246. *A Synthesis of* 5 : 6 : 7 : 8-*Tetrahydrophenanthridine and its Derivatives.*

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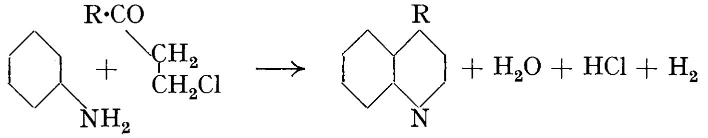
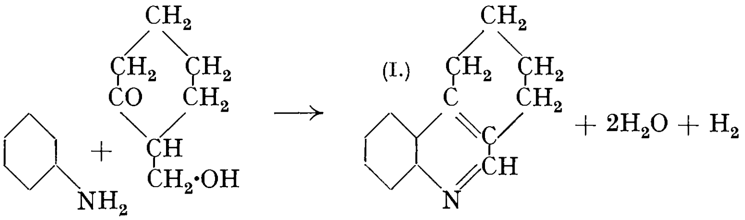
The phenanthridine ring system has hitherto received relatively slight attention in comparison with those of the quinoline and *iso*quinoline systems; yet it would be expected, like these, to be represented among natural products, and its presence has in recent years been detected in chelidonine and related alkaloids (v. Bruchhausen and Bersch, *Ber.*, 1930, **63**, 2520; Späth and Kuffner, *ibid.*, 1931, **64**, 370, 1125), tazettin (Späth and Kahovec, *ibid.*, 1934, **67**, 1501), and lycorin (Kondo and Uyeo, *ibid.*, 1935, **68**, 1756). The methods of synthesis at present available are essentially due to Pictet. On the one hand he applied pyrogenetic methods to benzylideneaniline and its derivatives (Pictet and Ankersmit, *Ber.*, 1889, **22**, 3339; *Annalen*, 1891, **266**, 138; Pictet and Erlich, *ibid.*, p. 157; also Etard, *Compt. rend.*, 1882, **95**, 730), and to methylcarbazole (*Ber.*, 1905, **38**, 1950). The unreliability of this in any case unattractive method was shown by Graebe (*Annalen*, 1904, **335**, 122), who found that Pictet's products from benzylidene-α- and -β-naphthylamines were in reality acridine derivatives. A more reliable procedure involves the internal condensation of 2-aminodiphenyl-2′-carboxylic acid (Pictet and Ankersmit, *loc. cit.*; Graebe and Wander, *Annalen*, 1893, **276**, 250; Graebe, *loc. cit.*) or 2-acylaminodiphenyls (Pictet and Hubert, *Ber.*, 1896, **29**, 1183). Although the last method has been recently improved, and applied to a number of cases by Morgan and Walls (J., 1931, 2447; 1932, 2225; 1934, 104), and its range has been enhanced by the development in recent years of the range of available diphenyl derivatives, the ideally flexible synthesis is still one in which the ring system is built up from separate benzene nuclei or their equivalents. Kondo and Uyeo (*loc. cit.*; *Ber.*, 1937, **70**, 1087, 1094) have achieved this by heating a mixture of an *o*-bromobenzaldehyde and an *o*-bromoaniline with copper powder at 200°. We have now been able to extend the synthesis of 4-alkyl- and 4-aryl-quinolines from aromatic amines and β-chloroethyl ketones (Kenner and Statham, *Ber.*, 1936, **69**, 16):

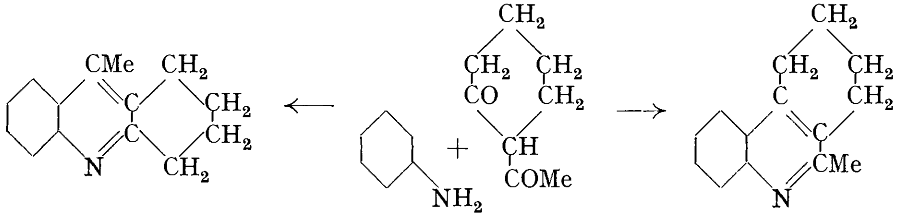


It seemed likely that a β-hydroxyethyl ketone might also be suitable for the purpose as well as being more accessible. Hence 2-hydroxymethyl*cyclo*hexan-1-one (Mannich and Brose, *Ber.*, 1923, **56**, 841) was treated with aniline and aniline hydrochloride in presence of stannic chloride under the conditions previously applied to the chloro-ketones:



