Fragmentation reactions promoted by cyanogen bromide

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The fragmentation of α-4-dimethylamino-3-methyl-1,2-diphenylbutan-2-ol to *cis* H/Ph 3-methyl-1,2-diphenylprop-2-ene, normally induced by treating the corresponding 2-chloro derivative with a base, also results when the alcohol itself is treated with cyanogen bromide; related γ-hydroxy acyclic tertiary amines similarly undergo fragmentation in this reaction. In contrast, cyclic analogues such as β-1,3-dimethyl-4-phenyl-4-piperidinol are not cleaved by cyanogen bromide (corresponding *N*-cyano derivatives are formed in low yield) even though β-4-chloro-1,3-dimethyl-4-phenylpiperidine is fragmented by potassium cyanide to *trans* H/Ph 5(*N*-cyanomethyl-*N*-methylamino)-3-phenylpent-2-ene.

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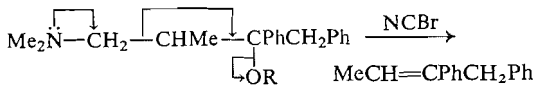
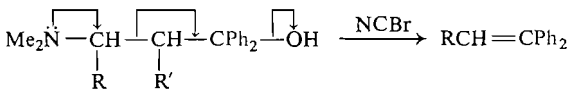
As part of a study of the von Braun *N*-demethylation procedure (1), the aminoalcohols **1***a*, **2***a*, and **2***b* were treated with cyanogen bromide. These compounds were chosen as reaction substrates because of the previous finding (1) that bases with oxygen functions delta to a dimethylamino group (e.g. methadone) are converted to cyclic products by cyanogen bromide (NCBr) instead of to *N*-cyano-*N*-methyl derivatives, the normal products of the von Braun reaction. An abnormal reaction course was also seen in the present experiments, the alcohols **1***a*, **2***a*, and **2***b* (OH γ- to NMe_2) being fragmented by NCBr at room temperature. Products isolated from the α-(±)-diastereoisomer of **1***a*, of known configuration (2), were *cis* H/Ph 3-methyl-1,2-diphenylprop-2-ene **3** (3) [ultraviolet (u.v.) and proton



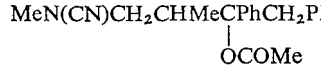
1 *a*) R = H; *b*) R = OCOMe **3**



2 *a*) R = H, R′ = Me
b) R = Me, R′ = H

4 *a*) R = Me
b) R = H

magnetic resonance (p.m.r.) spectra were identical with those of an authentic sample obtained from the 2-chloro analogue of **1***a* and sodium methoxide or pyridine] and α-**1***a* hydrobromide. No attempt was made to isolate the fragment complementary to the propene **3**. The diphenylpropan-1-ols **2***a* and **2***b* gave 1,1-diphenylprop-1-ene **4***a* and 1,1-diphenylethylene **4***b* respectively



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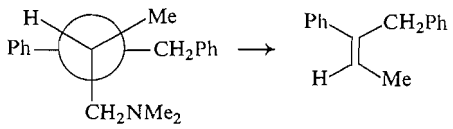
together with the corresponding substrate hydrobromides. No *N*-cyano derivatives were detected in any of the reaction products. The α-acetate **1***b* was also fragmented by NCBr giving *cis* **3**, but in this case the non-basic fraction contained the *N*-cyano-*N*-methyl acetate **5** in comparable amount (proton magnetic resonance evidence). Reaction between NCBr and the β-(±) diastereoisomer of **1***a* again gave the *cis* propene **3** as the major non-basic product. Hence, reaction of both α- and β-**1***a* appears to proceed through a common intermediate. This is probably a carbonium ion since if NCBr is regarded as analogous to an acyl halide, its reaction upon the tertiary benzylic alcohols **1** and **2** would be expected to give a reaction species of this nature.[1] The intermediate is represented in **6** by a conformer which satisfies the stereoelectronic requirements of fragmentation (4) and accounts for the exclusive or preponderant formation of the *cis* H/Ph



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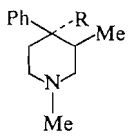
alkene **3**. Recovery of the α- rather than the β-**1***a* hydrobromide when β-**1***a* is treated with NCBr further supports the above interpretation of the reaction course. The β-ester **1***b* with NCBr gave a solid *N*-cyano-*N*-methyl ester **5** as the sole non-basic reaction product.

