

**Phenanthridine Derivatives:
Part I. Studies on the Cyclodehydration of some
Acylamido-2-Phenyl Cyclohexanes**

**Ahindra Chandra Das Gupta, Sibani Sankar Chakravorti,
Bijan Prasun Das* and U. P. Basu**

Cyclodehydration of *trans*-1-chloroacetyl-amido-2-phenylcyclohexane (II) with PoCl_3 /benzene afforded *trans*-1, 2, 3, 4, 4a, 10a-hexahydro-9-chloromethyl-phenanthridine, isolated in the form of its hydrochloride (III), the chloromethyl group of which did not interact with secondary amines. On the other hand, *trans*-1-[N-(piperidino/morpholino/diethylamino)]-acetyl-amido-2-phenylcyclohexanes (IV), obtained by treating II with piperidine, morpholine and diethylamine, could not be cyclised with PoCl_3 /benzene, P_2O_5 /benzene and PCl_5 /chloroform, but the amides (IV) on treatment with P_2O_5 /xylene furnished in each case 1-phenylcyclohexene (V) and the acetonitriles (VI) of the corresponding secondary amines respectively. However, by the action of PPA on (IV) the desired cyclised product, *trans*-1, 2, 3, 4, 4a, 10a-hexahydro-9-piperidinomethylphenanthridine (I; $\text{R}=\text{N}$ -piperidino) could only be isolated along with (V) as major side product in all the cases.

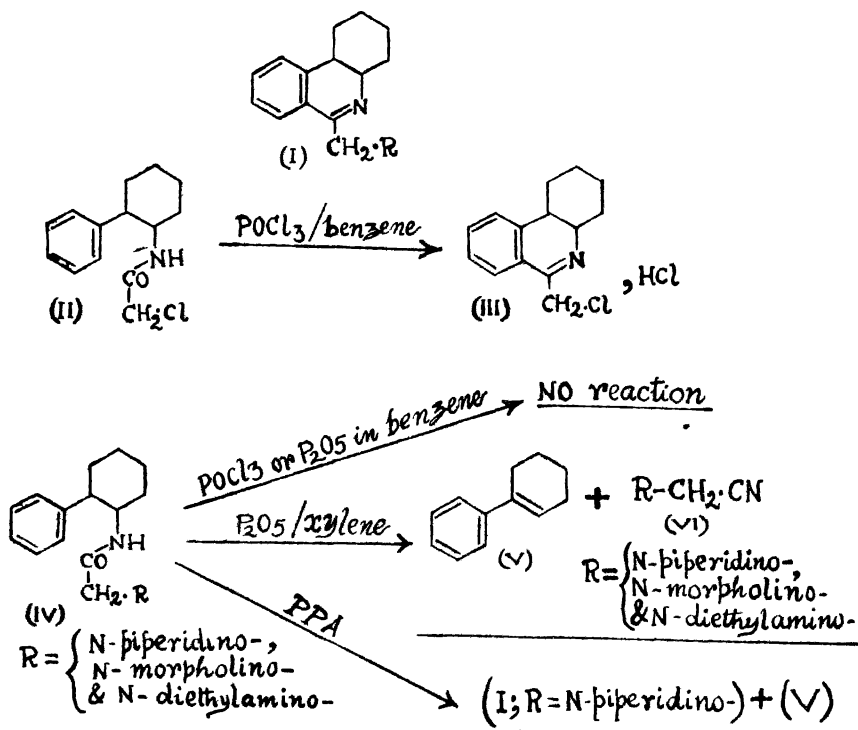
A systematic investigation on the synthesis of several 3, 4-dihydro-isoquinoline derivatives^{1,2} is being followed in this laboratory. In this connection it was considered to be of interest to have similar heterocyclic ring with 3, 4-cyclotetramethylene substitution giving rise to the phenanthridine skeleton as depicted in structure (I).

In the first approach towards the synthesis of compounds of structure (I), *trans*-1-amino-2-phenylcyclohexane^{2,3} was treated with chloroacetylchloride to give *trans*-1-chloroacetyl-amido-2-phenylcyclohexane (II), which on treatment with phosphorus oxychloride in boiling benzene, furnished *trans*-1, 2, 3, 4, 4a, 10a-hexahydro-9-chloromethylphenanthridine, isolated as its hydrochloride (III), the free base being unstable. Attempts to interact (III) with secondary amines (e.g. piperidine, morpholine, diethylamine) under different conditions⁴⁻⁶ to give (I) failed.

*Present address: Department of Chemistry University of Virginia, CHARLOTTESVILLE, VA 22903, U.S.A.

