192. *Tetrahydroacridones and Related Compounds as Antimalarials.*

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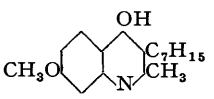
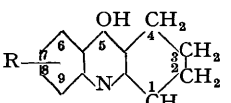
Tetrahydroacridones, 12-hydroxydihydro-β-quinindenes, and 2- and 4-hydroxyquinolines have been examined for antimalarial activity. Marked prophylactic action has been found against *P. gallinaceum* infections in chicks and the structural requirements for activity are outlined. The experimental conditions for the Conrad–Limpach ring-closure of β-arylamino-$\Delta^{\alpha\beta}$-unsaturated esters are discussed.

There are two approaches to the chemotherapy of malaria. The prophylactic approach aims at rendering the bite of the mosquito ineffective in producing an infection and the therapeutic approach aims at the eradication of an established infection; the former is directed at the sporozoites injected by the mosquito and the subsequent (primary) tissue phase development, while the latter aims at control during the later erythrocytic stages in the developmental cycle of the parasite. Quinine, mepacrine, and pamaquin, to which paludrine and several 4-dialkylaminoalkylaminoquinolines may now be added, are well-established examples of drugs possessing the latter type of action but, until recently, there have been few reports of drugs exhibiting causal prophylactic activity. Pamaquin has a slight prophylactic action (Kikuth and Mudrow, *Z. Immun-Forsch.*, 1939, **95**, 285; Mudrow, *Arch. Schiffs- u. Tropen-Hygiene*, 1940, **44**, 257). Certain sulphonamides (Sinton, Hutton, and Shute, *Ann. Trop. Med. Parasit.*, 1939, **33**, 37; Coatney and Cooper, *Publ. Hlth. Rep., Wash.*, 1944, **59**, 1455; Coggeshall, Porter, and Laird, *Proc. Soc. Exp. Biol. Med.*, 1944, **57**, 286; Freire and Paraense, *Rev. Brasil. Biol.*, 1944, **4**, 27) have a marked causal prophylactic action, as does paludrine (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 208), while *p*-methylsulphonylbenzamidine (Fuller, Tonkin, and Walker, *J.*, 1945, 633) and some arylguanidines (King and Tonkin, *J.*,.1946, 1063) have a slight effect. When the war in Europe ended, reports came to hand (Fitch, *Pharm. J.*, 1945, **155**, 182; *Combined Intelligence Objectives Sub-Committee*, 1945, Item No. 24, File No. XXIII–12; *idem*, File No. XXIV–20; *idem*, File No. XXV–54) that German workers had encountered causal prophylactic activity in certain 4-hydroxyquinolines, notably 4-hydroxy-7-methoxy-3-*n*-heptylquinaldine (I) (endochin), and the present authors at once recorded, in a preliminary way, similar observations with a chemically related series (*Nature*, 1945, **156**, 629); the present paper describes this work in detail.

An examination of a number of tetrahydroacridones (II), 12-hydroxy-2 : 3-dihydro-β-quinindenes (III) (for numbering, see Blount, Perkin, and Plant, *J.*, 1929, 1976), and 2- and 4-hydroxyquinolines for causal prophylactic activity in *Plasmodium gallinaceum* infections in chicks revealed definite activity in compounds conforming to type (IV), of which (I), (II), and



(I.)



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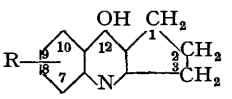
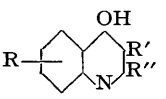


(III.)



(IV.)

(III) are representative, R′ and R″ being saturated hydrocarbon residues. For example, 3-methoxyacridone showed no activity while its tetrahydro-derivative, 7-methoxy-1 : 2 : 3 : 4-

