°C and 2 mm. pressure].

Analysis: Found - N = 8.6%;

$C_{18}H_{19}ON_2Cl$ requires N = 8.9%.

(23) Synthesis of 3 β -3'-methoxyphenylethyl quinazolone-4 (CXII)

To a refluxing mixture of quinazolone-4 (1 g) and powdered potassium hydroxide (2 g) in acetone (50 ml) was added β -meta-methoxyphenylethylbromide (1.5 g) in acetone (10 ml) over ten minutes. After refluxing for three hours, acetone was distilled off; the residue was diluted with water and extracted with benzene. From the benzene extract, after distilling off benzene and triturating the residue with petrol ether, was obtained 3 β -3'-methoxyphenyl-ethyl-quinazolone-4 (CXII) (0.075 g). It melted at 68-9°C. Crystallisation from benzene-petrol ether did not improve the melting-point. The quinazolone (CXII) was extremely soluble in alcohol, benzene, toluene and acetone. Its alcoholic solution fluoresced blue.

Analysis: Found - N = 10.15%;

$C_{17}H_{16}O_2N_2$ required N = 10%.

(24) Picrate of CXII

It was prepared just as the picrate of CVIII was prepared. It was crystallised from alcohol, m.p. 148-50°C.

Analysis: Found - N = 13.97%;

$C_{23}H_{19}O_9N_8$ requires N = 13.75%.

(25) Synthesis of 2-methyl-3-benzyl-quinazolone-4 (CXIV)

(a) A mixture of 2-methyl-quinazolone-4 (8.5 g) benzyl chloride (7 g) and powdered potassium hydroxide (12 g) in acetone (500 ml) was refluxed for six hours. Acetone was then distilled off; the residue was diluted with water and extracted with chloroform. Chloroform was distilled off from the chloroform extract; the residue was treated with hydrochloric acid to obtain the hydrochloride of CXIV. The hydrochloride was thoroughly washed with benzene, and the base was regenerated from the hydrochloride by addition of alkali. The base was again taken up in chloroform. After removing chloroform, an oily residue was left over, which, on trituration with petrol ether, gave a white powder (CXIV) (5 g ; m.p. 70°C).

2-Methyl-3-benzyl-quinazolone-4 (CXIV) was very soluble in alcohol, benzene and toluene. It was insoluble in aqueous alkali. With dilute hydrochloric acid it formed a sparingly soluble hydrochloride. Its alcoholic solution had a blue fluorescence.

Analysis: Found - C = 76.41, H = 5.53, N = 11.03%;

$C_{16}H_{14}ON_2$ requires C = 76.81, H = 5.6, N = 11.2%.

b) Bogert's method⁹⁵

Acetyl anthranil (0.9 g) and benzylamine (0.6 g) were heated together for thirty minutes at 150°C. On cooling, the melt solidified. It was thoroughly washed with sodium bicarbonate solution to obtain a crystalline solid (m.p. 118°C; yield - 0.9 g) [Bogert⁹⁵ reports the m.p. as 123°C].

The product thus obtained was very soluble in alcohol, benzene and toluene. It was soluble in dilute hydrochloric acid.

Two subsequent repetitions of the above experiment under identical conditions yielded a 70°C-melting solid identical with the product obtained by benzylating 2-methyl-quinazolone-4.

(26) Picrate of CXIV

The picrate of 2-methyl-3-benzyl-quinazolone-4 (m.p. 70°C) was prepared following the procedure for the preparation of the picrate of CVIII. It was crystallised from alcohol in plates, m.p. 200-2°C.

Analysis: Found - N = 14.11%; the monohydrate of the picrate
 $C_{22}H_{19}O_9N_5$ requires N = 14.09%.

(27) Hydrochloride of CXIV

2-Methyl-3-benzyl-quinazolone-4 (m.p. 70°C) (0.5 g) was dissolved in boiling dilute hydrochloric acid (50 ml. containing 3 ml. of concentrated hydrochloric acid), filtered and allowed to cool. The hydrochloride of CXIV (0.38 g) separated out in fat needles.

Melting Point: It melted around 240°C, solidified around 250°C, and melted again around 325°C with deep decomposition.

Analysis: Found - N = 9.2%; the monohydrate of the hydrochloride - $C_{16}H_{17}O_2N_2Cl$ - requires 9.2%.

(28) Hydrochloride of Bogert's compound

It was prepared by passing dry hydrogen chloride into a solution of Bogert's compound in dry benzene. It was crystallised from ethanelpetrol ether mixture.

