SYNTHESIS OF QUINOLIZINE DERIVATIVES

By T. R. Govindachari, F.A.Sc. and B. S. Thyagarajan

(Department of Chemistry, Presidency College, Madras)

Received October 13, 1953

Polycyclic structures incorporating the quinolizine[a] ring system are present in berberine and related alkaloids. An ingenious method for the synthesis of such types of benzo- and dibenzoquinolizidines was developed by Sugasawa and Sugimoto.[1] This consisted in the oxidation by alkaline ferricyanide of a quaternary salt formed between a β-aryl ethyl halide and a heterocyclic base, to the cyclic amide, followed by the cyclisation of the latter with phosphorous oxychloride to a quinolizinium halide. The method has been successfully applied for the synthesis of analogues of emetine.[2] However, only alkoxy substituted β-aryl ethyl halides and similarly substituted heterocyclic bases have so far been used in this method probably due to the belief that in the absence of such alkoxy substitution ring closure may not proceed at all. Indeed even though the simple N-β-phenethyl-2-pyridone and N-β-phenethyl-2-quinolone had been made by Sugasawa and Sugimoto[1] no attempts were made to cyclise them to the corresponding quinolizines.*

The object of the study presented in this paper was to ascertain whether benzo- and dibenzoquinolizines could be synthesised by the Sugasawa procedure in the absence of activating alkoxy substituents. Quaternary salts were formed between β-phenethyl bromide and pyridine, α-picoline, quinoline and isoquinoline. These bromides have been reported previously.[3] Quaternary salts were also formed between β-(1-naphthyl) ethyl bromide and pyridine, quinoline, 4-methyl quinoline, 7-methyl quinoline and isoquinoline. These salts have not been reported before. They were crystalline solids, sparingly soluble in water and not at all hygroscopic unlike the quaternary salts with β-phenethyl bromide.

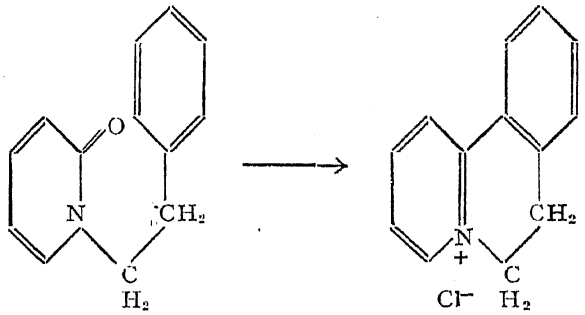
The oxidation of these quaternary salts was generally conducted at room temperature with alkaline potassium ferricyanide. N-β-phenethyl-α-picolinium bromide, N-β-phenethyl quinolinium bromide and N-β-(1-naphthyl) ethyl lepidinium bromide gave on oxidation only tarry oils under a variety of conditions. It was possible however to isolate the expected

* The material embodied in this paper formed part of a thesis submitted to the University of Madras in January 1953 for the Degree of Master of Science. While this paper was in preparation our attention has been drawn to a publication by Sugasawa *et al.* in the *J. Pharm. Soc. Jap.*, **72**, No. 10, p. 1275, in which the syntheses of three of the compounds prepared by us in the course of this study are reported.

oxidation product in crystalline condition by chromatographic fractionation of the tarry products, though in poor yields. The other quarternary salts were converted to the cyclic amides in excellent yield by oxidation with alkaline ferricyanide.

With the exception of N-β-phenethyl-6-methyl-2-pyridone, N-β-phenethyl-2-quinolone and N-β-(1-naphthyl) ethyl-4-methyl-2-quinolone, which were obtained in low yields, all the other cyclic amides were cyclised to the substituted quinolizinium salts by the action of phosphorous oxychloride and isolated as the quarternary iodides. The cyclisations have been found to proceed in excellent yields in all cases.

This remarkable ease of cyclisation is in striking contrast to the difficulty of cyclisation of acyl derivatives of β-phenethyl amine. The driving force in the present case appears to be the tendency of the heterocyclic part of the molecule to become fully aromatic.



The various quinolizinium iodides were reduced smoothly to the corresponding hydroquinolizines by reduction in alcohol medium in the presence of Adams' catalyst. The reduction products were purified by chromatography and characterised as hydrochlorides, picrates or picrolonates.

