(2) homopolar and (3) Ehrenfest-Raman. The influence of colloidalisation on the magnetic properties of metals in which these types of binding are present is mentioned. Attention is drawn to the experiments by Goetz on the effect of small quantities of foreign metals in bismuth crystals. The close analogy between colloidalisation and cold-working in the case of metals wherein the metallic type of binding is predominant, is considered in the light of Honda and Shimizu's theory. Brief mention is made of the investigations on nickel powders and films in the light of Heisenberg's theory.

The Chemistry of Antimalarials.

By Tejendra Nath Ghosh,

Department of Organic Chemistry, Indian Institute of Science, Bangalore.

THE toll of malaria in India and other parts of the world is increasing day by day. Malaria is described as a great, if not the greatest, obstacle to the physical, intellectual and economic progress of the people, the enormous mortality and labour inefficiency caused by this disease being a matter of dismay. The seriousness of the epidemic that raged last year in Ceylon may be realised from the fact that 74,000 deaths were caused by this disease during six months. The situation afforded an opportunity to test on a mass scale the value of quinine and of synthetic antimalarial drugs and the report thereon should prove of great value. In view of the fact that malaria causes an enormous waste of human efficiency, any well-planned chemical investigation undertaken as a campaign against malaria will indeed prove a beneficent factor in the amelioration of human distress and in the promotion of international welfare.

For the last half-century, quinine has been considered pre-eminently effective in the treatment of malaria and the selective cultivation of cinchona, in India and Java, has aimed at a maximum yield of quinine. Cinchona bark contains some twenty alkaloids. It is becoming increasingly clear, however, that several other alkaloids are at least as potent as quinine and instead of the expensive pure quinine, the crude mixed cinchona alkaloids are now being used. A comparative examination[1] of specially purified specimens of the principal cinchona alkaloids and their dihydro bases, has revealed that dihydroquinine is more active and that dihydroquinidine, cinchonidine and quinidine are less active than quinine. Our knowledge as to what particular group of the quinine molecule is responsible for its pronounced physiological activity is far from complete, for other alkaloids are known which show a similar physiological activity without possessing the various features of its constitution. Quinine has not been synthesised in the laboratory and, even if it had been, its industrial synthesis would, in any case, be too expensive. In view of the fact that the alkaloids of cinchona bark are not effective for certain therapeutic purposes, particularly for true causal prophylaxis, the prevention of relapses and the prevention of spread, the problem of finding a cheap and efficient quinine substitute is one of great importance.

In 1891 Grimaux and Arnaud prepared from cupreine, a series of homologues of quinine, one of which, ethyl cupreine, was tested clinically and found to be somewhat more active than quinine. Tappeiner, as long ago as 1895, found that certain quinoline derivatives, notably 2-phenylquinoline, kill paramæcia *in vitro* in greater dilutions than quinine itself, but they failed to have any curative action on malaria. Before the structure of quinine had been elucidated by Hesse, Königs, and Rabe, attempts at the synthesis of compounds which might be similar in constitution to quinine led Knorr to the synthesis of antipyrine and Skraup in 1883 to that of the hydroquinoline derivative, thalline. Neither of these has any antimalarial action, though both are stronger antipyretics than quinine. In the year 1913, Kaufmann[2] synthesised β-piperidino-α-hydroxy-(6-ethoxyquinolyl-4)-ethane which was toxic to paramæcia and had a marked antipyretic action in human fevers. Schulemann and his co-workers in the laboratories of I. G. synthesised a series of quinoline and acridine derivatives with

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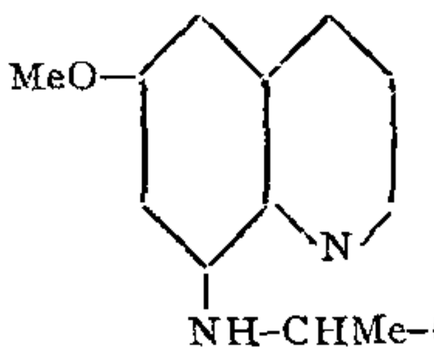
[1] Buttle, Henry and Trevan, *Biochem. J.*, 1934, **28**, 426.

[2] *Ber.*, 1913, **46**, 1823.