Melting Point: It melted around $240^{\circ}C$, solidified around $250^{\circ}C$, and melted again around $325^{\circ}C$ with decomposition.

(29) Preparation of o-Nitrobenzoic acid¹⁰³

This was obtained by oxidising o-nitro-toluene with alkaline potassium permanganate.

(30) Preparation of o-nitro-N-benzyl-benzamide (CXXVII)

o-Nitrobenzoic acid (1 g), dry benzene (5 ml) and thionyl chloride (3 ml) were refluxed together for one hour. Then the solvent and the excess of thionyl chloride were removed under suction. To a cooled solution of o-nitrobenzoyl chloride in dry benzene (2 ml) was added benzyl amine (1 ml) in benzene (3 ml) and petrol ether (10 ml). The crude benzamide (CXXVII) (1.1 g) melted around $100^{\circ}C$. It was crystallised from benzene, m.p. $122-3^{\circ}C$.

Analysis: Found - N = 10.88%;
 $C_{14}H_{12}O_3N_2$ requires N = 10.94%.

(31) Preparation of o-amino-N-benzyl-benzamide (CXXVIII)

o-Nitro-N-benzyl-benzamide (1 g) was gently refluxed with zinc dust (3 g) and 5% acetic acid (100 ml) for two hours. It was filtered hot, and the filtrate, on cooling, gave very pure CXXVIII (m.p. 123°C; 0.3 g). It was very soluble in alcohol. Its alcoholic solution had a blue fluorescence. It was crystallised from aqueous alcohol, m.p. 124°C.

Analysis: Found - N = 12.56%;

$C_{14}H_{14}ON_2$ requires N = 12.39%.

(32) Picrate of CXXVIII

It was prepared just as the picrates of the quinazolones were prepared. It was crystallised from aqueous alcohol, m.p. 156-8°C.

Analysis: Found - N = 14.89%; the monohydrate of the picrate -

$C_{20}H_{19}O_9N_5$ requires N = 14.8%.

(33) Preparation of o-acetylamino-N-benzyl-benzamide (CXXVI)

O-Amino-N-benzyl-benzamide (0.1 g) was heated with acetic anhydride (2 ml) for ten minutes on a water-bath. The reaction mixture was then poured into water and allowed to stand when a crystalline solid (0.1 g) separated out. It was crystallised from aqueous alcohol, m.p. 147-8°C.

Analysis: Found - N = 10.47%;

$C_{16}H_{16}O_2N_2$ requires N = 10.45%.

(34) Preparation of 2-formyl-3-benzyl-quinazolone-4 (CXV)

Freshly prepared selenium dioxide (0.42 g) was added to

2-methyl-3-benzyl-quinazolone-4 (m.p. 70°C) (1 g) in dioxane 25 ml. The mixture was gently refluxed for one hour. It was filtered after cooling. To rid the filtrate of finely divided selenium, it was run through a 3" column of alumina. After distilling off dioxane, the residue was triturated with petrol ether to obtain CXV (1 g; m.p. 130-5°C). It was crystallised from benzene in fine needles, m.p. 143-4°C.

Analysis: Found - C = 72.36, H = 4.59, N = 10.74%;
 $C_{16}H_{12}O_2N_2$ requires C = 72.73, H = 4.5, N = 10.6%.

(35) Dinitrophenylhydrazone of CXV

2-Formyl-3-benzyl-quinazolone-4 (0.2 g) in dioxane (1 ml) was boiled with 2,4-dinitro-phenylhydrazine (0.4 g) in alcohol (10 ml) and concentrated sulphuric acid (0.5 ml) for five minutes and cooled when the dinitrophenylhydrazone of CXV (0.25 g) crystallised out in needles. It was crystallised from dioxane-alcohol mixture, m.p. 275-7°C.

Analysis: Found - N = 19.08%;
 $C_{22}H_{16}O_5N_6$ requires N = 18.92%.

(36) Attempted cyclisation of CXV with concentrated sulphuric acid

CXV (0.4 g) was dissolved in ice-cold concentrated sulphuric acid (2 ml) with vigorous shaking. It was left at room temperature for thirty minutes and then poured into crushed ice when a rose-red solid was obtained. It was thoroughly washed with 5% alkali and then taken up in chloroform. The chloroform-insoluble fraction was deep

red in colour and melted around 300°C with decomposition. From the chloroform extract was obtained a rose-red powder which, after two crystallisations from chloroform and petrol ether, sintered above 270°C and melted with severe decomposition at 340-50°C.