Experimental

β-phenethyl bromide was made by the method of Rupe.[4]

β-1-naphthyl ethyl bromide was made by the method of Haworth and Mavin.[5]

N-β-*phenethyl pyridinium bromide*

Pyridine (5 g.) and β-phenethyl bromide (10 g.) were refluxed in dry toluene (50 ml.) for three hours. A white crystalline solid separated on cooling. It was filtered and washed with absolute ether. On recrystallisation from absolute alcohol-ether mixture it was obtained in the form of lustrous needles melting at 125–126°; yield, 14·5 g. (Found: N, 5·5%; $C_{13}H_{14}NBr$ requires N, 5·3%).

Sugasawa and Sugimoto[1] report the melting point of this compound as 112°.

N-β-phenethyl pyridinium iodide

A solution of N-β-phenethyl pyridinium bromide (0·5 g.) in water (5 ml.) was treated with a saturated aqueous solution of potassium iodide (5 ml.). The precipitated iodide was crystallised from a mixture of absolute alcohol and ether and was obtained in the form of glistening needles melting at 166° (Found: N, 4·7%; $C_{13}H_{14}NI$ requires N, 4·5%).

N-β-phenethyl-2-pyridone

A solution of N-β-phenethyl pyridinium bromide (2·6 g.) in water (25 ml.) was added dropwise to a vigorously stirred aqueous solution of potassium ferricyanide (11·8 g.) and sodium hydroxide (3 g.) in the minimum amount of water. The solution was stirred for six hours at room temperature. The brown solid which separated was filtered, washed with water, dried and recrystallised from benzene, yielding colourless plates melting at 105°. The aqueous filtrate on extraction with benzene gave a small amount of the same pyridone. Yield, 1·3 g. (Found: C, 78·1%; H, 6·5%; N, 7·4%; $C_{13}H_{13}NO$ requires C, 78·4%; H, 6·5%; N, 7·0%).

3 : 4-dihydro-9 : 10-dehydro-1 : 2-benzoquinolizinium iodide

A solution of the above pyridone (1·5 g.) in absolute benzene (25 ml.) was refluxed with phosphorous oxychloride (12 ml.) for three hours. The reaction mixture was cooled and treated with a large excess of petroleum ether (b.p. 40–60°). After an hour, the solvent was decanted off from the black oil which had settled at the bottom. The oil was dissolved in dilute hydrochloric acid (0·2N, 25 ml.), warmed and filtered. The clear filtrate was treated with excess of a saturated aqueous solution of potassium iodide. The precipitated product was filtered, washed with water, dried and recrystallised from alcohol, when it was obtained as a fine yellow powdery material melting at 190°; yield, 1·9 g. (Found: C, 50·1%; H, 3·6%; N, 4·6%; $C_{13}H_{12}NI$ requires C, 50·5%; H, 3·9%; N, 4·5%).

3 : 4 : 5 : 6 : 7 : 8-hexahydro-1 : 2-benzoquinolizine

A solution of the above benzoquinolizinium iodide (0·5 g.) in alcohol (100 ml.) was shaken with hydrogen at a pressure of 60 lb./sq. in. in the presence of Adams' catalyst (0·1 g.). When the absorption of hydrogen ceased, the solution was filtered to remove the catalyst and the filtrate distilled off to remove the solvent. The residue was dissolved in water and made alkaline. The liberated base was extracted with ether. On removal

of the solvent a reddish oil was obtained which could not be induced to solidify.

The picrate prepared in the usual way from this oil was recrystallised from alcohol when it was obtained in the form of yellow prisms melting at 123° (Found: C, 54·7%; H, 5·0%; N, 13·5%; $C_{19}H_{21}N_4O_7$ requires C, 54·7%; H, 5·0%; N, 13·4%).

The picrolonate prepared by mixing alcoholic solutions of the oil and picrolonic acid was crystallised from alcohol when it was obtained in the form of yellow needles melting at 208° (Found: C, 60·8%; H, 5·6%; N, 15·6%; $C_{25}H_{27}N_5O_5$ requires C, 61·1%; H, 5·8%; N, 15·5%).

The following compounds were prepared by methods analogous to those described above.

