736. *Indene and Related Compounds. Part III.*[1] *Ring Expansion of 2-Nitro-1-indanone Oxime to Isocarbostyril Derivatives.*[2]

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On being treated with ethanolic hydrochloric acid, 2-nitro-1-indanone oxime (I) undergoes a novel isomerization in which it is converted into the two isocarbostyril derivatives, 3-chloro-2-hydroxyisocarbostyril (II) and *N*-hydroxyhomophthalimide (IV), together with the degradation products hydroxylamine and homophthalic acid (III). From a study of their reactions, a possible mechanism for the isomerization is proposed.

IN a previous Paper [3] the nitrosation of indene with nitrous acid was shown to give indene pseudonitrosite, which was converted into 2-nitro-1-indanone oxime (I) when refluxed in an excess of ethanol for a long time. The purpose of the present investigation was to study the deoximation of the oxime (I) with various acidic reagents, but the ring-expanded compounds (II) and (IV) were obtained, unexpectedly.

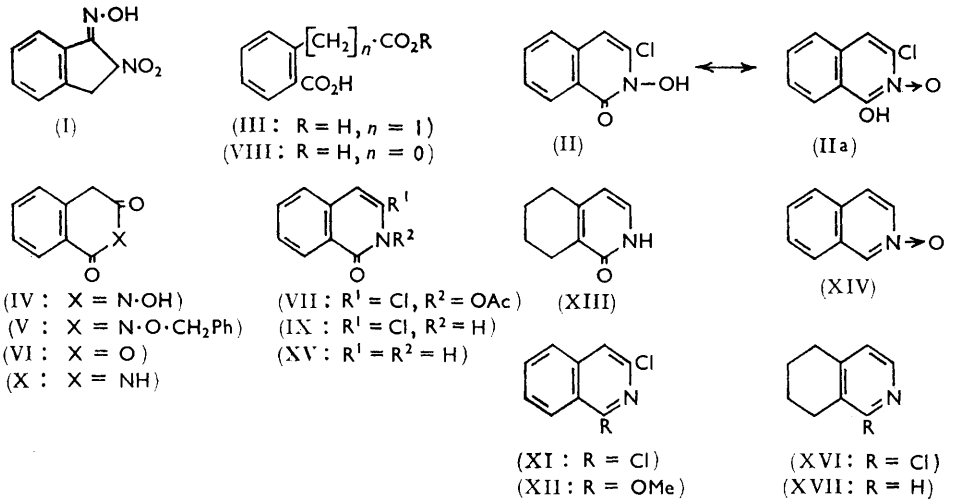
Attempted deoximation with sulphuric acid under various conditions [4] gave a resinous substance. However, hydrolysis of the oxime (I) with a mixture of 10% hydrochloric acid and ethanol or acetone afforded four compounds, namely, the isocarbostyril (II) which was the main product, hydroxylamine hydrochloride, homophthalic acid (III), and *N*-hydroxyhomophthalimide (IV). The elemental analyses of compounds (II) and (IV) agreed with the formulations, as did also the infrared spectra.

The compound (IV) [5] was identical with an authentic sample which was synthesized by catalytic hydrogenation, with palladium–strontium carbonate,[6] of *N*-benzyloxyhomophthalimide (V) which was obtained by condensation of homophthalic anhydride (VI) [7,8] and benzyloxyamine.[9]

The infrared spectrum of compound (II) showed maxima at 2600 (chelated OH), 1665 (C=O stretching), and 1620 cm.$^{-1}$ (C=C), and its Beilstein test was positive. Acetylation with acetic anhydride and sulphuric acid gave the compound (VII), which lacks OH

[1] Kigasawa, Hiiragi, Hayasaka, Sugahara, and Kametani, *J. Pharm. Soc. Japan*, 1964, **84**, 402.
[2] This forms Part CIV of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.
[3] Kametani and Sugahara, *J. Pharm. Soc. Japan*, 1964, **84**, 399.
[4] Hartman and Roll, *Org. Synth.*, Coll. Vol. III, 1955, 20.
[5] Ames and Grey, *J.*, 1955, 3518.
[6] Mozingo, *Org. Synth.*, 1946, **26**, 77.
[7] Graebe and Trümpy, *Ber.*, 1898, **31**, 375.
[8] Wislicenus, *Annalen*, 1886, **233**, 105.
[9] Janny, *Ber.*, 1883, **16**, 170; Behrend and Leuchs, *Annalen*, 1890, **257**, 206.

