Action of Alcoholic Potassium Hydroxide on 3 : 4-*Dihydro*-1-2′-*nitrobenzyl*isoquinolines.

By T. R. Govindachari and K. Nagarajan.

[Reprint Order No. 5228.]

3 : 4-Dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline ($C_{19}H_{20}O_5N_2$) in refluxing methanolic potassium hydroxide gave a compound $C_{19}H_{16}O_4N_2$ (A), a compound $C_{19}H_{18}O_5N_2$ (B), and 3 : 4-dihydro-6 : 7-dimethoxy*iso*carbostyril. Structures are suggested for the compounds A and B on the basis of their reactions and light absorptions. Four other 3 : 4-dihydro-1-2′-nitrobenzyl*iso*quinolines were also shown to yield compounds analogous to A, on treatment with methanolic potassium hydroxide, by loss of 4 hydrogen atoms and one oxygen atom.

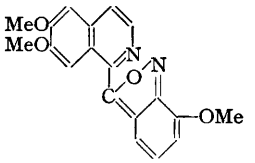
Several 1-benzyl-3 : 4-dihydro*iso*quinolines have been converted into the corresponding 1-benzoyl*iso*quinolines by treatment with hot methanolic potassium hydroxide (Späth, Reidl, and Kubiczek, *Monatsh.*, 1948, **79**, 72; Noller and Azima, *J. Amer. Chem. Soc.*, 1950, **72**, 17; Julian, Karpel, Magnani, and Meyer, *ibid.*, 1948, **70**, 180). During some synthetic work, we treated 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline with hot methanolic potassium hydroxide. From the warm solution, a yellow crystalline material separated, which was not the expected 1-benzoyl*iso*quinoline derivative.

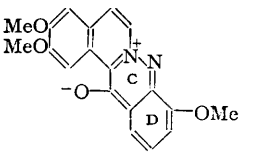
This product, designated A, had the molecular formula $C_{19}H_{16}O_4N_2$ and contained three methoxyl groups. It did not react with stannous chloride in boiling hydrochloric acid, nor did it yield a carbonyl derivative; it was unaffected by sodium borohydride, acetic anhydride, phosphorus pentachloride, hydrogen at 60 lb. in the presence of Adams catalyst in alcohol, or by hot concentrated potassium hydroxide solution, and it did not reduce Fehling's or Tollens's reagent. It was insoluble in cold 4N- but dissolved in hot 10N-hydrochloric acid. From this solution an orange-red hydrochloride crystallised on cooling, and this was also obtained by means of hydrogen chloride in benzene; in water it regenerated the original compound. Treatment of compound A with methyl iodide under pressure yielded a monomethiodide.

It was then of interest to see if other closely related compounds behaved similarly on treatment with hot methanolic potassium hydroxide. From 1-(α-hydroxy-3-methoxy-2-nitrobenzyl)-6 : 7-dimethoxy*iso*quinoline a small amount of 6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline was obtained, the original compound being mostly recovered. 6 : 7-Dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline was unaffected by hot methanolic potassium hydroxide, but yielded compound A on reduction with tin and acetic acid or with excess of sodium borohydride in warm methanol.

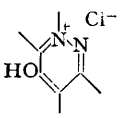
Analogy with the reduction of *o*-nitroacetophenone (Bamberger and Elger, *Ber.*, 1903, **36**, 1617) and *o*-nitrobenzophenone (Bamberger and Lindberg, *Ber.*, 1909, **42**, 1723) to

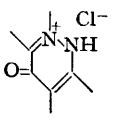
5-methyl- and 5-phenyl-3 : 4-benz*iso*oxazole by tin and acetic acid suggested that compound A might be a benz*iso*oxazole derivative (I). However, 3 : 4-benz*iso*oxazoles are unstable to alkali. 3 : 4-Benz*iso*oxazole itself is converted by dilute sodium hydroxide solution into anthranilic acid (Friedlaender and Henriques, *Ber.*, 1882, **15**, 2106) and 5-methyl-3 : 4-benz*iso*oxazole into *o*-aminoacetophenone (Bamberger, *Ber.*, 1909, **42**,

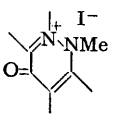
(I) 

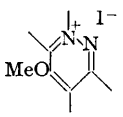
 (II)

1668). Besides, these compounds are powerful reducing agents giving positive reactions with Fehling's and Tollens's reagents. Structure (I) cannot therefore be valid for compound A. The only other alternative which can be advanced is (II). The ultra-violet absorption spectrum indicated the presence of a highly conjugated system. The infra-red absorption spectrum showed that NH, OH, CO, and NO_2 functions were not present. The infra-red absorption spectrum of the hydrochloride showed presence of an NH or OH function (2·96 μ) and absence of a CO function. On this basis, the hydrochloride should be assigned structure (III), although the hydrochloride would normally have been expected to be (IV). The methiodide showed a strong absorption at 5·86 μ and should therefore be assigned structure (V); however, its methoxyl content corresponded more closely to four methoxyl groups, which indicates structure (VI) for the methiodide; the reason for this anomaly is not evident.