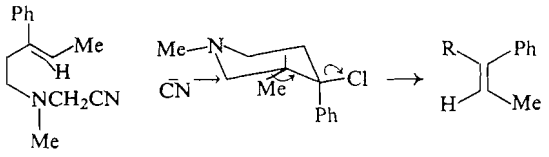
Some related reactions of the cyclic γ-hydroxy-tertiary amine **7** (β-prodinol, *cis* 3-Me/4-Ph) were next investigated. The 4-chloro analogue **7***b*, obtained by treating **7***a* with thionyl chloride (5), has

[1]Thanks to a referee for this suggestion.



7 *a*) R = OH,
b) R = Cl

the same configuration as the parent alcohol since its 3-methyl p.m.r. signal suffers a pronounced downfield shift (base, 52 Hz; HCl, 68 Hz from TMS in $CDCl_3$ at 60 MHz) when the basic center is protonated [the 3-methyl chemical shifts of α-isomers (*trans* 3-Me/4-Ph) of this type are little changed after *N*-protonation] (6). When **7***b* was treated with potassium cyanide in ethanol–water at the reflux temperature, a fragmentation reaction[2] occurred (cf. reaction between 3-β-chlorotropane and potassium cyanide) (7), the major product being 5-(*N*-methyl-*N*-cyanomethylamino)-3-phenylpent-2-ene **8**; this structure is substantiated by spectroscopic evidence (see Ex-

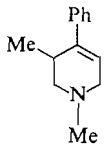


8 **9**

perimental). The predicted stereochemistry of **8**, based on reaction proceeding via the intermediate **9**, consistent with the stereoelectronic requirements of fragmentation (4) and the *cis* 3-Me/4-Ph configuration of **7***b*, is *trans* H/Ph. Support for this assignment is provided by the higher field chemical shift of the vinylic proton of **8** (336 Hz from TMS, base in $CDCl_3$) compared with that of the *cis* analogue **3** (365 Hz from TMS in $CDCl_3$) and comparative u.v. characteristics (**8** λ_{max} 231 mμ, ε 7600; **3** λ_{max} 245 mμ, ε 10 850 both in ethanol); these differences are consistent with a reduced degree of aromatic ring double bond coplanarity in the *trans* H/Ph derivative. β-Prodinol **7***a* and the tetrahydropyridine **10** were minor products of this reaction.

In view of the proneness of **7***b* to fragmentation, it was felt that NCBr should induce the cleavage of the precursor alcohol itself (**7***a*) by analogy with experiments upon the acyclic amino–alcohol

[2]The two fragments are, of necessity, linked together because of the ring system and no loss of carbon occurs.



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$Me_2NCH_2CMe{=}CPh_2$ **11**

$BrCH_2CMe{=}CPh_2$ **12**

1*a* and its chloro derivative. When β-prodinol was treated with NCBr in chloroform or benzene, however, the alcohol was recovered in high yield as the hydrobromide salt together with a small amount of the *N*-cyano-4-piperidinol (**7***a*, N—Me replaced by N—CN). The absence of a vinylic signal in the p.m.r. spectrum of the total hydrobromide showed that no fragmentation product formed. A similar result was obtained when 1-methyl-4-phenyl-4-piperidinol was used in this reaction, except that a small yield of the dehydrated alcohol also resulted. The process by which hydrogen bromide is generated in these reactions is not clear. The relative inertness of β-prodinol **7***a* (and the 3-desmethyl analogue) towards NCBr is possibly due to the highly hindered nature of its hydroxyl function (axial in preferred conformation and geminal to phenyl) (6).

Reaction of NCBr with the aminoalkene **11** gave 3-bromo-2-methyl-1,1-diphenylprop-1-ene **12**. This appears to be a normal tertiary-amino NCBr reaction in that one of the groups attached to nitrogen is cleaved, but is unusual in that the largest rather than the smallest *N*-substituent is lost.

Experimental

The p.m.r. spectra were recorded on a Varian A-60 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are expressed in τ units with TMS as standard. Infrared (i.r.) spectra of salts were recorded as Nujol mulls. The previously described (1) method for the reaction of tertiary amino substrates with NCBr was used. In the following specific cases, weight of substrate, reaction period, and temperature are given in parentheses after each example. Salts were crystallized from ethanol–ether.

(*a*) The α-butan-2-ol **1***a* (2) (11.2 g, 2 h, room) and NCBr (4.2 g) in $CHCl_3$ (40 ml) gave α-**1***a* hydrobromide (6.5 g), m.p. 235–237°, lit. (8) 235–236°, and 3-methyl-1,2-diphenylprop-2-ene (3.4 g) b.p. 104°/0.05 mm. Characteristics of the latter's u.v. and p.m.r. spectra were the same as those of the authentic *cis* H/Ph propene **3** (3).

