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BISCHLER–NAPIERALSKI REACTION—II*

SYNTHESIS OF SOME KETONIC *ISO*QUINOLINES

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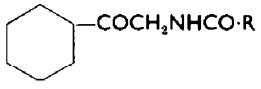
Abstract—Ethylene ketals of the type (I) cyclise in presence of phosphorus pentoxide in pyridine to give the ketal (II) which on hydrolysis yields 1-phenyl-6:7-dimethoxy-4-oxo-3:4-dihydro*iso*quinoline (III). 1-(4-oxo-*cyclo*hexyl)-6:7-dimethoxy-3:4-dihydro*iso*quinoline (VIII) and 2-oxo-3-methyl-9:10-dimethoxy-1:2:3:4:6:7-hexahydro-11bH-benzo[a]-quinolizine (XV) were also synthesised.

IN the first paper* of this series it was reported that substituted acyl-β-phenethylamides could be cyclised to the corresponding *iso*quinolines by treatment with phosphorus pentoxide in pyridine, and this has now been applied to compounds of the type



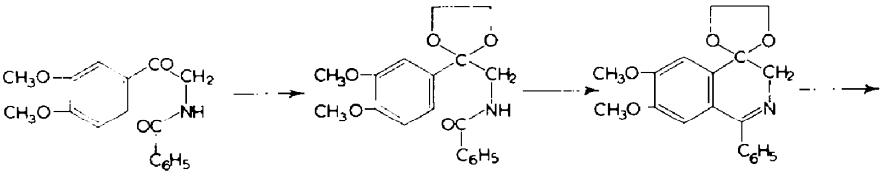
Buck first reported[1] that such compounds yielded 4-oxo*iso*quinoline derivative when treated with phosphoryl chloride, but later stated that the product really was an oxazole derivative.[2a,b] Cyclisation to *iso*quinoline derivatives can be achieved if the ketonic CO is protected by conversion to the ethylene ketal. Thus the ethylene ketal (I) from ω-benzamidoacetoveratrone is cyclised by phosphorus pentoxide in pyridine to 1-phenyl-4:4-ethylenedioxy-6:7 dimethoxy-3:4-dihydro*iso*quinoline (II) which on hydrolysis gives 1-phenyl-6:7-dimethoxy-4-oxo-3:4-dihydro*iso*quinoline (IIIa), or 1-phenyl-4-hydroxy-6:7-dimethoxy*iso*quinoline (IIIb), which on reduction by Huang-Minlon's method gives 1-phenyl-6:7-dimethoxy-3:4-dihydro*iso*quinoline (IV). In a similar manner 1-(4-oxo*cyclo*hexyl)-6:7-dimethoxy-3:4-dihydro*iso*quinoline (VIII) and 2-oxo-3-methyl-9:10-dimethoxy-1:2:3:4:6:7-hexahydro-11bH-benzo-[a]-quinolizine (XV) were synthesised. The latter is suitable for the synthesis of compounds related to emetine. The influence of various substituents in position 5 of the piperidone ring in (XII) on cyclisation is now being investigated.

EXPERIMENTAL

Ketal of ω-benzamidoacetoveratrone (I), ω-Benzamidoacetoveratrone[3] (1 g), ethylene glycol (0·3 g), *p*-toluenesulphonic acid (0·1 g) in benzene (50 cc) was refluxed for 3 hr in an apparatus provided with a Dean–Stark water separator 0·3 cc of water being collected. On cooling the benzene layer was washed with water, dried, and the solvent evaporated to a syrup (1·2 g) which solidified and crystallised from *n*-hexane in colourless needles (0·82 g, 75%) m.p. 109° (Found: C, 66·5; H, 5·9; N, 4·0; $C_{19}H_{21}O_5N$ requires: C, 66·5; H, 6·1; N, 4·1%).

* Part I. Nobuo Itoh and Shigehiko Sugasawa, *Tetrahedron* **1**, 45 (1957).

