*Experiments on the Synthesis of Azasteroids. Part II.**

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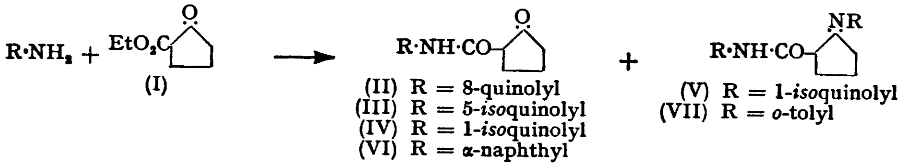
In attempts to synthesise diaza-derivatives of *cyclo*penta[*a*]phenanthrene the condensation of ethyl 2-oxo*cyclo*pentanecarboxylate with some heterocyclic amines has been examined.

Although many nitrogenous steroid derivatives occur in Nature, none has been found in which the hetero-atom is part of the *cyclo*penta[*a*]phenanthrene ring system. Moreover, few of this type have been synthesised. Bolt (*Rec. Trav. chim.*, 1938, **57**, 905) prepared 4-aza-derivatives from natural steroids, and Bachmann and Ramirez (*J. Amer. Chem. Soc.*, 1950, **72**, 2527) prepared lactams from deoxyequilenin and deoxy*iso*equilenin by ring closure of methyl *trans*- and *cis*-1-aminomethyl-1 : 2 : 3 : 4-tetrahydro-2-methylphenanthrene-2-carboxylate. Clemo and Mishra (*J.*, 1953, 192) prepared 15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene from α-naphthylamine by condensation with ethyl 2-oxo*cyclo*pentanecarboxylate (I), and attempts were made to extend this to reaction of the keto-ester with 8-aminoquinoline and 1- and 5-amino*iso*quinoline.

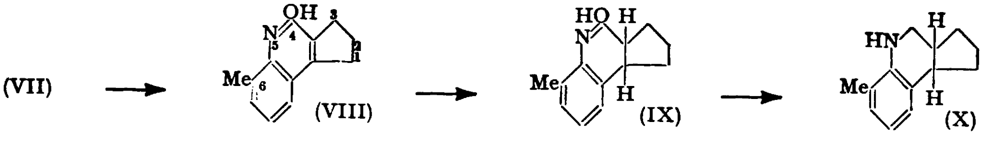
Condensation of 8-aminoquinoline with the keto-ester (I) at 180° gave the amide (II) which gave a deep blue colour with ferric chloride. Reaction of 5-amino*iso*quinoline under the same conditions formed the amide (III) (Mishra (Ph.D. Thesis, Durham, 1953). Attempts to cyclise these amides to compounds analogous to (VIII) proved unsuccessful. The use of hydrochloric acid (Albert, Brown, and Duewell, *J.*, 1948, 1284), sulphuric acid at temperatures above 60°, or phosphoric oxide and phosphoric acid (Smith, *J.*, 1953, 805) resulted in hydrolysis of the amide group, and small quantities of the parent amines were recovered.



(I)

(II) R = 8-quinolyl
(III) R = 5-*iso*quinolyl
(IV) R = 1-*iso*quinolyl
(VI) R = α-naphthyl

(V) R = 1-*iso*quinolyl
(VII) R = *o*-tolyl



(VIII) (IX) (X)

Treatment of 1-amino*iso*quinoline with the keto-ester (I) under the conditions described above gave a mixture of a keto-amide (IV) and an imino-amide (V) : the former, but not the latter, gave a violet colour with ferric chloride. For cyclisation of the keto-amide (IV),

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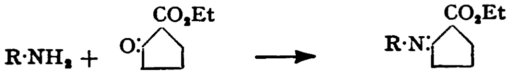
* Part I, *J.*, 1953, 192.

prior reduction of the heterocyclic ring is necessary, but all attempts to effect this resulted in cleavage of the amide bond or recovery of starting material.

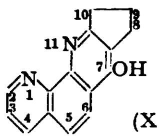
Condensation of 5-amino-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline, prepared by reduction of 5-amino*iso*quinoline methiodide (cf. Barltrop and Taylor, *J.*, 1951, 108), with the keto-ester (I) was also examined as it was thought that position 6 would thus be activated towards dehydrating agents. A red-brown gum was obtained which was insoluble in ether and could not be purified by distillation and on treatment with the reagents mentioned above merely afforded small amounts of 5-amino-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline. Since Clemo and Mishra (*loc. cit.*) were able to cyclise the naphthalide (VI) it appears that the influence of the heterocyclic nitrogen atom weakens the amide link, which is thus readily hydrolysed.