tetrahydroacridone (V), was the most active substance encountered, being, on a weight basis, about twice as active as sulphadiazine and four times as active as endochin (I), our investigations being ultimately extended to include comparison with this substance. Access to compounds of types (II), (III), and (IV) was obtained by condensation of the appropriate aromatic primary amines and β-keto-esters, followed by thermal cyclization of the resulting β-arylamino-$\Delta^{\alpha\beta}$-unsaturated esters. This reaction was described first for ethyl acetoacetate by Conrad and Limpach (*Ber.*, 1887, **20**, 944) who simply heated the intermediate products to about 250° and rarely obtained yields greater than 30%. The reaction was used by numerous workers in the interval and many years elapsed before Limpach (*Ber.*, 1931, **64**, 969; D.R.-P. 455,387) made the significant improvement of effecting ring-closure by adding the intermediate products to liquid paraffin preheated to 250—280° and claimed yields of over 90%. Our own experience has been that decomposition is frequently excessive under Limpach's conditions as the products separate on the walls of the reaction vessel and there become overheated, and the yields are not as good as those claimed; other criticisms have been advanced by Maurin (*Ann. Chim.*, 1935, **4**, 309). Ashley *et al.* (*Proc. Roy. Soc.*, 1933, *B*, **113**, 295) used molten paraffin wax which was subsequently removed by a solvent. It was obvious to us that the best thermal control and mixing could be obtained by using a vigorously boiling inert solvent of suitable boiling point. For several years, therefore, we have used vigorously boiling diphenyl (b. p. 255°) for this purpose and have obtained clean products in good yield thereby; American workers (Price and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 1204; Steck, Hallock, and Holland, *ibid.*, p. 1241) have recently described the use of diphenyl ether and the eutectic of diphenyl and diphenyl ether (Dowtherm A) for this purpose, the latter having the advantage of being liquid at room temperature. Other high boiling inert solvents should be equally suitable, quinoline, for example, having been applied for this purpose (Dr. F. H. S. Curd, private communication).

With *o*- and *p*-substituted amines the constitutions of the products formed in the Conrad–Limpach reaction are unequivocal. With *m*-substituted amines, however, two products may be obtained since ring-closure may take place at either the 2- or the 6-position of the arylamino-group; both were isolated in the ring-closures of ethyl 2-*m*-anisidino*cyclo*hex-1-enecarboxylate, which yielded 8- (VI) and 6-*methoxy*-1 : 2 : 3 : 4-*tetrahydroacridone* (VII), and ethyl β-*m*-anisidino-α-*n*-heptylcrotonate, which yielded endochin (I), m. p. 213—214°, and the isomeric 4-*hydroxy*-5-*methoxy*-3-n-*heptylquinaldine* (VIII), m. p. 219—220°. Leonard, Herbrandson, and Van Heyningen (*J. Amer. Chem. Soc.*, 1946, **68**, 1279) have recently studied the latter ring-closure but do not record the isolation of (VIII) and claim, on the basis of analytical data, to have isolated the demethylated substance, 4 : 5-dihydroxy-3-*n*-heptylquinaldine, m. p. 218—218·5° (corr.), in addition to (I), m. p. 218·5—219·5° (corr.). In both these cases ring-closure at the position para to the methoxyl group greatly preponderated, in contrast with the purely aromatic series where approximately equal proportions of 2- and 4-methoxyacridones are formed in the ring-closure of *N*-*m*-anisylanthranilic acid (Lehmstedt and Schrader, *Ber.*, 1937, **70**, 838). An authentic specimen of (VI) was obtained by applying the Niementowski–Borsche–Tiedtke reaction to 4-methoxyanthranilic acid and *cyclo*hexanone, but the yield was poor because of the ease with which this particular anthranilic acid undergoes decarboxylation. The melting points of 7-methoxy- (V) and 7-ethoxy-1 : 2 : 3 : 4-tetrahydroacridone (X) recorded here differ from those recorded in the literature (see pp. 1036, 1037), but we have carefully repeated these preparations and have fully confirmed our own observations.

Tests for causal prophylactic activity in *P. gallinaceum* infections in 10-day old chicks were carried out using the technique previously outlined (Fuller, Tonkin, and Walker, *loc. cit.*; King and Tonkin, *loc. cit.*) and the results are recorded in the Table. The minimal effective doses are those, given orally twice daily for the first four days and commencing two hours before infection, which gave definite indications of activity in comparison with untreated controls. In some cases no parasites were observed in the blood during the period of observation; sub-inoculations into clean chicks from such birds were carried out in a few cases and, if no infection resulted in the recipients, the donors were considered as having been sterilized of their infections (S). Where no sub-inoculations were carried out the result is recorded as presumably sterilized (? S). These observations (S and ? S) were, of course, made on higher dosages than those recorded as minimal. In a number of cases tests for therapeutic activity were carried out and the results are recorded in the Table; + denotes definite action, +— slight action, and — no action. The following substances, prepared by known methods, were also examined for prophylactic action and found to be inactive: 2 : 4-dihydroxyquinoline, 4-hydroxyquinaldine, 4-hydroxy-6-methoxyquinaldine, 4-hydroxy-8-methoxyquinaldine, 2-hydroxy-6-methoxy-lepidine, 1 : 2 : 3 : 4-tetrahydroacridone, and 3-methoxyacridone. From an inspection of the

