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Part XI. N-Alkyl-3-phenyl Chelidamic Acid Derivatives

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It is apparent that as far as literature is concerned the main points of departure for any researches in the field of synthetic antimalarials are the models of plasmochin, quinine, atabrine and the isomer of plasmochin-paludrine being an exception in this sense. Though some workable theories as to the mode of action of certain chemotherapeutic agents have been evolved recently, in the main, chemotherapy is still an empirical science.

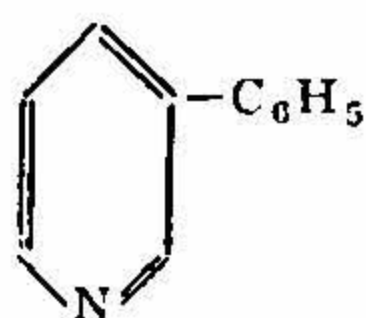
A study of the above four antimalarials reveals that they all may be considered as quinoline derivatives. Thus atabrine may be considered as 2:3 benzoquinoline derivative, quinine and plasmochin as γ -substituted quinolines. But if we go further into this structure we see that, more fundamentally, each is a pyridine derivative as well and with the exception of plasmochin each is a γ -substituted pyridine derivative. Based on this fundamental consideration, investigations on the ultimate pyridine analogues of these compounds were started to ascertain whether or not the activity inherent in the quinoline and acridine nuclei was also manifested in the simple pyridine structure.

It has been pointed out by former workers (Curd & Rose, *J.C.S.*, 1946, 343) that the quinoline nucleus of pamaquin and the acridine nucleus of atabrine are heterocyclic systems foreign to the animal body and it was considered that one feasible approach to the synthesis of less toxic compounds would be to build up antimalarial structures on the basis of some ring system of biological importance, since for such compounds the body would possess more tolerance. The present choice fell on the pyridine nucleus for more than one reason. Firstly, the chemistry of the ring system has become familiar in the course of work on sulpha pyridine and it has moreover been learnt that some of the sulphanilamide derivatives are active against malaria. Coggeshall (*J. Inf. Dis.*, 1941, 69, 108; *Am. J. Trop. Med.*, 1938, 18, 715); Manwell, *et al.* (*Proc. Soc. Expt. Biol. Med.*, 46, 523). Secondly, it is one of the vital molecules occurring in many systems of physiological importance as the vitamins and coenzymes.

Though many α - and β -substituted derivatives of pyridine were prepared by American workers, with various side chains, the results were far from encouraging with regard to their antimalarial activity. (Harry, Mosher, *et. al.*, "Advancing fronts in Chemistry," II, 53.) The γ -substituted amino alkyl amino pyridines, however, showed antimalarial activity. This indicated that the position opposite the ring nitrogen is a favoured position and the activity of acridine and quinoline antimalarials is in some way connected with this fundamental structural unit.

Recently, many pyridine derivatives as S. N. 6686, 7446, 2767, 14937, 4240 and a host of others have been found to possess some activity against *P. gallinaceum* in chicks. (Wesilogle, "A Survey of Antimalarial Drugs," U.S.A.). Gilman and Spartz prepared some quinoline derivatives as open models of atebaine (*J.A.C.S.*, 1944, 66, 621). These compounds also showed activity against chick malaria and hence it was thought that open models of quinolines, namely phenyl pyridines might also give useful antimalarials.

