455. *Syntheses of Heterocyclic Compounds. Part V.*[1] 3,4-*Cycloalkenoquinolines.*

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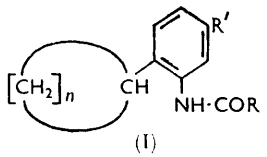
Treatment of acylated cycloalkylanilines (I) with polyphosphoric acid yielded the title compounds (II) by ring-closure on to a paraffinic methylene group. A convenient preparation of phenylcycloalkanes is also described.

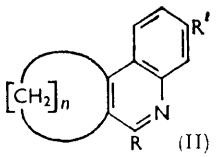
Numerous cyclodehydrations of suitably substituted acylamino-compounds with various reagents have been reported. Cyclisation usually occurs on to an " aromatic " carbon atom as in the Bischler–Napieralski reaction,[2] or involves an " aromatic " methyl group as in the Madelung indole synthesis.[3] We have now found that ring-closure with a paraffinic methylene group is possible when *o*-acylaminophenylcycloalkanes (I; $n = 4$, 5, 6) are treated with polyphosphoric acid at about 150°. For instance, from the cyclohexyl compound (I; R = R′ = H, $n = 5$) the tetrahydrophenanthridine (II; R = R′ = H, $n = 4$) was obtained, rather than the expected hexahydro compound (III; R = H, $n = 4$). Dehydrogenation, which is not uncommon in polyphosphoric acid reactions[4] at sufficiently high temperature, presumably occurred after ring-closure since phenylcyclohexane remained unchanged when heated under the conditions of the reaction. The product was identified by comparison (m. p. and infrared spectrum) with an authentic specimen made by condensing aniline with the Mannich base from cyclohexanone, formalin, and diethylamine hydrochloride by the method of Hollingsworth and Petrow.[5]

[1] Part IV, Meth-Cohn and Suschitzky, *J.*, 1963, 4666.
[2] Whaley and Govindachari, *Org. Reactions*, 1951, **6**, 74.
[3] Madelung, *Ber.*, 1912, **45**, 1128, 3521.
[4] Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962; Wenham and Whitehurst, *J.*, 1956, 3857.
[5] Hollingsworth and Petrow, *J.*, 1948, 1537; 1960, 263.

Similarly, the benzoyl derivative (I; R = Ph, R′ = H, $n = 5$) gave the tetrahydrophenanthridine (II; R = Ph, R′ = H, $n = 4$). This structure follows from a selenium dehydrogenation to the known 6-phenylphenanthridine and from an unambiguous synthesis by interaction of 5,6,7,8-tetrahydrophenanthridine and phenyl-lithium. The acetyl compound (I; R = Me, R′ = H, $n = 5$) and the diacyl derivative (I; R = Ph, R′ = NH·COPh, $n = 5$) cyclised to the respective quinolines (II; R = Me, R′ = H, $n = 4$) and (II; R = Ph, R′ = NH_2, $n = 4$) though in the latter case with deacylation. The diformyl compound (I; R = H, R′ = NH·CHO, $n = 5$), however, was completely



(I)



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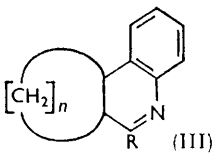
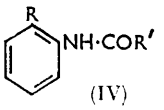


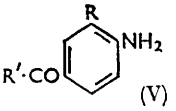
(III)

deformylated to the parent amine, and the ketone (I; R = Me, R′ = COMe) gave intractable tars. The product obtained from the chloro-compound (I; R = Ph, R′ = Cl, $n = 5$) did not give a correct analysis, although its ultraviolet and nuclear magnetic resonance spectra were consistent with the phenanthridine structure (II; R = Ph, R′ = Cl, $n = 4$). Several cyclo-pentyl (I; R′ = H, $n = 4$) and -heptyl analogues (I; R′ = H, $n = 6$) could also be converted with polyphosphoric acid into the corresponding heterocyclic systems (II; $n = 3$ or 5). The best yields (up to 18%) were generally given by the benzoyl derivatives, and the lowest by the formyl compounds (9—13%). Some of these cycloalkene systems had previously been made by a Mannich reaction [5] (cf. above) or by a modified Skraup condensation [6] of the appropriate hydroxymethylcycloalkanone with nitroaniline. Neither route is, however, suitable for preparation of quinolines with a substituent in the pyridine ring (cf. II) as has been done by the polyphosphoric acid method. The ultraviolet spectra of all the cycloalkenoquinolines are very similar (cf. Experimental section).