Table and the preceding list, it is obvious that activity was only to be found in substances conforming to type (IV), as mentioned above. The necessity for the presence of a substituent in the benzene ring is clearly indicated by the inactivity of the simple 1 : 2 : 3 : 4-tetrahydroacridone and, of the substituents examined, methoxyl was more favourable than chloro-, which was more favourable than the ethoxyl group as indicated by the order of activities, (V) > (XI) > (X), and (XXIV) = (XXVI) > (XXV). The effect of the position of the methoxyl group in the benzene ring was marked, the position corresponding to the 7-position of quinoline being as a rule favourable as indicated by endochin (I), in which R′ and R″ of (IV) are of unequal size, but where R′ and R″ are of equal size as in (V), (VI), and (IX) the position corresponding to the 6-position of quinoline appeared to be most favourable, and weighting the alicyclic ring had a dystherapeutic effect.

Experimental.

General Method for the Synthesis of 1 : 2 : 3 : 4-*Tetrahydroacridones,* 12-*Hydroxy*-2 : 3-*dihydro*-β-*quinindenes, and* 4-*Hydroxyquinolines.*—Equimolecular amounts, usually 0·1 g.-mol., of the appropriate aromatic primary amine and β-keto-ester were mixed—with warming, if necessary, in the case of solid amines—and the mixture, treated with one drop of concentrated hydrochloric acid (Coffey, Thomson, and Wilson, *J.*, 1936, 856), was set aside in a partly evacuated desiccator for several days at 37°. The crude β-arylamino-$\Delta^{\alpha\beta}$-unsaturated esters were cyclized by being added slowly to a weight of boiling diphenyl four times that of the combined starting materials. Evolution of alcohol took place readily and the boiling solutions were refluxed for 15 minutes after the end of the addition. On cooling, the products usually crystallised when the temperature fell to about 100°. When cold, the diphenyl was removed with ether, and the crude products, usually cream-coloured, were crystallised from suitable

Antimalarial Activity in P. gallinaceum *Infections.*

	Prophylactic Test.		Therapeutic Test.
Tetrahydroacridones :	Min. effective dose (mg./100 g. chick).	Remarks.	
(V) 7-Methoxy-	12·5	?S	+
(VI) 8-*Methoxy-*	25		+−
(IX) 9-Methoxy-	37·5		−
(X) 7-Ethoxy-	inactive		
(XI) 7-Chloro-	100	slight act.	−
(XII) 7-Methyl-	inactive *		
(XIII) 7 : 8-Dimethoxy-	inactive *		
(XIV) 7-Methoxy-3-methyl-	inactive *		
(XV) 8-*Methoxy*-3-*methyl*-	50	S	
(XVI) 9-*Methoxy*-3-*methyl*-	50		
(XVII) 7-*Methoxy*-1-*methyl*-	62·5	toxic	
(XVIII) 8-*Methoxy*-1-*methyl*-	*ca.* 25	S	
(XIX) 9-*Methoxy*-1-*methyl*-	50	toxic	
(XX) 7-*Methoxy*-3-*ethyl*-	inactive *		
(XXI) 8-*Methoxy*-3-*ethyl*-	100	?S	
(XXII) 9-*Methoxy*-3-*ethyl*-	inactive *		
(XXIII) 7-*Methoxy*-1-*ethyl*-	100	very slight	
Dihydro-β-quinindenes :			
(XXIV) 12-*Hydroxy*-9-*methoxy*-	37·5		+
(XXV) 12-*Hydroxy*-9-*ethoxy*-	inactive		
(XXVI) 12-*Hydroxy*-9-*chloro*-	31		+
4-Hydroxyquinaldines :			
(XXVII) 6-*Methoxy*-3-*ethyl*-	inactive	toxic	
(XXVIII) 6-*Methoxy*-3-n-*heptyl*-	inactive *		
(I) 7-Methoxy-3-*n*-heptyl-	50	S	+
(XXIX) 8-*Methoxy*-3-n-*heptyl*-	*ca.* 100		
Sulphadiazine	25		