5 : 6 : 7-8-*Tetrahydrophenanthridine* (I) was readily isolated from the products, and its identity established by its dehydrogenation with selenium or zinc dust to phenanthridine itself, identical with a specimen prepared by Pictet's process from benzylideneaniline. Further, since Borsche had shown that in certain instances tetrahydroacridines, as well as tetrahydrophenanthridines, may result from the condensation of aromatic amines with 2-acyl*cyclo*hexanones (*Ber.*, 1908, **41**, 2203; *Annalen*, 1910, **377**, 106), the difference

of the new base from tetrahydroacridine was established by direct comparison of the two :



Systematic study showed the new reaction to be applicable with varying yields to alkyl-, halogenated, and alkoxy-derivatives of aniline, although halogen and alkoxy-substituents did not survive the dehydrogenation process. α-Naphthylamine also furnished a phenanthridine, corresponding in its properties with the compound described by Graebe (*loc. cit.*). From β-naphthylamine, however, two isomeric tetrahydro-bases and two dehydrogenated derivatives were obtained. A detailed account of this work is deferred until it can more suitably be presented in relation to the results of the condensation of ethyl β-aminocrotonate with the methylol derivative.

Although the use of stannic chloride determined the practical success of the synthesis of 4-alkylquinolines, and it was consequently employed in the above instances, further experiments by Dr. R. L. Wain have shown it to be unnecessary. As a further simplification the methylol can be used with equal success in the form of the solution resulting from the interaction of aqueous formaldehyde solution and *cyclo*hexanone. As the latter can be carried out on a large scale, there is an economy of time and labour which to some extent compensates the moderate yields.

EXPERIMENTAL.

2-Hydroxymethyl*cyclo*hexan-1-one was prepared essentially according to the directions of Mannich and Brose (*loc. cit.*) by addition of lime (6·4 g.) during 30 minutes to a well-stirred mixture of *cyclo*hexanone (1720 c.c.), 40% formaldehyde solution (1065 c.c.), and water (160 c.c.). When the initial temperature was 19°, the rate of reaction soon accelerated and in order to prevent a temperature of 38° from being exceeded it was necessary to apply vigorous cooling, first by water and then by ice, when the mixture was at 28—30°. As soon as the temperature had begun to fall after reaching its maximum, the cooling medium was withdrawn, and subsequent procedure followed that of the above authors. 2-Hydroxymethyl-4-methyl*cyclo*hexanone resulted similarly from a mixture of 4-methyl*cyclo*hexanone (56 g.), 40% formaldehyde solution (70 g.), alcohol, and 0·8% sodium hydroxide solution (100 c.c.). After about 45 minutes the rise in temperature of the light brown mixture was restrained by water-cooling, and the mixture subsequently stirred at the ordinary temperature for 5 hours. The methylol (9 g.), b. p. 138—145°/40 mm., isolated as in the previous case, furnished a p-*nitrophenylhydrazone*, orange-yellow needles, m. p. 144—145° (Found : N, 14·8. $C_{14}H_{19}O_3N_3$ requires N, 15·2%). Attempts to prepare similar derivatives of 2-methyl*cyclo*hexanone and *cyclo*pentanone were unsuccessful.

Condensation of Formaldehyde with α-Tetralone.—A mixture of α-tetralone (58·4 g.), 40% formaldehyde solution (30 g.), alcohol (130 c.c.), and water (70 c.c.) was treated with 40% sodium hydroxide solution (0·5 c.c.). After ½ hour, when the temperature had risen 10°, the purple-red mixture was cooled and left for 2¼ hours. The product, separated as before, yielded 25 g., b. p. up to 90° and chiefly 84—86°/0·2—0·3 mm., and 15·5 g., b. p. 100—127°/0·2—0·4 mm. The latter fraction gradually solidified and yielded plates, m. p. 106—107°, after recrystallisation from alcohol. The compound decolorised bromine and its analysis indicated that it was 2-*methylene-α-tetralone* (Found : C, 83·2; H, 6·5. $C_{11}H_{10}O$ requires C, 83·5; H, 6·3%).