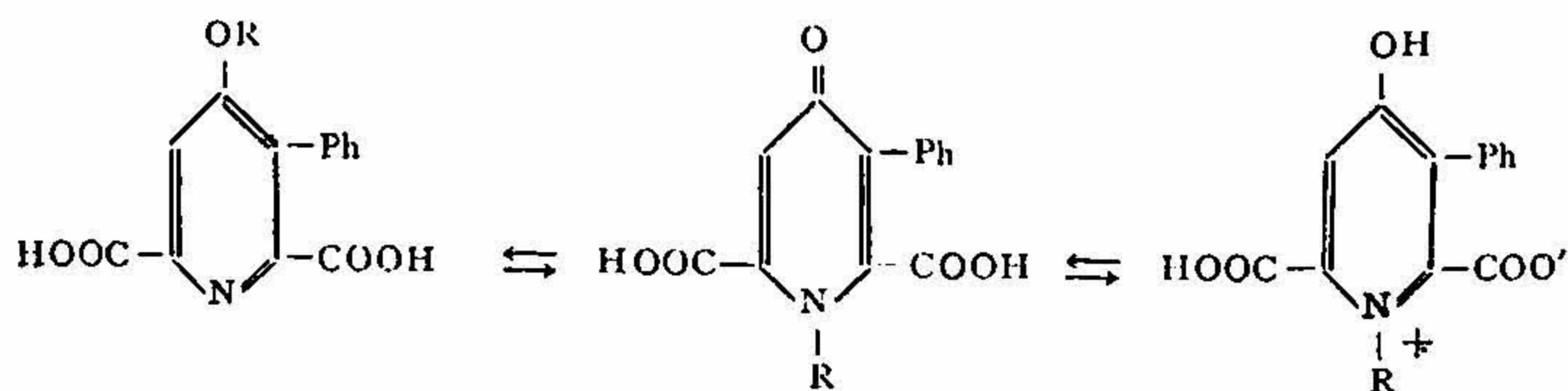
In the present scheme of work 3-phenyl-pyridine (I) where we have a free phenyl group instead of the fused benzo group of quinoline, was chosen as the nucleus and synthesis of N-substituted-3-phenyl γ -pyridone, 2:6-dicarboxylic acid derivatives (type II) as possible antimalarials has been described in this paper.



3-Phenyl pyridine

(I)

The presence of the $-(\text{COOH})$ groups makes it possible to prepare the easily soluble sodium salts, and further increases the possibility of tautomerism as indicated below in the molecule, which is one of the conditions for antimalarial activity.



R = alkyl or diethylamino ethyl, etc.

(II)

also give active antimalarial compounds because of their similarity in structure to the active acridine compounds mentioned above and hence the pyrone (IV) was reacted with diethylaminoethylamine and diethylaminoisopentylamine to yield the corresponding pyridones (type II).

EXPERIMENTAL

Phenyl acetone was prepared by passing a mixture of the vapours of phenyl acetic acid and glacial acetic acid over heated thoria kept at 450° C. (*Org. Synthesis*, Vol. XVI, 47).

Condensation of phenyl acetone with ethyl oxalate: Formation of Ethyl 3-phenylchelidonate (III).—A solution of sodium ethylate was made by dissolving 12 g. sodium in absolute alcohol (150 c.c.). One half of the sodium ethylate was taken in a three-necked flask with stirrer and condenser, protected from moisture. When a scum started to form, a mixture of dry phenyl acetone (34 g.) and diethyl oxalate (37 g.) was quickly added. This was stirred till the solution became turbid. A mixture of diethyl oxalate (37 g.) and the rest of the sodium ethylate was then added and the whole stirred for four hours. Afterwards a portion of the alcohol (40 c.c.) was removed from the mixture by distillation and the mass after thorough cooling poured into 200 g. of ice. A mixture of concentrated hydrochloric acid (75 c.c.) and water (75 c.c.), well cooled in ice was then slowly added to the sodium salt with good stirring to give a creamy yellow precipitate of the phenyl chelidonic ester. The crude ester was crystallised from alcohol to give pale yellow plates, m.p. 130° C., yield 60 g. (Found: C, 64.94; H, 4.4. $C_{17}H_{16}O_1$ requires, C, 64.6; H, 4.9 per cent.)

3-Phenyl-chelidonic acid—Hydrolysis of (III).—The ester (60 g.) was heated on a steam-bath for 20 hours with concentrated HCl (75 c.c.). It was allowed to cool and the crude acid collected and recrystallised from hot water, m.p. 160°, yield 45 g. (Found: C, 60.4; H, 2.84; $C_{13}H_8O_5$ requires, C, 60.0; H, 3.1 per cent.)

