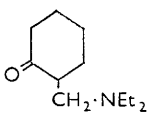
50. *Some Derivatives of 5,6,7,8-Tetrahydrophenanthridine.*

By B. L. Hollingsworth and V. Petrow.

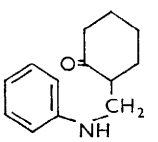
The syntheses of 5,6,7,8-tetrahydrophenanthridines described in an earlier publication [1] are herein extended to some new derivatives.

A new synthesis of 5,6,7,8-tetrahydrophenanthridine (III) involving reaction of diethylaminomethylcyclohexanone hydrochloride (as I) with an arylamine, its hydrochloride, and stannic chloride hydrate was reported in an earlier publication,[1] which also described the conversion of the tetrahydrophenanthridine (III) and its 1-methyl and 1,3-dimethyl derivatives into the 9-aminotetrahydrophenanthridines by amination with sodamide. Biological study of the 9-amino-derivatives revealed pronounced analeptic activity,[2] which led us to extend the chemistry of the series.

Employment of ethyl *p*-aminobenzoate in the above synthesis led to ethyl 5,6,7,8-tetrahydrophenanthridine-3-carboxylate, converted *via* the carboxamide into 3-amino-5,6,7,8-tetrahydrophenanthridine. The corresponding dimethylamino-derivative was prepared from *p*-dimethylaminoaniline and was smoothly converted into 9-amino-3-dimethylamino-5,6,7,8-tetrahydrophenanthridine by reaction with sodamide. Attempts to aminate the 3-chloro- and the 3-methoxy-derivative of 5,6,7,8-tetrahydrophenanthridine led to intractable tars. 5,6,7,8-Tetrahydro-1,4-dimethylphenanthridine was recovered quantitatively unchanged after being heated with sodamide in diethylaniline at 170°, behaviour in marked contrast with the ease with which 5,6,7,8-tetrahydro-1,3-dimethylphenanthridine passes into its 9-amino-derivative.



(I)



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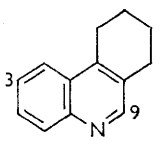

(III)

Nitration of 5,6,7,8-tetrahydrophenanthridine by a modification of the method of Dufton [3] led to the isolation of only one nitro-derivative. This differed from the known 5,6,7,8-tetrahydro-1-nitro-[4] and -3-nitrophenanthridine.[1] It is tentatively identified as 5,6,7,8-tetrahydro-4-nitrophenanthridine by analogy with Dufton's observation [3] that nitration of quinoline leads to the formation of 5- and 8-nitroquinoline.

We had previously postulated [1] that the foregoing synthesis of tetrahydrophenanthridines (III) proceeds through 2-anilinomethylcyclohexanone (II) as intermediate but had been unable at the time to prepare this material for study. We now find that reduction of 2-phenyliminomethylcyclohexanone with anhydrous formic acid, followed by treatment with picric acid leads to the separation of 2-anilinomethylcyclohexanone picrate in *ca.* 20% yield. The free base (II), as expected, passes smoothly into 5,6,7,8-tetrahydrophenanthridine on reaction with aniline hydrochloride and stannic chloride hydrate, an observation which establishes the feasibility of the proposed reaction scheme.

Experimental

M. p.s are corrected.

Ethyl 5,6,7,8-Tetrahydrophenanthrdine-3-carboxylate.—Cyclohexanone (100 g.), formaldehyde (18 g.), and diethylamine hydrochloride (22 g.) were heated under reflux until reaction occurred

[1] Hollingsworth and Petrow, *J.*, 1948, 1537.
[2] Thorp, Ph.D. Thesis, London, 1947.
[3] Dufton, *J.*, 1892, **61**, 782; cf. Morgan and Walls, *J.*, 1932, 2225.
[4] Kenner, Ritchie, and Statham, *J.*, 1937, 1169.

(6 min.). The crude product was treated with ethyl *p*-aminobenzoate (16·5 g.), ethyl *p*-aminobenzoate hydrochloride (20·2 g.), and stannic chloride hydrate (40 g.), and the mixture was heated under reflux for 16 hr. It was cooled and made faintly alkaline with sodium hydroxide solution, and the basic fraction was extracted with ether and treated in alcohol (100 ml.) with picric acid (20 g.) in alcohol (150 ml.), yielding *ethyl* 5,6,7,8-*tetrahydrophenanthridine*-3-*carboxylate picrate*, lemon-yellow needles, m. p. 212—213° (decomp.) (Found: N, 11·8. $C_{16}H_{17}O_2N,C_6H_3O_7N_3$ requires N, 11·6%). The base was liberated from the picrate and distilled. The fraction, b. p. about 200°/20 mm., solidified and yielded almost colourless needles [from light petroleum (b. p. 80—100°)] (30%) of the *ester*, m. p. 75° (Found: C, 75·2; H, 6·7; N, 5·4. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%).