[1] J. S. Buck, *J. Amer. Chem. Soc.* **52**, 3610 (1930).
[2a] J. S. Buck, *J. Chem. Soc.* 740 (1933); [b] R. Robinson, *J. Chem. Soc.* 275 (1933).
[3] R. Robinson, *J. Chem. Soc.* **95**, 2167 (1909).



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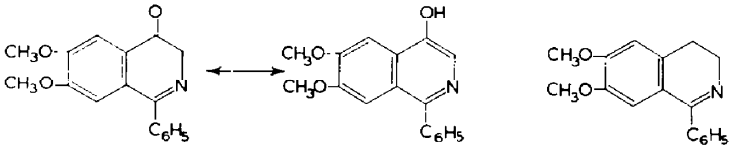

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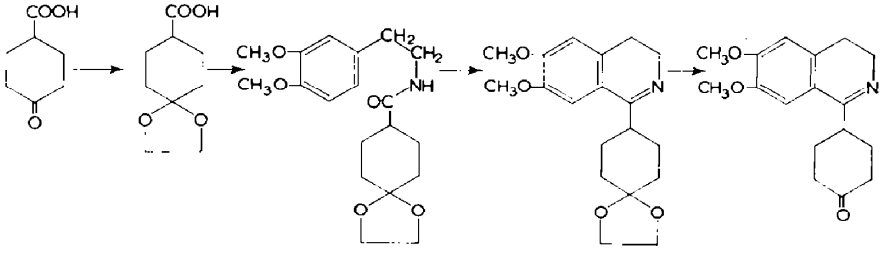
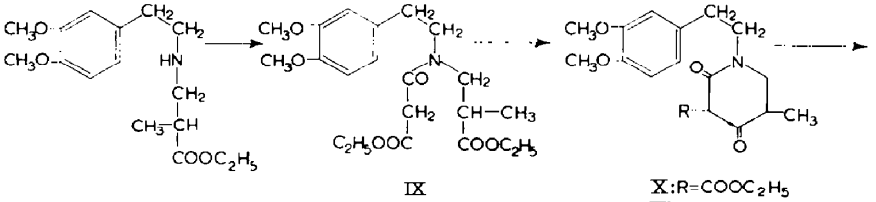
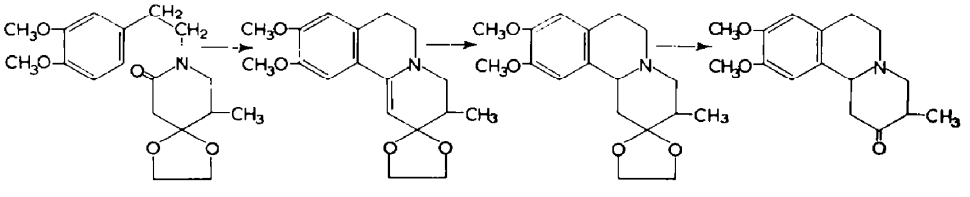


V VI VII VIII



IX

X: R = $COOC_2H_5$
XI: R = H



XII XIII XIV XV

1-*Phenyl*-4:4-*ethylenedioxy*-6:7-*dimethoxy*-3:4-*dihydro*isoquinoline (II). The ketal (I, 0·5 g) in pyridine (30 cc) was refluxed (oil-bath) and to the solution a mixture of phosphorus pentoxide (5 g) and purified sea sand (50 g) was added in four portions during 2 hr and boiling maintained for 6 hr. The dark brown pyridine layer was decanted, the residue washed with pyridine (3 × 10 cc) and the washings combined with the pyridine layer. Evaporation of the pyridine *in vacuo* left a reddish syrup, which was dissolved in benzene, filtered and the solvent removed leaving a reddish yellow syrup (0·38 g, 80%). The latter solidified and was crystallised from *n*-hexane in pale yellow needles m.p. 137° (Found: C, 70·7; H, 6·1; N, 4·3. $C_{19}H_{19}O_4N$ requires: C, 70·3; H, 5·9; N, 4·3%). The *picrate* formed yellow needles m.p. 162–163° from ethanol (Found: C, 54·0; H, 4·2; N, 10·3. $C_{25}H_{22}O_{11}N_4$ requires: C, 54·15; H, 4·0; N, 10·1%).