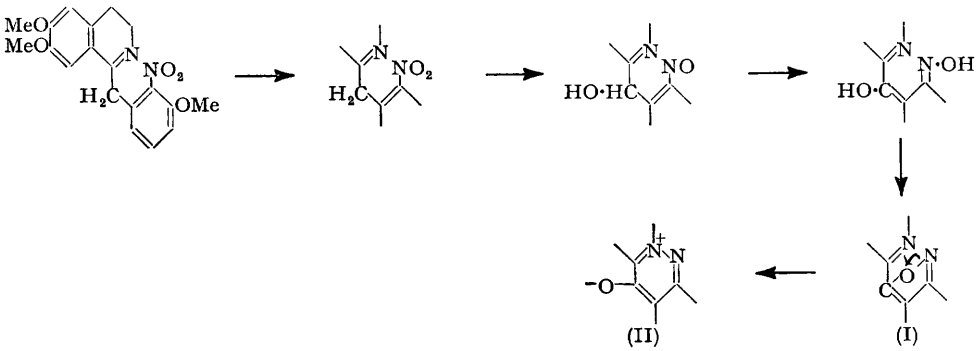

(III)


(IV)


(V)


(VI)

A compound (II) could arise from 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline by the annexed reactions. Similarly, the benz*iso*oxazole (I) is probably the intermediate in the reduction of 6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline to (II). The formation of the tetracyclic structure of type (II) seems to be a general reaction of 3 : 4-dihydro-1-2′-nitrobenzyl*iso*quinolines with hot methanolic potassium hydroxide: 3 : 4-dihydro-1-(3-methoxy-2-nitrobenzyl)-6 : 7-


(II) (I)

methylenedioxy-, 3 : 4-dihydro-6 : 7-dimethoxy-1-2′-nitrobenzyl-, 3 : 4-dihydro-1-(3 : 4-dimethoxy-2-nitrobenzyl)-6 : 7-dimethoxy-, and 3 : 4-dihydro-1-2′-nitrobenzyl-*iso*quinoline all yielded products having four hydrogen atoms and one oxygen atom less than the initial compound. The ultra-violet absorption spectra of these products were closely similar to

that of compound A (see Table). The products were obtained in varying yields which seemed to be influenced by the nature of the substitution in the benzyl portion of the molecule.

In the oxidation of 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline with methanolic potassium hydroxide, three other products besides compound A were isolated. One of these was 3 : 4-dihydro-6 : 7-dimethoxy*iso*carbostyril (Späth and

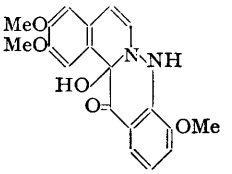
Absorption maxima (mμ) *of products from substituted* 1-*benzyl*-3 : 4-*dihydro*isoquinolines *by methanolic potassium hydroxide.*

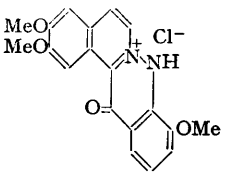
Subst. in benzyl group	Subst. in *iso*quinoline ring	Formula of product	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε
3-OMe-2-NO_2	6 : 7-$(OMe)_2$	$C_{19}H_{16}O_4N_2$ †	225	4·61	262 *	4·39	385	4·21
2-NO_2	6 : 7-$(OMe)_2$	$C_{18}H_{14}O_3N_2$	221	4·61	252	4·56	380	4·32
3-OMe-2-NO_2	6 : 7-O_2CH_2	$C_{18}H_{12}O_4N_2$	232	4·57	262 *	4·37	385	4·22
3 : 4-$(OMe)_2$-2-NO_2	6 : 7-$(OMe)_2$	$C_{20}H_{18}O_5N_2$	232	4·55	262 *	4·37	383	4·07
2-NO_2	—	$C_{16}H_{10}ON_2$	245	4·31	275	3·68	370	4·23

* Inflexion. † Substance A.

