STUDIES IN INTRAMOLECULAR INTERACTION OF AROMATIC NITRO GROUP WITH ORTHO SIDECHAIN

Part 1.—A New Synthesis of Quinoline N-Oxide Derivatives

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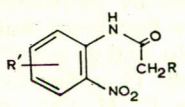
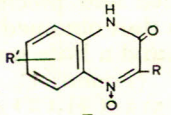
o-Nitroveratrylidenesuccinic acid (III), a nitrobenzene derivative with an active methylene group in its *ortho* side-chain, has been cyclised with the help of aqueous alkali to give directly an *N*-oxide of a quinoline derivative, $C_{12}H_{11}NO_5$. Its structure has been proved to be 3-carboxy-6,7-dimethoxyquinoline 1-oxide(Va), through its rearrangement with acetic anhydride to 2-hydroxy-6,7-dimethoxyquinoline-3-carboxylic acid*(VIa), which has been synthesised by an unambiguous route.

Recently an unusual synthesis of the *N*-oxides of quinoxaline derivatives has been reported from these laboratories.[2,3] It has been accomplished through the cyclizations of α-substituted-*o*-nitroacetanilides (I) with the help of basic catalysts, whereby 3-hydroxyquinoxaline *N*-oxide derivatives(II) are obtained directly.



I



II

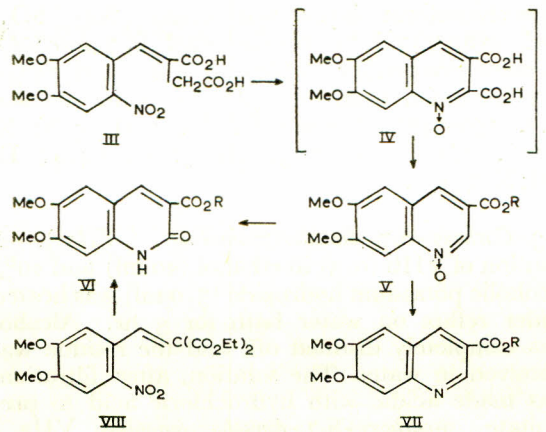
R=CN, Ph, $C_6H_4Cl(p)$, or $C_6H_4NO_2(p)$
R′=H, Cl, EtO, or MeO

In this novel synthesis advantage has been taken of the presence of a suitably activated methylene group in the side chain in *ortho* position of a nitrobenzene derivative. The anion generated from the active methylene attacks the nitro group in *ortho* position and thereby an N–C bond is directly formed, resulting in the formation of a six membered *N*-heterocycle bearing an oxide function on its nitrogen atom. Syntheses on similar lines have also been simultaneously reported from other Laboratories.[4,5] The reactions involving direct interaction of the aromatic nitro group with the *ortho* side chain have recently been reviewed.[6] These reactions have been used for the formation of a number of other *N*-heterocycles. The formation of 3-hydroxybenzotriazine *N*-oxide from 2-nitrophenylurea;[7] 1-hydroxybenzotriazole from 2-nitrophenylhydrazine;[8] 6-cyanophenanthridine 5-oxide from 2-(2′-nitrophenyl)-phenylacetonitrile;[9] 1-hydroxy-2-phenylbenzimidazole from *N*-benzyl -2-nitroaniline;[10] benzo (*c*) cinnoline 1-oxide from 2-(2′-nitrophenyl)aniline[9] may be cited as some of the examples. On the same lines a method has been successfully devised for an unusual direct synthesis of *N*-oxides of quinolines, and is being reported in this paper.[11]

The *N*-oxides of quinolines are usually obtained by the oxidation of quinolines themselves. No synthesis resulting in the direct formation of the *N*-oxides of quinoline derivatives seems to have been recorded so far. Perhaps the only exception is the report of Loudon *et al*,[12,13] about the synthesis of 1,2-dihydro-1-hydroxy-2-oxoquinolines and 1,4-dihydro-1-hydroxy-4-oxoquinolines, which in their tautomeric form can be regarded as 2-hydroxy-and 4-hydroxy-quinoline *N*-oxides. *o*-Nitrobenzylidenesuccinic acid and its derivatives, have all the requisites for the interaction of the nitro group with active methylene of the *ortho* side chain in the presence of a basic catalyst. It was envisaged that, if successful, this would give a novel route for the direct synthesis of *N*-oxides of quinoline derivatives.

