A survey of literature relating to quinazolines revealed that 4-benzyl quinazolines have not received much attention. Fetscher and Bogert attempted the synthesis of 4-veratryl-6:7-dimethoxy quinazoline, true analogue of papaverine by a method analogous to Pictet papaverine synthesis, but without success. Palit had previously reported failure to cyclise sym-acetyl phenyl urea to 4-methyl-2-quinazolone. The unsuccessful attempts of Bogert and co-workers to cyclise acetyl, phenylacetyl and homoveratroyl derivatives of 3:4-dimethoxyphenyl urea confirm the failure of this method in this series.

A successful route to 4-alkyl quinazolines is the action of alcoholic ammonia on acyl O-amino ketones under pressure. This method has been modified by Schofield, Theobald and Swain by passing a continuous stream of ammonia for 4-5 hours through molten ammonium acetate containing the requisite ketone, the temperature being maintained at about 165-70°C. This communication is a report on the application of this method. The first step is to obtain o-acetamido- or o-amino phenyl benzyl ketone. Fetscher and Bogert applied three different methods for preparing o-amino deoxy veratroin without any success. Goodwin and Lothrop applied the inverse addition of benzyl magnesium chloride to acetanthranil to obtain o-amino desoxy benzoin without being able to isolate any tangible product. We first attempted to prepare o-amino phenyl benzyl ketone by Hofmann reaction on benzalphtalamide. Hypohalite reaction on the amide (I) gave benzalphthalimide (IV) and benzaldehyde. The imide was recovered unchanged when subjected to Hofmann reaction and smell of benzaldehyde was prominent. The formation of the imide from the amide could be explained by the enolisation of the keto group, replacement of hydroxy by bromine and elimination of hydrogen bromide in the alkaline medium.
The formation of benzaldehyde in both reactions could possibly be explained by the oxidation of the benzal group by the hypohalite. The resistance of the imide to undergo reaction was unexpected. The application of Friedal-Craft reaction of phenacetyl chloride on p-acetanisidide produced only intractable tars. Attention was now turned to the method employed by Hauser and Walker,\(^6\) Bowman,\(^7\) and by Albert and Hampton.\(^8\) o-Nitrobenzoyl chloride was condensed with magnesium ethoxy derivative of phenyl diethyl malonate, yielding o-nitrobenzoyl-phenyl diethyl malonate. Attempts to acid hydrolyse the product to yield o-nitro phenyl benzyl ketone failed. Alkaline conditions cleaved the o-nitro benzoyl group to O-nitro benzoic acid. It is relevant to note that Blumer and Sorkin\(^9\) did not succeed to hydrolyse and decarboxylate 3-nitro-6-methyl-benzoyl-n butyl diethyl malonate to afford the corresponding ketone. The only product they could isolate was 3-nitro-o-toluic acid. Applying Gabriel's method,\(^10\) o-phthalimido-benzoyl chloride was condensed with magnesium ethoxy phenyl diethyl malonate and the product hydrolysed without isolation, only phthalimido benzoic acid could be obtained.

Success was achieved in obtaining o-acetamido phenyl benzyl ketone in good yield by the ozonolysis of 2-methyl-3-benzyl indole. When this part of the work was completed a paper by Schofield and Okenden\(^11\) appeared on ozonolysis of 2: 3-disubstituted indoles. When o-acetamido phenyl benzyl ketone was treated with gaseous ammonia in molten ammonium acetate, a yellow base of m.p. 142-43\(^\circ\) was obtained in satisfactory yield. The compound was expected to be 2-methyl-4-benzyl quinazoline. Analysis of the compound showed it to have the formula \(C_{16}H_{14}N_2O\), instead of \(C_{16}H_{14}N_2\), pointing to the oxidation of a methylene group at some stage of the reaction. Infra-red spectrum of the compound (see Fig. 8) shows that there is absorption at both 1381 cm.\(^{-1}\) and 1667 cm.\(^{-1}\) indicating the presence of a C-methyl
group, an αβ-unsaturated ketone and a diaryl ketone. The compound \( C_{16}H_{12}N_{2}O \) is 4-benzoyl-2-methyl-quinazoline.

\[
\begin{align*}
\text{V} & \quad \text{VI} \\
\text{VII}
\end{align*}
\]

This is the first reported instance of the formation of a 4-benzoyl quinazoline. Oxidation of a methylene group during synthesis is not without precedent. Quinazoline can be considered to be a quinoline as well as an isoquinoline derivative. The oxidation of a 1-benzyl group in an isoquinoline to the benzoyl group during synthesis has been observed by Haworth, Perkin and Buch, and by Gulland and Haworth. A recent publication by Meerwein, Laassh, Mersch and Nentwig reported the preparation of two nuclear substituted 2-phenyl-4-benzyl quinazolines by an entirely different
method. Attempts were made to synthesise 4-benzyl quinazoline by the condensation of benzimid chloride with phenyl acetonitrile in the presence of anhydrous aluminium chloride, but the expected 4-benzyl quinazoline could not be isolated. The problem of preventing the oxidation of the methylene group during the synthesis and the synthesis of substituted 4-benzyl quinazolines are being pursued.