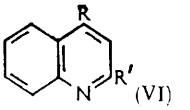
An extension of this cyclisation to the analogous 1-alkylanilines seemed of interest. However, treatment of the acylated *o*-toluidine (IV; R = Me, R′ = Ph) with polyphosphoric acid was recently shown [7] to give the amino-ketone (V; R = Me, R′ = Ph) by intermolecular acylation. The ethyl compound (IV; R = Et, R′ = Ph) suffered deacylation to the parent amine. Only in the case of a branched alkyl group, namely the cumene (IV; R = Pr^i, R′ = H, Me, or Ph), was cyclisation to the corresponding quinoline (VI; R = Me, R′ = H, Me, or Ph) successful. It thus appears that the success of cyclisation depends on the geometry of the alkyl substituent which is provided either by an alicyclic ring or a branched chain. The necessity of initially involving a tertiary carbon atom in the cyclodehydration, to give a spiran which, by ring-enlargement, gives a 6-membered nitrogen-ring system, may be the reason for this steric requirement.



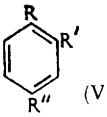
(IV)



(V)



(VI)



(VII)

The intermediates required for the preparation of the title compounds (II) were made by condensing benzene with the appropriate cyclic alcohol in polyphosphoric acid to give the cycloalkanes (VII; R = C_5H_9, C_6H_{11}, C_7H_{13}, R′ = R″ = H) in fair yield. Attempts

[6] Case, *J. Org. Chem.*, 1956, **21**, 1069.
[7] Denton and Suschitzky, *J.*, 1963, 4741.

to obtain the nitro-compounds (VII; R = cycloalkyl, R′ = NO_2, R″ = H) by mononitration and separation of the resulting isomeric mixture, as described in the literature [8,9] for 2-nitrophenylcyclohexane, proved tedious. Dinitration to the phenylcycloalkanes (VII; R = cycloalkyl, R′ = R″ = NO_2) and selective removal of one nitro-group by reduction and deamination gave the required mononitro-compounds more efficiently. 2,4-Dinitrophenylcyclohexane was best prepared by stepwise nitration as was 2,4-dinitrocumene (VII; R = Pr′, R′ = R″ = NO_2). Reduction and acylation of the nitro-compounds to the required amides (IV) were done in the usual way.

Experimental

Polyphosphoric acid was commercial tetraphosphoric acid (Albright and Wilson) containing 80—85% of phosphorus pentoxide.

Phenylcycloalkanes.—The appropriate cyclic alcohol (50 g.) and benzene (135 g.) were run slowly with vigorous stirring into polyphosphoric acid (500 g.) on an oil-bath at 80—85°. This temperature was maintained for 1·25 hr., and the mixture was cooled and diluted with twice its volume of water. The organic layer was combined with a benzene extract (100 ml.) of the aqueous portion. Fractional distillation of the organic extract gave, in the respective experiments, phenylcyclopentane (48%), b. p. 215—217°, phenylcyclohexane (59%), b. p. 237°, and phenylcycloheptane (35%), b. p. 83—85°/1 mm.; yields are based on weight of alcohol used.

