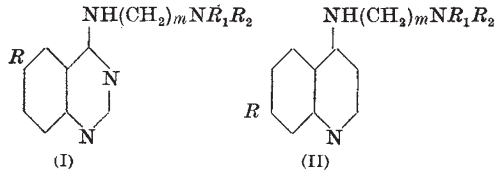
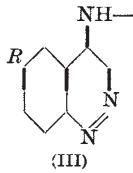
however, exhibited by certain 6-substituted 4-basicalkylaminoquinolines[3], and the closely analogous 7-substituted derivatives (formula II), according to the patent literature[4], are also active.



(I) (II)

In view of these considerations, the investigation of the cinnoline ring-system from the antimalarial point of view is of interest, on account of the close formal similarity which it bears to the quinoline and quinazoline prototypes; and preliminary results indicate that activity may be expected in suitably substituted compounds of this group.

The following substances of general formula III, prepared by us in the course of work carried out in the University of Durham (Durham Division), have been tested against *Plasmodium gallinaceum* in chicks by the technique described by Curd, Davey and Rose[5].



(III)

Compound	Dose (mgm./kgm.)	Activity
(*a*) R = H; X = CH(Me)$(CH_2)_3$. M.p. 103° (found: C, 71·35; H, 8·95; N, 19·5. $C_{17}H_{26}N_4$ requires C, 71·3; H, 9·15; N, 19·55 per cent); dihydrochloride, m.p. 132° (found: C, 51·55; H, 8·2; N, 14·1; Cl, 18·45. $C_{17}H_{26}N_4$, 2HCl, $2H_2O$ requires C, 51·6; H, 8·15; N, 14·2; Cl, 18·0 per cent).	250 120	Marked Slight
(*b*) R = OMe; X = CH(Me)$(CH_2)_3$. M.p. 160° (found: C, 67·9; H, 8·45; N, 18·2. $C_{18}H_{28}ON_4$ requires C, 68·3; H, 8·9; N, 17·7 per cent).	80	None
(*c*) R = H; X = $(CH_2)_2$. M.p. 145° (found: C, 68·8; H, 8·45; N, 22·05. $C_{14}H_{20}N_4$ requires C, 68·8; H, 8·2; N, 22·95 per cent); dihydrochloride, m.p. 246° (found: C, 47·8; H, 7·5; N, 16·3; Cl, 20·55. $C_{14}H_{20}N_4$, 2HCl, $2H_2O$ requires C, 47·6; H, 7·4; N, 15·85; Cl, 20·1 per cent).	200 120	Doubtful None

The biological tests were carried out in the Blackley Laboratories of Imperial Chemical Industries, Ltd., and we are indebted to I.C.I., Ltd., for permission to publish the findings.

A further point of interest in connexion with these results is that they lend support to the hypothesis of Schönhofer[3] that antimalarial activity is related to the formal possibility of prototropy between the 'normal' molecule (amino-aromatic) and the imino-quinonoid form.

An extended investigation based on these preliminary results is now in progress.

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Antimalarial Activity and Toxicity of a Metabolic Derivative of Quinine

The preparation and properties of a metabolic product of quinine has previously been described[1,2], but the results of the studies on the toxicity and antimalarial activity of this compound were not released for publication at that time.

Recently, Marshall[3] has reported that a similarly prepared degradation product does not reduce the peripheral parasitemia of *Plasmodium gallinaceum* in chicks and he concludes that "after the administration of quinine in malaria treatment, a proportion of the alkaloid is converted by the liver of the host into an inactive metabolite".

In our experience, the metabolic product of quinine is suppressive when given intravenously to chicks infected with *P. gallinaceum* in doses of 40–70 mgm./kgm./day (six birds). The degree of suppression is about equal to that obtained in our routine screening test with 15 mgm./kgm./day of quinine. The $L.D._{50}$ of this substance, given intravenously to week-old chicks, is 100–120 mgm./kgm., while that of quinine is 30–40 mgm./kgm. Thus it can be seen that its chemotherapeutic index is of the same order of magnitude as that of quinine.

When the metabolic derivative of quinine is added to the diet of ducks infected with *P. lophuræ*, it shows a definite antimalarial activity; but it is less than 1/20 that of quinine[4].

Its suppressive action on the respiration of chicken red blood cells parasitized with *P. gallinaceum* is almost as effective as quinine, but it is less effective in repressing both aerobic and anaerobic glycolysis[5].

These results do not support Marshall's view that the metabolism of quinine results in an inherently less efficient drug, since the reduction in activity and toxicity may well be a matter of decreased penetration into the cell. Therefore, derivatives of quinine (or other quinoline compounds similarly metabolized) with substitutions in the 2-position designed to block the oxidation may prove to be even more effective than quinine itself.

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Synthetic Liquid Penicillin Medium with Glycerine as the Sole Source of Carbon Atom

Penicillin was first obtained from nutrient broth medium by Sir Alexander Fleming. For systematic investigation of this important antibacterial substance, modified Czapek–Dox medium, with glucose as the sole source of carbon, was used by Clutterbuck, Lovell and Raistrick in 1932. Since then, various modifications of Czapek–Dox medium have been tried either to enhance the growth of the mould or to increase the yield of penicillin. But in all these modifications, either sugar or carbohydrate has been chosen as the principal source of carbon. In our experiments with different synthetic liquid media for producing penicillin, we have observed that glycerine can effectively replace either sugar or carbohydrate, hitherto exclusively employed in the liquid media. This observation has an important bearing on commercial production, as glycerine is much cheaper than either glucose or lactose; if it could be suitably adopted for large-scale manufacture, it would eventually reduce considerably the cost of penicillin.

Media used	No. of days of incubation	*p*H	Anti-bacterial titre
2% v./v. Glycerine medium (*A*)	4	6·1	40
	5	6·4	100
	6	6·2	150
	7	6·4	200
	8	6·4	100
4% v./v. Glycerine medium (*A*)	4	6·1	40
	5	6·1	100
	6	6·1	150
	7	6·2	200
	8	6·0	350

We believe we are the first to record a basic change in the source of carbon in synthetic liquid media for penicillin production.

The following glycerine medium (*A*) was used in all our experiments: sodium nitrate, 3·0 gm.; potassium chloride, 0·5 gm.; magnesium sulphate ($MgSO_4.7H_2O$), 0·5 gm.; ferrous sulphate ($FeSO_4.7H_2O$), 0·01 gm.; potassium dihydrogen phosphate, 1 gm.; 'Bacto-Peptone', 10 gm.; glycerine, 20 c.c. or 40 c.c., according as 2 per cent or 4 per cent v./v. was desired; distilled water to make 1 litre. Very satisfactory results were obtained if, instead of distilled water, 1,000 c.c. extract derived from 100 gm. of wheat-bran were employed. 200 c.c. of this medium was used for each sowing bottle.

The organism used was a culture of *Pen. notatum*, G.C. 419 supplied by Dr. B. Mundkar, from the collection of the Imperial Agricultural Research Institute, Delhi. Antibacterial activity was recorded in duplicate in standard nutrient broth medium with Oxford *A. Staph. aureus* strain, in the usual manner.

Further, it has also been noticed that increasing the concentration of glycerine to more than 4 per cent v./v. in the medium does not increase the antibacterial titre.

Detailed work in this connexion will be published later.

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