5,6,7,8-*Tetrahydrophenanthridine*-3-*carboxylic acid*, needles, m. p. 312° (Found: C, 73·7; H, 5·5; N, 6·3. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·7; N, 6·2%), was obtained (95%) when the foregoing ester (11·9 g.) was hydrolysed with 10% alcoholic potassium hydroxide solution (100 ml.) under reflux for 18 hr. The solvent was evaporated under reduced pressure, the residue neutralised with sulphuric acid, and the precipitated white solid (10·1 g.) collected, dried, and recrystallised from alcohol–light petroleum (b. p. 80—100°) (charcoal).

5,6,7,8-Tetrahydrophenanthridine-3-carboxylic acid (3 g.) was converted into the acid chloride by phosphorus oxychloride (15 ml.) and phosphorus pentachloride (1 g.) under reflux in 1 hr. Phosphorus halides were removed under reduced pressure, and the warm residue was dissolved in dry benzene (75 ml.) and slowly added to ice-cold aqueous ammonia (225 ml.; *d* 0·880) with stirring. After being kept overnight at 20°, the benzene was removed under reduced pressure and the solid collected and purified from aqueous acetone. The *amide* formed cream needles, m. p. 250—252° (Found: C, 72·9; H, 6·3; N, 12·0. $C_{14}H_{14}ON_2,\frac{1}{4}H_2O$ requires C, 72·8; H, 6·2; N, 12·1%). Attempts to prepare the acid chloride by the use of thionyl chloride alone or in benzene or by use of phosphorus oxychloride led to tars.

3-*Amino*-5,6,7,8-*tetrahydrophenanthridine*.—The powdered amide (1 g.) was added to an ice-cold stirred solution of bromine (1 g.) in 10% potassium hydroxide solution (12 ml.). After 45 min. at 0°, additional 10% potassium hydroxide solution (8 ml.) was added, and the mixture heated on the water-bath for 30 min. After being kept overnight at 0°, the precipitated solid (0·45 g.) was collected and crystallised from aqueous alcohol (charcoal), giving 3-*amino*-5,6,7,8-*tetrahydrophenanthridine* as a cream-coloured powder, m. p. 168—170° (Found: N, 13·9. $C_{13}H_{14}N_2$ requires N, 14·1%), identical in m. p. and mixed m. p. with material obtained by the reduction of 5,6,7,8-tetrahydro-3-nitrophenanthridine.[1]

3-*Benzamido*-5,6,7,8-*tetrahydrophenanthridine*, m. p. 224—225° (Found: C, 79·4; H, 5·8; N, 9·0. $C_{20}H_{18}ON_2$ requires C, 79·5; H, 6·0; N, 9·2%) after crystallisation from aqueous alcohol or alcohol–light petroleum (b. p. 80—100°), was obtained by treatment of the amine with benzoyl chloride in pyridine.

3-*Dimethylamino*-5,6,7,8-*tetrahydrophenanthridine*, m. p. 95—96°, bright yellow needles [from light petroleum (b. p. 60—80°)], m. p. 95—96° (Found: C, 79·4; 8·2; N, 12·1. $C_{15}H_{18}N_2$ requires C, 79·6; H, 8·0; N, 12·4%), was prepared (25%) from *NN*-dimethyl-*p*-phenylenediamine. The *picrate* separated from alcohol (charcoal) in orange-yellow needles, m. p. 250—251° (decomp.) (Found: N, 15·7. $C_{15}H_{18}N_2,C_6H_3O_7N_3$ requires N, 15·4%). The base exhibited a weak blue fluorescence in alcohol.

3-*Diethylamino*-5,6,7,8-*tetrahydrophenanthridine*, needles, m. p. 100—101° (Found: C, 75·8; H, 7·7; N, 10·1. $C_{18}H_{20}ON_2$ requires C, 76·6; H, 7·7; N, 10·0%) after crystallisation from light petroleum (b. p. 80—100°) (charcoal), was obtained (50%) from the acid chloride and diethylamine in benzene.