1-*Phenyl*-6:7-*dimethoxy*-4-*oxo*-3:4 *dihydro*isoquinoline (III). The hydrochloride of (III) was obtained as a colourless crystalline hygroscopic solid by heating (steam-bath) the ketal (II, 0·3 g) in HCl (5 cc, 10%) for 2 hr and subsequent evaporation. Treatment of the aqueous solution of the hydrochloride with potassium carbonate gave the base (III) which was dissolved in benzene dried, and the solvent evaporated leaving a yellow syrup (0·2 g, 79%) which rapidly darkened in air. The base was characterised as its 2:4-dinitrophenylhydrazone, red needles m.p. 201–203° (decomp.) from ethanol (Found: C, 60·1; H, 4·5; N, 15·0. $C_{23}H_{19}O_6N_5$ requires: C, 60·0; H, 4·1; N, 15·2%).

1-*Phenyl*-6:7-*dimethoxy*-3:4-*dihydro*isoquinoline (IV). The base (III, 0·3 g) was reduced by treatment with KOH (0·2 g) hydrazine hydrate (0·2 g) and ethylene glycol (0·5 g) and heating in an oil-bath for 2 hr at 140° and then at 170° for 2 hr. The red product was extracted with benzene and the solution washed, dried and the solvent removed leaving a viscous mass (70 mg) which partially solidified. It was obtained as colourless prisms from *n*-hexane, m.p. 121° and was identified with an authentic specimen. The yield was 42 mg (14%).

4:4-*Ethylenedioxy*cyclo*hexane carboxylic acid* (V). This was prepared by heating a mixture of ethyl 4-oxo-*cyclo*hexanecarboxylate[4] (6·1 g), ethylene glycol (2·5 g), *p*-toluenesulphonic acid (0·1 g) in benzene (50 cc) for 4 hr, using the apparatus previously mentioned. After collecting 1 cc of water, an oil b.p. 140–145°/15 mm (6 g, 83%) was obtained, and this was hydrolysed by refluxing with NaOHaq. and methanol. The acid (V) was obtained from the sodium salt by neutralisation with dilute HCl with cooling. The acid was extracted with ether and obtained as a colourless oil (2·6 g, 50%) b.p. 131–136°/2 mm. A small portion of this oil treated with dilute HCl gave the corresponding ketonic acid m.p. 67–68° which was not depressed on mixing with an authentic specimen.[4]

4′:4′*Ethylenedioxy*-cyclo*hexane-carbox*-(3:4-*dimethoxyphenethyl*)-*amide* (VI). The acid (V, 2·6 g) in ether was converted to the chloride with thionyl chloride (1·2 g). The solvent and excess of thionyl chloride were removed *in vacuo* and the reddish residue (2·5 g) was dissolved in benzene, and the solution treated with 3:4-dimethoxyphenethylamine (1 g) in the presence of potassium carbonate (1·5 g). The amide (VI) was obtained as a yellow gum which solidified (1·5 g) and crystallised from a mixture of benzene and *n*-hexane as colourless needles (0·8 g) m.p. 109–110° (Found: C, 65·7; H, 7·4; N, 3·9. $C_{19}H_{27}O_5N$ requires: C, 65·3; H, 7·7; N, 4·0%). On refluxing a

[4] R. H. Martin and R. Robinson, *J. Chem. Soc.* 491 (1943).

solution of the ketal amide (0·2 g) in ethanol (10 cc) with HCl (2 cc, 2%) for 2 hr, the *ketonic amide* was obtained in quantitative yield as colourless needles m.p. 143–145° from *n*-hexane (Found: C, 66·6; H, 7·4; N, 4·3. $C_{17}H_{23}O_4N$ requires: C, 66·9; H, 7·5; N, 4·6%). The 2:4-*dinitrophenylhydrazone* was obtained as orange needles m.p. 206–207° (decomp.) from ethanol (Found: C, 56·7; H, 5·2; N, 14·2. $C_{23}H_{27}O_7N_5$ requires: C, 56·9; H, 5·5; N, 14·4%).