* Highest dose tested : 100 mg.

solvents. Diphenyl was used in the same arbitrarily selected proportion throughout, but recent work (Price and Roberts, *loc. cit.*) indicates that there may be an optimal concentration for each particular ring-closure.

7-*Methoxy*-1 : 2 : 3 : 4-*tetrahydroacridone* (V).—Obtained in an overall yield of 86% from *p*-anisidine and ethyl *cyclo*hexanone-2-carboxylate, the compound crystallised from alcohol or, better, pyridine in flat rectangular plates, m. p. 313° (Found : C, 73·6; H, 6·6; N, 6·3. Calc. for $C_{14}H_{15}O_2N$: C, 73·4; H, 6·6; N, 6·1%). Basu and Das Gupta (*J. Indian Chem. Soc.*, 1937, **14**, 468) record m. p. 295°; Hughes and Lions (*J. Proc. Roy. Soc., New South Wales*, 1938, **71**, 458) record m. p. 284°; Bukhsh and Desai (*Proc. Indian Acad. Sci.*, 1939, *A*, **10**, 262) record m. p. 285—286°. The intermediate ethyl 2-*p*-anisidino-*cyclo*hex-1-enecarboxylate separated from methyl alcohol in prisms, m. p. 70° (Found : C, 69·7; H, 7·7;

N, 5·4. Calc. for $C_{16}H_{21}O_3N$: C, 69·9; H, 7·6; N, 5·1%). Hughes and Lions (*loc. cit.*) record m. p, 71°; Bukhsh and Desai (*loc. cit.*) record m. p. 71—72°.

8-*Methoxy*-1 : 2 : 3 : 4-*tetrahydroacridone* (VI).—(*a*) 4-Methoxyanthranilic acid (4 g.) (preparation below) and *cyclo*hexanone (4 g.) were mixed and heated to 220° fairly rapidly and the mixture was kept at 220—230° for an hour. The mixture was cooled and treated with ether to remove *m*-anisidine, arising from decarboxylation, and unreacted *cyclo*hexanone. The insoluble 8-*methoxytetrahydroacridone* (0·3 g.; 5%) separated from spirit in small hexagonal plates, m. p. 309° (Found: C, 73·0; H, 6·5; N, 6·3. $C_{14}H_{15}O_2N$ requires C, 73·4; H, 6·6; N, 6·1%). The *m*-anisidine, arising as a by-product, was characterised as the acetyl derivative, m. p. and mixed m. p. 80°.

(*b*) The crude cyclization product obtained in 72% yield from *m*-anisidine and ethyl *cyclo*hexanone-2-carboxylate was a mixture of the 8- and 6-methoxy-compounds which could not be separated satisfactorily by crystallisation. The mixture (17 g.) was therefore dissolved in twice its weight of warm glacial acetic acid and then treated with 1½ volumes of concentrated hydrochloric acid. The hydrochloride, which separated on cooling in the ice-chest, was collected and drained thoroughly. The base (10·7 g.), regenerated from the solid hydrochloride with aqueous ammonia, then separated from spirit in hexagonal plates, m. p. and mixed m. p. 309° (Found: C, 73·1; H, 6·5; N, 6·3%).

6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydroacridone* (VII).—The acetic–hydrochloric acid mother liquors from the above experiment, on evaporation to dryness and treatment with aqueous ammonia, afforded the crude 6-*methoxy*-isomer (5·9 g.) which separated from spirit in flattened needles (1·4 g.), m. p. 326°, depressed to 284° on admixture with the 8-methoxy-compound formed in the same reaction (Found: C, 73·5; H, 6·5; N, 6·1. $C_{14}H_{15}O_2N$ requires C, 73·4; H, 6·6; N, 6·1%).

