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A Cyclization of β -Arylethylisocyanates to 3,4-Dihydroisocarbostyrils

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A β -arylethylisocyanate derived from β -(3,4-methylenedioxyphenyl) (**3a**)-, β -(3,4-dimethoxyphenyl) (**3b**)-, β -(3,4,5-trimethoxyphenyl) (**3c**)- or β -(3-methoxyphenyl) (**3d**)-propionic acid was treated with anhydrous phosphoric acid at room temperature to give, in moderate yield, 6,7-methylenedioxy (**4a**)-, 6,7-dimethoxy (**4b**)-, 6,7,8-trimethoxy (**4c**)-, or 6-methoxy (**4d**)- and 8-methoxy (**4d'**)-3,4-dihydroisocarbostyrils.

In the case of β -(4-benzyloxy-3-methoxyphenyl) (**3e**)- or β -(3-benzyloxy-4-methoxyphenyl) (**3f**)-propionic acid, however, only 8-benzyl-7-hydroxy-6-methoxy (**4e**)- or 5-benzyl-6-hydroxy-7-methoxy (**4f**)-3,4-dihydroisocarbostyril, respectively, was obtained in low yield.

Keywords—cyclization; rearrangement; anhydrous H_3PO_4 ; β -arylpropionic acids; β -arylethylisocyanates; 3,4-dihydroisocarbostyrils

In connection with synthetic studies²⁾ on lycorine-type alkaloids, the preparation of 1,2,3,4,4a α ,5,6,10b β -octahydrophenanthrid-6-one (**2**)³⁾ from an isocyanate (**1**) was required on a large scale.

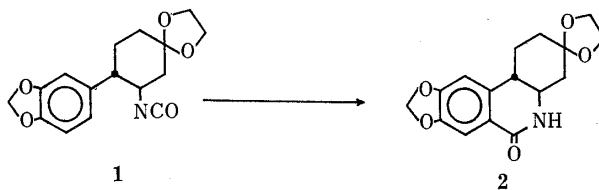


Chart 1

Although polyphosphoric acid (PPA),⁴⁾ boron trifluoride-etherate,⁵⁾ and phosphoryl chloride-stannic chloride⁶⁾ are known to be useful reagents for cyclization, we decided to employ anhydrous phosphoric acid (anhyd. H_3PO_4),⁷⁾ for this purpose. This paper deals with the preparation of several 3,4-dihydroisocarbostyrils from appropriate β -arylethylisocyanates.

The corresponding propionic acids (**3**) were successively transformed to acid chlorides and acid azides, Curtius rearrangement of which gave the starting isocyanates. Treatment of the isocyanates in methylene chloride with anhyd. H_3PO_4 afforded the 3,4-dihydroisocarbostyrils (**4**) in fair to good yields, as shown in Table I.

The structures of **4a**,⁸⁾ **4b**,⁸⁾ **4c**,⁹⁾ and **4d**⁸⁾ were confirmed by their spectral data (NMR, IR) and by comparison of their melting points with those in the literature. On the other hand, the structure **4d'** was strongly suggested by the presence of one-proton double doublets at δ 7.25 ($J=7$ and 8 Hz) in the nuclear magnetic resonance (NMR) spectrum.

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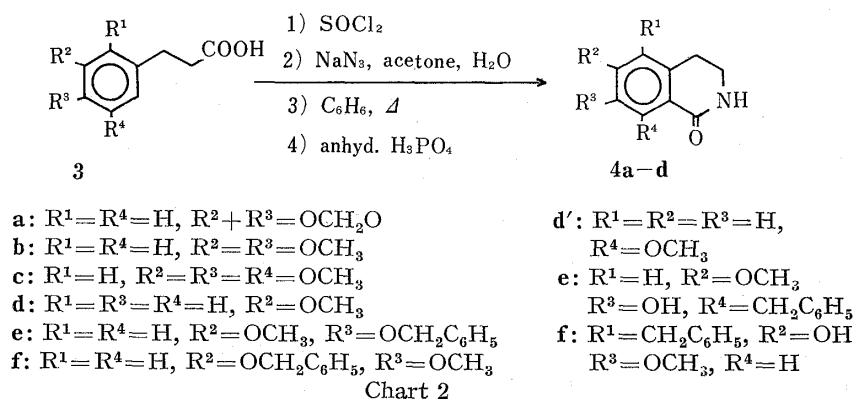


TABLE I. Melting Points and Yields of 3,4-Dihydroisocarbostyrils (4)

Starting material	Product (%)	mp ^{d)}
3a ^{b)}	4a (65.5)	183—184° (lit. ^{e)} 181°
3b ^{d)}	4b (60.0)	171.5—172° (lit. ^{e)} 170—171°
3c ^{e)}	4c (47.0)	137—188° (lit. ^{f)} 136.5—137.5°
3d ^{g)}	4d (36.0) ^{h)}	137—138° (lit. ^{e)} 139°

- a) They were recrystallized from C_6H_4 -*n*-hexane.
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 h) A regioisomer (4d'), mp 146—147° (CCl_4 -*n*-hexane) (*Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.34; H, 6.30; N, 7.92), was obtained in 6% yield.

In the case of **3e**,¹⁰⁾ however, the only isolable product was 8-benzyl-3,4-dihydroisocarbostyril (**4e**), the yield being 7%. Similarly, **3f**¹¹⁾ gave **4f** in 5% yield. The structures of **4e** and **4f** were assigned on the basis of NMR spectra; namely the absence of a one-proton singlet attributable to C_8 -H and the presence of a benzylic two-proton singlet, shifted appreciably downfield, at δ 4.70 in the former, and the presence of a one-proton singlet at δ 7.50 due to C_8 -H and of a benzylic two-proton singlet at δ 4.11 in the latter.

