309. *New Syntheses of Heterocyclic Compounds. Part IX. Tetrahydrophenanthridines.*

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Work on the relationship between structure and analeptic activity (Petrow, *J.*, 1946, 200, 884, 888) has been extended by the preparation of some 9-*amino*- and 9-*aminotetrahydrophenanthridines* by direct amination of the corresponding bases.

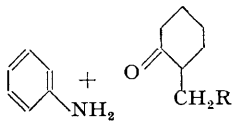
Tetrahydrophenanthridines have been synthesised by (*a*) reaction between 1-diethylaminomethyl*cyclo*hexan-2-one hydrochloride, aniline hydrochloride, and stannic chloride hydrate in boiling *cyclo*hexanone, (*b*) condensation of chloromethyl*cyclo*hexanone, aniline, and aniline hydrochloride in boiling alcohol, (*c*) reduction and ring closure of certain aryliminomethyl-*cyclo*hexanones by heating them with anhydrous formic acid.

A study of the biological properties of the diazaphenanthrenes described in Parts V, VII, and VIII (Petrow, *J.*, 1946, 200, 884, 888) has revealed that certain of these compounds are specific stimulants of the central nervous system, possessing outstanding analeptic properties of the type shown by picrotoxin; but whereas the dose of picrotoxin required to counteract increasing degrees of barbiturate anæsthesia follows a logarithmic pattern, a linear relationship holds with the diazaphenanthrenes (Thorp, forthcoming publication).

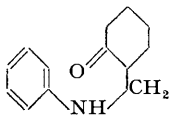
Common features among active compounds of this series appear to be (*a*) a structure analogous to 9-aminophenanthrene, (*b*) a ring nitrogen in position 10, and (*c*) two methyl groups, preferably at positions 1 and 3. Combination of all three factors leads to 9-amino-1 : 3-dimethylphenanthridine, the synthesis of which formed the immediate object of this investigation.

Although this compound was readily formed by the direct amination of 1 : 3-dimethylphenanthridine, the preparation of the latter by the published methods was not entirely satisfactory. This difficulty was overcome by developing a new synthesis of the tetrahydrophenanthridine, from which the required base was readily prepared by selenium dehydrogenation.

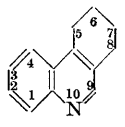
Kenner, Ritchie, and Statham (*J.*, **1937**, 1169) have described the preparation of tetrahydrophenanthridine (III) in moderate yield by condensation of hydroxymethyl-*cyclo*hexanone (I; R = OH) with aniline and aniline hydrochloride in boiling alcoholic solution. β-Hydroxy-ketones do not usually react directly with arylamines, and (I; R = OH) gave no evidence of reaction with aniline on prolonged standing at room temperature. At the same time, 1 : 3-ketols are readily dehydrated in the presence of acids to give αβ-unsaturated ketones (cf. diacetone alcohol ⟶ mesityl oxide) which, by virtue of their structure, react with aniline to give β-anilino-ketones. These facts lead to the conclusion that dehydration of hydroxymethyl-*cyclo*hexanone (I; R = OH) to methylene*cyclo*hexanone takes place in the Kenner synthesis (above), followed by addition of aniline to give (II) and ring closure to (III).



(I.)

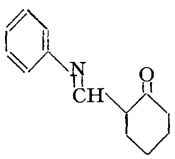


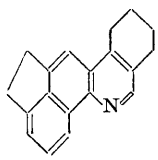
(II.)



(III.)

(IV.)





(V.)

2-Methylene*cyclo*hexanone, recently prepared by Mannich (*Ber.*, **1941**, **74**, 554) by high-vacuum distillation of the Mannich base (I; R = NMe_2), is characterised by rapid dimerisation to a *spiro*-compound (*ibid.*, p. 565). Preliminary experiments soon confirmed the highly unstable character of " monomeric methylene*cyclo*hexanone ", and its use in a tetrahydrophenanthridine synthesis was abandoned. An alternative route to compounds of type (II) appeared to lie in the *in situ* preparation of methylene*cyclo*hexanone in the presence of the aromatic base. The practical character of such an approach was first demonstrated by du Feu, McQuillin, and Robinson (*J.*, **1937**, 53), who condensed the methiodide of the Mannich base from 2-methyl*cyclo*hexanone with ethyl acetoacetate and sodium methoxide, obtaining the corresponding methyloctalone. Mannich, Koch, and Borkowsky (*Ber.*, **1937**, **70**, 355) have carried out a similar condensation using the Mannich base in place of its methiodide.