absorption but has maxima at 1820 (C=O) and 1680 cm.$^{-1}$ (lactam C=O). The high frequency at 1820 cm.$^{-1}$ is attributed to an anhydride carbonyl, and compound (VII) is in fact an anhydride of a hydroxamic with a carboxylic acid. Furthermore, hydrolysis of compound (II) with concentrated hydrochloric acid also yielded homophthalic acid (III);

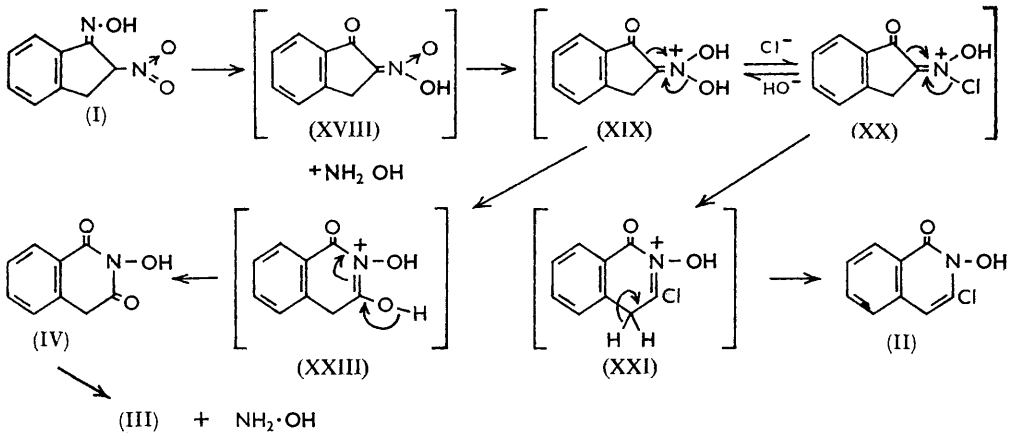


oxidation of (II) with potassium permanganate gave phthalic acid (VIII). Attempted dehalogenation of compound (II) with zinc in ethanol gave an unexpected compound, (IX), m. p. 216°, which was identical with an authentic sample, m. p. 216—218°, obtained from homophthalimide (X) *via* 1,3-dichloroisoquinoline (XI) and 3-chloro-1-methoxyisoquinoline (XII) according to Gabriel.[10] Furthermore, the absence of *N*-oxide absorption at 1325 and 1185 cm.$^{-1}$, both generally present as strong bands in isoquinoline *N*-oxide,[11] does not appear to rule out the alternative. This may be a 1-hydroxyisoquinoline *N*-oxide (IIa), existing very likely as a hydrogen-bonded chelate, *i.e.*, the normal *N*-oxide frequency might well be absent, but the presence of a lactam CO band at 1665 cm.$^{-1}$ strongly suggests the preponderance of (II) rather than the tautomeric *N*-oxide (IIa).

Catalytic hydrogenation of (II) with platinum oxide in hot methanol gave 5,6,7,8-tetrahydroisocarbostyril[12] (XIII), which shows maxima at 1670 (lactam C=O) and 1630 cm.$^{-1}$ (C=C or C=N stretching). This was identical with the isocarbostyril derivative (XIII) obtained from isoquinoline *N*-oxide (XIV) *via* isocarbostyril[13] (XV). Furthermore, catalytic hydrogenation with palladium–charcoal of 1-chloro-5,6,7,8-tetrahydroisoquinoline (XVI), which was obtained by halogenation of (XIII) with phosphoryl chloride in a sealed tube, gave 5,6,7,8-tetrahydroisoquinoline[14] (XVII).

Perhaps the simplest mechanism to explain the formation of (II) and (IV) would initially involve hydrolysis of the hydroxyimino-group and formation of the *aci*-form of the nitro-group in acid media to yield (XVIII). In low acid concentration, addition of a proton would lead to the intermediate (XIX). Substitution of chlorine in (XIX) under strongly acidic conditions would lead to (XX) which by an acid-catalysed isomerization affords (XXI) and thence (II). A similar isomerization of (XIX) would lead to (XXIII) which would presumably give (IV). We suggest that compound (IV) led to the formation of (III) as the result of a hydrolysis accelerated by acid.

[10] Gabriel, *Ber.*, 1886, **19**, 1653, 2354; 1900, **33**, 980.
[11] Moriconi, Greegan, Donovan, and Spano, *J. Org. Chem.*, 1963, **28**, 2215.
[12] Ochiai and Kawazoe, *Pharm. Bull.*, 1957, **5**, 606.
[13] Robison and Robison, *J. Org. Chem.*, 1956, **21**, 1338.
[14] Grewe and Mondon, *Chem. Ber.*, 1948, **81**, 279.