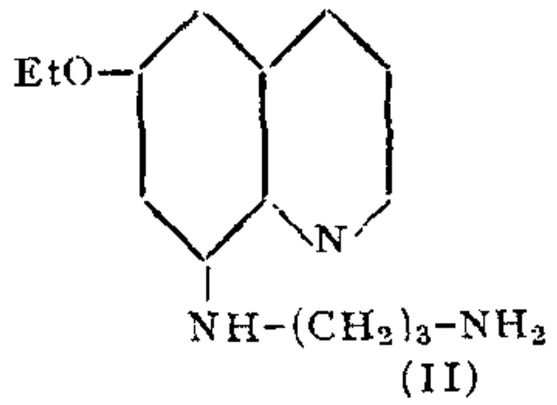
a basic side-chain and these were tested by Roehl and Kikuth on canaries. The Bayer Company, in 1926, announced the preparation of a relatively simple compound, plasmoquine, which was stated to possess a specific action on the malarial parasite; this synthesis has proved to be the first step into a new field of chemotherapy.

Since the discovery of plasmoquine to which structure (I) has been assigned by the I. G. Farbenind. A.-G., several workers have synthesised compounds similar to plasmoquine in structure.



(I)

The derivatives of 8-aminoquinoline have special interest in connection with the subject of antimalarials; thus Baldwin[3] condensed 8-amino-6-ethoxyquinoline with γ-bromopropylphthalimide and obtained a product which, on hydrolysis, yielded the compound (II) similar in structure to plasmoquine.



(II)

The method developed by Baldwin has been extended by several workers,[4] and several products possessing powerful antimalarial properties[5] (against bird malaria) have been obtained. A few of them resemble plasmoquine and are nearly equal to it in potency. Fourneau and his collaborators[6] tested a series of such compounds on rice finch and found 8-diethylamino-propylamino-6-methoxy-quinoline to be equal, if not superior to plasmoquine and this has now been placed on the market under the name of plasmocid. Brahmachari and his co-workers[7] prepared some alkylaminoquinoline derivatives amongst which special mention may be made of 6-methoxy-8-amino*iso*-propylaminoquinoline, structurally related to plasmoquine.

Whilst extending the above line of research for the preparation of new antimalarials, one should bear in mind that even small variations in the substituents (though of no interest from a purely chemical point of view) produce effects of marked biological significance. For instance, the 6-methoxyquinolines are more potent than the similarly substituted 6-ethoxyquinolines, and the length of the alkylaminoalkyl chain in position 8 of 8-amino-6-ethoxyquinoline has a considerable bearing on the activity. Magidson and Strukov[8] claim that the 6-hydroxy-derivatives are in some cases more active than the corresponding alkoxy-derivatives, the efficiency decreasing with the size of the alkoxy-group. In evaluating a drug, its therapeutic efficiency and toxicity are both taken into consideration, and in the study of antimalarials of the type of plasmoquine the aim should be to obtain products possessing lower toxicity combined with an equal or increased therapeutic efficiency.

Gunn and Marshall[9] reported that harmaline, although inferior to quinine, possesses curative value in acute malaria, whilst harmine, though valueless in acute cases, prevents recurrence of attacks in cases of relapsing malaria in which administration of quinine is without value. Robinson[10] has synthesised pyrroloquinolines having similarity in structure to harmine and harmaline. Pyrryl indoles, synthesised by Rây and his co-workers,[11] are likely to possess antimalarial properties, in view of their similarity to harmine. Preliminary trials have indicated that they have antipyretic properties. Glyoxalinquinolines, synthesised by Narang and Rây,[12] have been found to possess antimalarial properties and appear to be actively toxic to paramœcia in a dilution of 1 : 1000. Rây and his collaborators[13] have synthesised some derivatives

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[3] *J. Chem. Soc.*, 1929, 2959.

[4] Kermack and Smith, *J. Chem. Soc.*, 1931, 3096; Baldwin and Robinson, *ibid.*, 1934, 1264; Meisel and Robinson, *ibid.*, 1934, 1267.

[5] Tate and Vincent, *Parasitology*, 1933, **25**, 411.

[6] Fourneau, Trefouel, Bovet and Benoit, *Ann. Inst. Pasteur*, 1931, **46**, 514.

[7] Brahmachari and Das Gupta, *J. Indian Chem. Soc.*, 1932, **9**, 37, 207.

[8] *Arch. Pharm.*, 1933, **271**, 359.

[9] *Proc. Roy. Soc. Edin.*, 1920, **15**, 145.

[10] *J. Chem. Soc.*, 1929, 2948.