2,4-*Dinitrophenylcycloalkanes.*—The phenylcycloalkane (30 g.) was added dropwise with stirring to an ice-cold mixture of nitric acid (*d* 1·42; 60 ml.) and concentrated sulphuric acid (130 ml.) during 20 min. The mixture was set aside until it reached room temperature, slowly heated to about 80° on a water-bath with efficient stirring, and maintained at this temperature for 40 min. When cool, it was poured on to ice and extracted with ether (200 ml.). The extract was washed free from acid (dilute sodium hydroxide and water), dried ($MgSO_4$), and the nitro-compound isolated by driving off the solvent. 2,4-*Dinitrophenylcyclopentane* (69%) had b. p. 146—148°/0·6 mm. (Found: C, 55·6; H, 5·1; N, 12·2. $C_{11}H_{12}N_2O_4$ requires C, 55·9; H, 5·1; N, 11·9%). 2,4-Dinitrophenylcycloheptane (36%) had b. p. 162—164°/0·5 mm. On reduction and benzoylation it gave 2,4-*dibenzamidophenylcycloheptane*, m. p. 221° (Found: C, 78·3; H, 7·15. $C_{27}H_{28}N_2O_2$ requires C, 78·6; H, 6·85%). 2,4-Dinitrophenylcyclohexane was made from 4-nitrophenylcyclohexane (25 g.) by nitration, as described above, with nitric acid (*d* 1·42; 25 ml.) and concentrated sulphuric acid (25 ml.). It formed yellow plates (24 g.), m. p. 56° (from ethanol) (lit.,[8] 57°) (Found: C, 57·8; H, 5·6. Calc. for $C_{12}H_{14}N_2O_4$: C, 57·6; H, 5·6%). 2,4-Dinitrocumene, similarly prepared from 4-nitrocumene (40 g.), had b. p. 128—130°/1·3 mm. (40 g.).

Aminophenylcycloalkanes.—The 2,4-dinitro-compound (40 g.) was dissolved in hot ethanol (*ca.* 300 ml.), and ammonium hydroxide solution (*d* 0·88; 80 ml.) was added. The mixture was refluxed, and saturated with hydrogen sulphide every 2 hr. Precipitated sulphur was filtered off at convenient intervals. After 12 hr., ethanol was distilled off and the nitro-amine isolated by diluting the residue with water and extracting with ether. 4-*Amino-2-nitrophenylcyclopentane* (70%) had b. p. 160°/0·6 mm. (Found: N, 13·2. $C_{11}H_{14}N_2O_2$ requires N, 13·6%). 4-Amino-2-nitrophenylcyclohexane (75%) had m. p. 66° (lit.,[8] 66—67°), and 4-amino-2-nitrophenylcycloheptane (49%), b. p. 150—152°/0·5 mm., was characterised as its *monobenzoyl derivative*, m. p. 92° (Found: C, 71·0; H, 6·55. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·55%). 4-Amino-2-nitrocumene (85%) had m. p. 48° (lit.,[10] 51—52°).

Reduction of 2,4-dinitrophenylcyclohexane with iron and hydrochloric acid gave the diamine, m. p. 106° (lit.,[8] 108°). Its NN′-*diformyl derivative* had m. p. 130° (Found: C, 68·25; H, 7·35. $C_{14}H_{18}N_2O_2$ requires C, 68·25; H, 7·35%). Its NN′-*dibenzoyl derivative* had m. p. 270—271° (Found: C, 77·8; H, 6·6. $C_{26}H_{26}N_2O_2$ requires C, 78·4; H, 6·5%).

2-*Nitrophenylcycloalkanes.*—The above amines (25 g.) were diazotised in the usual way and the filtered diazonium salt solution run into hypophosphorous acid (250 ml.; 30% w/v) at 0°. This mixture was kept at 0° for 12 hr. and at room temperature for a further 12 hr. The nitro-compounds were obtained by steam-distillation. 2-*Nitrophenylcyclopentane* (65%) had b. p.

[8] Mayes and Turner, *J.*, 1929, 500.
[9] Neunhoeffer, *J. prakt. Chem.*, 1932, **133**, 95.
[10] Haworth, Lamberton, and Woodcock, *J.*, 1947, 182.