We now find that diethylaminomethyl*cyclo*hexanone hydrochloride (Mannich and Honig, *Arch. Pharm.*, **1927**, **265**, 598) (I; R = NEt_2,HCl) condenses readily with a mixture of aniline hydrochloride, aniline, and stannic chloride hydrate in boiling *cyclo*hexanone to give tetrahydrophenanthridine (III) in 45% yield. There seems little doubt that this reaction proceeds through the intermediate formation of methylene*cyclo*hexanone ⟶ (II) ⟶ (III). Its value lies in the simplicity of the experimental technique. The intermediate (I; R = NEt_2,HCl) does not require isolation, and the complete reaction can be carried out in one vessel by consecutive addition of the appropriate reagents. Other primary aromatic amines (see experimental section) can be equally well employed in place of aniline in this new synthesis, although the reaction fails with 1-naphthylamine, *m*-aminoacetophenone, and 5-aminoacenaphthene.

Since the initial work of Kenner, Ritchie, and Statham (*loc. cit.*), Décombe (*Comp. rend.*, **1941**, **213**, 579) has described the conversion of hydroxymethyl*cyclo*hexanone (I; R = OH) into the corresponding chloro-ketone (I; R = Cl). Kenner and Statham (*Ber.*, **1936**, **69**, 16) have previously shown that quinolines can be prepared from 2-chloroethyl ketones and primary arylamines. We now find that (I; R = Cl) readily condenses with aniline and aniline hydrochloride in boiling alcoholic solution to give (III), although in only 35% yield. This reaction undoubtedly takes place through the intermediate formation of (II), a fact we have made use of in yet a third route to the tetrahydrophenanthridine system. Compounds such as phenyliminomethyl*cyclo*hexanone (IV) have *trans*-configurations, and thus resist all attempts at ring closure to (III) (see Petrow, *J.*, **1942**, 694). Selective reduction of the azomethine linkage of (IV) would clearly give the anilino-ketone (II), readily convertible into (III). We now find that anhydrous formic acid—a reagent enjoying wide use in the reduction of azomethines—will not

only reduce the anil linkage of such compounds as 5-*acenaphthenyliminomethyl*cyclo*hexanone*, but will achieve ring closure in the same operation to give the tetrahydrophenanthridine (III). The reaction fails with substituted anilines and 2-aminopyridine, but succeeds with the naphthylamines and 5-aminoacenaphthene (giving V).

9-Aminophenanthridine, 9-*aminotetrahydrophenanthridine*, and their 1-*methyl*, 3-*methyl*, and 1 : 3-*dimethyl* derivatives were prepared by reaction of the corresponding bases with sodamide in diethylaniline at 170°. Their biological examination is being reported elsewhere (Thorp, *loc. cit.*).

Experimental.

M. p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s in parentheses are those given by Kenner, Ritchie and Statham (*loc. cit.*).

5 : 6 : 7 : 8-*Tetrahydrophenanthridine*.—(*a*) *cyclo*Hexanone (50 g.), formalin (9 g.), and diethylamine hydrochloride (11 g.) were heated under reflux until reaction occurred (5 minutes). Heating was then discontinued until the initial exothermic condensation was complete. The crude mixture containing the Mannich base hydrochloride in excess of *cyclo*hexanone was treated with aniline (9·3 g.), aniline hydrochloride (12·8 g.), and stannic chloride hydrate (13 g.), and heated under reflux for a further 16 hours. The mixture was made alkaline with sodium hydroxide solution and the basic fraction isolated with ether. The fraction, b. p. 110—230°/20 mm., on treatment with picric acid (15 g.) in spirit (150 ml.), gave 5 : 6 : 7 : 8-tetrahydrophenanthridine picrate, yellow needles from spirit (charcoal), m. p. 212—213° (decomp.) (212—214°, decomp.) (Found : N, 13·4. Calc. for $C_{13}H_{13}N,C_6H_3O_7N_3$: N, 13·6%). The base, liberated from the picrate by treatment with excess of aqueous ammonia, formed colourless plates from light petroleum (b. p. 40—60°), m. p. 63° (64°) (Found : C, 85·1 ; H, 7·0 ; N, 7·4. Calc. for $C_{13}H_{13}N$: C, 85·3 ; H, 7·1 ; N, 7·6%), not depressing the melting point of an authentic specimen prepared by the method of Kenner *et al.* (*loc. cit.*). (*b*) Omission of stannic chloride hydrate in (*a*) reduced the yield to 15%. (*c*) Omission of aniline hydrochloride gave yields of less than 5%.