9-*Methoxy*-1 : 2 : 3 : 4-*tetrahydroacridone* (IX).—Obtained in 60% yield from *o*-anisidine and ethyl *cyclo*hexanone-2-carboxylate, the compound separated from *n*-butyl alcohol in plates, m. p. 286—288° (Found: C, 73·5; H, 6·6; N, 6·4. Calc. for $C_{14}H_{15}O_2N$: C, 73·4; H, 6·6; N, 6·1%). Hughes and Lions (*loc. cit.*) record m. p. 278°; Bukhsh and Desai (*loc. cit.*) record m. p. 277—279°.

7-*Ethoxy*-1 : 2 : 3 : 4-*tetrahydroacridone* (X).—Obtained in 87% yield from *p*-phenetidine and ethyl *cyclo*hexanone-2-carboxylate, the compound separated from pyridine in needles or from alcohol in prisms, m. p. 292—293° (Found: C, 74·1; H, 7·1; N, 5·8. Calc. for $C_{15}H_{17}O_2N$: C, 74·1; H, 7·0; N, 5·8%). Hughes and Lions (*loc. cit.*) record m. p. > 300°; Bukhsh and Desai (*loc. cit.*) record m. p. >350°. The intermediate ethyl 2-*p*-phenetidino*cyclo*hex-1-enecarboxylate separated from alcohol in long prisms, m. p. 87° (Found: C, 70·0; H, 8·0; N, 4·9. Calc. for $C_{17}H_{23}O_3N$: C, 70·6; H, 8·0; N, 4·9%). Hughes and Lions (*loc. cit.*) record m. p. 87°; Bukhsh and Desai (*loc. cit.*) record m. p. 88°.

7-*Chloro*-1 : 2 : 3 : 4-*tetrahydroacridone* (XI).—Obtained in 74% yield from *p*-chloroaniline and ethyl *cyclo*hexanone-2-carboxylate, the compound crystallised from alcohol in microscopic prisms, m. p. > 330° (Found: C, 67·0; H, 5·3; N, 6·2. Calc. for $C_{13}H_{12}ONCl$: C, 66·9; H, 5·1; N, 6·0%). Basu and Das Gupta (*loc. cit.*) record m. p. 380°. The intermediate ethyl 2-*p*-chloroanilino*cyclo*hex-1-enecarboxylate separated from aqueous alcohol in short prisms, m. p. 67°, whereas Basu and Das Gupta (*loc. cit.*) record m. p. 90° (Found: C, 64·7; H, 6·7; N, 5·2. Calc. for $C_{15}H_{18}O_2NCl$: C, 64·4; H, 6·4; N, 5·0%).

7-*Methyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XII).—Obtained in 40% yield from *p*-toluidine and ethyl *cyclo*hexanone-2-carboxylate, the compound separated from aqueous acetic acid in thin laths, m. p. > 330° (Found: C, 78·9; H, 7·1; N, 6·8. Calc. for $C_{14}H_{15}ON$: C, 78·9; H, 7·0; N, 6·6%). Sen and Basu (*J. Indian Chem. Soc.*, 1930, **7**, 435) record m. p. 340°; Reed (*J.*, 1944, 425) records m. p. 374°.

7 : 8-*Dimethoxy*-1 : 2 : 3 : 4-*tetrahydroacridone* (XIII).—Obtained in 65% yield from 4-aminoveratrole and ethyl *cyclo*hexanone-2-carboxylate, the compound separated from aqueous alcohol in microscopic plates, m. p. > 330° (Found: C, 69·9; H, 6·6; N, 5·6. Calc. for $C_{15}H_{17}O_3N$: C, 69·5; H, 6·6; N, 5·4%). Lions (*ibid.*, p. 242) records m. p. > 300°.

12-*Hydroxy*-9-*methoxy*-2 : 3-*dihydro*-β-*quinindene* (XXIV).—Obtained in 59% yield from *p*-anisidine and ethyl *cyclo*pentanone-2-carboxylate, the *compound* separated from alcohol in fine needles, m. p. > 330° with prior darkening (Found: C, 72·7; H, 6·3; N, 6·7. $C_{13}H_{13}O_2N$ requires C, 72·6; H, 6·1; N, 6·5%). The intermediate *ethyl* 2-p-*anisidino*cyclo*pent*-1-*enecarboxylate* separated from aqueous alcohol in short needles, m. p. 54—55° (Found: C, 69·0; H, 7·3. $C_{15}H_{19}O_3N$ requires C, 68·9; H, 7·3%).