In view of this, *o*-toluidine was condensed with the keto-ester (I). The product gave no colour with ferric chloride and was the imino-amide (VII). Treatment with sulphuric acid cyclised it to 2 : 3-dihydro-4-hydroxy-6-methyl*cyclo*penta[*c*]quinoline (VIII). Reduction with sodium amalgam in boiling ethanol formed the tetrahydro-compound (IX) and further reduction with lithium aluminium hydride gave the hexahydro-compound (X). Attempts to use the 6-methyl group as the starting point in the synthesis of a second heterocyclic ring have not yet succeeded.

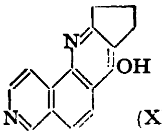
Reaction of the keto-ester (I) with amines under reflux in alcoholic solution results in the formation of imino-esters : under these conditions the Schiff's bases (XI), (XII), and (XIII) were obtained. Ethyl 2-8′-quinolylimino*cyclo*pentanecarboxylate (XI) gave no picrate, and treatment with methyl iodide gave an unstable dimethiodide. The imino-ester (XII) gave a crystalline picrate; the ester (XIII) from *o*-toluidine gave no picrate, nor could it be isolated in a pure condition.



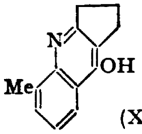
(XI) R = 8-quinolyl
(XII) R = 5-*iso*quinolyl
(XIII) R = *o*-tolyl



(XIV)



(XV)



(XVI)

Ring closure of these compounds at 250° in paraffin or diphenyl ether–diphenyl (Conrad and Limpach, *Ber.*, 1887, **20**, 944; 1931, **64**, 969) gave the phenolic bases (XIV), (XV), and (XVI) respectively.

EXPERIMENTAL

2-*Oxo*-N-8′-*quinolyl*cyclo*pentanecarboxyamide* (II).—8-Aminoquinoline (5 g.) (Coates and Cook, *J.*, 1943, 401) and ethyl 2-oxo*cyclo*pentanecarboxylate (I) (5·5 g.) were heated at 170—180° for 4 min., and the gummy *amide* cooled. When stirred under ether the gum solidified. From light petroleum (b. p. 60—80°) it formed pale yellow crystals (3·7 g.), m. p. 100—102° (Found : C, 71·1; H, 5·6; N, 10·9. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as an orange-red solvate, m. p. 232—235° (Found : C, 57·4; H, 5·1. $C_{21}H_{18}O_5N_6,C_2H_5{\cdot}OH$ requires C, 57·6; H, 5·0%).

2-*Oxo*-N-5′-iso*quinolyl*cyclo*pentanecarboxyamide* (III).—5-Amino*iso*quinoline (5 g.) (Misani and Bogert, *J. Org. Chem.*, 1945, **10**, 358) and the keto-ester (I) (5·5 g.) were condensed and worked up as described above. The solid *product* crystallised from benzene or alcohol as colourless plates (3·9 g.), m. p. 120—122° (Found : C, 71·1; H, 5·9; N, 11·3. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·1%). The *picrate* crystallised from alcohol as yellow needles, m. p. 210—214° (decomp.) (Found : C, 52·3; H, 3·7. $C_{21}H_{17}O_9N_5$ requires C, 52·4; H, 3·5%).

2-*Oxo*-N-1′-iso*quinolyl*cyclo*pentanecarboxyamide* (IV).—1-Amino*iso*quinoline (7 g.) (Bergström *et al.*, *ibid.*, 1946, **11**, 239) and the keto-ester (I) (7·6 g.), condensed as described above, gave a yellow-brown solid product which was extracted with cold methanol to give a yellow solution. After treatment with charcoal and concentration, this deposited the yellow *amide* (IV) (3·7 g.), m. p. 176—178° (Found : C, 70·6; H, 5·8; N, 11·6. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·1%). The *picrate* crystallised as prisms (from ethanol), m. p. 177—180° (Found: C, 52·7; H, 3·7. $C_{21}H_{17}O_9N_5$ requires C, 52·4; H, 3·5%).