5 : 6 : 7 : 8-*Tetrahydrophenanthridine.*—(a) A mixture of 2-hydroxymethyl*cyclo*hexanone (12·8 g.), aniline (18·6 g.), aniline hydrochloride (18·6 g.), stannic chloride hydrate (40·6 g.), and alcohol (20 c.c.) was heated at 100° for 7 hours. On fractional distillation of the basic products, the portion, b. p. 100—230°/20 mm., yielded a yellow *picrate* (7·8 g.), m. p. 210—212° after crystallisation from alcohol (Found : C, 55·3; H, 4·2; N, 13·7. $C_{13}H_{13}N,C_6H_3O_7N_3$ requires C, 55·3; H, 3·9; N, 13·6%). The free *base*, liberated from the picrate, separated from light petroleum (b. p. 40—60°) in plates, m. p. 64° (Found : C, 85·0; H, 7·1; N, 7·7. $C_{13}H_{13}N$ requires C, 85·2; H, 7·1; N, 7·6%). In contrast with phenanthridine, it showed no fluorescence

in concentrated sulphuric acid solution. A mixture of the base with authentic tetrahydroacridine (m. p. 54°; Borsche, *loc. cit.*) was liquid at the ordinary temperature. Alternatively the base was isolated by treating the basic fraction, b. p. 90—340°/17 mm., with an equal volume of acetic anhydride at 100° for 1 hour. From the product an *acetyl* derivative was separated, m. p. 228·5—230°, and after successive crystallisation from dilute alcohol, methyl alcohol (twice), and water was obtained as needles (Found : N, 10·1%). This was not further investigated.

(b) The same yield of picrate was obtained from a repetition of the above experiment in which stannic chloride was omitted and the amount of aniline was halved.

(c) Comparative experiments having shown that the crude reaction mixture from the condensation of formaldehyde with *cyclo*hexanone could be used under the conditions just indicated on the basis of a 70% conversion into hydroxymethyl derivative, the reaction mixture from 100 g. of *cyclo*hexanone was, immediately after neutralisation with acetic acid, treated with aniline (65 g.), aniline hydrochloride (91 g.), and alcohol (50 c.c.) as in (a). The basic fraction (98 g.), b. p. 100—250°/33 mm., yielded 57 g. of nearly pure picrate.

Phenanthridine resulted when the tetrahydro-derivative (1·8 g.) was heated at 270—280° for ½ hour with selenium powder (1·5 g.), and then for a further 12 hours at 320°. The basic product, separated by direct distillation, was purified through its picrate (1·6 g.), m. p. 247—248° after crystallisation from alcohol (Found : C, 55·6; H, 3·0; N, 13·7. Calc. for $C_{13}H_9N,C_6H_3O_7N_3$: C, 55·9; H, 2·9; N, 13·7%). The free base separated from ligroin in plates, m. p. 107° (Found : C, 86·9; H, 5·2; N, 7·9%), and did not depress the m. p. of a sample prepared from benzylideneaniline. Its *platinichloride* shrank at 217° and melted at 219—221° (decomp.) [Found : Pt, 24·7. $(C_{13}H_9N)_2,H_2PtCl_6$ requires Pt, 25·3%].

In the preparation of the following compounds the above procedure (a) was followed, the acetylation method being employed for the preliminary purification of the tetrahydrophenanthridine. Doubtless the yields indicated would also be attained without the use of stannic chloride.