1-Methyl-5 : 6 : 7 : 8-tetrahydrophenanthridine, white plates from alcohol–light petroleum, m. p. 80—81° (80·5°) (Found : C, 85·5 ; H, 7·6 ; N, 7·0. Calc. for $C_{14}H_{15}N$: C, 85·3 ; H, 7·6 ; N, 7·1%), was prepared from *o*-toluidine. The picrate formed yellow needles from spirit (charcoal), m. p. 201—202° (decomp.) (203—204°) (Found : N, 13·1. Calc. for $C_{14}H_{15}N,C_6H_3O_7N_3$: N, 13·1%). Yield 40%.

2 (*or* 4)-*Methyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine*, a light yellow oil purified by vacuum distillation (b. p. 210°/20 mm.) (Found : C, 84·6 ; H, 8·2 ; N, 6·9. $C_{14}H_{15}N$ requires C, 85·3 ; H, 7·6 ; N, 7·1%), was prepared from *m*-toluidine. The *picrate* formed long yellow needles from spirit (charcoal), m. p. 226° (decomp.) (Found : N, 13·1. $C_{14}H_{15}N,C_6H_3O_7N_3$ requires N, 13·1%). Yield 15%.

3-Methyl-5 : 6 : 7 : 8-tetrahydrophenanthridine, small white plates from light petroleum (b. p. 60—80°), m. p. 72° (73·5°) (Found : C, 85·3 ; H, 7·7 ; N, 7·2. Calc. for $C_{14}H_{15}N$: C, 85·3 ; H, 7·6 ; N, 7·1%), was prepared from *p*-toluidine. The picrate formed very small yellow spangles from spirit (charcoal), m. p. 231° (decomp.) (231—232°, decomp.) (Found : N, 13·1. Calc. for $C_{14}H_{15}N,C_6H_3O_7N_3$: N, 13·1%). Yield 50%.

7-Methyl-5 : 6 : 7 : 8-tetrahydrophenanthridine, white plates from light petroleum (b. p. 40—60°), m. p. 45° (45°) (Found : C, 85·3 ; H, 7·3 ; N, 6·9. Calc. for $C_{14}H_{15}N$: C, 85·3 ; H, 7·6 ; N, 7·1%), was prepared from aniline and 5-methyl-1-(diethylaminomethyl)*cyclo*hexan-2-one hydrochloride, obtained from 4-methyl*cyclo*hexanone. The picrate formed gleaming yellow needles from spirit (charcoal), m. p. 196—197° (decomp.) (195°—196°, decomp.) (Found : N, 13·1. Calc. for $C_{14}H_{15}N,C_6H_3O_7N_3$: N, 13·1%). Yield 12%.

1 : 3-Dimethyl-5 : 6 : 7 : 8-tetrahydrophenanthridine, white plates from light petroleum (b. p. 40—60°), m. p. 50—51° (49·5—50·5°) (Found : C, 85·4 ; H, 7·9 ; N, 6·8. Calc. for $C_{15}H_{17}N$: C, 85·4 ; H, 8·1 ; N, 6·6%), was prepared from *m*-xylidine. The picrate formed light yellow needles from spirit (charcoal), m. p. 212—213° (decomp.) (212·5°, decomp.) (Found : N, 12·3. Calc. for $C_{15}H_{17}N,C_6H_3O_7N_3$: N, 12·7%). Yield 20%.