1. T. N. Ghosh, B. K. Ghosh and B. Bhattacharya, *J. Sci. Industr. Res.*, 1962, **21B**, 133.
2. T. R. Govindachari, K. Nagarajan, B. R. Pai and N. Arumugam, *J. Chem. Soc.*, 1956, 4280.
3. T. Masamune, M. Ohno, M. Koshi, S. Ohuchi and T. Iwadara, *J. Org. Chem.*, 1964, **29**, 1419.
4. J. H. Burckhalter and R. I. Leib, *J. Org. Chem.*, 1961 **26**, 4078.
5. B. K. Ghosh, B. Bhattacharya and T. N. Ghosh, *J. Sci. Industr. Res.*, 1962, **21B**, 387.
6. S. L. Shapiro, E. S. Isaacs and L. Freedman, *J. Org. Chem.*, 1961, **26**, 74.

In an alternate approach⁷, the secondary amines (piperidine, morpholine, diethylamine) were condensed with (II) to afford the amides (IV; R=N-piperidino N-morpholino- and N-diethylamino-). The amides (IV) could not be cyclised with



either phosphorus oxychloride or phosphorus pentoxide in boiling benzene and phosphorus pentachloride in chloroform⁸, the starting amides (IV) being recovered. Treatment of the amides (IV) with phosphorus pentoxide in boiling xylene gave, instead of usual cyclodehydration product, the hydrocarbon, 1-phenyl cyclohexene⁹⁻¹¹ (V), and the acetonitriles¹²⁻¹⁴ (VI) corresponding to the secondary amines. However, the amide (IV; R=N-piperidino-) could be cyclised with polyphosphoric acid, but in a very poor yield; the major side product in this case also was 1-phenylcyclohexene (V). But the amides (IV; R=N-morpholino and N-diethylamino-) on treatment with polyphosphoric-

7. S. Sugawara, K. Sakurai, M. Huzisawa and N. Sugimoto, *J. Pharm. Soc. Japan*, 1940, **60**, 140; *Chem. Abs.*, 1940, **34**, 5086.
8. J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 1928, 581.
9. P. Sabatier and A. Mailhe, *Compt. rend.*, 1904, **138**, 1323.
10. J. Szmuszkowicz and E. J. Modest, *J. Amer. Chem. Soc.*, 1948, **70**, 2542.
11. C. F. Coelsch, *J. Amer. Chem. Soc.*, 1951, **73**, 295.
12. A. Lespagnol, E. Cuingnet and M. Debaert, *Bull. Soc. Chim. France*, 1960, **2**, 383.
13. R. A. Henry and W. M. Dehn, *J. Amer. Chem. Soc.*, 1950, **72**, 2804.
14. L. Henry, *Rec. trav. Chim.*, 1905, **24**, 173.

acid furnished only 1-phenylcyclohexene (V), presumably the desired cyclised products could not be isolated due to their resinous nature.

Formation of the nitriles (VI) during cyclodehydration of the amides (IV) parallels the observation of Mc. Coubrey and Mathieson¹⁵, who during cyclisation of the *m*- and *p*-nitro benzoyl derivatives of β phenethylamines obtained the nitrobenzonitriles in considerable proportions. Formation of the hydrocarbon (V) from the amides (IV) also seems parallel to the observation of Cook *et al*¹⁶ in that the acetyl derivative of 1, 2-diphenyl ethylamine when heated with phosphorus pentoxide in xylene affords stilbene with the elimination of acetamide. Similar observation during cyclodehydration of 8-ethoxyquinoline-5 N-(α -methyl- β phenethyl)-carboxamide has also been recorded by Ghosh *et al*¹⁷ in that they isolated only the corresponding nitrile.

EXPERIMENTAL

All recorded melting and boiling points are uncorrected. UV absorption spectra were taken in ethanol solution and measured in Hilger Spectrophotometer model H700 using quartz cells.

trans-1 Chloroacetyl-amido-2-phenyl cyclohexane (II)—Chloroacetyl chloride (90 g.) was added dropwise to an ice cooled mixture of *trans*-1-amino-2-phenylcyclohexane^{2,3} (100 g) and sodium hydroxide solution (20%; 200 ml.) at 0° under stirring during 30 min. The greenish viscous mass was extracted with ether. The ethereal extract was washed successively with dilute hydrochloric acid and water and dried (sodium sulphate). The residue left after removal of the ether was distilled at 210–5°/12–15 mm to furnish on cooling a pale yellow semisolid mass (75 g.). This on trituration with acetone-petroleum ether (60–80°) afforded a solid which crystallised from aqueous ethanol in colourless microcrystalline powder, m. p. 132–3°; λ_{\max} 252, 258 m μ (log ϵ 3.36, 3.37) (Found: N, 5.70; Cl, 13.99. $C_{14}H_{18}NOCl$ requires N, 5.56; Cl, 14.11%).