3:4:5:6-tetrahydro-1:2:7:8-dibenzoquinolizine

N-β-phenethyl isoquinolinium bromide.—It was crystallised from a mixture of absolute alcohol and ether and was obtained in the form of shining needles melting at 173° (Found: N, 4·8%; $C_{17}H_{16}NBr$ requires N, 4·5%). *N-β-phenethyl isoquinolinium iodide* was crystallised from alcohol when it was obtained in the form of colourless needles melting at 177° (Found: N, 4·0%; $C_{17}H_{16}NI$ requires N, 3·9%). *N-β-phenethyl isoquinolone-1* was obtained by oxidation of the quarternary bromide with alkaline ferricyanide. Crystallisation from benzene gave pale yellow plates melting at 102°. 3 g. of the quarternary bromide yielded 2·1 g. of the isoquinolone (Found: C, 82·2%; H, 6·2%; N, 5·9%; $C_{17}H_{15}NO$ requires C, 81·9%; H, 6·0%; N, 5·6%). *3:4-dihydro-9:10-dehydro-1:2:7:8-dibenzoquinolizinium iodide*, obtained by the cyclisation of the above isoquinolone was recrystallised from water. It separated as yellow needles melting at 120°. After drying at 100° for three hours *in vacuo* it melted at 155°. 2 g. of the isoquinolone gave 2·4 g. of the quinolizinium iodide (Found: C, 56·6%; H, 3·8%; N, 4·1%; $C_{17}H_{14}NI$ requires C, 56·8%; H, 3·9%; N, 3·9%).

3:4:5:6-tetrahydro-1:2:7:8-dibenzoquinolizine was obtained by catalytic reduction of the above iodide and was obtained in the form of an oil. When the oil was treated with hydrochloric acid the hydrochloride was formed which on recrystallisation from dilute alcohol was obtained as a fine powder, melting at 207° (Found: C, 74·7%; H, 6·9%; N, 5·3%; $C_{17}H_{19}NCl$ requires C, 74·9%; H, 7·0%; N, 5·1%). The picrolonate of the above base was crystallised from alcohol when it was obtained as yellow needles melting at 169° (Found: C, 64·5%; H, 5·1%; N, 14·2%; $C_{27}H_{28}N_6O_6$ requires C, 64·8%; H, 5·2%; N, 14·0%).

N-β-phenethyl-α-picolinium bromide was obtained as colourless needles by crystallisation from alcohol and was found to melt at 198° (Found: N, 5·2%; $C_{14}H_{16}NBr$ requires N, 5·0%). *N-β-phenethyl-6-methyl-2-pyridone* obtained by alkaline ferricyanide oxidation of the above quarternary salt and subsequent chromatographic fractionation of the oily material was a colourless crystalline solid. On recrystallisation from petroleum ether it was obtained in the form of colourless plates melting at 108° (Found: C, 78·6%; H, 6·7%; N, 6·9%; $C_{14}H_{15}NO$ requires C, 78·9%; H, 7·0%; N, 6·6%).

N-β-phenethyl-2-quinolone. The quarternary bromide formed between β-phenethyl bromide and quinoline could not be obtained in the form of a solid and the oily material as such was oxidised with alkaline ferricyanide. The product again was an oil which on chromatographic fractionation over alumina and recrystallisation from petroleum ether, was obtained in the form of colourless plates melting at 98° (Found: C, 81·8%; H, 5·9%; N, 5·6%; $C_{17}H_{15}NO$ requires C, 81·9%; H, 6·0%; N, 5·6%).

N-β-(1-naphthyl) ethyl pyridinium bromide was obtained as colourless needles by crystallisation from alcohol. It melted at 110° (Found: N, 4·6%; $C_{17}H_{16}NBr$ requires N, 4·5%). *N-β-(1-naphthyl) ethyl pyridinium iodide* was crystallised from alcohol when it separated in the form of colourless needles melting at 120° (Found: N, 4·0%; $C_{17}H_{16}NI$ requires N, 3·9%). *N-β-(1-naphthyl) ethyl-2-pyridone.* It was obtained as colourless plates by recrystallisation from alcohol. It melted at 72° (Found: C, 81·7%; H, 6·0%; N, 5·7%; $C_{17}H_{15}NO$ requires C, 81·9%; H, 6·0%; N, 5·6%). *3:4-dihydro-9:10-dehydro-1:2:1':2'-naphthoquinolizinium iodide*, obtained by the cyclization of the above pyridone, was recrystallised from aqueous alcohol when it separated as a fine white powder melting at 172° (Found: C, 49·2%; H, 4·4%; N, 3·7%; $C_{17}H_{14}NI \cdot 3H_2O$ requires C, 49·4%; H, 4·8%; N, 3·4%). *3:4:5:6:7:8-hexahydro-1:2:1':2'-naphthoquinolizine* was obtained by the catalytic reduction of the above iodide. It was an oil, treatment of which with hydrochloric acid gave the hydrochloride. The latter was recrystallised from water when it was obtained in the form of a fine white powder melting at 218° (Found: C, 78·1%; H, 6·3%; N, 4·5%; $C_{21}H_{21}NCl$ requires C, 78·1%; H, 6·5%; N, 4·3%). The hexahydro base gave a crystalline picrate which on recrystallisation from alcohol was obtained as yellow needles, melting at 157° (Found: C, 62·5%; H, 4·3%; N, 11·0%; $C_{27}H_{23}N_4O_7$ requires C, 62·9%; H, 4·5%; N, 10·9%).