3-Phenyl-chelidamic acid: (type II, R = H).—Chelidonic acid (2 g.) was evaporated to dryness with excess of liquor ammonia, twice. The product was dissolved in alcohol and the solution diluted with water to give a yellow micro crystalline substance, m.p. 210–15°. (Found: C, 60.81; H, 3.12; N, 5.3. $C_{13}H_9NO_5$ requires C, 60.2; H, 3.5; N, 5.5 per cent.)

N-Methyl-3-phenyl-chelidamic acid: (type II, R = CH₃).—3-Phenyl chelidonic acid (2.6 g.) was dissolved in the minimum quantity of alcohol and a solution of methylamine (0.3 g.) in alcohol added to it. The whole was refluxed for half an hour. On cooling a crystalline solid separated. This

was collected, purified as the sodium salt, and the acid precipitated with dil. HCl. The product was recrystallised from alcohol to give colourless plates. Yield 2 g., m.p. 160°. (Found: C, 64.75; H, 4.47; N, 5.0. $C_{14}H_{11}O_5N$ requires C, 64.4; H, 4.22; N, 5.1 per cent.)

N-Isopropyl-3-phenylchelidamic acid: (type II, $R = CHMe_2$).—3-Phenyl-chelidonic acid (2.6 g.) dissolved in the minimum of alcohol was added to a solution of isopropylamine (0.6 g.) in alcohol and the whole after refluxing for one half hour, allowed to cool. The product separated was collected, purified and recrystallised from alcohol to give orange red crystals, m.p. 154°, yield 1.8 gm. (Found: N, 4.5; $C_{15}H_{11}O_5N$ requires N, 4.66 per cent.)

*N-(α -methyl-*n*-butyl)-3-phenylchelidamic acid*: (type II, $R = CH_2-CH_2-CH_2-CHCH_3$).—Phenyl chelidonic acid (2.6 g.) and the amine (0.8 g.) were reacted as before. The product was purified and crystallised from alcohol and water to give pale red crystals, m.p. 145°, yield 1.5 g. (Found: N, 3.80; $C_{18}H_{19}O_5N$ requires N, 4.1 per cent.)

N-Isoamyl-3-phenyl-chelidamic acid: (type II, $R = CH_2-CH_2-CHMe_2$).—3-Phenyl-chelidonic acid (2.6 g.) and iso-amyl amine (0.8 g.) were reacted as before using alcohol as solvent. The product purified and crystallised from alcohol gave yellow glistening plates, m.p. 162°, yield 1.6 g. (Found: N, 3.9; $C_{18}H_{19}O_5N$ requires N, 4.1 per cent.)

1-(Diethylamino ethyl)-3-phenyl-chelidamic acid: (type II, $R = \cdot CH_2-CH_2-NEt_2$).—A mixture of diethylamino ethyl amine (1.2 g.) and 3-phenyl chelidonic acid (2.6 g.) was refluxed for one hour in alcohol. The mass separated on cooling was collected, purified as the hydrochloride and the base crystallised from alcohol and water twice, m.p. 147°, yield 2.2 g. (Found: N, 7.58; $C_{19}H_{22}O_5N_2$ requires N, 7.99 per cent.)

1-(α -Methyl- δ -diethylamino butyl)-3-phenyl-chelidamic acid: (type II, $R = \cdot CHMe-CH_2-CH_2-CH_2-NEt_2$).—The phenyl chelidonic acid and the amine were reacted in the same way as before, α -methyl- δ -diethylamino butylamine (1.58 g.) being used instead. The product was purified as before and crystallised from alcohol to give a red microcrystalline product, m.p. 172°, yield 2.1 g. (Found: N, 7.15; $C_{22}H_{25}O_5N_2$ requires N, 7.0 per cent.)

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