Stobbes condensation of 2-nitrobenzaldehyde with diethyl succinate to obtain 2-nitrobenzylidenesuccinic acid (or its ester) has been reported[14] to give only resinous products, probably due to the interfering reactions of the nitro group in the presence of basic catalyst with which these condensations are carried out. To avoid this complication it became necessary to synthesise a suitable benzylidenesuccinic acid in which the nitro group could be introduced in the appropriate position in the molecule as a second step through the nitration of the compound. To achieve this purpose veratraldehyde was condensed with ethyl succinate to obtain veratrylidenesuccinic acid.[15] Nitration according to the procedure of Cartwright and Haworth[16] gave *o*-nitroveratrylidenesuccinic acid (III). On being warmed with aqueous alkali III dissolved, and the solution slowly changed colour and finally became dark red. Acidification of

*For the sake of keeping uniformity with the allied work published earlier from these laboratories, 2-quinoline and 2-quinoxalone derivatives have been named as the derivatives of 2-hydroxyquinoline and 2-hydroxyquinoxaline respectively, in this paper as well.



(a) R=H (b) R=Et(c) R=Me

the solution precipitated a high melting dark brown acidic product, which was purified by dissolution in aqueous sodium bicarbonate and reprecipitation with acid. The elementary analysis and neutralization equivalent of this new compound indicated it to be different from the expected 2,3-dicarboxy-6,7-dimethoxyquinoline 1-oxide(IV) and agreed well with the formula $C_{12}H_{11}NO_5$ for a monocarboxylic compound. Apparently the alkali salt of the intermediate IV, as soon as it was formed, in the strongly alkaline conditions, lost its carboxylate group at position 2. This was not entirely unexpected. As in an analogous reaction in quinoxaline series, Tennant[5] has reported that under strongly alkaline conditions quinoxaline *N*-oxides bearing a carbonylic substituent at C-2, lose this substituent and replace it with hydrogen; Ahmad *et al.*[2] have proposed a mechanism for it.

The constitution of the new acid was established to be 3-carboxy-6,7-dimethoxyquinoline 1-oxide (Va) on the basis of the following evidence:

1. The new compound lacked the absorption bands for the nitro group in its IR spectrum, indicating that the nitro group of the *o*-nitroveratrylidenesuccinic acid had irreversibly reacted during this reaction.

2. The new compound underwent the well-known rearrangement[17] of the *N*-oxides of quinolines to carbostyrils[18] on being heated with acetic anhydride, and gave isomeric 2-hydroxy-6,7-dimethoxyquinoline-3-carboxylic acid (VIa). An authentic sample of VIa was prepared, for comparison, through an unambiguous route,[19] by the condensation of *o*-nitroverateraldehyde and ethyl malonate to give diethyl *o*-nitroveratrylidenemalonate (VIII), which on reduction cyclised to ethyl 2-hydroxy-6,7-dimethoxyquinoline-3-carboxylate (VIb). The hydrolysis of VIb with alkali gave VIa.

3. The acid VIa obtained by the rearrangement of Va with acetic anhydride, on sublimation *in vacuo*, decarboxylated and gave 6,7-dimethoxycarbostyril (VI, H for CO_2R) identical with an authentic sample.[19]

4. The ethyl and methyl esters(Vb and Vc) of the new acid were prepared by the usual method. The ethyl ester(Vb) was deoxygenated[20] with phosphorus trichloride to obtain ethyl 6,7-dimethoxyquinoline-3-carboxylate(VIIb), which on hydrolysis with alkali gave 6,7-dimethoxyquinoline-3-carboxylic acid(VIIa). The IR spectra of VIIa and VIIb were very similar to that of quinoline-3-carboxylic acid and its ethyl ester.