(37) Synthesis of 2-Hydroxyethylquinazolone-4 (CXXX)

An intimate mixture of 2-methyl-quinazolene-4 (2 g), paraformaldehyde (1 g) and ammonium chloride (2 g) in paraffin (15 ml) was heated on an oil-bath for one hour. A reaction set in around 160°C and lasted for five minutes. After cooling the reaction mixture, the paraffin was decanted off; the residue was thoroughly washed with petrol ether and then with hot water. It was later taken up in glacial acetic acid and precipitated with ammonia. The brownish-yellow powder (1 g) thus obtained was crystallised from dilute acetic acid.

Melting Point: Shrinks around 270°C, and melts around 281-3°C (Menti reports 268-70°C for the melting-point).

It was very soluble in glacial acetic acid and alkali.

Analysis: Found - N = 14.84%;

$C_{10}H_{10}O_2N_2$ requires N = 14.73%.

(38) Preparation of β -Bromo-propionic acid

Ethylene cyanohydrin¹⁰⁴ was prepared by treating ethylene chlorohydrin with potassium cyanide. β -Bromopropionic acid¹⁰⁵ was obtained by refluxing ethylene cyanohydrin with 48% hydrobromic acid.

(39) Preparation of o-Bromopropionamido-benzoic acid (CXXXI)

β -Bromo-propionic acid (9 g) was refluxed with thionyl chloride (15 ml) for 90 minutes. After distilling off the excess of thionyl chloride from β -bromopropionyl-chloride, it was cooled and added to a cooled solution of anthranilic acid (6 g) in water (90 ml) containing potassium hydroxide (4.5 g) and sodium acetate (15 g). After rendering the reaction mixture acidic to Congo red with hydrochloric acid, CXXXI (9.4 g) was obtained as a white powder. It was crystallised from benzene in small needles, m.p. 150-2°C.

Analysis: Found - N = 5.1%;
 $C_{10}H_{10}O_3N$ Br requires N = 5.15%.

(40) Preparation of o-chloracetamidobenzoic acid (CXXXII)

Starting from chlor-acetyl chloride and sodium anthranilate and following the procedure for the preparation of CXXXI, chloracetamidobenzoic acid was obtained in good yields.

(41) Preparation of o-chlor-acetamide-benzamide (CXXXIII)

o-Chloracetamido-benzoic acid (1 g) was gently refluxed with acetic anhydride (10 ml) for thirty minutes. After distilling off the excess of acetic anhydride at 30 mm., the residue was poured into 20% ammonia (10 ml). A crystalline solid was obtained. It was crystallised from alcohol in needles, m.p. 182-3°C.

Analysis: Found - N = 13.41%;
 $C_9H_9O_2N_2Cl$ requires N = 13.18%.

(42) Synthesis of 2-methyl-3-hydroxy-methyl-quinazolone-4 (CXXXV)

A mixture of 2-methyl-quinazolone-4 (1 g) paraformaldehyde (2 g), piperidine (1 ml) and glacial acetic acid (2 drops) was refluxed in absolute alcohol (10 ml) for four hours. From the reaction mixture part of the alcohol was distilled off when a crystalline high-melting solid (0.25 g) separated out. It was filtered and washed with alcohol.

It was sparingly soluble in water, alcohol, dilute hydrochloric acid and dilute alkali, m.p. 325-7°C.

Analysis: Found - N = 14.76%;

$C_{10}H_{10}O_2N_2$ requires N = 14.73%.

(43) Debenzylation in the hydrochloride of 2-methyl-3-benzyl-quinazolone-4

The hydrochloride of 2-methyl-3-benzyl-quinazolone-4 (0.8 g) was heated to 250°C and maintained at that temperature for thirty minutes. The product was then thoroughly washed with 5% sodium-bicarbonate solution. It was then taken up in alcohol, charcoal treated, and diluted with water to obtain 2-methyl-quinazolone-4 (150 mg). Mixed melting-point of this with an authentic sample of 2-methyl-quinazolone-4 proved the identity of the components.

The above experiment was repeated. The product was not washed with sodium-bicarbonate solution. It was crystallised from water (m.p. 340°C with deep decomposition). Mixed melting-point of this with an authentic sample of the hydrochloride of 2-methyl-quinazolone-4 showed that the components of the mixture were identical with each other.