Lewis acid-catalyzed rearrangement of benzyl phenyl ether has been well documented,¹²⁾ and the above rearrangement must have been induced by protons before or after cyclization.

Since more effective agitation is possible in anhyd. H_3PO_4 than PPA, the present method appears to be of some synthetic utility.

Experimental¹³⁾

A General Procedure—A solution in CH_2Cl_2 (1.5 ml) of an isocyanate was prepared by treatment with aq. NaN_3 in acetone of an acid chloride from **4a**—**c** (4.17 mmol) followed by heating in C_6H_6 , then

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 13) All melting points are uncorrected. IR spectra were taken with a Hitachi 215 spectrometer. NMR spectra were run on a Hitachi R-24B spectrometer in $CDCl_3$ solution using $(CH_3)_4Si$ as an internal standard, unless otherwise noted. The following abbreviations are used; s: singlet; bs: broad singlet; d: doublet; dd: double doublets; td: triple doublets; t: triplet; m: multiplet. Mass spectra were run on a Hitachi RMU-7M double-focusing mass spectrometer at 70 eV with direct insertion. Preparative TLC (prep. TLC) was performed using silica gel HF₂₅₄ (Merck) or basic alumina HF₂₅₄ (Merck).

this solution was treated with anhyd. H_3PO_4 (5 g, prepared from 85% H_3PO_4 and a calculated amount of P_2O_5) at room temperature for 2 hr. Purification of the product was carried out by prep. TLC or recrystallization. The results are shown in Table I. A typical experimental procedure is described below.

3,4-Dihydro-6-methoxy- and 3,4-Dihydro-8-methoxy-isocarbostyrils (4d and 4d')—A solution in CH_2Cl_2 (1.5 ml) of an isocyanate (509 mg) derived from **3d** (751 mg) was added dropwise to anhyd. H_3PO_4 (5 g) with stirring over a period of 5 min and stirring was continued at room temperature for 2 hr. The reaction mixture was poured into saturated aq. K_2CO_3 and the product was taken up in CHCl_3 . Usual work-up gave a solid (340 mg), which was recrystallized from C_6H_6 -*n*-hexane to give **4d** (196 mg). A mixture (139 mg) from the mother liquor was separated by prep. TLC (SiO_2 , acetone-AcOEt=2:1) giving an additional crop of **4d** (72 mg) and **4d'** (35 mg) (mobility; **4d**>**4d'**). **4d'**; NMR δ : 2.85 (2H, t, $J=6$ Hz, C_4 -H), 3.40 (2H, m, C_5 -H), 3.80 (3H, s, OCH_3), 6.70 (1H, d, $J=8$ Hz, ar. H), 6.80 (1H, d, $J=7$ Hz, ar. H), 7.25 (1H, dd, $J=8, 7$ Hz, C_6 -H); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3400 (NH), 1660 (NHCO); MS m/e : 177 (M^+).

8-Benzyl-3,4-dihydro-7-hydroxy-6-methoxyisocarbostyril (4e)—An isocyanate (662 mg) from **3e**¹⁰ (1.08 g) was treated in the manner described above for **3d** to give a reaction mixture, which was made alkaline with 10% NaOH. The alkaline layer was, after washing with CHCl_3 , made acidic with 10% HCl and the product was taken up in CHCl_3 . Usual work-up gave an amorphous mass (131 mg), purification of which by prep. TLC (SiO_2 , AcOEt: acetone=2:1) provided **4e** (76 mg, 7%), mp 172—172.5° (C_6H_6). *Anal.* Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3$: C, 72.05; H, 6.05; N, 4.95. Found: C, 71.97; H, 6.05; N, 4.99. NMR¹⁴ δ : 2.80 (2H, t, $J=7$ Hz, C_4 -H), 3.30 (2H, td, $J=7, 3$ Hz, C_3 -H), 3.82 (3H, s, OCH_3), 4.70 (2H, s, CH_2 Ph), 6.72 (1H, s, C_5 -H), 6.80—7.30 (5H, m, C_6H_5), 7.42 (1H, s, OH, disappeared on addition of D_2O); IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3530 (OH), 3170 (NH), 1650 (NHCO); MS m/e 283 (M^+).

Despite extensive purification of the neutral portion, no identifiable product could be obtained.

5-Benzyl-3,4-dihydro-6-hydroxy-7-methoxyisocarbostyril (4f)—A phenolic residue (498 mg) derived from **3f**¹¹ (2.39 g) as described above was chromatographed on SiO_2 (Kanto Chemicals) (elution with C_6H_6 -iso-PrOH=60:1) to afford a product (250 mg), which was purified by prep. TLC (Al_2O_3 , C_6H_6 -iso-PrOH=8:1), giving **4f** (115 mg, 5%), mp 194—195° (CCl_4). *Anal.* Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3 \cdot 1/4\text{H}_2\text{O}$: C, 70.94; H, 6.13; N, 4.87. Found: 70.69; H, 6.17; N, 5.14. NMR¹⁴ δ : 2.78 (2H, t, $J=7$ Hz, C_4 -H), 3.40 (2H, td, $J=7, 3$ Hz, C_3 -H), 3.88 (3H, s, OCH_3), 4.10 (2H, s, CH_2 Ph), 6.70—7.00 (1H, bs, NH), 7.18 (5H, s, C_6H_5), 7.50 (1H, s, C_5 -H), 8.12 (1H, s, OH, disappeared on addition of D_2O); IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3450 (OH), 3200 (NH), 1660 (NHCO); MS m/e : 283 (M^+).

No identifiable product could be obtained from the neutral portion.

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14) This was taken with a JEOL 4H-100 spectrometer in acetone- d_6 solution.