12-*Hydroxy*-9-*ethoxy*-2 : 3-*dihydro*-β-*quinindene* (XXV).—Obtained in 59% yield from *p*-phenetidine and ethyl *cyclo*pentanone-2-carboxylate, the *compound* crystallised from alcohol in aggregates of irregular plates, m. p. approx. 300° with previous darkening (Found: C, 73·4; H, 6·1; N, 6·2. $C_{14}H_{15}O_2N$ requires C, 73·4; H, 6·6; N, 6·1%). The intermediate *ethyl* 2-p-*phenetidino*cyclo*pent*-1-*enecarboxylate* separated from spirit in short prisms, m. p. 53° (Found: C, 70·0; H, 7·7; N, 5·1. $C_{16}H_{21}O_3N$ requires C, 69·9; H, 7·6; N, 5·1%).

9-*Chloro*-12-*hydroxy*-2 : 3-*dihydro*-β-*quinindene* (XXVI).—Obtained in 60% yield from *p*-chloroaniline and ethyl *cyclo*pentanone-2-carboxylate, the *compound* crystallised from aqueous acetic acid in long needles, m. p. approx. 330° with prior darkening (Found: C, 65·8; H, 4·5; N, 6·6. $C_{12}H_{10}ONCl$ requires C, 65·8; H, 4·6; N, 6·4%).

7-*Methoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XIV).—Obtained in 40% yield from *p*-anisidine and ethyl 4-methyl*cyclo*hexanone-2-carboxylate, the compound separated from 50% alcohol or aqueous pyridine in microscopic rectangular plates, m. p. 346—347° (Found: C, 73·9; H, 7·1; N, 6·1. Calc for $C_{15}H_{17}O_2N$: C, 74·1; H, 7·0; N, 5·8%). Basu and Das Gupta (*loc. cit.*) record m. p. 335°.

8-*Methoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XV).—Presumably contaminated initially with the 6-methoxy-isomer in the reaction product obtained in 56% yield from *m*-anisidine and ethyl 4-methyl*cyclo*hexanone-2-carboxylate, the *compound* separated from pyridine in microscopic needles, m. p. 324° (Found: C, 74·2; H, 6·8; N, 6·1. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%).

9-*Methoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XVI).—Obtained in 62% yield from *o*-anisidine and ethyl 4-methyl*cyclo*hexanone-2-carboxylate, the *compound* separated from alcohol in rectangular plates, m. p. 270—273° (Found: C, 73·7; H, 7·1; N, 6·1. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%).

7-*Methoxy*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XVII).—Obtained in 41% yield from *p*-anisidine and ethyl 6-methyl*cyclo*hexanone-2-carboxylate, the *compound* separated from aqueous alcohol in

rectangular plates, m. p. 280—281° (Found: C, 73·8; H, 7·0; N, 5·7. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%).

8-*Methoxy*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XVIII).—Obtained in 23% yield from *m*-anisidine and ethyl 6-methyl*cyclo*hexanone-2-carboxylate, the *compound* crystallised from spirit in fine needles, m. p. 277—278° (Found: C, 74·0; H, 7·2; N, 5·6. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%).

9-*Methoxy*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XIX).—Obtained in 24% yield from *o*-anisidine and ethyl 6-methyl*cyclo*hexanone-2-carboxylate, the *compound* separated from ethyl acetate in small cubes, m. p. 245—246° (Found: C, 74·0; H, 7·4; N, 5·9. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%).

7-*Methoxy*-3-*ethyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XX).—Obtained in 72% yield from *p*-anisidine and ethyl 4-ethyl*cyclo*hexanone-2-carboxylate, the *compound* separated from alcohol in rectangular plates, m. p. 334° (Found: C, 74·9; H, 7·1; N, 5·7. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4; N, 5·4%).