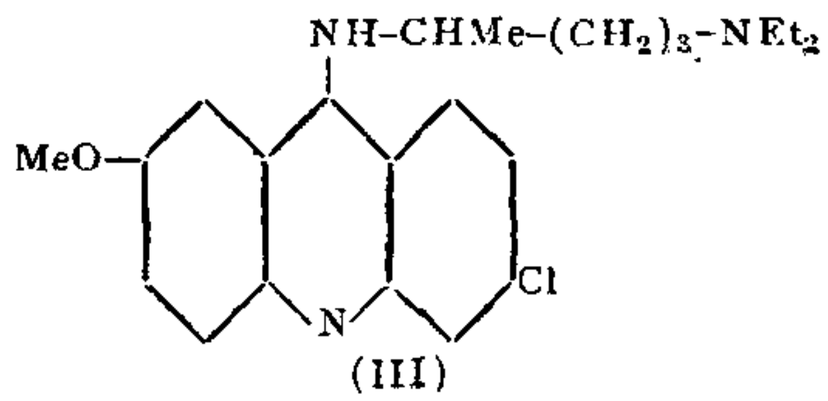
[11] Aggarwal, Qureshi and Rây, *J. Amer. Chem. Soc.*, 1932, **54**, 3988.

[12] *J. Chem. Soc.*, 1931, 970.

[13] Ahluwalia, Kochhar and Ray, *J. Indian Chem. Soc.*, 1932, **9**, 215.

of cotarnine. These have been found to have antipyretic properties but Chopra and his co-workers[14] have found, however, that anhydrocotarnineresorcinol hydrochloride has no antimalarial action.

Atebrin (III), a synthetic antimalarial which is as remarkable as plasmoquine, was discovered by Mauss and Mietzsch in 1930. These investigators[15] found atebrin to be very effective against the schizont modification of the malarial parasite and consider that it should be very successful in conjunction with plasmoquine, which is effective against the gamete modification.



(III)

According to the discoverers of atebrin, the most varied acridine derivatives of the above type and other ring systems containing similar basic aliphatic side-chains (*e.g.*, triphenylmethane, thiazine, xanthine; see *Klin. Woch.*, 1933, **12**, 1276) are active antimalarials. Walls[16] has recently synthesised a phenanthridine derivative containing the same basic side-chain as atebrin. The pharmacological examination shows that phenanthridine is notably less active than its otherwise closely analogous isomeride acridine and differs from the latter in its lack of dermatitic and sternutative action.

The recent use of salvarsan and stovarsol in benign tertian malaria, as well as that of mercurochrome (dibromohydroxy-mercurifluorescein) suggests that the study of organo-metallic compounds would constitute an useful line of enquiry.

The difficulty of forming an accurate estimate of the value of any particular antimalarial agent arises from the fact that the actual infection cannot be transmitted to laboratory animals. This difficulty was partially removed when Roehl devised his technique of testing such drugs in bird malaria, using canaries as test animals, but ultimately one is dependent on clinical trials for confirmation.

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[14] Chopra, Mukherjee and Campbell, *Indian J. Med. Research*, 1933, **21**, 255.

[15] Mietzsch and Mauss, *Angew. Chem.*, 1934, **47**, 633.

[16] *J. Chem. Soc.*, 1935, 1405.

The Detection of Adulteration of Butterfat (Ghee).

(A Suggested Solution of an All-India Problem.)

By Prof. Dr. N. N. Godbole, M.A., B.Sc., Ph.D. (Berlin),
Benares Hindu University, Benares.

THE adulteration of butterfat (ghee) has been penalised by all the Provincial Governments of India and some of these have already taken very serious steps to punish the dealers in this important article of food, whenever the adulteration has been detected and proved in a law-court. Every province has got a special Chemical Analyser, whose business it is to examine and report on the samples of ghee (as also other food-stuffs) submitted to him for report. The act dealing with the prevention of food adulteration empowers the trying magistrates to decide the cases before them on the strength of the reports submitted by the special officers. In the interests of the vast public, it is but necessary to punish those who sell adulterated ghee (as also other adulterated food-stuffs). The responsibility which rests on the Chemical Analysers to the various Governments is therefore very great indeed. In the interests of justice and also in the interests of the public for whom justice is administered, it is of paramount importance that the investigation of the adulteration must be both scientific and correct.

In our investigation of this problem, we have come across certain points which need a very careful consideration. The main problem is, what are the correct physical and chemical constants of butter and butterfat from the scientific point of view? What are the limits of these? How is the purity or impurity of both butter and butterfat to be ascertained? Is there, in the first place, a correct knowledge of the composition of Indian butter or butterfat, from cows and buffaloes, either separately or mixed? Are the differ-