N-β-(1-naphthyl) ethyl isoquinolinium bromide was obtained as pale brown needles by crystallisation from absolute alcohol-ether mixture. It

melted at 158° (Found: N, 3·9%; $C_{21}H_{18}NBr$ requires N, 3·8%). *N*-β-(1-*naphthyl*) *ethyl isoquinolinium iodide* was obtained as yellow powder on recrystallisation from alcohol. It melted at 190° (Found: N, 3·5%; $C_{21}H_{18}NI$ requires N, 3·4%).

N-β-(1-*naphthyl*) *ethyl*-1-*isoquinolone* was prepared by oxidation of the bromide with alkaline ferricyanide and was obtained as colourless plates by recrystallisation from alcohol. It melted at 97°. 7 g. of the bromide gave 4·3 g. of the isoquinolone (Found: C, 83·7%; H, 5·5%; N, 4·3%; $C_{21}H_{17}NO$ requires C, 84·2%; H, 5·6%; N, 4·6%). 3:4-*dihydro*-9:10-*dehydro*-1:2:1′:2′-*naphtho*-7:8-*benzoquinolizinium iodide* was made by the cyclisation of the above isoquinolone. 2·6 g. of the iodide was obtained from 2 g. of the former. On recrystallisation from alcohol it separated as a yellow powder melting at 192° (Found: C, 61·4%; H, 3·8%; N, 3·7%; $C_{21}H_{16}NI$ requires C, 61·6%; H, 3·9%; N, 3·4%).

3:4:5:6-*tetrahydro*-1:2:1′:2′-*naphtho*-7:8-*benzoquinolizine* was obtained by the catalytic reduction of the above base and subsequent chromatographic fractionation of the oil got. It was recrystallised from alcohol when it separated as colourless white plates melting at 98° (Found: C, 88·5%; H, 7·2%; N, 5·1%; $C_{21}H_{20}N$ requires C, 88·1%; H, 7·0%; N, 4·9%). The picrate of the above base on recrystallisation from alcohol was obtained as a yellow powder melting at 209° (Found: C, 63·2%; H, 4·7%; N, 11·1%; $C_{27}H_{23}N_4O_7$ requires C, 62·9%; H, 4·5%; N, 10·9%). The picrolonate of the base was crystallised from alcohol and was obtained as a yellow powdery solid melting at 190° (Found: C, 67·4%; H, 5·3%; N, 12·9%; $C_{31}H_{28}N_5O_5$ requires C, 67·6%; H, 5·1%; N, 12·7%).

N-β-(1-*naphthyl*) *ethyl quinolinium bromide* was obtained as a colourless powdery solid on recrystallisation from water. It melted at 172° (Found: N, 3·7%; $C_{21}H_{18}NBr$ requires N, 3·8%). *N*-β-(1-*naphthyl*) *ethyl quinolinium iodide* prepared from the above bromide was recrystallised from alcohol when it separated in the form of fine needles, melting at 204° (Found: N, 3·5%; $C_{21}H_{18}NI$ requires N, 3·4%). *N*-β-(1-*naphthyl*) *ethyl*-2-*quinolone* obtained by the oxidation of the bromide was crystallised from dilute alcohol when it separated in the form of pale brown flakes melting at 172° (Found: C, 83·9%; H, 5·6%; N, 4·3%; $C_{21}H_{17}NO$ requires C, 84·3%; H, 5·7%; N, 4·7%).

3:4-*dihydro*-9:10-*dehydro*-1:2:1′:2′-*naphtho*-5:6-*benzoquinolizinium iodide*, the product obtained on cyclisation of the above quinolone was crystallised from alcohol when it was got as a yellow powdery solid melting at 193° (Found: C, 61·4%; H, 3·8%; N, 3·6%; $C_{21}H_{16}NI$ requires C, 61·6%; H, 3·9%; N, 3·4%).