8-*Methoxy*-3-*ethyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XXI).—Obtained in 64% yield from *m*-anisidine and ethyl 4-ethyl*cyclo*hexanone-2-carboxylate, the *compound* was purified with some difficulty from the 6-methoxy-isomer, formed simultaneously, by crystallisation from methyl alcohol and separated in fine flattened needles, m. p. 291° (Found: C, 74·8; H, 7·4; N, 5·6. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4; N, 5·4%). A pure specimen of the 6-methoxy-isomer was not isolated.

9-*Methoxy*-3-*ethyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XXII).—Obtained in 64% yield from *o*-anisidine and ethyl 4-ethyl*cyclo*hexanone-2-carboxylate, the *compound* separated from spirit in microscopic prisms, m. p. 218—219° (Found: C, 74·6; H, 7·2; N, 5·6. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4; N, 5·4%). The intermediate *ethyl* 2-*o*-*anisidino*-5-*ethyl*cyclo*hex*-1-*enecarboxylate* separated from methyl alcohol in rectangular plates, m. p. 60° (Found: C, 70·8; H, 8·5; N, 4·9. $C_{18}H_{25}O_3N$ requires C, 71·3; H, 8·3; N, 4·6%).

7-*Methoxy*-1-*ethyl*-1 : 2 : 3 : 4-*tetrahydroacridone* (XXIII).—Obtained in 40% yield from *p*-anisidine and ethyl 6-ethyl*cyclo*hexanone-2-carboxylate, the *compound* separated from methyl alcohol in rectangular plates, m. p. 252—253° (Found: C, 74·9; H, 7·7; N, 5·8. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4; N, 5·4%).

4-*Hydroxy*-6-*methoxy*-3-*ethylquinaldine* (XXVII).—Obtained in 46% yield from *p*-anisidine and ethyl α-ethylacetoacetate, the *compound* separated from pyridine in fine needles, m. p. 290° (Found: C, 72·0; H, 7·0; N, 6·6. $C_{13}H_{15}O_2N$ requires C, 72·0; H, 7·0; N, 6·5%).

4-*Hydroxy*-6-*methoxy*-3-n-*heptylquinaldine* (XXVIII).—Obtained in 77% yield from *p*-anisidine and ethyl α-*n*-heptylacetoacetate, the *compound* separated from methyl alcohol in fine rectangular plates, m. p. 236—237° (Found: C, 75·6; H, 8·9; N, 5·0. $C_{18}H_{25}O_2N$ requires C, 75·3; H, 8·7; N, 4·9%).

4-*Hydroxy*-7-*methoxy*-3-n-*heptylquinaldine* (*Endochin*) (I) *and* 4-*Hydroxy*-5-*methoxy*-3-n-*heptylquinaldine* (VIII).—A mixture of isomers was obtained in 61% yield from *m*-anisidine and ethyl α-*n*-heptylacetoacetate, which were allowed to interact in the first stage for 7 days at 37°. Crystallisation from methyl alcohol readily afforded the bulk (*ca.* 2/3) of the product, consisting of (I), which separated in fine flattened needles, m. p. 213—214° (Found: C, 75·7; H, 8·5; N, 5·2. Calc. for $C_{18}H_{25}O_2N$: C, 75·3; H, 8·7; N, 4·9%). *Combined Intelligence Objectives Sub-Committee*, 1945, Item No. 24, File No. XXV—54 (p. 38) records m. p. 207—212°; Leonard *et al.* (*loc. cit.*) record m. p. 218·5—219·5° (corr.).

The mother liquors on concentration to small bulk afforded an obvious mixture (7·9 g.), m. p. 180—185°. This mixture on treatment with N-hydrochloric acid (100 c.c.) gave a sticky gum which slowly hardened. The solid was collected and the acid filtrate yielded only traces of material (< 0·1 g.) on treatment with excess of ammonia. The solid dissolved readily in methyl alcohol and the clear solution was evaporated to a syrupy consistency. On addition of water (*ca.* 40 c.c.) a sticky gum reappeared, giving way, on addition of methyl alcohol (*ca.* 20 c.c.), to fine needles. These were collected, the mother liquors being retained (see below), and, on treatment in methyl alcoholic solution with aqueous ammonia, afforded a further amount (4·4 g.) of (I), m. p. and mixed m. p. 213—214°. The aqueous methyl alcohol mother liquors, on treatment with aqueous ammonia, afforded (VIII) (2·95 g.), m. p. 213°, depressed to 173—193° on admixture with (I). The pure *compound* separated from a small volume of methyl alcohol, or from a larger volume of 50% ethyl alcohol, in clusters of fine needles, m. p. 219—220° (Found: C, 75·4; H, 8·5; N, 4·7; OMe, 10·2. $C_{18}H_{25}O_2N$ requires C, 75·3; H, 8·7; N, 4·9; OMe, 10·8%).

