The Synthesis of Narciclasic Aldehyde and Related Isocarbostyrils

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The synthesis of several isocarbostyrils is reported, including formyl derivatives at C-4, like narciclasic aldehyde (I) and the homologous aldehyde (XV).

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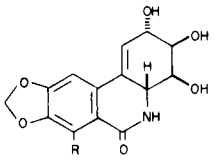
Narciclasic aldehyde (I) (1) was obtained from narciclasine (II) by diazomethane methylation to *O*-methylnarciclasine (III) (1) followed by periodic acid oxidation (1); it represents a key degradation product in the elucidation (1-4) of the structure of this *Amaryllidaceae* alkaloid. The structure of I as 4-formyl-6,7-methylenedioxy-8-methoxyisocarbostyril was determined on the basis of spectroscopic results mainly; now we report the first total synthesis (5) of narciclasic aldehyde.

Amongst the various possible methods for the synthesis of substituted isocarbostyrils, we preferred as most suitable the transformation of isoquinolines into isocarbostyrils, followed by the introduction of the formyl group at position 4.

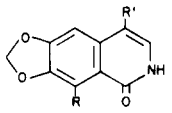
The required 6,7-methylenedioxy-8-methoxyisoquinoline (IV) (6) was easily prepared starting from 2-methoxy-3,4-methylenedioxybenzaldehyde (7) by means of the novel Birch modification (8,9) of the Pomeranz-Fritsch cyclization. The isoquinoline (IV) was transformed into the related *N*-oxide (V); low yields and some isolation difficulties were encountered in the isomerization of V to the isocarbostyril (VI), performed as reported (10) for the case of unsubstituted isocarbostyril (VII).

Direct Vilsmeyer formylation at position 4 is reported (11) for *N*-alkylisocarbostyrils, but failed in our hands on isocarbostyril itself (VII). In contrast, the transformation of the 4-bromo into the 4-cyano and then into the 4-formyl derivatives, previously (11) tested only on *N*-alkylisocarbostyrils, gave us satisfactory results also on 4-bromoisocarbostyril (VIII) (12) that was converted into IX and X.

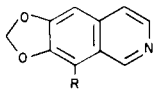
This pathway was therefore applied to 6,7-methylenedioxy-8-methoxyisocarbostyril (VI). Bromination afforded XI easily, whereas the transformation into the 4-cyano derivative (XII) gave poor yields and a byproduct identified as 6,7-methylenedioxy-8-hydroxyisocarbostyril (XIII). Finally, the reduction of XII afforded 4-formyl-6,7-methylenedioxy-8-methoxyisocarbostyril (I), identical with narciclasic aldehyde, thus confirming the structure previously proposed (1).



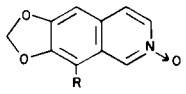
II R OH
III R OCH_3
XIV R H



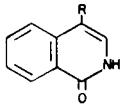
I R = OCH_3 R' = CHO
VI R = OCH_3 R' = H
XI R = OCH_3 R' = Br
XII R = OCH_3 R' = CN
XIII R = OH R' = H
XV R = H R' = CHO
XVIII R = H R' = H
XIX R = H R' = Br
XX R = H R' = CN



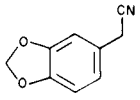
IV R OCH_3
XVI R H



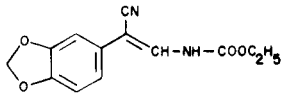
V R = OCH_3
XVII R = H



VII R = H
VIII R = Br
IX R = CN
X R = CHO



XXI



XXII

Table I

Nmr Spectra of Isocarbostyril Derivatives (DMSO-d_6)

		H-3	H-4	H-5	H-6	H-7	H-8
Isocarbostyril	(VII)	7.17	6.52	←	7.3-7.8	→	8.25
Isocarbostyril	(XVIII)	7.04	6.42	7.10			7.50
Isocarbostyril	(VI)	7.00	6.33	6.87			
Bromo derivative	(VIII)	7.55		←	7.4-8.0	→	8.31
Bromo derivative	(XIX)	7.42		7.14			7.54
Bromo derivative	(XI)	7.34		6.92			
Cyano derivative	(IX)	8.27		←	7.7-8.1	→	8.38
Cyano derivative	(XX)	7.92		7.07			7.60
Cyano derivative	(XII)	8.06		6.80			
Formyl derivative	(X)	8.13		8.26	← 7.3-8.0	→	8.98
Formyl derivative	(XV)	8.08		8.41			7.57
Formyl derivative	(I)	8.00		8.30			

Other signals: OCH_3 3.85-3.90; OCH_2O 6.12-6.21; CHO 9.50-9.75.