95°/0·6 mm. (Found: C, 69·5; H, 7·25. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·9%). 2-Nitrophenylcyclohexane (61%) was a pale yellow solid, m. p. 42° (lit.,[9] 45°). 2-Nitrophenylcycloheptane (47%), b. p. 104°/0·9 mm., was reduced without further purification. 2-Nitrocumene (65%) had b. p. 115—117°/12 mm. (lit.,[11] 117—119°/12 mm.).

2-*Aminophenylcycloalkanes*.—The 2-nitro-compound (20 g.), dissolved in a minimum of ethanol, was slowly added to a vigorously stirred boiling mixture of water (150 ml.), ammonium chloride (10 g.), and reduced iron powder (10 g.). After 4—5 hr. the mixture was steam-distilled and the amine obtained in a nearly quantitative yield from the aqueous distillate by ether extraction. 2-*Aminophenylcyclopentane* had b. p. 98°/2 mm. (Found: C, 81·85; H, 9·15. $C_{11}H_{15}N$ requires C, 82·0; H, 9·4%). It gave a *formyl derivative*, m. p. 88° (Found: C, 76·7; H, 8·4. $C_{12}H_{15}NO$ requires C, 76·2; H, 8·0%), an *acetyl derivative*, m. p. 112° (Found: C, 76·4; H, 8·2. $C_{13}H_{17}NO$ requires C, 76·8; H, 8·4%), and a *benzoyl derivative*, m. p. 128° (Found: C, 81·5; H, 6·7. $C_{18}H_{19}NO$ requires C, 81·5; H, 7·2%). 2-Aminophenylcyclohexane [9] was obtained as an oil quickly darkening on exposure to air. It gave an acetyl (m. p. 101°) and a benzoyl (m. p. 156°) derivative as described.[9] Its *formyl derivative* had m. p. 114° (Found: C, 77·0; H, 8·4. $C_{13}H_{17}NO$ requires C, 76·8; H, 8·4%). 2-Aminophenylcycloheptane had b. p. 104—106°/1 mm., and yielded a *formyl derivative*, m. p. 73° (Found: C, 77·4; H, 8·9. $C_{14}H_{19}NO$ requires C, 77·4; H, 8·8%) and a *benzoyl derivative*, m. p. 144° (Found: C, 82·0; H, 8·1. $C_{20}H_{23}NO$ requires C, 81·9; H, 7·9%). 2-Aminocumene gave formyl, acetyl, and benzoyl derivatives with m. p.s 69, 70, and 147°, respectively, as given in the literature.[12–14]

4-*Acetyl*-2-*nitrophenylcyclohexane*.—4-Acetylphenylcyclohexane (10 g.) [8] was nitrated as described above, to give the 2-*nitro-compound*, yellow needles, m. p. 59—60° (from aqueous ethanol) (Found: C, 67·8; H, 6·8. $C_{14}H_{17}NO_3$ requires C, 68·0; H, 6·9%); 2,4-*dinitrophenylhydrazone*, needles, m. p. 216° (from ethanol) (Found: C, 57·1; H, 4·9. $C_{20}H_{21}N_5O_6$ requires C, 56·5; H, 4·95%).

4-*Acetyl*-2-*aminophenylcyclohexane*.—A solution of the above nitro-compound (10 g.) in benzene (100 ml.) was reduced at normal pressure and room temperature over Raney nickel with hydrogen. The *amine* formed pale yellow needles, m. p. 100° [from light petroleum (b. p. 100—120°)] (Found: C, 77·65; H, 8·7. $C_{14}H_{19}NO$ requires C, 77·4; H, 8·8%); *formyl derivative*, m. p. 124° (Found: C, 72·9; H, 7·9. $C_{15}H_{19}NO_2$ requires C, 73·3; H, 7·8%); *acetyl derivative*, m. p. 154° (Found: C, 73·7; H, 8·2. $C_{16}H_{21}NO_2$ requires C, 74·1; H, 8·2%); *benzoyl derivative*, m. p. 150° (Found: C, 78·4; H, 7·3. $C_{21}H_{23}NO_2$ requires C, 78·5; H, 7·2%).

