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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 studies[2] on lycorine–type alkaloids, the preparation of 1,2,-3,4,4aα,5,6,10bβ-octahydrophenanthrid-6-one (**2**)[3] from an isocyanate (**1**) was required on a large scale.

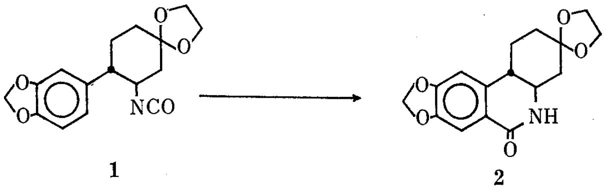

Chart 1

Although polyphosphoric acid (PPA),[4] boron trifluoride-etherate,[5] and phosphoryl chloride-stannic chloride[6] 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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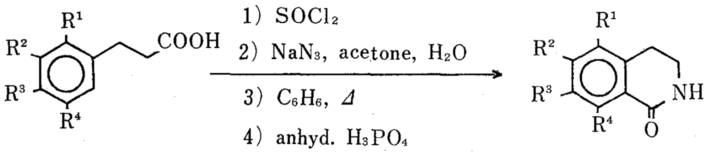

3

4a–d

a: $R^1=R^4=H$, $R^2+R^3=OCH_2O$
b: $R^1=R^4=H$, $R^2=R^3=OCH_3$
c: $R^1=H$, $R^2=R^3=R^4=OCH_3$
d: $R^1=R^3=R^4=H$, $R^2=OCH_3$
e: $R^1=R^4=H$, $R^2=OCH_3$, $R^3=OCH_2C_6H_5$
f: $R^1=R^4=H$, $R^2=OCH_2C_6H_5$, $R^3=OCH_3$

d′: $R^1=R^2=R^3=H$, $R^4=OCH_3$
e: $R^1=H$, $R^2=OCH_3$ $R^3=OH$, $R^4=CH_2C_6H_5$
f: $R^1=CH_2C_6H_5$, $R^2=OH$ $R^3=OCH_3$, $R^4=H$

Chart 2

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

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

a) They were recrystallized from C_6H_6–*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 $CDCl_3$ solutoin 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 HF_{254} (Merck) or basic alumina HF_{254} (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_3–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 $\nu_{max}^{CHCl_3}$ 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 whcih by prep. TLC (SiO_2, AcOEt: acetone=2 : 1) provided **4e** (76 mg, 7%), mp 172—172.5° (C_6H_6). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.05; H, 6.05; N, 4.95. Found: C, 71.97; H, 6.05; N, 4.99. NMR[14] 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_2), 4.70 (2H, s, $\underline{CH_2}$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 ν_{max}^{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 $C_{17}H_{17}NO_3 \cdot 1/4H_2O$: C, 70.94; H, 6.13; N, 4.87. Found: 70.69; H, 6.17; N, 5.14. NMR[14] 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, $\underline{CH_2}$Ph), 6.70—7.00 (1H, bs, NH), 7.18 (5H,s, C_6H_5), 7.50 (1H, s, C_8–H), 8.12 (1H, s, OH, disappeared on addition of D_2O); IR ν_{max}^{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 solutoin.

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