The positive result in the synthesis of I prompted us to synthesize also the homologous aldehyde, *i.e.*, 4-formyl-6,7-methylenedioxyisocarbostyril (XV), derived from periodic acid oxidation of margetine (XIV) (13), a minor alkaloid accompanying narciclasine in daffodil bulbs.

Across the pathway starting from 6,7-methylenedioxyisoquinoline (XVI) (14) we had to contend with very poor yields in the conversion of the *N*-oxide (XVII) into 6,7-methylenedioxyisocarbostyril (XVIII): however, the steps XVIII → XIX → XX → XV could be accomplished and the aldehyde was obtained. Much better results were obtained from the pathway explored by Wenkert (15) and applied by us here to 3,4-methylenedioxyphenylacetonitrile (XXI) (16): this product was converted into XXII and then into 4-cyano-6,7-methylenedioxyisocarbostyril (XX), that underwent final transformation into the required aldehyde (XV). Product XXII was obtained in two forms, probably the two geometric isomers, *cis* and *trans*: they showed slight differences in their spectra, and both could be cyclizated to XX.

The protons signals of the nmr spectra of the isocarbostyril derivatives were compared and the results are tabulated in Table I.

EXPERIMENTAL

All melting points were taken on a Reichert Kofler microscope and are uncorrected. Ir spectra were determined as nujol mull on a Perkin Elmer Infracord 137 spectrophotometer; nmr spectra were obtained with a Jeol C-60 H spectrometer (TMS as internal reference). Mass spectra were registered on a Hitachi Perkin Elmer 270 instrument. Column chromatography was done on 0.063-0.200 mm neutral silica gel 60 (E.Merck).

6,7-Methylenedioxy-8-methoxyisocarbostyril (VI).

The trisubstituted isoquinoline (IV) was prepared as reported in the General Part, m.p. 144° (from ethanol); nmr (deuteriochloroform): δ 4.24 (s, OCH_3), 6.10 (s, OCH_2O), 6.84 (s, H-5), 7.50 (d, J 6.5 Hz, H-3), 8.55 (d, J 6.5 Hz, H-4), 9.47 (s, H-1). A solution of IV (6.6 g.) in acetic acid (10 ml.) was heated at 65°, treated with 30% hydrogen peroxide (3.5 ml.), added with more hydrogen peroxide (3 ml.) after 3 hours, then left at 65° for 9 hours. Work-up of the solution, as described (10) for isoquinoline, gave the *N*-oxide (V) (5 g.), yellow amorphous powder, m.p. ~185° dec., (not characterized). The crude *N*-oxide was dissolved in acetic anhydride (32 ml.), the solution was heated at reflux for 5 hours (compare 10), then evaporated under reduced pressure. The residue (6.5 g.) was boiled for 1 hour with 5% aqueous sodium hydroxide (70 ml.), then the resulting solution was neutralized by bubbling carbon dioxide and evaporated to dryness. The residue was percolated through silica gel, eluent chloroform; VI (1 g.) was isolated as white prisms, m.p. 235° (from ethanol); ir: 3100 (NH), 1640 (C=O) cm^{-1}; nmr, see Table I.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.44; H, 4.21; N, 6.28.

6,7-Methylenedioxyisocarbostyril (XVIII).