Further work is in progress.

Experimental

Melting points are uncorrected and were determined on Gallenkamp MF370 m.p. apparatus. IR spectra were measured in Nujol mull using Perkin-Elmer Model 137B.

Diethyl 6-nitroveratrylidenemalonate(VIII) was obtained by the condensation of 6-nitroveratraldehyde[21] and diethyl malonate by the reported method.[19]

Ethyl 2-hydroxy-6,7-dimethoxyquinoline-3-carboxylate (VIb).— Compound VIII (5.0 g) in ethanol (200 ml) was hydrogenated using a 10% Pd–C catalyst (1.0 g). After theoretical amount of hydrogen had been absorbed, the catalyst was filtered off and the filtrate was concentrated under reduced pressure to about 50 ml volume. On cooling this solution, a yellow solid (3.5 g, yield 89%) separated out, which, on crystallization from ethanol, gave yellow needles of VIb, m.p. 272° (lit.[19] m.p. 271–272°).

Compound VIb when hydrolysed with aqueous alkali gave an authentic sample of 2-hydroxy-6,7-dimethoxyquinoline-3-carboxylic acid (VIa).[19]

Veratrylidenesuccinic Acid[15a].—Sodium (7.0 g; 3 atoms) was dissolved in absolute ethanol(140 ml). Ethyl succinate(19.0 g; 1.1 moles) was then added, followed by veratraldehyde (17.0 g; 1.0 mole), and the mixture was heated under reflux on a water bath for 2 hr. Alcohol was slowly distilled off and was replaced with an equal amount of water, by the addition of water from time to time. The aqueous solution was cooled and almost neutralized with hydrochloric acid and then extracted with ether. The aqueous

phase on being made strongly acidic precipitated veratrylidenesuccinic acid(19.0 g, yield 73%) which was crystallized from chloroform as light yellow prisms, m.p. 173–174° (lit.[15b] m.p. 175°).

6-*Nitroveratrylidenesuccinic Acid* (*III*)[16].—Nitric acid (*d* 1.42; 150 ml) was added to a solution of veratrylidenesuccinic acid (15.0 g) in glacial acetic acid (300 ml) maintained at 0–5°. The mixture was stirred at room temperature for ½ hr and then poured on ice. The resulting solid (9.0 g) was collected by filtration. The filtrate on concentration gave more solid (3.0 g; total yield 68.4%). Crystallization from dilute acetic acid gave pale yellow silky needles of the nitro acid(III), m.p. 214–215°(lit.[16] m.p. 215°).

3-*Carboxy*-6,7-*dimethoxyquinoline* 1-*oxide* (*Va*).—6-Nitroveratrylidenesuccinic acid (III; 5.0 g) dissolved in 20% aqueous potassium hydroxide (20 ml) was heated on water bath for ½ hr. The solution changed colour from yellow to red and finally became dark red. The cooled solution on acidification precipitated a brown solid, which was purified by dissolution in aqueous sodium bicarbonate and reprecipitation with hydrochloric acid. Pure solid (3.5 g, yield 87%) on crystallization from excess hot ethanol gave white micro-needles of the *carboxy*-N-*oxide*(Va), m.p. 282–283° (decomp.). Found: C, 57.6; H, 4.8; N, 5.6%. Calc. for $C_{12}H_{11}NO_5$: C, 57.8; H, 4.45; N, 5.6%.