5,6,7,8-*Tetrahydro*-3-*hydroxyphenanthridine* was obtained when 3-methoxy-5,6,7,8-tetrahydrophenanthridine (3 g.) was suspended in constant-boiling hydrobromic acid (15 ml.) and gently refluxed for 2 hr. The precipitated hydrobromide was separated, suspended in potassium hydroxide solution (5 g. in 70 ml. of water), and heated to the b. p. The mixture was then filtered from a small quantity of resin. The potassium salt was decomposed by warming it with an excess of acetic acid, and the precipitated white solid (2·5 g.) collected and recrystallised from alcohol–light petroleum (b. p. 80—100°) (charcoal), giving needles, m. p. 288—289° (80%) (Found: C, 76·4; 76·8; 76·7; H, 6·5, 6·6; N, 7·1. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·5; N, 7·0%). Difficulty has previously been experienced in the analysis of hydroxy-derivatives of this type. The *picrate* separated from alcohol in yellow needles, m. p. 221—223° (decomp.) (Found: N, 13·4. $C_{13}H_{13}ON,C_6H_3O_7N_3$ requires N, 13·1%).

3-*Benzoyloxy*-5,6,7,8-*tetrahydrophenanthridine* separated in needles, m. p. 138—139° (Found: N, 4·7. $C_{20}H_{17}O_2N$ requires N, 4·6%), from aqueous alcohol or from alcohol–light petroleum (b. p. 80—100°).

9-*Amino*-3-*dimethylamino*-5,6,7,8-*tetrahydrophenanthridine*.—3-Dimethylamino-5,6,7,8-tetrahydrophenanthridine (4 g.), diethylaniline (15 ml.), and sodamide (4 g.) were heated in a wax-bath at 160°. Vigorous evolution of gas took place, and in 30 min. the mixture set to a black solid. The mixture was heated for a further 3½ hr. at 160°, and the solid, when cold, decomposed with water (25 ml.). The precipitated black solid (2 g.) was collected and dissolved in hot 32% acetic acid (charcoal), and the solution was made faintly alkaline with potassium hydroxide solution and boiled for 5 min. After cooling, a brownish-yellow solid was collected and crystallised from alcohol–light petroleum (b. p. 80—100°). 9-*Amino*-3-*dimethylamino*-5,6,7,8-*tetrahydrophenanthridine* formed long flat yellow needles, m. p. 185—187° (Found: C, 74·5; H, 7·8; N, 17·6. $C_{15}H_{19}N_3$ requires C, 74·7; H, 7·9; N, 17·4%).

The *acetate*, m. p. 222—223° (Found: N, 14·0. $C_{15}H_{19}N_3,C_2H_4O_2$ requires N, 13·9%), formed straw-coloured needles from alcohol–light petroleum (b. p. 80—100°), and was obtained (~100%) by dissolving the base in an excess of hot 33% acetic acid and just neutralising the solution with ammonia.

5,6,7,8-*Tetrahydro*-2(or 4)-*methylphenanthridine*, a light yellow oil purified by vacuum-distillation (b. p. 210°/20 mm.), was prepared from *m*-toluidine. In 3 months over phosphoric oxide it partially solidified and then formed plates, m. p. 57° (Found: C, 85·1; H, 7·4; N, 7·5. $C_{14}H_{15}N$ requires C, 85·3; H, 7·6; N, 7·1%) from light petroleum (b. p. 40—60°) (charcoal). The *picrate* formed yellow needles (from alcohol), m. p. 231—232° (decomp.) (Found: N, 13·2. $C_{14}H_{15}N,C_6H_3O_7N_3$ requires N, 13·1%). The liquid basic residue, purified by vacuum-distillation (b. p. 215°/20 mm.), formed an almost colourless oil (Found: C, 85·4; H, 7·6; N, 7·2%). This compound is provisionally identified as 5,6,7,8-*tetrahydro*-2-*methylphenanthridine*. Its *picrate* formed long yellow needles (from alcohol), m. p. 230—231° (decomp.) (Found: N, 13·1%). In admixture with 5,6,7,8-tetrahydro-4-methylphenanthridine picrate, the m. p. was 223—226° (decomp.).