Dobrowsky, *Ber.*, 1925, **58**, 1274). A second, m. p. 205—207°, was isolated in quantity too small for further investigation. A third, designated B, had the molecular formula $C_{19}H_{18}O_5N_2$. This was basic, but salt formation with hydrochloric acid or picric acid involved elimination of a molecule of water, yielding salts isomeric with the corresponding salts of compound A. The ultra-violet absorption spectra of the compounds A and B differed. The infra-red absorption spectrum of compound B showed the presence of a carbonyl group (6·15 μ) and more than one NH or OH group (2·75, 2·88, 2·97, 3·13 μ);

(VII)





(VIII)

the infra-red absorption spectrum of its hydrochloride showed the presence of a CO group (6·08 μ), an NH or OH group (2·87, 3·03 μ), and a salt structure (4·43, 4·97, 5·05 μ). On this basis, compound B and its hydrochloride are assigned structures (VII) and (VIII).

Attempts to confirm the structures proposed are in progress.

Experimental

Analyses are partly by Mr. S. Selvavinayagam.

Action of Methanolic Potassium Hydroxide.—(a) *On* 3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-(3-*methoxy*-2-*nitrobenzyl*)*iso*quinoline. A solution of the base (Govindachari and Pai, *J. Org. Chem.*, 1953, **18**, 1352) (4·5 g.) in 10% methanolic potassium hydroxide (75 ml.) was refluxed on a water-bath for 8 hr., during which the originally clear brown solution deposited yellow crystals. The solution was cooled and the precipitate was filtered off and washed with methanol (filtrate A). Crystallisation of the residue from alcohol yielded *compound A* as yellow needles (1·7 g.), m. p. 179° [Found : C, 67·7, 67·8; H, 4·5, 4·7; N, 8·4, 8·3; OMe, 25·7%; *M*, ebullioscopically in benzene, 340, 349. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8; N, 8·3; OMe, 27·7%; *M*, 336].

The *hydrochloride*, prepared by passing dry hydrogen chloride into a solution of compound A in benzene, crystallised from alcohol–ether as yellow needles, m. p. 178° (decomp.). A red form was obtained by cooling a solution of the base in concentrated hydrochloric acid, but crystallisation from alcohol–ether yielded the yellow form, m. p. 178° (decomp.) (Found : C, 60·9; H, 4·3; N, 7·7; Cl, 9·7. $C_{19}H_{17}O_4N_2Cl$ requires C, 61·2; H, 4·6; N, 7·5; Cl, 9·5%). The *picrate*, prepared in benzene, crystallised from benzene as yellow needles, m. p. 205° (decomp.) (Found :

C, 52·5; H, 3·1; N, 12·7. $C_{25}H_{19}O_{11}N_5$ requires C, 53·1; H, 3·4; N, 12·4%). The compound A (0·5 g.) was heated in chloroform (5 ml.) with methyl iodide (5 ml.) at 100° for 18 hr. The solvent was then removed and the residue was dissolved in boiling alcohol (75 ml.). The solution was concentrated to 10 ml., then cooled, the amorphous precipitate removed, and the filtrate diluted with ether to turbidity. Pale yellow needles of the *methiodide* were obtained which after recrystallisation from alcohol–ether melted at 178° (Found: C, 49·7; H, 4·4; N, 5·8; OMe, 29·2. $C_{20}H_{19}O_4N_2I$ requires C, 50·2; H, 4·0; N, 5·9; 4OMe, 25·9, 3OMe, 19·5%).

The methanolic filtrate A was evaporated to dryness and a solution of the residue in benzene was repeatedly extracted with N-hydrochloric acid (benzene layer B). The acid extract was rendered alkaline and extracted with benzene and the solvent removed after drying (K_2CO_3). The residue in a small volume of benzene was passed through a column of alumina, and the column washed with benzene (500 ml.). The eluate yielded a solid (0·5 g.) which was repeatedly extracted with light petroleum (b. p. 40—60°); the soluble portion (0·05 g.) melted at 205—207° (Found: C, 51·9; H, 7·0; N, 7·1%); the insoluble portion, *compound* B, on recrystallisation from dilute alcohol, gave yellow needles, m. p. 117—118° (Found: C, 64·7; H, 5·6; N, 8·0; OMe, 24·1. $C_{19}H_{18}O_5N_2$ requires C, 64·4; H, 5·1; N, 7·9; 3OMe requires OMe, 26·3%). The *hydrochloride*, prepared as above, and crystallised from alcohol, had m. p. 195° (decomp.) (Found: C, 61·4; H, 5·2; N, 7·8. $C_{19}H_{17}O_4N_2Cl$ requires C, 61·2; H, 4·6; N, 7·5%). The *picrate* prepared in benzene and crystallised from benzene, had m. p. 187° (decomp.) (Found: C, 53·1; H, 3·5; N, 12·3. $C_{25}H_{19}O_{11}N_5$ requires C, 53·1; H, 3·4; N, 12·4%).