1 : 4-Dimethyl-5 : 6 : 7 : 8-tetrahydrophenanthridine, yellowish white needles from light petroleum (b. p. 40—60°), m. p. 63—64° (63—63·5°) (Found : C, 85·3 ; H, 8·1 ; N, 6·6. Calc. for $C_{15}H_{17}N$: C, 85·4 ; H, 8·1 ; N, 6·6%), was prepared from *p*-xylidine. The picrate formed yellow needle clusters from spirit (charcoal), m. p. 181—182° (decomp.) (180—181°) (Found : N, 12·5. Calc. for $C_{15}H_{17}N,C_6H_3O_7N_3$: N, 12·7%). Yield 20%.

1-*Methoxy*-5 : 6 : 7 : 8-*tetrahydrophenanthridine*, yellowish plates from light petroleum (b. p. 80—100°), m. p. 106° (Found : C, 78·5 ; H, 7·2 ; N, 6·6. $C_{14}H_{15}ON$ requires C, 78·7 ; H, 7·0 ; N, 6·6%), was prepared from *o*-anisidine. The *picrate* formed mustard-yellow prisms from spirit (charcoal), m. p. 214° (decomp.) (Found : N, 12·9 ; $C_{14}H_{15}ON,C_6H_3O_7N_3$ requires N, 12·7%). Yield 25%.

3-Methoxy-5 : 6 : 7 : 8-tetrahydrophenanthridine, white needles from light petroleum (b. p. 60—80°), m. p. 109—110·5° (110—111°) (Found : N, 6·4. Calc. for $C_{14}H_{15}ON$: N, 6·6%), was prepared from *p*-anisidine. The picrate formed yellow needles from spirit (charcoal), m. p. 240—241° (241—242°) (Found : N, 12·7. Calc. for $C_{14}H_{15}ON,C_6H_3O_7N_3$: N, 12·7%). Yield 50%.

3-*Nitro*-5 : 6 : 7 : 8-*tetrahydrophenanthridine*, white spangles from aqueous acetone, m. p. 172—173° (Found : C, 68·6 ; H, 5·2 ; N, 12·1. $C_{13}H_{12}O_2N_2$ requires C, 68·5 ; H, 5·3 ; N, 12·3%), was prepared from *p*-nitroaniline. The *picrate* formed small yellow needles from acetone–spirit (charcoal), m. p. 203° (decomp.) (Found : N, 15·1. $C_{13}H_{12}O_2N_2,C_6H_3O_7N_3$ requires N, 15·3%). Yield 50%.

3-Chloro-5 : 6 : 7 : 8-tetrahydrophenanthridine, small white needles from light petroleum (b. p. 40—60°), m. p. 90° (90°) (Found : C, 71·7 ; H, 5·7 ; N, 6·5. Calc. for $C_{13}H_{12}NCl$: C, 71·5 ; H, 5·6 ; N, 6·4%), was prepared from *p*-chloroaniline. The picrate formed yellow needles from spirit (charcoal), m. p. 213° (decomp.) (214°, decomp.) (Found : N, 12·5. Calc. for $C_{13}H_{12}NCl,C_6H_3O_7N_3$: N, 12·5%). Yield 30%.

3-*Phenyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine*, felted white masses from aqueous alcohol, m. p. 122—123° (Found : C, 88·2; H, 6·7; N, 5·3. $C_{19}H_{17}N$ requires C, 88·0; H, 6·6; N, 5·4%), was prepared from *p*-aminodiphenyl. The *picrate* formed yellow needles from spirit (charcoal), m. p. 235° (decomp.) (Found : N, 11·4. $C_{19}H_{17}N,C_6H_3O_7N_3$ requires N, 11·5%). Yield 70%.

5 : 6 : 7 : 8-*Tetrahydro*-1 : 2-*benzphenanthridine*.—1-(1-Naphthyliminomethyl)*cyclo*hexan-2-one (50 g.) (Petrow, *loc. cit.*) in anhydrous formic acid (400 ml.) was heated under reflux for 20 hours. Formic acid (300 ml.) was removed under reduced pressure and the residue poured into excess of aqueous ammonia. The precipitated base was collected, dissolved in spirit, and treated with picric acid (60 g.) in spirit (500 ml.), giving 5 : 6 : 7 : 8-tetrahydro-1 : 2-benzphenanthridine picrate, very small yellow spangles from spirit (charcoal), m. p. 218° (decomp.) (218°, decomp.) (Found : N, 12·5. Calc. for $C_{17}H_{15}N,C_6H_3O_7N_3$: N, 12·1%). The base formed white needles from light petroleum (b. p. 60—80°), m. p. 118—119° (118°) (Found : C, 87·6; H, 6·5; N, 6·2 Calc. for $C_{17}H_{15}N$: C, 87·6; H, 6·4; N, 6·2%). Yield 60%.