4-*Chloro*-2-*nitrophenylcyclohexane*.—4-Chlorophenylcyclohexane [8] was nitrated as described above. The crude mixture of nitro-compounds, after separation, was warmed on a steam-bath with an excess of piperidine for 6 hr., taken up in benzene, and extracted with dilute hydrochloric acid. This treatment removed the 4-chloro-3-nitrophenyl isomer as a piperidino-compound. The benzene layer was evaporated, and left 4-*chloro*-2-*nitrophenylcyclohexane* as a yellow oil (46·0%), b. p. 136—137°/0·65 mm. (Found: C, 59·8; H, 5·8. $C_{12}H_{14}ClNO_2$ requires C, 60·1; H, 5·85%).

2-*Amino*-4-*chlorophenylcyclohexane*.—A solution of the above nitro-compound (8·0 g.) in benzene (100 ml.) gave, on reduction with hydrogen over Raney nickel, the amine as a pale yellow oil. Its *formyl derivative* had m. p. 140° (Found: C, 65·6; H, 6·8. $C_{13}H_{16}ClNO$ requires C, 65·7; H, 6·75%), and its *benzoyl derivative* had m. p. 152—153° (Found: C, 72·5; H, 6·35. $C_{19}H_{20}ClNO$ requires C, 72·6; H, 6·4%).

3,4-*Cycloalkenoquinolines*.—(*a*) The unsubstituted quinolines (II; R = R′ = H, *n* = 3, 4, 5) were made by heating together the appropriate cyclic ketone (50 g.), formalin (8 g.), and diethylamine hydrochloride (10 g.) for 30 min. To the crude Mannich base were added aniline (9 g.), aniline hydrochloride (12 g.), and stannic chloride hydrate (12 g.). The mixture was refluxed for 20 hr. and worked up as described.[5] The crude bases, obtained by fractionation *in vacuo*, were purified by conversion into the picrates which were decomposed with aqueous sodium hydroxide (20%). The m. p.s of all picrates and parent bases agreed with those quoted in the literature.[5,6]

(*b*) A solution of the appropriate acyl derivative (I) (1—5 g.) in polyphosphoric acid (20—100 g.) was stirred at 150—160° for about 1·5 hr. The mixture was poured into ice-water,

[11] Bogert and Sterling, *J. Org. Chem.*, 1939, **4**, 20.
[12] Arient and Dvořák, *Chem. listy*, 1956, **50**, 1636.
[13] von Braun, Bayer, and Blessing, *Ber.*, 1924, **57**, *B*, 392.
[14] Stroh, Ebersberger, Haberland, and Hahn, *Angew. Chem.*, 1957, **69**, 124.