The benzene layer B was dried (Na_2SO_4), concentrated, and poured on a column of alumina, which was then washed with dry benzene. A yellow band was rapidly removed. Evaporation of the eluate from this zone gave compound A, m. p. 179° (0·1 g.). Subsequent elution with benzene containing 2% of alcohol gave a colourless solid, crystallising from benzene in plates (0·05 g.), m. p. 171—172° alone or mixed with 3 : 4-dihydro-6 : 7-dimethoxy*iso*carbostyril (Found: C, 63·5; H, 6·3; N, 6·8. Calc. for $C_{11}H_{13}O_3N$: C, 63·8; H, 6·3; N, 6·8%).

(b) *On* 3 : 4-*dihydro*-1-(3-*methoxy*-2-*nitrobenzyl*)-6 : 7-*methylenedioxy*isoquinoline. The base (0·3 g.) (Barger and Schlittler, *Helv. Chim. Acta*, 1932, **15**, 381) was refluxed with a solution of potassium hydroxide (3 g.) in methanol (100 ml.) for 12 hr. The *product* that separated was filtered off, after cooling, and crystallised from alcohol as orange needles (0·1 g.), m. p. 208° (Found: C, 67·4, 67·3; H, 3·8, 3·6; N, 9·0. $C_{18}H_{12}O_4N_2$ requires C, 67·5; H, 3·7; N, 8·8%).

(c) *On* 3 : 4-*dihydro*-1-(3 : 4-*dimethoxy*-2-*nitrobenzyl*)-6 : 7-*dimethoxy*isoquinoline. The base (1 g.) (Gulland and Haworth, *J.*, 1928, 1834) was refluxed with a solution of potassium hydroxide (3 g.) in methanol (50 ml.) for 10 hr. The *product* that separated crystallised from alcohol as yellow needles (0·15 g.), m. p. 150° (Found: C, 65·1; H, 5·0; N, 7·6. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 4·9; N, 7·7%).

(d) *On* 3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-2′-*nitrobenzyl*isoquinoline. The base (2 g.) (Gulland and Haworth, *J.*, 1928, 581) was heated under reflux with a solution of potassium hydroxide (6 g.) in methanol (100 ml.) for 12 hr. The solvent was then removed and the residue partitioned between benzene and N-hydrochloric acid. The benzene layer was washed with water, dried, concentrated to a small volume, and poured on alumina. Elution with benzene yielded a *product* which crystallised from alcohol in yellow needles (0·01 g.), m. p. 184—185° (Found: C, 71·0; H, 4·7; N, 9·3. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·2%). Elution with benzene containing 1% of alcohol then gave plates (0·17 g.) (from benzene), m. p. 172° alone or mixed with 3 : 4-dihydro-6 : 7-dimethoxyisocarbostyril.

The hydrochloric acid extract (above) was rendered alkaline and extracted with benzene. The sticky material recovered from the benzene was chromatographed on alumina and yielded a greenish-yellow *substance* (0·15 g.), crystallising from benzene in needles, m. p. 166° (Found: C, 70·1; H, 5·6; N, 9·2. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·2; N, 9·1%). This is probably a dihydro-derivative of the compound $C_{18}H_{14}O_3N_2$, m. p. 184°.