1-(4′:4′-*Ethylenedioxy*cyclo*hexyl*)-6:7-*dimethoxy*-3:4-*dihydro*isoquinoline (VII). The amide (VI, 0·5 g) in pyridine (30 cc) was cyclised with phosphorus pentoxide (5 g) as described above. The reddish syrup (0·5 g) was dissolved in benzene, washed and dried and the solvent evaporated leaving a reddish syrup which could not be crystallised. It was converted to the *picrate* which crystallised as yellow needles m.p. 103–104° from ethanol (Found: C, 52·3; H, 5·4; N, 9·5. $C_{25}H_{28}O_{11}N_4$, $\frac{1}{2}H_2O$ requires: C, 52·7; H, 5·2; N, 9·8%). The yield of picrate was good (75%).

1-(4′-*oxo*-cyclo*hexyl*)-6:7-*dimethoxy*-3:4-*dihydro*isoquinoline (VIII). A solution of (VII, 0·3 g) in HCl (5 cc, 10%) was heated (steam-bath) for 2 hr. On cooling, the solution was shaken with benzene to remove undissolved matter and treated with charcoal, filtered and the filtrate treated with potassium carbonate. The base was extracted with benzene, dried and the solvent evaporated leaving a yellow syrup (0·24 g) which darkened in the air. The *picrate*, yellow needles m.p. 161° (decomp.) from ethanol (Found: C, 53·3; H, 4·8; N, 10·5. $C_{23}H_{24}O_{10}N_4$ requires: C, 53·5; H, 4·65; N, 10·85%).

The 2:4-*dinitrophenylhydrazone*, yellow needles m.p. 179–180° (decomp.) from ethanol (Found: C, 59·5; H, 5·6; N, 15·2. $C_{23}H_{25}O_8N_5$ requires: C, 59·1; H, 5·35; N, 14·9%).

1-(3′:4′-*Dimethoxyphenethyl*)-4-*oxo*-5-*methyl-piperid*-2-*one* (XI). To a solution of ethyl N-(3:4-dimethoxyphenethyl)-N(2′-ethoxycarbonylpropyl)-malonamidate[5] (IX, 16 g) in xylene (50 cc), sodium dust (0·8 g) was added and the mixture refluxed (oil-bath) for 3 hr when the evolution of H ceased and the sodium compound of the ketonic ester (X) separated. After cooling, the xylene layer was decanted and the sodium compound was dissolved in ice cold water acidified with dilute HCl, and the ketonic ester extracted with benzene yielding (X, 14·2 g). It gave a reddish ferric chloride reaction. The crude ester was subjected to ketonic fission by dissolving in acetic acid (10%) and refluxing for 3 hr when the evolution of CO_2 ceased. The solution was neutralised with sodium bicarbonate solution, extracted with benzene and the solution repeatedly extracted with sodium hydroxide solution (10%). The ketopiperidone was obtained from the aklaline solution by acidifying with HCl and extracting with benzene, dried and the solvent evaporated leaving a syrup (7·2 g, 64%) which solidified, and crystallised from benzene and *n*-hexane in colourless needles m.p. 94–95° (Found: C, 66·25; H, 7·1; N, 4·6. $C_{16}H_{21}O_4N$ requires: C, 65·95; H, 7·3; N, 4·8%). (XI) gave no ferric chloride reaction. Infra-red spectrum Nujol 1655 cm^{-1} (lactam C=O), Nujol 1722 cm^{-1} (ketone C=O). The 2:4-*dinitrophenyl hydrazone* formed yellowish red needles m.p. 202–203° (decomp.) from ethanol (Found: C, 55·9; H, 5·6; N, 15·5. $C_{22}H_{25}O_7N_5$ requires: C, 56·05; H, 5·3; N, 14·9%).