The disubstituted isoquinoline (XVI) (8,14) had m.p. 122° (from cyclohexane); nmr (deuteriochloroform): δ 6.18 (s, OCH_2O), 7.61 (d, J 6 Hz, H-3), 8.32 (d, J 6 Hz, H-4), 7.28 and 7.40 (s, H-5 and H-8), 9.05 (s, H-1). Treatment of XVI (6.25 g.) with peracetic acid as described for V yielded the *N*-oxide (XVII) (6.5 g.), yellow amorphous powder (not characterized). The crude *N*-oxide was allowed to react with acetic anhydride and then with sodium hydroxide, as described for V; only a poor yield of XVIII (100 mg.) was obtained, white microcrystals, m.p. 270° (from ethanol); ir: 3100 (NH), 1640 (C=O) cm^{-1}; nmr, see Table I.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.38; H, 3.90; N, 7.35.

4-Cyanoisocarbostyril (IX).

A mixture of 4-bromoisocarbostyril (VIII) (12) (600 mg.) and cuprous cyanide (600 mg.) in *N*-methyl-2-pyrrolidone (10 ml.) was heated at reflux for 3 hours, then poured while hot into a 25% aqueous solution of sodium cyanide (50 ml.) under careful stirring. The resulting solution was extracted with dichloromethane; after the slow, tedious evaporation of *N*-methyl-2-pyrrolidone, the residue was percolated through silica gel, eluent benzene. 4-Cyanoisocarbostyril (IX) (300 mg.) was obtained as white needles, m.p.

258-259° (from benzene); ir: 3100 (NH), 2190 (CN), 1660 (C=O) cm^{-1}; nmr, see Table I.

Anal. Calcd. for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.45; H, 3.48; N, 16.69.

4-Formylisocarbostyril (X).

A mixture of IX (160 mg.), sodium hypophosphite (400 mg.), water (2.5 ml.), acetic acid (2.5 ml.), pyridine (5 ml.) and Raney Ni (500 mg.) was heated at 45° and stirred for 4 hours. The warm solution filtered from the catalyst was diluted with water and extracted with dichloromethane. The organic layer was washed with water, dried and evaporated; 4-formylisocarbostyril (X) (30 mg.) was isolated, white prisms, m.p. 236-237° (from benzene); ir: 3100 (NH), 2700 (aldehyde C-H), 1700 (aldehyde C=O), 1660 (lactame C=O); nmr, see Table I.

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.18; H, 3.89; N, 8.23.

4-Bromo-6,7-methylenedioxy-8-methoxyisocarbostyril (XI).

The isocarbostyril (VI) (1 g.) was dissolved in acetic acid (20 ml.) and treated under stirring with a solution of bromine (1 g.) in acetic acid (10 ml.); after 3 hours the solution was heated at 40° for 1 hour, then diluted with water. The precipitate yielded XI (850 mg.), yellowish crystals, m.p. 279-281° (from ethanol); nmr, see Table I.

Anal. Calcd. for $C_{11}H_8BrNO_4$: C, 44.32; H, 2.71; N, 4.70; Br, 26.81. Found: C, 44.18; H, 2.62; N, 4.58; Br, 27.05.

4-Cyano-6,7-methylenedioxy-8-methoxyisocarbostyril (XII) and 6,7-Methylenedioxy-8-hydroxyisocarbostyril (XIII).

Product XI (800 mg.) was treated with cuprous cyanide as described above for the preparation of IX. Chromatography on silica gel, eluent chloroform, gave 6,7-methylenedioxy-8-hydroxyisocarbostyril (XIII) (100 mg.), colorless needles, m.p. 295° (from chloroform or by sublimation under high vacuum); MS: 205 (M^+, 100%), 147, 119, 91; nmr (DMSO-d_6): δ 6.12 (s, OCH_2O), 6.55 (d, J 7 Hz, H-4), 6.70 (s, H-5), 7.13 (q collapsing to a d, J 7 Hz, with deuterium oxide, H-3), 11.50 (broad, NH), 13.30 (chelated phenolic OH). The product was remethylated to VI by methanolic diazomethane solution.

Continuing the elution with chloroform, XII (50 mg.) was obtained as a white amorphous powder, m.p. 290-292° (from chloroform); ir: 3100 (NH), 2200 (CN), 1655 cm^{-1} (C=O); nmr, see Table I; MS: 244 (M^+, 100%), 216, 201, 198, 170, 88.

Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 58.80; H, 3.22; N, 11.58.

4-Formyl-6,7-methylenedioxy-8-methoxyisocarbostyril (I).

The reduction of XII (40 mg.) was performed as described above for 4-cyanoisocarbostyril (IX). The aldehyde (I) (10 mg.) was isolated as colorless powder, m.p. 284-285° (from ethanol); it was identical (ir, uv, nmr, MS, m.m.p.) with authentic narciclasic aldehyde (1).

4-Bromo-6,7-methylenedioxyisocarbostyril (XIX).

The bromination of XVIII (80 mg.) was done under the conditions indicated above for the homologue (VI). The bromo derivative (XIX) (50 mg.) was isolated as a yellowish powder, dec. ~270° without melting (from chloroform); nmr, see Table I.

Anal. Calcd. for $C_{10}H_6BrNO_3$: Br, 27.74. Found: Br, 27.90.

4-Cyano-6,7-methylenedioxyisocarbostyril (XX) from XIX.

The bromo derivative (XIX) (40 mg.) was subjected to cuprous cyanide treatment as described above for the preparation of IX. Product XX was obtained in poor yield (3 mg.) as a colorless powder which was sublimed under high vacuum. It does not melt until 340°, and was shown to be identical (MS) with the product prepared as described below.

4-Cyano-6,7-methylenedioxyisocarbostyril (XX) from 3,4-methylenedioxyphenylacetonitril (XXI).

Product XXI (16) (9 g.) and ethyl formate (5 ml.) were dissolved in ether (40 ml.) containing potassium methoxide (from 2 g. of potassium). After stirring at room temperature for 6 hours, the precipitate was filtered, washed with ether and decomposed with 10% acetic acid. The crude product (8 g.) was collected, dried on phosphoric anhydride and dissolved in toluene (170 ml.) with ethyl carbamate (3.7 g.) and concentrated sulphuric acid (0.2 ml.); then the solution was distilled slowly to a residual volume of 15 ml., cooled and filtered. Chromatography of the precipitate on silica gel, eluent chloroform, gave in the order two (XXII) products, m.p. 118-119° (2.1 g.) and m.p. 148-149° (0.9 g.). Both gave almost identical nmr and MS spectra: nmr (deuteriochloroform): δ 1.34 (t, J 7 Hz, CH_3-CH_2-O), 4.27 (q, J 7 Hz, CH_3-CH_2-O), 6.00 (s, OCH_2O); however, their ir spectra, both in nujol and chloroform solution, have several differences in the fingerprint region: 3200 (NH), 2210 (CN), 1725 (C=O), 800 cm^{-1} (C=CH); MS: 260 (M^+), 215, 188, 157, 129. Therefore the products are believed to be *cis-trans* geometric isomers (17).

Anal. (on the low-melting product) Calcd. for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.13; H, 4.49; N, 10.64.

A solution of the low-melting product (1.8 g.) in diphenyl ether (10 ml.) was refluxed for 1 hour, then cooled, diluted with light petrol, and the precipitate was collected and washed with chloroform: the cyano derivative (XX) (400 mg.) was isolated as white microcrystals, sublimated under high vacuum, that did not melt until 340°; MS: 214 (M^+, 100%); nmr see Table I.

Anal. Calcd. for $C_{11}H_6N_2O_3$: C, 61.68; H, 2.82; N, 13.08. Found: C, 61.79; H, 2.70; N, 12.93.

The identical reaction, performed on the high-melting product (800 mg.) gave also XX (200 mg.).

4-Formyl-6,7-methylenedioxyisocarbostyril (XV).

Product XX (350 mg.) was reduced with sodium hypophosphite as described above for the preparation of 4-formylisocarbostyril (X); usual treatment gave XV (70 mg.), colorless crystals, m.p. 320° (from ethanol); ir: 3400 and 3100 (NH), 1650 cm^{-1} (C=O); nmr, see Table I; MS: 217 (M^+, 100%), 216, 189, 188, 161, 146, 133.

Anal. Calcd. for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.71; H, 3.12; N, 6.33.

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