(e) *On* 3 : 4-*dihydro*-1-2′-*nitrobenzyl*isoquinoline. This compound has not been reported previously. Kay and Pictet (*J.*, 1913, **103**, 947) and Gadamer, Oberlin, and Schoeler (*Arch. Pharm.*, 1925, **263**, 81) reported that it could not be obtained from *o*-nitrophenyl-*N*-phenethylacetamide, but the following procedure was successful. The amide (Kay and Pictet, *loc. cit.*) (2 g.) was refluxed in dry toluene (80 ml.) with phosphoric oxide (12 g.) for 2 hr., during which more phosphoric oxide (13 g.) was added in portions. The mixture was then cooled, the excess of oxide was decomposed by crushed ice, and the aqueous layer separated and extracted with ether to remove non-basic material. The aqueous solution was then cooled and rendered alkaline and the liberated 3 : 4-*dihydro*-1-2′-*nitrobenzyl*isoquinoline extracted with ether, purified by one more passage through acid, and obtained after crystallisation from alcohol as

tan-coloured needles (0·49 g.), m. p. 115—116° (Found : C, 72·0; H, 5·3; N, 10·8. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3; N, 10·5%).

The above base (0·9 g.) was heated with methanolic potassium hydroxide (10%; 20 ml.) for 12 hr. The solvent was then removed and the residue was taken up in benzene. Basic material was removed by dilute hydrochloric acid and the sticky mass which was recovered from the benzene layer was purified by chromatography on alumina. Elution with benzene yielded a *product* (0·2 g.) which, crystallised from alcohol, had m. p. 106—107° (Found : C, 78·5; H, 3·9; N, 11·5. $C_{16}H_{10}ON_2$ requires C, 78·1; H, 4·1; N, 11·4%).

Reduction of 6 : 7-*Dimethoxy*-1-(3-*methoxy*-2-*nitrobenzoyl*)iso*quinoline.*—(a) *With tin and acetic acid.* A solution of 6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline (0·6 g.) (Govindachari and Nagarajan, *J.*, 1954, 2537) in boiling glacial acetic acid (6 ml.) was treated with tin foil (0·3 g.), then diluted with water (100 ml.) and repeatedly extracted with benzene. The extract was washed with water, dried (Na_2SO_4), concentrated to a small volume, and poured on alumina. Elution with benzene removed a yellow band rapidly, which gave compound A (0·15 g.), m. p. 179° (from alcohol).

(b) *With sodium borohydride in hot methanol.* The base (0·5 g.) in absolute methanol (30 ml.) was heated with sodium borohydride (1 g.) on a steam-bath for 6 hr. On cooling, a few crystals separated. These, recrystallised from alcohol, had m. p. 228—231° (Found : C, 66·0; H, 5·2; N, 8·7%). This *substance* was not further characterised or identified.

The filtrate was diluted with water (200 ml.) and extracted with benzene. The extract was concentrated to 10 ml. and poured on alumina. Washing with benzene (500 ml.) removed a yellow band from which compound A (0·15 g.) was isolated as yellow needles, m. p. 179° (from alcohol).

Subsequent elution with benzene containing 1% of alcohol gave 1-(α-hydroxy-3-methoxy-2-nitrobenzyl)-6 : 7-dimethoxy*iso*quinoline (Govindachari and Nagarajan, *loc. cit.*). This was the sole product if the reduction was carried out with cooling, below 30°.

Reduction of 6 : 7-*Dimethoxy*-1-2′-*nitrobenzoyl*iso*quinoline with Tin and Acetic Acid.*—This *base* was prepared by oxidation of 3 : 4-dihydro-6 : 7-dimethoxy-1-2′-nitrobenzyl*iso*quinoline (1 g.) with potassium dichromate (2 g.) in hot 70% acetic acid (5 ml.) for 1 hr. The material that separated was filtered off after cooling, and crystallised from alcohol as yellow plates, m. p. 200° (decomp.) (Found : C, 63·9; H, 4·4; N, 8·5. $C_{18}H_{14}O_5N_2$ requires C, 63·9; H, 4·1; N, 8·3%).

A solution of this base (0·3 g.) in boiling acetic acid (7 ml.) was treated with tin foil (0·15 g.). After all the tin had dissolved, the solution was diluted with water (100 ml.). The yellow precipitate was filtered off and recrystallised from alcohol, giving yellow flakes (0·2 g.), m. p. 185—187°, identical with the product $C_{18}H_{14}O_3N_2$ obtained by use of methanolic potassium hydroxide.

We are grateful to Professor A. R. Todd, F.R.S., and Prof. Roger Adams for valuable suggestions and for infra-red measurements, and to Dr. R. N. Haszeldine and Dr. E. J. Corey for interpretation of infra-red absorption spectra. We thank Dr. B. R. Pai for experimental assistance and helpful discussions and the Government of India for the award of a studentship to one of us (K. N.).

PRESIDENCY COLLEGE, MADRAS. [*Received, March 22nd,* 1954.]