3:4:7:8-tetrahydro-1:2:1':2'-naphtho-5:6-benzoquinolizine was obtained by catalytic reduction of the above base and purified by recrystallisation from alcohol after passing through a column of alumina. It was obtained in the form of colourless flakes melting at 113° (Found: C, 88·4%; H, 7·2%; N, 5·0%; $C_{23}H_{23}N$ requires C, 88·1%; H, 7·0%; N, 4·5%). The picrate of the base was crystallised from alcohol when it separated as yellow needles melting at 77° (Found: C, 63·1%; H, 4·6%; N, 10·9%; $C_{29}H_{26}N_4O_7$ requires C, 62·9%; H, 4·8%; N, 10·9%).

N-β-(1-naphthyl) ethyl-7-methyl quinolinium bromide, prepared in the usual way was crystallised from alcohol ether and was obtained in the form of colourless plates melting at 194° (Found: N, 3·9%; $C_{22}H_{20}NBr$ requires N, 3·7%). *N-β-(1-naphthyl) ethyl-7-methyl isoquinolinium iodide* was crystallised from alcohol and was obtained as a pale yellow powder melting at 228° (Found: N, 3·5%; $C_{22}H_{20}NI$ requires N, 3·1%). *N-β-(1-naphthyl) ethyl-7-methyl-2-quinolone*, obtained by the oxidation of the bromide was recrystallised from petroleum ether when it separated in the form of pale brown flakes melting at 136° (Found: C, 84·2%; H, 6·3%; N, 4·8%; $C_{22}H_{19}NO$ requires C, 84·4%; H, 6·1%; N, 4·5%). *3:4-dihydro-9:10-dehydro-1:2:1':2'-naphtho-5:6:1'':2''-benzo-4''-methyl benzoquinolizinium iodide* obtained from the above quinolone was crystallised from alcohol when it separated as pale yellow powder melting at 181° (Found: C, 62·2%; H, 4·6%; N, 3·4%; $C_{22}H_{18}NI$ requires C, 62·4%; H, 4·3%; N, 3·3%).

3:4:7:8-tetrahydro-1:2:1':2'-naphtho-5:6:1'':2''-benzo-4''-methyl benzoquinolizine was obtained by the reduction of the foregoing iodide and on recrystallisation from alcohol after chromatographic purification it separated in the form of colourless needles melting at 131° (Found: C, 88·3%; H, 7·5%; N, 4·9%; $C_{22}H_{23}N$ requires C, 88·0%; H, 7·3%; N, 4·7%). The picrate of the above base prepared in the usual way was crystallised from alcohol when it was obtained as yellow needles melting at 145° (Found: C, 63·8%; H, 4·5%; N, 10·7%; $C_{28}H_{26}N_4O_7$ requires C, 63·8%; H, 4·9%; N, 10·5%).

N-β-(1-naphthyl) ethyl-4-methyl quinolinium bromide was crystallised from absolute alcohol-ether when it separated in the form of shining plates melting at 196° (Found: N, 3·9%; $C_{22}H_{20}NBr$ requires N, 3·7%).

N-β-(1-naphthyl) ethyl-4-methyl-2-quinolone obtained by the oxidation of the above bromide was an oil which on chromatographic fractionation gave a crystalline solid. The latter on recrystallisation from petroleum ether was obtained as a colourless powder melting at 98° (Found: C, 84·1%; H, 6·1%; N, 4·7%; $C_{22}H_{19}NO$ requires C, 84·3%; H, 6·1%; N, 4·5%).

Summary

The scope of the Sugasawa method for the synthesis of quinolizinium derivatives has been investigated. Several benzo, naphtho and naphthobenzo quinolizinium compounds have been synthesised in excellent yields, although the ring on which cyclisation was effected did not carry any activating substituents.

References

1. Sugasawa and Sugimoto — *Ber.*, 1939, **72**, 977.
2. Pailer, Schweglberger and Rechberger — *Monatsh.*, 1952, **83**, 513.
3. Harwell and Kornberg — *J.A.C.S.*, 1946, **68**, 860.
4. Roser — *Ann.*, 1913, **398**, 114.
5. Haworth and Mavin — *J.C.S.*, 1933, 1018.