Action of phosphorus oxychloride on (II): Formation of trans 1, 2, 3, 4, 4a, 10a-hexahydro-9-chloromethylphenanthridine hydrochloride (III): A mixture of the compound (II, 10 g.), phosphorus oxychloride (10 ml.) and dry benzene (150 ml.) was heated under reflux on a steam bath for about 6 hrs. The cooled mixture was treated with crushed ice and the aqueous layer separated, treated with charcoal and filtered. The filtrate was basified with sodium hydroxide solution (30%) and the liberated base (an oil) was extracted with ether. The ethereal layer was then extracted with dilute hydrochloric acid (1:1) and the extract on evaporation to dryness furnished a solid, crystallising from dry ether-ethanol mixture in yellow microcrystalline powder, m. p. 189–90°; λ_{\max} 232, 258 m μ (log ϵ 3.35, 3.83) (Found: N, 4.99; Cl, 26.32. $C_{14}H_{17}NCl_2$ requires N, 5.18; Cl, 26.29%).

15. A. McCoubrey and D. W. Mathieson, *J. Chem. Soc.*, 1949, 696.

16. J. W. Cook, G. T. Dickson, E. Drummond and J. D. London, *J. Chem. Soc.*, 1949, 1074

17. T. N. Ghosh, S. S. Chakravorti and B. Bhattacharya, *Indian J. Chem.*, 1963, 1, 168.

trans-1-(*N*-Piperidino) *acetylamido*-2-*phenyl cyclohexane* (IV; *R*=*N* piperidino)—To a solution of *trans*-1-chloroacetylamidocyclohexane (II, 25 g.) in dry benzene (200 ml.), piperidine (17 g.) was added when an exothermic reaction ensued. The mixture was allowed to stand at room temperature for 1 hr. with occasional swirling, refluxed for 2 hr. and the piperidine hydrochloride filtered off. The filtrate on shaking with benzoyl chloride in presence of sodium hydroxide solution (50%) furnished a brown oil which was extracted with ether, washed with water and dried (sodium sulphate). The solvent was removed and the residue distilled (214—5°/3-4 mm) to afford a gummy product which on trituration with petroleum ether (b. p. 60—80°) yielded a colourless solid, crystallising from ethanol (charcoal) in colourless microcrystalline powder, m.p. 115—6°. (Found: N, 9.27. $C_{19}H_{28}N_2O$ requires N, 9.33%).

trans-1-(*N*-Morpholino) - *acetylamido*-2-*phenylcyclohexane* (IV; *R*=*N*-Morpholino)—This was prepared from the amide (II, 25 g.) dissolved in dry benzene (200 ml.) and morpholine (19g.), following the procedure described in case of (IV; *R*=*N*-piperidino-) and the liquid obtained after removal of the solvent distilled at 230-5°/2-3 mm. as a pink oil which on trituration with acetone-petroleum ether (b. p. 60—80°) mixture afforded a colourless solid crystallising from aqueous ethanol in colourless microcrystalline powder, m. p. 123—4°. (Found: N, 9.35. $C_{18}H_{26}N_2O_2$ requires N, 9.27%).

trans-1-(*N*-Diethyl)-*acetylamido*-2-*phenylcyclohexane* (IV; *R*=*N*-diethylamino)—Diethylamine (12 g.) was mixed with the compound (II, 20 g.). After the initial exothermic reaction was over the product was heated under reflux at 110° for 2 hr., cooled and washed with water. The residual dark brown viscous product was extracted with ether, the ethereal layer washed with water and dried (sodium sulphate). After removal of the ether the residue was distilled *in vacuo* at 220-5°/2 mm. to furnish a deep brown oil. (Found: N, 9.54. $C_{18}H_{28}N_2O$ requires N, 9.72%).

Action of phosphorus pentoxide on (IV; *R*=*N*-piperidino); *Formation of 1-phenylcyclohexene* (V) and *N-piperidinoacetonitrile* (VI; *R*=*N*-piperidino-)—In a flask protected from moisture, a mixture of the amide (IV; *R*=*N*-piperidino-; 10 g.), phosphorus pentoxide (94 g.) and xylene (500 ml.) was refluxed under stirring in an oil bath for about 4 hr. The mixture was cooled and the xylene layer (fraction A) decanted and collected over calcium chloride. The solid residue was treated with crushed ice and the aqueous layer separated, washed with ether, treated with charcoal and filtered. The filtrate on basification with sodium hydroxide solution (50%) furnished an oily product which was repeatedly extracted with ether. The ethereal solution was washed with water, dried (sodium sulphate), ether distilled off and the residue (fraction B) on distillation at 125-30°/25 mm furnished a colourless liquid, characterised as piperidino acetonitrile (Lit¹² b. p. 95°/15 mm). (Found: N, 22.45. Calc. for $C_7H_{12}N_2$; N, 22.58%). Its picrate was crystallised from ethanol in shining yellow needles, m. p. 164°. (Found: N, 19.93. $C_7H_{12}N_2$, $C_6H_3N_3O_7$ requires N, 19.82%)