N-1′-iso*Quinolyl*-2-1′-iso*quinolyliminocyclopentanecarboxyamide* (V), the solid residue from the methanol extraction of the above product and from ethanol, formed pale straw-coloured prisms (0·6 g.), m. p. 183—185° (Found: C, 76·3; H, 5·4; N, 14·4. $C_{24}H_{20}ON_4$ requires C, 75·9; H, 5·3; N, 14·7%).

5-*Amino*-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*iso*quinoline*.—A solution of 5-amino*iso*quinoline methiodide (10 g.) and diethylamine (9 ml.) in methanol (120 ml.) was hydrogenated over Raney nickel at 150°/80 atm. for 3 hr. The catalyst was filtered off and the solvent removed. Distillation of the gummy residue gave the *base* as a pale yellow liquid (4·9 g.), b. p. 139—142°/0·1 mm. (Found: C, 74·1; H, 8·8; H, 16·9. $C_{10}H_{14}N_2$ requires C, 74·2; H, 8·6; N, 17·2%). It gave a *dipicrate*, m. p. 177—179° (from ethanol) (Found: C, 42·8; H, 3·6. $C_{22}H_{20}O_{14}N_8$ requires C, 42·6; H, 3·2%).

N-o-*Tolyl*-2-o-*tolyliminocyclopentanecarboxyamide* (VII).—*o*-Toluidine (10 g.) and the keto-ester (I) (15 g.) were heated at 170—180° for 5 min. The melt solidified on cooling and was extracted with cold methanol to give a brown solution. Treatment of the methanol extract with charcoal gave a yellow solution which deposited the *imino-amide* (VII) as long, pale yellow needles (16 g.), m. p. 131—133° (Found: C, 78·3; H, 7·5; N, 9·5. $C_{20}H_{22}ON_2$ requires C, 78·5; H, 7·2; N, 9·15%).

2 : 3-*Dihydro*-4-*hydroxy*-6-*methyl*cyclo*penta*[c]*quinoline* (VIII).—The toluidide (VII) (8 g.) was added slowly to cooled sulphuric acid (15 ml.) with stirring. The mixture was heated on a water-bath until the vigorous reaction had ceased and then for a further 10 min. The deep brown liquid was poured on crushed ice (400 g.) and made alkaline with 20% sodium hydroxide solution, and the solid was collected. Recrystallisation of the precipitated solid from alcohol gave the cyclo*pentaquinoline* (VIII) as colourless plates (4·6 g.), m. p. 254—256° (Found: C, 78·3; H, 6·7; N, 7·2. $C_{13}H_{13}ON$ requires C, 78·45; H, 6·5; N, 7·1%).

2 : 3 : 3a : 9b-*Tetrahydro*-4-*hydroxy*-6-*methyl*cyclo*penta*[c]*quinoline* (IX).—The base (VIII) (3 g.) and sodium hydrogen carbonate (1 g.) in alcohol (120 ml.) were heated on a water-bath with vigorous stirring. Sodium amalgam (160 g.; 4%) was added in portions during 4 hr., and the stirring and heating were continued for a further 5 hr. The solution was filtered whilst hot and the filtrate evaporated to dryness. Extraction of the residue with benzene gave, after concentration of the extract, the *tetrahydro-compound* (IX) as colourless prisms (2 g.), m. p. 129—131° (Found: C, 77·7; H, 7·7; N, 6·5. $C_{15}H_{15}ON$ requires C, 77·7; H, 7·5; N, 6·95%).

2 : 3 : 3a : 4 : 5 : 9b-*Hexahydro*-6-*methyl*cyclo*penta*[c]*quinoline* (X).—A solution of the above base (IX) (1 g.) in ether (40 ml.) was added to a cooled ethereal solution of lithium aluminium hydride (15 ml.; 80-vol.). The mixture was refluxed for 6 hr., then set aside overnight. Excess of lithium aluminium hydride was decomposed with crushed ice, and the ether layer separated. The aqueous solution was extracted twice with ether and the combined ether solutions were dried (Na_2SO_4). Removal of the solvent gave a brown *base* which distilled as a pale yellow liquid (0·8 g.), b. p. 109—112°/0·4 mm. (Found: C, 83·5; H, 9·05; N, 7·8. $C_{13}H_{17}N$ requires C, 83·5; H, 9·1; N, 7·5%). The *picrate* separated from ethanol as bright yellow prisms, m. p. 177—180° (Found: C, 54·6; H, 5·1. $C_{19}H_{20}O_7N_6$ requires C, 54·8; H, 4·8%).