2:2-*Ethylenedioxy*-3-*methyl*-9:10-*dimethoxy*-3:4:6:7-*tetrahydro*-2H-*benzo*[a]*quinolizine* (XIII). The ketone (XI) was converted to ketal (XII) as described above, and

[5] K. Mizukami, *Chem. Pharm. Bull. Japan* **6**, 312 (1958).

obtained as a yellow syrup (85%) which was free from the ketone (XI). Infra-red spectrum (capillary 1645 cm^{-1}, lactam C=O, no band in the ketonic region). The crude ketal (1 g) was cyclised with phosphorus pentoxide (5 g) in pyridine with sea sand for 6 hr. The product, obtained as a yellow jelly (0·8 g) was dissolved in acetic acid (5%), filtered through a wet filter and the base liberated by addition of potassium carbonate and extracted with benzene which on evaporation left a syrup (0·3 g, 38%). The *picrate* crystallised in yellow needles from ethanol m.p. 200° (effervescence) (Found: C, 49·6; H 4·6; N 10·1. $C_{24}H_{26}O_{11}N_4$, 1·5 H_2O requires: C, 50·3; H, 5·1; N, 9·8%. $C_{24}H_{26}O_{11}N_4$, $2H_2O$ requires C, 49·5; H, 5·0; N, 9·6%).

2:2-*Ethylenedioxy*-3-*methyl*-9:10-*dimethoxy*-1:2:3:4:6:7-*hexahydro*-11bH-*benzo*[a]*quinolizine* (XIV). The reduction of (XIII) (0·2 g) was carried out in presence of Raney nickel, 1 molar equivalent of hydrogen being absorbed in 2 hr. The product was obtained as a syrup which did not crystallise. The *picrate* was obtained as yellow needles from ethanol m.p. 203–204° (decomp.) (Found: C, 52·8; H, 5·3; N, 10·2. $C_{24}H_{28}O_{11}N_4$ requires: C, 52·55; H, 5·1; N, 10·2%).

2-*Oxo*-3-*methyl*-9:10-*dimethoxy*-1:2:3:4:6:7-*hexahydro*-11bH-*benzo*[a]*quinolizine* (XV). The ketal (XIV) is readily hydrolysed with HCl (5%) by heating (steam-bath) for 2 hr. On working up the product as described above (XV) was obtained as a yellow jelly which solidified and crystallised from *n*-hexane in colourless needles m.p. 139° and was identified by comparison with an authentic specimen of (XV) synthesised by Mizukami by a different method (Found: C, 67·55; H, 7·95; N, 5·1. Calc. for $C_{16}H_{21}O_3N$, $0·5H_2O$, C, 67·6; H, 7·7; N, 4·9%). The *picrate* crystallises in yellow needles from ethanol m.p. 197–198° (decomp.) (Found: C, 52·2; H, 5·1; N, 11·1. $C_{22}H_{24}O_{10}N_4$ requires: C, 52·4; H, 4·8; N, 11·1%). The *hydrochloride* of the base crystallises as colourless plates from ethanol m.p. 198–199° (decomp.) (Found: C, 58·2; H, 7·85; N, 4·4. $C_{16}H_{22}O_3NCl$, H_2O requires: C, 58·3; H, 7·3; N, 4·2%). The 2:4-*dinitrophenylhydrazone hydrogen sulphate* crystallises in yellow prisms from ethanol m.p. 173–174° (Found: C, 47·8; H, 5·3; N, 12·9. $C_{22}H_{25}O_6N_5$, H_2SO_4 requires: C, 47·7; H, 4·9; N, 12·7%).

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