3-*Methyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine picrate*, from *p*-toluidine (27% yield), had m. p. 231—232° (decomp.) (Found : N, 13·0. $C_{14}H_{15}N,C_6H_3O_7N_3$ requires N, 13·1%). The free *base* crystallised from ligroin in plates, m. p. 73·5° (Found : C, 85·1; H, 7·8; N, 7·2. $C_{14}H_{15}N$ requires C, 85·3; H, 7·6; N, 7·1%). 3-Methylphenanthridine separated from ligroin in pale yellow needles, m. p. 89° (Found : C, 86·7; H, 5·9; N, 7·6. Calc. for $C_{14}H_{11}N$: C, 87·0; H, 5·7; N, 7·3%), and yielded a yellow picrate, m. p. 266° (decomp.) (Found : N, 13·2. Calc. for $C_{14}H_{11}N,C_6H_3O_7N_3$ requires N, 13·3%). Pictet and his collaborators (*loc. cit.*) give 131° and 202° as m. p.'s of the base and its picrate respectively. In a repetition of their experiment a picrate was obtained which melted at 245—250° (decomp.) after several recrystallisations, and its mixture with the picrate, m. p. 266°, melted at 255—260°. 1-*Methyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine picrate*, from *o*-toluidine (21% yield), had m. p. 203—204° (decomp.) (Found : N, 13·2. $C_{14}H_{15}N,C_6H_3O_7N_3$ requires N, 13·1%); the free *base* formed plates, m. p. 80·5° (Found : C, 85·2; H, 7·7; N, 7·0. $C_{14}H_{15}N$ requires C, 85·3; H, 7·6; N, 7·1%). 1-Methylphenanthridine had m. p. 95·5° (Found : C, 87·0; H, 5·8; N, 7·6. Calc. for $C_{14}H_{11}N$: C, 87·0; H, 5·7; N, 7·3%), and its picrate, m. p. 234° (decomp.) (Found : N, 13·4. Calc. for $C_{14}H_{11}N,C_6H_3O_7N_3$: N, 13·3%). Pictet and his collaborators (*loc. cit.*) give 70° and 220° as m. p.'s of the base and its picrate respectively.

1 : 3-*Dimethyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine picrate*, from *m*-xylidine (23% yield), had m. p. 212·5° (decomp.) (Found : N, 12·8. $C_{15}H_{17}N,C_6H_3O_7N_3$ requires N, 12·7%). The free *base* had m. p. 49·5—50·5° (Found : C, 85·2; H, 8·0. $C_{15}H_{17}N$ requires C, 85·3; H, 8·1%).

1 : 3-*Dimethylphenanthridine*, m. p. 84·5° (Found : C, 86·8; H, 6·3; N, 6·8. $C_{15}H_{13}N$ requires C, 87·0; H, 6·3; N, 6·8%), furnished a *picrate*, m. p. 261° (decomp.) (Found : N, 12·9. $C_{15}H_{13}N,C_6H_3O_7N_3$ requires N, 12·8%). It exhibited a weaker blue fluorescence than phenanthridine in concentrated sulphuric acid.

1 : 4-*Dimethyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine*, from *p*-xylidine (b. p. 221—223° after purification by crystallisation of its hydrochloride, m. p. 211°, from dilute hydrochloric acid; acetyl derivative, m. p. 144—145°; benzoyl derivative, m. p. 153°), was obtained in the crude state, b. p. 90—250° (mainly 210—215°)/25 mm. (15% yield), and finally purified by repeated crystallisation from light petroleum (b. p. below 40°); it formed long needles, m. p. 63—63·5° (yield, 6·5%) (Found : C, 84·9; H, 8·1; N, 6·9. $C_{15}H_{17}N$ requires C, 85·3; H, 8·1; N, 6·6%); the *picrate* had m. p. 180—181° (decomp.) (Found : N, 12·9. $C_{15}H_{17}N,C_6H_3O_7N_3$ requires N, 12·7%).

1 : 4-*Dimethylphenanthridine* formed pale yellow clusters of needles, m. p. 76·5°, which showed

no fluorescence in concentrated sulphuric acid solution (Found: C, 86·8; H, 6·4; N, 6·9. $C_{15}H_{13}N$ requires C, 87·0; H, 6·3; N, 6·8%); the *picrate* had m. p. 222° (Found: N, 12·8. $C_{15}H_{13}N,C_6H_3O_7N_3$ requires N, 12·8%).