3-Chloro-5,6,7,8-tetrahydrophenanthridine, white needles from light petroleum (b. p. 40—60°), m. p. 90°, was prepared from *p*-chloroaniline. 3-*Chloro*-5,6,7,8-*tetrahydrophenanthridine* 10-*oxide* was formed when this base (2 g.), in glacial acetic acid (8 ml.), was heated with 30% hydrogen peroxide (4 ml.) on the water-bath for 3 hr. The mixture was poured into water and neutralised with ammonia, and the precipitated solid (1·7 g.) recrystallised from alcohol–light petroleum (b. p. 80—100°), giving light yellow plates, m. p. 169—170° (Found: C, 66·4; H, 5·2; N, 5·9. $C_{13}H_{12}ONCl$ requires C, 66·8; H, 5·1; N, 6·0%).

3-*Chloro*-5,6,7,8-*tetrahydrophenanthridine nitrate*, m. p. 152—153° (decomp.) (Found: C, 55·8; H, 4·9; N, 9·8. $C_{13}H_{12}NCl,HNO_3$ requires C, 55·6; H, 4·6; N, 10·0%), was obtained (90%) when the base was dissolved in excess of hot 3N-nitric acid. Yellow crystals were deposited on cooling, which recrystallised from alcohol (charcoal) as needles.

5,6,7,8-*Tetrahydrophenanthridine nitrate*, needles (from alcohol) (charcoal), m. p. 156—157° (decomp.) (Found: C, 63·0; H, 5·8; N, 11·4. $C_{13}H_{13}N,HNO_3$ requires C, 63·4; H, 5·7; N, 11·4%), was prepared (85%) similarly.

Nitration of Tetrahydrophenanthridine.—5,6,7,8-Tetrahydrophenanthridine nitrate (3·3 g.) was added in portions to a stirred mixture of concentrated sulphuric acid (6 ml.) and 30% oleum (4 ml.) at 0°. After 30 min. at 0° the mixture was heated on the water-bath for 1 hr., then cooled, poured into water (100 ml.), and neutralised with potassium hydroxide solution. The precipitated solid (1·6 g.) was collected and purified from light petroleum (b. p. 60—80°). 5,6,7,8-*Tetrahydro*-4-*nitrophenanthridine* formed needles, m. p. 119—120° (Found: C, 68·4; H, 5·1; N, 12·2. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%). No second compound was isolated.

The foregoing nitro-compound (1·5 g.) was suspended in alcohol (80 ml.) and water (20 ml.) containing a little hydrochloric acid. Reduced iron (6 g.) was added in portions to the boiling mixture, and the whole was heated under reflux for a further 2 hr., then filtered and evaporated to dryness in a vacuum. The residue was treated in pyridine (15 ml.) with benzoyl chloride (1 ml.). Next morning the mixture was diluted with water and neutralised with ammonia, a yellowish-brown solid (0·65 g.) being precipitated. This crystallised from aqueous spirit, yielding 4-*benzamido*-5,6,7,8-*tetrahydrophenanthridine*, cubes, m. p. 149—150° (Found: C, 79·9; H, 6·0; N, 9·0. $C_{20}H_{18}ON_2$ requires C, 79·5; H, 6·0; N, 9·2%).

2-*Anilinomethylcyclohexanone*.—2-Phenyliminomethylcyclohexanone (50 g.) in anhydrous formic acid (400 ml.) was heated under reflux for 20 hr. Formic acid (300 ml.) was removed in a vacuum, and the residue was poured into excess of aqueous ammonia. The precipitated base was treated in alcohol with picric acid (50 g.) in spirit (400 ml.), giving 2-*anilinomethylcyclohexanone picrate* (20%), yellow needles, m. p. 228—229° (decomp.) (Found: N, 12·8. $C_{13}H_{17}ON,C_6H_3O_7N_3$ requires N, 12·9%). The *base* formed light yellow spangles, m. p. 88—89° (Found: C, 77·3; H, 8·3; N, 6·9. $C_{13}H_{17}ON$ requires C, 77·1; H, 8·4; N, 6·9%) after crystallisation from light petroleum (b. p. 60—80°). 2-Anilinomethylcyclohexanone (5 g.), aniline hydrochloride (4 g.), and stannic chloride hydrate (5 g.) in alcohol (100 ml.) were heated under reflux for 8 hr., giving 5,6,7,8-tetrahydrophenanthridine (70%), m. p. and mixed m. p. 63°.

Queen Mary College (University of London), E.1.
(Present addresses:
B. L. H.: Ministry of Supply, Waltham Abbey, Essex.
V. P.: The British Drug Houses, London, E.1.)

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