EXPERIMENTAL

_Hofmann degradation experiments._—Benzalphtalamide and imide were prepared according to the method of Natelson and Gottfried. The amide (5 gm.) dissolved in 10% sodium hydroxide solution (20 ml.) was treated with freshly prepared hypobromite solution at 0° with stirring. After the addition of the hypobromite was complete, the mixture was heated slowly on the water-bath at 80°. Smell of benzaldehyde was noticed. The cooled alkaline solution was extracted with chloroform. The chloroform extract was washed with dilute hydrochloric acid. Basification of the acid extract yielded no product. The chloroform extract was dried and the solvent removed. The resulting solid (m.p. 180–81° from benzene) was benzalphtalamide. When the reaction was carried out with the imide, it was recovered unchanged.

**(O-Nitro benzo)-phenyl-diethyl-malonate.—**Phenyl diethyl malonate was obtained by carbethoxylation of ethyl phenyl acetate with diethyl carbonate according to Gaubert and Smith. An ethereal solution of its magnesium derivative was prepared by standard procedure. A slightly more than equivalent quantity of O-nitro benzoyl chloride in ether was added slowly to the magnesium derivative under stirring, the addition being so regulated that gentle boiling was maintained. After completion of addition the mixture was refluxed for an hour and then left to stand overnight. The magnesium complex was decomposed with cold dilute sulphuric acid and the acid layer extracted with ether. The combined ethereal solution was washed with sodium carbonate (10%), water, dried and ether removed. The resulting oily product solidified on standing in the ice-chest. On crystallisation from ethanol it melted at 103–04°. Found: C, 62.5%; H, 5.1%; N, 3.8%. Calculated for C_{20}H_{19}NO_7, C, 62.3%; H, 4.9%; N, 3.6%.

All attempts to hydrolyse the product to the desoxybenzoin failed.

_Cyclisation of O-acetamido phenyl benzyl ketone._—O-Acetamido phenyl benzyl ketone was obtained by ozonolysis of 2-methyl-3-benzyl-indole. The ketone (5 gm.) and 50 gm. of dry ammonium acetate were taken in a 300 ml. R.B.-flask and slowly heated to 165° by immersion in an oil-bath, in an
atmosphere of ammonia. A continuous stream of ammonia was passed through the melt for 4 hours. It was then cooled, taken up in water and the aqueous solution left in the ice-chest. A small quantity of a solid separated after some time. The mixture was repeatedly extracted with ethyl acetate and the extract washed with dilute acid. The acid extract was basified with cold, dilute ammonia and then repeatedly extracted with ethyl acetate. After drying over anhydrous magnesium sulphate, ethyl acetate was removed under reduced pressure affording an oil which solidified on standing in the ice-chest. Crystallised from light petrol small yellow shining crystals of m.p. 138-39° were obtained. Found: (1) C, 77.56%; H, 4.95%; N, 11.2%. (2) C, 77.64%; H, 4.85%; N, 11.4%. Calculated for C₁₆H₁₂N₂O, C, 77.41%; H, 4.85%; N, 11.2%.

The presence of the keto-group was confirmed by infra-red spectrum.

ACKNOWLEDGEMENT

I take this opportunity to express my thanks to Dr. K. N. Menon for suggesting this problem and for guidance during the course of this work. I thank Government of India for a scholarship and Dr. Gurubakh Singh of the National Physical Laboratory for the infra-red spectrum.

SUMMARY

The synthesis of 4-benzoyl-2-methyl quinazoline is reported.

LITERATURE

   —— and Nabenhauer J. Ibid., 1924, 46, 1702.
   Bishler, A. and Lang, M. Ber., 1895, 28, 279.
   —— and Burkart, E. Ibid., 1893, 26, 1350.
8. Albent, A. and Hampton, A. Schofield, K. and Osborn, A. R. 
   Ibid., 1955, 2100.
9. Blumer, M. E. and Sorkin, E. 
10. Gabriel, S. and Lowenberg, B. 
    Ber., 1918, 51, 1493.
11. Schofield, K. and Ockenden, D. W. 
    Ibid., 1924, 2176.
    Ibid., 1928, 581.
    Ber., 1956, 89, 224.
15. Natelson, S. and Gottfried, S. P. 
16. Gaubert, P. and Smith, F. R. 
    C.A., 1946, 40, 9934.