basified with aqueous sodium hydroxide (40%), and extracted with small portions of ether. The solvent layer was dried ($MgSO_4$) and evaporated, leaving an oily residue. Addition of an ethanolic solution of picric acid produced a picrate which was purified from ethanol, and yielded the appropriate quinoline (II) on decomposition with aqueous sodium hydroxide (20%) on a water-bath. Yields are based on the amount of pure picrate obtained. 3,4-Cyclopentenoquinoline (9%) was a pale yellow oil, $\lambda_{max.}$ 237, 279, 306, and 320 mμ (log ε 3·91, 3·40, 3·18, and 3·28). Its 2-*phenyl derivative* (14·5%), m. p. 74° (Found: C, 87·7; H, 6·2. $C_{18}H_{15}N$ requires C, 88·1; H, 6·2%), $\lambda_{max.}$ 252, 287, 315, and 330 mμ (log ε 4·32, 3·73, 3·66, and 3·61), gave a *picrate*, m. p. 205° (Found: C, 60·55; H, 4·3. $C_{24}H_{18}N_4O_7$ requires C, 60·7; H, 3·8%). 7,8,9,10-Tetrahydrophenanthridine (3,4-cyclohexenoquinoline) (10%), m. p. 60°, $\lambda_{max.}$ 230, 284, 310, and 323 mμ (log ε 4·21, 3·66, 3·47, and 3·53), was purified by sublimation *in vacuo*. Its 6-*methyl derivative* (II; R = Me, R′ = H, *n* = 4) (10%), m. p. 85° (Found: C, 84·6; H, 7·5. $C_{14}H_{15}N$ requires C, 85·2; H, 7·6%), $\lambda_{max.}$ 233, 281, 307, 315, and 321 mμ (log ε 4·37, 4·05, 3·66, 3·19, and 3·36), gave a *picrate*, m. p. 215—218° (decomp.) (Found: C, 56·1; H, 4·3%. $C_{20}H_{18}N_4O_7$ requires C, 56·3; H, 4·3%), and its 6-*phenyl derivative* (18·2%), m. p. 79° (Found: C, 87·6; H, 6·9. $C_{19}H_{17}N$ requires C, 88·0; H, 6·6%), $\lambda_{max.}$ 246, 287, 312, and 324 mμ (log ε 3·89, 3·63, 3·54, and 3·54), gave a *picrate*, m. p. 211° (Found: C, 60·9; H, 4·0. $C_{25}H_{20}N_4O_7$ requires C, 61·4; H, 4·13%). 3-Amino-7,8,9,10-tetrahydro-6-phenylphenanthridine (II; R = Ph, R′ = NH_2, *n* = 4) was identified as its *picrate*, m. p. 250° (decomp.) (Found: C, 59·4; H, 4·55. $C_{25}H_{21}N_5O_7$ requires C, 59·6; H, 4·2%). The cycloheptenoquinoline (II; R = R′ = H, *n* = 5) (13%) had m. p. 67°, $\lambda_{max.}$ 227, 288, 306, and 320 mμ (log ε 4·59, 3·49, 3·36, and 3·37). Its 2-*phenyl derivative* (II; R = Ph, R′ = H, *n* = 5) (12·25%) was a colourless oil, $\lambda_{max.}$ 248, 285, 312, and 325 mμ (log ε 4·60, 3·58, 3·52, and 3·52) yielding a *picrate*, m. p. 206—208° (decomp.) (Found: C, 61·7; H, 4·2. $C_{26}H_{22}N_4O_7$ requires C, 62·2; H, 4·4%).

(*c*) 7,8,9,10-Tetrahydro-6-phenylphenanthridine was also made by adding the tetrahydro-compound (1 g.) in ether (10 ml.) to a solution of phenyl-lithium [from bromobenzene (0·86 g.), lithium (0·08 g.), and anhydrous ether (20 ml.)] under nitrogen. The mixture was stirred for 1 hr. and poured into aqueous hydrochloric acid (4N; 50 ml.). The precipitated hydrochloride, on treatment with dilute aqueous sodium hydroxide, gave an oil whose picrate had m. p. 210°. The picrate when treated with aqueous sodium hydroxide gave a solid (0·6 g.), m. p. 78° undepressed on admixture with the 6-phenyl compound prepared under (*b*).

Cyclisation of 2-Aminocumenes.—Heating the formyl, acetyl, and benzoyl derivative of 2-aminocumene in polyphosphoric acid, as in (*b*), gave 4-methyl-, 2,4-dimethyl-, and 4-methyl-2-phenyl-quinoline, respectively, in small yield. The last compound was made unambiguously for comparison by Goldberg and Levine's method.[15]

6-*Phenylphenanthridine.*—On heating a mixture of selenium powder (2 g.) and 7,8,9,10-tetrahydro-6-phenylphenanthridine (0·3 g.) on an oil-bath at 250° for 30 min. and then at 320° for 12 hr., 6-phenylphenanthridine, m. p. 104° (lit.,[16] 106°), was obtained by extraction with light petroleum. Its picrate had m. p. 248° (from ethanol) (lit.,[16] 251°).

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[15] Goldberg and Levine, *J. Amer. Chem. Soc.*, 1955, **77**, 3647.
[16] Galt and Loudon, *J.*, 1959, 885.