4-*Hydroxy*-8-*methoxy*-3-n-*heptylquinaldine* (XXIX).—Obtained in 60% yield from *o*-anisidine and ethyl α-*n*-heptylacetoacetate, the *compound* crystallised from methyl alcohol in fine prisms, m. p. 155—156° (Found: C, 75·1; H, 8·9; N, 5·1. $C_{18}H_{25}O_2N$ requires C, 75·3; H, 8·7; N, 4·9%).

2-*Nitro*-4-*methoxyphenyl Cyanide*.—3-Nitro-4-aminoanisole was submitted to the Sandmeyer reaction using a technique previously described (Fuller, Tonkin, and Walker, *loc. cit.*), affording a 75% yield of recrystallised material separating from methyl alcohol in small plates, m. p. 139° (Found: N, 15·7. Calc. for $C_8H_6O_3N_2$: N, 15·7%). Cook *et al.* (*J.*, 1945, 861), using cuprous cyanide, obtained a somewhat lower yield (crude) and record m. p. 140°.

2-*Nitro*-4-*methoxybenzoic Acid*.—The preceding cyanide (50 g.) was refluxed for 5 hours with a mixture of equal volumes of glacial acetic acid, concentrated sulphuric acid, and water (each 100 c.c.), crystals separating after about 1½ hours. The cooled mixture was treated with about 2 volumes of water and the product was collected and re-precipitated (45 g.) from solution in aqueous ammonia; m. p. 195—196° as recorded by Simonsen and Rau (*J.*, 1917, **111**, 235) and by Ashley, Perkin, and Robinson (*J.*, 1930, 393).

4-*Methoxyanthranilic Acid*.—The preceding nitro-acid (45 g.) was dissolved in a slight excess of 2N-ammonia and hydrogenated in the presence of palladised strontium carbonate (5 g.) at 45 atm. The calculated fall in pressure was observed in about 20 minutes and absorption of hydrogen then ceased. The filtered solution was acidified to about pH 4 and the product (35·4 g.) was collected; m. p. 180° (efferv.). On account of ready decarboxylation, recrystallisation from *ca.* 40% aqueous acetic acid was wasteful but afforded fine prisms, m. p. 180—181° (efferv.). Friedländer, Bruckner, and Deutsch (*Annalen*, 1912, **388**, 46) record m. p. 166° (decomp.); Ullmann and Dootson (*Ber.*, 1918, **51**, 20) record m. p. 172° (decomp.).

Ethyl α-n-*Heptylideneacetoacetate*.—A mixture of freshly distilled oenanthal (100 g.) and ethyl

acetoacetate (114 g.) was cooled in a freezing mixture and saturated with dry hydrogen chloride. After 18 hours in the ice-chest the mixture was poured into water and extracted with ether. The extract was washed well with water, dried, and fractionated, affording a colourless oil (158 g.), b. p. 150—152°/14 mm. (Found: C, 69·1; H, 10·0. Calc. for $C_{13}H_{22}O_3$: C, 69·0; H, 9·7%). Knoevenagel (*Ber.*, 1898, **31**, 737) used piperidine as catalyst and recorded b. p. 145°/10 mm.

Ethyl α-n-Heptylacetoacetate.—The preceding unsaturated ester (145 g.) was hydrogenated in ethyl alcohol (400 c.c.) with palladised strontium carbonate (7 g.) at 45 atm. The calculated fall in pressure was observed in about 20 minutes and no further absorption of hydrogen took place. The product, a colourless oil (133 g.), distilled at 144—146°/11 mm. (Found: C, 68·3; H, 10·5. Calc. for $C_{13}H_{24}O_3$: C, 68·4; H, 10·5%). Wojcik and Adkins (*J. Amer. Chem. Soc.*, 1934, **56**, 2424) record b. p. 130—132°/7 mm.

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