5 : 6 : 7 : 8-Tetrahydro-3 : 4-benzphenanthridine, long white needles from light petroleum (b. p. 80—100°), m. p. 100—101° (101°) (Found : C, 87·4; H, 6·5; N, 6·2. Calc. for $C_{17}H_{15}N$: C, 87·6; H, 6·4; N, 6·0), was prepared from 1-(2-naphthyliminomethyl)*cyclo*hexan-2-one (Petrow, *loc. cit.*). The picrate formed small yellow needles from spirit, m. p. 252—253° (decomp.) (245—246°, decomp.) (Found : N, 11·8. Calc. for $C_{17}H_{15}N,C_6H_3O_7N_3$: N, 12·1%). Yield 75%.

1 : 2 : 3 : 4-*Tetrahydro*-11-*aza*-6 : 7-*acechrysene* (V), small cream needles from aqueous alcohol, m. p. 134—135° (Found : C, 88·0; H, 6·7; N, 5·5. $C_{19}H_{17}N$ requires C, 88·0; H, 6·6; N, 5·4%), was prepared from 1-(5-*acenaphthenyliminomethyl*)cyclo*hexan*-2-*one* [orange-yellow needles from spirit (charcoal), m. p. 137—138° (Found : C, 82·2; H, 7·0; N, 5·1. $C_{19}H_{19}ON$ requires C, 82·3; H, 6·9; N, 5·1%), obtained by the condensation of 5-aminoacenaphthene with formyl*cyclo*hexanone]. The *picrate* formed long yellow needles from spirit (charcoal), m. p. 229° (decomp.) (Found : N, 11·8. $C_{19}H_{17}N,C_6H_3O_7N_3$ requires N, 11·6%). Yield 50%.

9-*Amino*-5 : 6 : 7 : 8-*tetrahydrophenanthridine*.—Dry 5 : 6 : 7 : 8-tetrahydrophenanthridine (5 g.), dry diethylaniline (25 g.), and sodamide (6 g.) were heated in a wax-bath at 160—170°. Vigorous evolution of gas took place, and in 15 minutes the mixture set to a buff solid. The mixture was heated for a further 5 hours at 170°, and the solid, when cold, decomposed with water (25 ml.). After standing overnight, the solids (4 g.) were collected and crystallised from aqueous alcohol. 9-*Amino*-5 : 6 : 7 : 8-*tetrahydrophenanthridine* formed small gleaming white plates, m. p. 165° (Found : C, 78·7; H, 7·0; N, 14·3. $C_{13}H_{14}N_2$ requires C, 78·7; H, 7·1; N, 14·1%).

The *acetate*, white needles from light petroleum (b. p. 80—100°), m. p. 212—213° (Found : C, 69·8; H, 6·9; N, 11·0. $C_{13}H_{14}N_2,C_2H_4O_2$ requires C, 69·8; H, 7·0; N, 10·9%), was obtained by dissolving the base in excess hot acetic acid (33%), and just neutralising the solution with ammonia. Yield nearly theoretical.

5 : 6 : 7 : 8-Tetrahydrophenanthridone was obtained when 9-amino-5 : 6 : 7 : 8-tetrahydrophenanthridine (5 g.), in dilute hydrochloric acid (300 ml.), was treated with an ice-cold solution of sodium nitrite (4 g.) in water (40 ml.) with constant stirring. The mixture was heated on the water-bath for 1 hour, neutralised with ammonia, and the precipitated buff solids (4 g.) recrystallised from aqueous alcohol (charcoal), giving small white needles m. p. 272° (Found : C, 78·4; H, 6·5; N, 7·0. Calc. for $C_{13}H_{14}ON_2$: C, 78·4; H, 6·5; N, 7·1%). Yield 75%. (Sen and Basu, *J. Indian Chem. Soc.*, 1929, **6**, 310, record m. p. 273° for 5 : 6 : 7 : 8-tetrahydrophenanthridone.)