3-*Bromo*-5 : 6 : 7 : 8-*tetrahydrophenanthridine picrate*, from *p*-bromoaniline (23·5% yield), had m. p. 221—222° (decomp.) (Found: N, 11·6. $C_{13}H_{12}NBr,C_6H_3O_7N_3$ requires N, 11·4%). The free *base* had m. p. 110° (Found: C, 59·5; H, 4·8; N, 5·6. $C_{13}H_{12}NBr$ requires C, 59·5; H, 4·6; N, 5·4%).

3-*Chloro*-5 : 6 : 7 : 8-*tetrahydrophenanthridine picrate*, from *p*-chloroaniline (26% yield), had m. p. 214° (decomp.) (Found: N, 12·6. $C_{13}H_{12}NCl,C_6H_3O_7N_3$ requires N, 12·5%). The free *base* had m. p. 90° (Found: C, 71·6; H, 5·6; N, 6·6. $C_{13}H_{12}NCl$ requires C, 71·7; H, 5·5; N, 6·4%).

1-*Nitro*-5 : 6 : 7 : 8-*tetrahydrophenanthridine picrate*, obtained from *o*-nitroaniline in very poor yield, had m. p. 216—217° (decomp.) (Found: N, 14·9. $C_{13}H_{12}N_2O_2,C_6H_3O_7N_3$ requires N, 15·3%), and yielded an oily base.

3-*Methoxy*-5 : 6 : 7 : 8-*tetrahydrophenanthridine picrate*, from *p*-anisidine (34% yield), had m. p. 241—242° (decomp.) (Found: N, 12·8. $C_{14}H_{15}ON,C_6H_3O_7N_3$ requires N, 12·7%). The free *base* had m. p. 110—111° (Found: C, 78·7; H, 7·1; N, 6·8. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·0; N, 6·6%).

1 : 4-Dimethoxy-5 : 6 : 7 : 8-tetrahydrophenanthridine picrate, from 2 : 5-dimethoxyaniline, had m. p. 194—195° (decomp.) (yield, 5·3%). The free *base* had m. p. 86·5—87° (Found: C, 73·9; H, 7·1; N, 6·1. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%).

7-*Methyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine picrate*, from 2-hydroxymethyl-4-methyl*cyclo*hexanone and aniline, had m. p. 195—196° (decomp.) (yield, 21%) (Found: N, 13·4. $C_{14}H_{15}N,C_6H_3O_7N_3$ requires N, 13·1%). The free *base* had m. p. 45° (Found: C, 84·9; H, 7·7; N, 7·3. $C_{14}H_{15}N$ requires C, 85·3; H, 7·6; N, 7·1%). 7-*Methylphenanthridine*, m. p. 88° (Found: C, 86·9; H, 5·8; N, 7·4. $C_{14}H_{11}N$ requires C, 87·0; H, 5·7; N, 7·2%), formed a *picrate*, m. p. 236—237° (decomp.) (Found: N, 13·3. $C_{14}H_{11}N,C_6H_3O_7N_3$ requires N, 13·3%).

Tetrahydro-α-naphthaphenanthridine picrate, from α-naphthylamine, had m. p. 215—216° (decomp.) (yield, 15%) (Found: N, 12·1. $C_{17}H_{15}N,C_6H_3O_7N_3$ requires N, 12·1%). The free *base* had m. p. 118° (Found: C, 87·2; H, 6·6; N, 6·2. $C_{17}H_{15}N$ requires C, 87·5; H, 6·4; N, 6·0%). α-Naphthaphenanthridine, m. p. 135° (Found: C, 88·8; H, 4·9; N, 6·1. Calc. for $C_{17}H_{11}N$: C, 89·1; H, 4·8; N, 6·1%), formed a picrate, m. p. 255° (decomp.) (Found: N, 12·1. Calc. for $C_{17}H_{11}N,C_6H_3O_7N_3$: N, 12·2%). Graebe (*loc. cit.*) records m.p.'s 135·5° and 256° for the base and its picrate respectively.

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