(44) Preparation of N-benzyl-quinazolone-4 (CXXXVI)

N-benylation of quinazolone-4 was effected with benzyl chloride, potassium hydroxide and acetone, just as in the case of 2-methyl-quinazolone-4. The yield of CXXXVI was 47% (Bogert¹⁰⁶, employing methanol instead of acetone as solvent, reports 37.5%). N-Benzyl-quinazolone-4 was crystallised from alcohol, m.p. 116-8°C (Bogert¹⁰⁶ reports 116°C; Baker⁹⁸ and co-workers report 112-4°C).

Analysis: Found - N = 11.71%;

$C_{15}H_{12}ON_2$ requires N = 11.87%.

(45) Hydrochloride of CXXXVI

It was prepared and purified just as the hydrochloride of CVIII was prepared and purified, m.p. 215.7°C.

Analysis: Found - N = 10.14%;

$C_{15}H_{13}ON_2Cl$ requires N = 10.28%.

Unlike in the case of the hydrochloride of 2-methyl-3-benzyl-quinazolone-4, no thermal debenylation was observed at 250°C in the case of the hydrochloride of CXXXVI.

(46) Preparation of 2-ethyl-3-benzyl-quinazolone-4 (CXXXVII)

The N-benylation of 2-ethyl-quinazolone-4 was effected with benzyl chloride, potassium hydroxide and acetone, just as in the case of 2-methyl-quinazolone-4. The yield of CXXXVII was 40%. It was crystallised from aqueous alcohol, m.p. 108-9°C.

Analysis: Found - C = 77.52, H = 6.2, N = 10.69%;

$C_{17}H_{16}ON_2$ requires C = 77.27, H = 6.06, N = 10.6%.

(47) Picrate of CXXXVII

Just as the picrate of the other quinazolones, the picrate of CXXXVII was prepared. It was crystallised from aqueous alcohol, m.p. 148-50°C.

Analysis: Found - N = 13.79%; the monohydrate of the picrate - $C_{23}H_{21}O_9N_5$ requires N = 13.7%.

(48) Hydrochloride of CXXXVII

The hydrochloride of CXXXVII was prepared following the procedure for the preparation of the hydrochloride of 2-methyl-3 β -3',4'-dimethoxyphenylethyl-quinazolone-4 (vide Experiment No.19). It was crystallised from alcohol-benzene mixture, m.p. 178-81°C.

Analysis: Found - N = 9.196%; $C_{17}H_{17}ON_2Cl$ requires N = 9.32%.

As anticipated, no thermal debenylation was observed at 250°C in the case of the hydrochloride of 2-ethyl-3-benzyl-quinazolone-4.

(49) Preparation of 2,3-dimethyl-quinazolone-4 (CXIX)

Methyl iodide (10 ml) in acetone (120 ml) was added slowly over twenty minutes to a refluxing mixture of 2-methyl-quinazolone-4 (4 g) and powdered potassium hydroxide (6 g) in acetone (400 ml). After refluxing the mixture for one hour, acetone was distilled off. The residue was diluted with water and extracted with chloroform. After ~~distilling off chloroform~~ distilling off chloroform, 2,3-dimethylquinazolone-4 (3 g) was obtained, m.p. 71°C (Reported¹⁰⁷ m.p. 72°C).

(50) Hydrochloride of CXIX

The hydrochloride of CXIX was obtained by evaporating a solution of CXIX in dilute hydrochloric acid to dryness. It was crystallised from alcohol.

Melting Point: Melted around 255° with evolution of gas, solidified around 260°C, and melted again around 300°C.

Analysis: Found - N=12.42%; the monohydrate of the hydrochloride $C_{10}H_{13}O_2N_2Cl$ requires N=12.26%.

(51) Thermal demethylation in the hydrochloride of 2,3-dimethyl-quinazolone-4

This was studied just as debenzylation in the hydrochloride of 2-methyl-3-benzyl-quinazolone-4 (Vide Experiment No.43). The product of thermal demethylation of the hydrochloride of CXIX, after purification, was found to be identical with the hydrochloride of 2-methyl-quinazolone-4.

(52) Preparation of 2-ethyl-3-methyl-quinazolone-4 (CXXXVIII)

This was prepared from 2-ethyl-quinazolone-4 following the procedure for the preparation of 2,3-dimethyl-quinazolone-4, yield 92%. It was crystallised from aqueous alcohol, m.p. 117-8°C (Reported¹⁰⁸ m.p. 121°C).

(53) Hydrochloride of CXXXVIII

This was prepared and purified just as the hydrochloride of 2,3-dimethyl-quinazolone-4, m.p. 218-20°C.

Analysis: Found - N = 12.54%;

$C_{11}H_{13}ON_2Cl$ requires N = 12.47%.

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