9-*Amino*-1-*methyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine* formed small gleaming white plates from aqueous alcohol, m. p. 121—122° (Found, C, 79·5; H, 7·8; N, 12·9. $C_{14}H_{66}N_2$ requires C, 79·4; H, 7·6; N, 13·2%). Yield 45%.

9-*Amino*-3-*methyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine* formed very fine white needles from alcohol–light petroleum (b. p. 80—100°), m. p. 169—170° (Found : C, 79·2; H, 7·3; N, 13·3. $C_{14}H_{16}N_2$ requires C, 79·4; H, 7·6; N, 13·2%). Yield 50%. The *acetate* formed small gleaming white plates from alcohol–light petroleum (b. p. 80—100°) (charcoal), m. p. 204—205° (Found : C, 70·6; H, 7·3; N, 10·6. $C_{14}H_{16}N_2,C_2H_4O_2$ requires C, 70·6; H, 7·4; N, 10·3%). Yield 90%.

9-*Amino*-1 : 3-*dimethyl*-5 : 6 : 7 : 8-*tetrahydrophenanthridine* formed fine white needles from alcohol–light petroleum (b. p. 80—100°) (charcoal), m. p. 136—137° (Found : C, 79·2; H, 7·9; N, 12·3. $C_{15}H_{18}N_2$ requires C, 79·7; H, 8·0; N, 12·4%). Yield 60%.

9-*Amino*-5 : 6 : 7 : 8-*tetrahydro*-3 : 4-*benzphenanthridine* formed white needles from alcohol–light petroleum (b. p. 80—100°), m. p. 241—242° (Found : C, 82·2; H, 6·6; N, 11·3. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·5; N, 11·3%). Yield 80%.

9-*Amino*-1-*methylphenanthridine*.—1-Methyl-5 : 6 : 7 : 8-tetrahydrophenanthridine (10 g.) was dehydrogenated by heating with powdered selenium (10 g.) at 300° for 5 hours. The cooled product was extracted with boiling absolute alcohol and filtered from selenium. The product crystallised from alcohol–light petroleum in white plates, m. p. 95° (95·5°); picrate, m. p. 233—234° (decomp.) (234°, decomp.). The mixed m. p. with 1-methyl-5 : 6 : 7 : 8-tetrahydrophenanthridine (m. p. 80°) was 61—63°. Yield 85%.

1-Methylphenanthridine (7 g.), diethylaniline (25 ml.), and sodamide (8 g.) were heated at 160° for 4 hours. After a few minutes, the mixture had set to a pasty black solid. The product was decomposed with water (15 ml.), left overnight, and the dark brown solid collected and crystallised from alcohol–light petroleum (b. p. 80—100°) (charcoal). 9-*Amino*-1-*methylphenanthridine* formed white needles, m. p. 116—117° (Found : C, 80·8; H, 5·3; N, 14·0. $C_{14}H_{12}N_2$ requires C, 80·7, H, 5·7; N, 13·8%). Yield 50%. The mixed melting point with 9-amino-1-methyl-5 : 6 : 7 : 8-tetrahydrophenanthridine was 90—92°.

9-*Amino*-3-*methylphenanthridine* separated from alcohol–light petroleum (b. p. 80—100°) (charcoal) in clusters of needles, m. p. 170—171° (Found : C, 80·6; H, 5·5; N, 14·0. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·7; N, 13·8%). Yield 60%. The mixed melting point with 9-amino-3-methyl-5 : 6 : 7 : 8-tetrahydrophenanthridine (m. p. 169—170°) was 150—153°.

9-*Amino*-1 : 3-*dimethylphenanthridine* formed small white needles from aqueous alcohol (charcoal), m. p. 142—143° (Found : C, 80·8; H, 6·3; N, 12·7. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·3; N, 12·6%).

Yield 55%. The mixed melting point with 9-amino-1 : 3-dimethyl-5 : 6 : 7 : 8-tetrahydrophenanthridine (136—137°), was 118—120°.

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