Experimental

3-Chloro-2-hydroxyisocarbostyril (II) *and N-Hydroxyhomophthalimide* (IV).—10% Hydrochloric acid (200 ml.) was added with stirring to a solution of 2-nitro-1-indanone oxime [3] (I) (6·6 g.) in ethanol (or acetone) (100 ml.), and the stirred mixture was refluxed at 60—80° for 3 hr. The oxime (I) precipitated as an oil during the addition but gradually dissolved during the reaction to give a clear solution. After the reaction, the ethanol (or acetone) was removed under reduced pressure, and the crystals which separated were recrystallized from aqueous ethanol to afford *3-chloro-2-hydroxyisocarbostyril* (II) (2·3 g.) as pale brown needles, m. p. 193° (decomp.) (Found: C, 55·5; H, 3·0; N, 7·2. $C_9H_6ClNO_2$ requires C, 55·2; H, 3·0; N, 7·2%), $\nu_{max.}$ 2600 (OH), 1665 (C=O), 1620 and 1590 (ring) cm.$^{-1}$ (KBr),* $\lambda_{max.}$ (in EtOH) 249, 292, and 328 mμ (log ε 3·86, 3·95, and 3·71).†

The aqueous layer from the above was extracted with ether. The ethereal extract, after being washed and dried (Na_2SO_4), yielded homophthalic acid (III) (1·9 g.), needles, m. p. and mixed m. p. 181° (decomp.) (from aqueous ethanol), whose infrared spectrum was identical with that of an authentic sample.

The aqueous residue was then extracted with ethyl acetate. Evaporation of the washed and dried (Na_2SO_4) solvent gave *N*-hydroxyhomophthalimide (IV) as yellow crystals (0·9 g.). Recrystallization from propan-2-ol afforded pale yellow plates, m. p. 201—202° (Found: C, 60·8; H, 4·1; N, 7·9. Calc. for $C_9H_7NO_3$: C, 61·0; H, 4·0; N, 7·9%). This product was identical with that obtained from benzyloxyhomophthalimide.[5]

The aqueous layer remaining from the above extraction was acidified with hydrochloric acid and evaporated to dryness under reduced pressure. The residue was twice extracted with ethanol; evaporation of the solvent yielded hydroxylamine hydrochloride (2·4 g.).

2-Acetoxy-3-chloroisocarbostyril (VII).—A drop of concentrated sulphuric acid was added to a solution of isocarbostyril (II) (1 g.) in acetic anhydride (2 ml.), and the mixture was stirred at room temperature for a brief period during which time crystals separated. After being allowed to stand for a few hours, the mixture was poured into ice–water, and the crystalline precipitate (1 g.) filtered off. Recrystallization from ethanol afforded *2-acetoxy-3-chloroisocarbostyril* (VII) as cubes, m. p. 135—137° (Found: C, 55·7; H, 3·4; N, 5·9. $C_{11}H_8ClNO_3$ requires C, 55·6; H, 3·4; N, 5·9%), $\nu_{max.}$ (KBr) 1820 (anhydride C=O) and 1680 (lactam C=O) cm.$^{-1}$.

3-Chloroisocarbostyril (IX).—A solution of the above isocarbostyril (II) (1 g.), in aqueous ethanol to which had been added ammonium chloride (0·3 g.) and zinc powder (3·0 g.), was heated under reflux in an oil-bath for 5 hr. The hot mixture was filtered and concentrated, to yield crystals, which were collected on a filter, washed with water, and dried, to give the isocarbostyril (IX) (0·65 g.), needles, m. p. 216—218° (from benzene) (Found: C, 60·6; H, 3·4; N, 8·1. Calc. for C_9H_6ClNO: C, 60·2; H, 3·3; N, 7·8%), $\nu_{max.}$ (KBr), 2800 (OH) and 1680

* Cf. infrared absorptions reported for 2-hydroxy-3-methylisocarbostyril: $\nu_{max.}$ (KBr) 1661 (C=O), 1629 and 1600 (C=C) cm.$^{-1}$.[11]

† Cf. ultraviolet absorptions reported for 2-hydroxy-3-methylisocarbostyril: $\lambda_{max.}$ (EtOH) 249 and 291 mμ (ε 9100 and 8500).