3-*Ethoxycarbonyl*-6,7-*dimethoxyquinoline* 1-*oxide* (*Vb*).—Dry hydrogen chloride was passed through a solution of Va(1.0 g) in absolute ethanol (200 ml) for ½ hr. The solution was then heated under reflux for 2 hr. On cooling, the *ethyl ester* (0.7 g, yield 63.6%) separated out, which was recrystallized from ethanol (charcoal) to give white shining needles of Vb m.p. 214–215°. Found: C, 60.5; H, 5.4; N, 5.1%. Calc. for $C_{14}H_{15}NO_5$: C, 60.6; H, 5.4; N, 5.05%.

3-*Methoxycarbonyl*-6,7-*dimethoxyquinoline* 1-*oxide* (*Vc*).—Compound Va(1.0 g) was similarly treated with absolute methanol (200 ml) to give white shining needles (from methanol) of the *methyl ester* (Vc) (yield 58%), m.p. 211–212°. Found: C, 59.2; H, 5.0; N, 5.8%. Calc. for $C_{13}H_{13}NO_5$: C, 59.3; H, 5.0; N, 5.3%.

Ethyl 6,7-*dimethoxyquinoline*-3-*carboxylate* (*VIIb*).—A solution of phosphorus trichloride (1.0 ml) in dry chloroform(10 ml) was added to cold solution of Vb(1.0 g) in dry chloroform(20 ml). The mixture was heated under reflux for 10 min. After cooling it was shaken with cold 10% aqueous ammonia(20 ml) and then with water (20 ml). The chloroform layer was dried (Na_2SO_4) and evaporated to obtain *ethyl* 6,7-*dimethoxyquinoline*-3-*carboxylate* (VIIb) (0.7 g, yield 74%). Crystallization from ethanol gave white needles, m.p. 140–141°. Found: C, 65.1; H, 5.8; N, 5.7%. Calc. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8; N, 5.4%.

3-*Carboxy*-6,7-*dimethoxyquinoline* (*VIIa*).—A solution of VIIb (0.5) in ethanol (20 ml) and 10% alcoholic potassium hydroxide (5.0 ml) was heated under reflux on water bath for 3 hr. Alcohol was completely distilled off, and the residue was dissolved in water. The solution, after filtration, was made acidic with hydrochloric acid to precipitate 3-*carboxy*-6,7-*dimethoxyquinoline*(VIIa) (0.3 g, yield 67%). Crystallization from methanol–benzene gave white micro-needles, m.p. 267–268°. Found: C, 61.1; H, 5.0; N, 6.0%. Calc. for $C_{12}H_{11}NO_4$: C, 61.8, 4.7; N, 6.0%.

Rearrangement of 3-*carboxy*-6,7-*dimethoxyquinoline* 1-*oxide*(*Va*) *with Acetic Anhydride*.—Compound Va (1.0 g) was heated under reflux with acetic anhydride (25 ml) for 2 hr. The colour of the solution changed to reddish brown and on cooling a solid separated out. Acetic anhydride was completely removed under reduced pressure. The residue was triturated with cold water, and the solid (0.7 g yield 74%) filtered off. Crystallization from acetic acid (charcoal) gave pale yellow needles of a compound, m.p. 310° (decomp.). Found: C, 58.2; H, 4.4; N, 5.7%. Calc. for $C_{12}H_{11}NO_5$: C, 57.8; H, 4.4; N, 5.6%.

This compound was identical (IR spectrum and mixed m.p.) with an authentic sample of 2-hydroxy-6,7-dimethoxyquinoline-3-carboxylic acid(VIa) synthesized by an unambiguous route (see p. 355).

Compound VIa exhibits a strong bluish-green flourescence in its solution in acetic acid or ethanol.

The constitution of the product of rearrangement of Va with acetic anhydride was further confirmed to be 2-hydroxy-6,7-dimethoxyquinoline-3-carboxylic acid by its sublimation at 350°/0.5 mm, whereby it was decarboxylated to give a compound m.p. 232–234°, which was identical (IR spectrum and mixed m.p.) with an authentic sample of 6,7-dimethoxycarbostyril (VI; H for CO_2R) obtained by the method of Somasekhara and Phadke.[19]

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