The xylene layer (vide fraction A) on concentration *in vacuo*, gave a red oil which distilled at 130°-5°/20-25 mm. The distillate was characterised as 1-phenylcyclohexene (Lit⁹ b. p. 128°/16 mm) by the formation of maleic anhydride adduct, crystallising from ethanol in cream coloured microcrystals, m.p. 156-7° (Lit¹⁰ m.p. 160°). Its

nitrosochloride derivative crystallised from methanol in colourless microcrystalline powder, m.p. 127—9° [Lit¹¹ m.p. 133—4° (dec.)].

Action of phosphorus pentoxide on (IV; R=N-morpholino): Formation of 1-phenylcyclohexene (V) and N-morpholinoacetonitrile (VI; R=N-morpholino)—A mixture of (IV; R=N-morpholino), phosphorus pentoxide (94 g.) and xylene (150 ml.) was heated under reflux for 4 hr. under stirring. After following the same procedure as described above, 1-phenylcyclohexene (b. p. 132°/20 mm) was isolated from the xylene layer and characterised.

The ethereal extract of the usual basified aqueous layer on distillation *in vacuo* afforded only N-morpholino acetonitrile (b. p. 138—40°/18-20 mm; m.p. 60—1°; Lit¹³ m.p. 60—1°). (Found: N, 22.13. Calc. for C₆H₁₀N₂: N, 22.22%). Its picrate was crystallised from ethanol in yellow microcrystals, m.p. 152.3°. (Found: N, 19.96. C₆H₁₀N₂O, C₆H₃N₃O₇ requires N, 19.71%).

Action of phosphorus pentoxide on (IV; R=N-diethylamino): Formation of 1-phenylcyclohexene (V) and N-diethylaminoacetonitrile (VI; R=N-diethylamino)—The amide (IV; R=N-diethylamino; 10 g.), phosphorus pentoxide (94 g.) and xylene (225 ml.) were mixed and heated under stirring for 4 hr. and worked up as above. From the xylene layer 1-phenylcyclohexene (V) was obtained and N-diethylaminoacetonitrile (VI; R=N-diethylamino). (b. p. 110.2°/4 mm.; Lit¹⁴ b. p. 170°/10 mm.) isolated from the ethereal extract of the basified aqueous layer was characterised by its elemental analysis (Found: N, 24.92. Calc. for C₆H₁₂N₂: N, 25.00% and the formation of its picrate, crystallising from ethanol in yellow needles, m.p. 147.8° (Found: N, 20.61. C₆H₁₂N₂, C₆H₃N₃O₇ requires N, 20.52%).

Action of polyphosphoric acid on (IV; R=N-Piperidino): Formation of trans-1,2,3,4,4a,10a-hexahydro-9-piperidinomethyl phenanthridine (I; R=N-piperidino) and 1-phenylcyclohexene (V)—To polyphosphoric acid prepared from phosphorous pentoxide (93.5 g) and orthophosphoric acid (85 per cent; 60 ml.) the compound (IV; R=N-piperidino) was added under stirring. The mixture was then heated in an oil bath at 135—40° for 8 hr. and left overnight. The mixture was treated with ice and water and then extracted with ether. The ethereal extract (fraction A), dried over anhydrous sodium sulphate, on concentration afforded a liquid which was distilled at 130°/20 mm and characterised as 1-phenylcyclohexene (V). The acidic aqueous layer (fraction B) was treated as before to furnish a liquid distilling at 195.8°/1.2 mm. This on standing was converted into a solid product which on trituration and subsequent crystallisation from aqueous ethanol yielded a colourless microcrystalline powder, m.p. 220°; λ_{max} 240 m μ (log ϵ 3.32) (Found: C, 80.62; H, 9.15; N, 9.78. C₁₉H₂₆N₂ requires C, 80.85; H, 9.21; N, 9.92%). Its picrate was crystallised from ethanol in yellow microcrystals, m.p. 135°. (Found: N, 14.78. C₁₉H₂₆N₂, 2C₆H₃N₃O₇ requires N, 15.13%).

The same reaction as described above was followed in case of the amides (IV; R=N=morpholino and IV. R=N-diethylamino-) and in both the cases only 1-phenylcyclohexene (V) was obtained and characterised.

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