(C=O) cm.$^{-1}$ $\lambda_{max.}$ (EtOH) 227, 288, and 328 mμ (log ε 4·03, 4·01, and 3·70). The Beilstein test was positive. This substance was identical with the product obtained by hydrolysis of 3-chloro-1-methoxyisoquinoline (XII).[10]

5,6,7,8-*Tetrahydroisocarbostyril* (XIII).—The isocarbostyril (II) (2 g.) in methanol (100 ml.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (0·2 g.) and concentrated hydrochloric acid (1 ml.). During the reaction the mixture was shaken, and warmed by an infrared lamp (100 v, 250 w). Hydrogen uptake (4 moles) was complete within 6 hr. Filtration and removal of the solvent *in vacuo* gave a brown oil which was decomposed with water. The resulting acidic solution was basified with aqueous ammonia and extracted with ethyl acetate. The solvent layer was washed with water, dried (Na_2SO_4), and evaporated, to give 5,6,7,8-tetrahydroisocarbostyril (XIII) (1·4 g.), needles, m. p. 212—214° (from aqueous ethanol or water) (Found: C, 72·8; H, 7·1; N, 9·6. Calc. for $C_9H_{11}NO$: C, 73·0; H, 6·7; N, 9·5%), $\nu_{max.}$ (KBr) 2800 (OH), 1690 (C=O), and 1640 (C=C) cm.$^{-1}$, $\lambda_{max.}$ (in EtOH) 234 and 291 mμ (log ε 3·69 and 3·81), $\lambda_{max.}$ (in 2N-HCl) 275 mμ (log ε 3·83), $\lambda_{max.}$ (in 2N-NaOH) 235 and 291 mμ (log ε 3·87 and 3·75). Recrystallization of its *picrate* from ethanol afforded yellow needles, m. p. 160—161·5° (Found: C, 48·0; H, 3·8; N, 15·2. $C_9H_{11}NO,C_6H_3N_3O_7$ requires C, 47·8; H, 3·5; N, 14·9%).

The above carbostyril (XIII) was identified, by infrared spectrum and melting point, with the product obtained by catalytic hydrogenation of isocarbostyril [13] (XV) under the same conditions as above.

5,6,7,8-*Tetrahydroisoquinoline* (XVII).—A mixture of (XIII) (0·5 g.) and phosphoryl chloride (3 ml.) was heated in a sealed tube at 150° (oil-bath) for 2 hr. After the reaction, excess of phosphoryl chloride was distilled off under reduced pressure, and the residue was decomposed with ice–water. The acidic solution was basified with 10% sodium hydroxide and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated, to yield 1-chloro-5,6,7,8-tetrahydroisoquinoline (XVI) (0·4 g.) as an oil.

The above base (XVI) (0·4 g.) in methanol (50 ml.) was hydrogenated at atmospheric pressure in the presence of 10% palladium–charcoal (0·4 g.). Hydrogen uptake (1 mole) was complete within 30 min. Filtration and removal of the solvent *in vacuo* gave 5,6,7,8-tetrahydroisoquinoline (XVII) as a brown oil (0·32 g.). The picrate formed yellow leaves (from ethanol), m. p. 143—145° (lit.,[14] 144°).

Oxidation of the Carbostyril (II).—Potassium permanganate (4 g.) was gradually added to a solution of (II) (1·5 g.) and potassium hydroxide (5 g.) in water (50 ml.), and the mixture was stirred and heated on a water-bath at 70° for 3 hr. After the reaction, excess of potassium permanganate was decomposed with sodium hydrogen sulphate. The resulting alkaline solution was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The solvent layer was washed with water and dried (Na_2SO_4). Removal of the solvent gave phthalic acid (0·6 g.), m. p. and mixed m. p. 230° (decomp.) (when rapidly heated) (from water).

Hydrolysis of the Carbostyril (II).—A mixture of (II) (2 g.), concentrated hydrochloric acid (20 ml.), and ethanol (20 ml.) was heated in an oil-bath for 4 hr. Ethanol was distilled off, and the residue was extracted with benzene. The solvent was washed with water, and extracted with 5% sodium hydrogen carbonate solution. The resulting alkaline solution was acidified with 10% hydrochloric acid and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. Removal of the benzene extract gave ethyl 2-carboxyphenylacetate (0·4 g.), needles (from benzene), m. p. 106—107·5° (lit.,[8] 107—108°) (Found: C, 63·2; H, 5·8. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·8%). Hydrolysis of the above ester with 10% sodium hydroxide gave homophthalic acid (III).

The above aqueous layer was extracted with ether, and the solvent was again extracted with 5% sodium hydrogen carbonate, which was then acidified with 10% hydrochloric acid and extracted with ether. Distillation of the ethereal extract afforded a liquid (0·3 g.), b. p. 161°/1·5 mm., which solidified to give homophthalic anhydride as needles, m. p. 141—142° (lit.,[8] 140·5—141°), identical with an authentic sample.

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