Ethyl 2-8′-*Quinolyliminocyclopentanecarboxylate* (XI).—8-Aminoquinoline (5 g.), the keto-ester (I) (5·5 g.), and hydrochloric acid (2 drops; 1 : 1) in ethanol (25 ml.) were refluxed for 6 hr. The solvent was distilled off, and the gummy residue stirred under ether and kept in a refrigerator overnight. Crystallisation of the now solid residue from ethanol gave orange prisms (4·9 g.), m. p. 86—87° (Found: C, 72·6; H, 6·6; N, 10·4. $C_{17}H_{18}O_2N_2$ requires C, 72·4; H, 6·4; N, 9·9%). Treatment with methyl iodide in acetone at 80° in a sealed tube gave unstable red crystals, m. p. 188—190° (Found: C, 40·2; H, 3·95. $C_{17}H_{18}O_2N_2,2CH_3I$ requires C, 40·3; H, 4·25%).

9 : 10-*Dihydro*-7-*hydroxy*-1 : 11-*diaza*cyclo*penta*[b]*phenanthrene* (XIV).—The imino-ester (XI) (4 g.) was added to hot diphenyl ether–diphenyl (60 ml.) with stirring and the temperature raised to 250° for 10 min. The cooled solution was filtered and the brown residue washed well with benzene. Crystallisation from alcohol (charcoal) gave the *diaza-compound* as pale yellow needles (2·2 g.), m. p. 265—268° (Found: C, 76·2; H, 5·3; N, 11·6. $C_{15}H_{12}ON_2$ requires C, 76·4; H, 5·1; N, 11·9%). Its *picrate* crystallised from ethanol as bright yellow leaflets, m. p. 233—237° (decomp.) (Found: C, 54·0; H, 3·4. $C_{21}H_{15}O_8N_5$ requires C, 54·2; H, 3·2%).

Ethyl 2-5′-iso*Quinolyliminocyclopentanecarboxylate* (XII).—Reaction of 5-amino*iso*quinoline (5 g.) as in the preceding case yielded the *imino-ester* (5·6 g.), m. p. 123—125° (from ethanol) (Found: C, 72·6; H, 6·1; N, 10·3. $C_{17}H_{18}O_2N_2$ requires C, 72·4; H, 6·4; N, 9·9%). The *picrate* crystallised from alcohol as orange-yellow rhombohedra, m. p. 189—191° (Found: C, 54·1; H, 4·4. $C_{23}H_{21}O_9N_5$ requires C, 54·0; H, 4·1%).

9 : 10-*Dihydro*-7-*hydroxy*-3 : 11-*diaza*cyclo*penta*[b]*phenanthrene* (XV).—The Schiff's base (XII) (5 g.) was cyclised as described for (XI). After being washed with benzene the crude *diaza-compound* crystallised from ethanol as white needles (2·9 g.), m. p. 323—326° (Found: C, 76·1; H, 5·5; N, 11·7. $C_{15}H_{12}ON_2$ requires C, 76·4; H, 5·1; N, 11·9%). The *picrate* formed yellow prisms, m. p. 265—270° (decomp.) from alcohol (Found: C, 54·5; H, 3·6. $C_{21}H_{15}O_8N_5$ requires C, 54·2; H, 3·2%).

2 : 3-*Dihydro*-9-*hydroxy*-5-*methyl*cyclo*penta*[b]*quinoline* (XVI).—A solution of *o*-toluidine (5 g.), the keto-ester (I) (7·5 g.), and hydrochloric acid (2 drops; 1 : 1) in ethanol (25 ml.) was refluxed for 6 hr. After removal of the solvent, the gummy residue was added to a 1 : 3 mixture (50 ml.) of diphenyl and diphenyl ether at 100° and then heated at 250° with stirring for 10 min. The solution was cooled, and the brown solid product collected, washed with benzene and crystallised from alcohol. The *base* (XVI) was isolated as a white solid (3 g.), m. p. 307—310° (decomp.) (Found: C, 78·6; H, 6·7; N, 7·3. $C_{13}H_{13}ON$ requires C, 78·45; H, 6·5; N, 7·05%).

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