(*b*) The α-acetate **1***b* (2) (14.6 g, 3 h, room) and NCBr (4.8 g) in $CHCl_3$ (40 ml) gave α-**1***b* hydrobromide, (7.5 g), ν_{max} 2650 ($\overset{+}{N}H$), 1735 (C=O) and 3350 cm^{-1} (H_2O), and the *cis* H/Ph propene **3** (4 g) b.p. 104°/0.05 mm.

Anal. Calcd. for $C_{21}H_{28}BrNO_2 \cdot H_2O$: C, 59.4; H, 7.1. Found: C, 60.0; H, 7.05.

The p.m.r. spectrum of the total non-basic fraction in $CDCl_3$ displayed signals due to the *N*-cyanomethyl derivative of **1***b* [singlets 7.33 (NMe) and 8.1 (OCOMe) and doublet 8.95 τ, *J* 6.5 Hz (3-Me)] as well as those due to the *cis* propene **3**.

(*c*) The β-butan-2-ol **1***a* (2) (3 g, 12 h, room) and NCBr (1 g) in $CHCl_3$ (20 ml) have **1***a* hydrobromide (2 g), m.p. 234–236° established as the α-diastereoisomer since its i.r. spectrum showed bands at 3080 and 3240 cm^{-1}, typical of the α-form and absence of β-bands (9). The major component of the non-basic product (0.5 g) was the *cis* propene **3** (p.m.r. comparisons).

(*d*) The β-acetate **1***b* (2) (1.5 g, 2 h, room) and NCBr (0.5 g) in $CHCl_3$ (20 ml) gave 2-acetoxy-4-*N*-cyano-*N*-methylamino-3-methyl-1,2-diphenylbutane (0.4 g), m.p. 131–132° from ether, ν_{max} 2195 (NCN) and 1730 cm^{-1} (C=O); p.m.r. characteristics in $CDCl_3$: singlets 7.23 (NMe) and 7.97 (COMe), doublet 8.95 τ, *J* 6.5 Hz (3-Me).

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 75.0; H, 7.2; N, 8.3. Found: C, 75.2; H, 7.3; N, 8.3.

(*e*) β-Prodinol **6***a* (10) (10.2 g, 2 h, room) and NCBr (5.3 g) in $CHCl_3$ (50 ml) or benzene (50 ml) gave **6***a* hydrobromide (6.5 g), m.p. 203–205°.

Anal. Calcd. for $C_{13}H_{20}BrNO$: C, 52.9; H, 7.1. Found: C, 52.5; H, 7.1.

1-Cyano-3-methyl-4-phenyl-4-piperidinol (0.18 g), m.p. 106–108° from hexane–methanol, was also isolated.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.1; H, 7.45; N, 13.9. Found: C, 72.2; H, 7.6; N, 13.85.

The total hydrobromide had a p.m.r. spectrum in DMSO-d_6 very similar to that of β-**6***a* hydrochloride and lacked signals in the vinylic region.

The same treatment of 1-methyl-4-phenyl-4-piperidinol (1.6 g) gave 1-cyano-4-phenyl-4-piperidinol (40 mg), m.p. 138–140° from hexane–methanol.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.2; H, 7.0; N, 14.85. Found: C, 71.0; H, 7.0; N, 14.7.

The piperidinol hydrobromide (0.5 g) and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, isolated as a hydrochloride m.p. 252–253°, lit. (11) 251–253°, were also obtained.

(*f*) The amino-propanol **2***a* (10.8 g, 2 h, room) and NCBr (4.2 g) in $CHCl_3$ (40 ml) gave **2***a* hydrobromide (6.5 g), m.p. 228–230°, ν_{max} 2650 cm^{-1} ($\overset{+}{N}$—H).

Anal. Calcd. for $C_{18}H_{24}BrNO$: C, 61.7; H, 6.9. Found: C, 61.4; H, 6.9.

The non-basic product of this reaction, 1,1-diphenylprop-1-ene (2 g), m.p. 46–48° from ethanol, lit. (12) b.p. 143–145°/11 mm, had u.v. and p.m.r. characteristics similar to those reported (12).

Anal. Calcd. for $C_{15}H_{14}$: C, 92.7; H, 7.3. Found: C, 92.85; H, 7.3.

(*g*) The amino-propanol **2***b* (10.8 g, 3 h, room) and NCBr (4.3 g) in $CHCl_3$ (40 ml) gave **2***b* hydrobromide (7 g), m.p. 229–231°. Anal. Found: C, 61.6; H, 6.7.

The non-basic product of this reaction, 1,1-diphenylethylene (2.2 g), b.p. 102°/0.5 mm, lit (12) b.p. 128°/10 mm, had u.v. and p.m.r. characteristics similar to those reported (12).

(*h*) The amino-alkene **10** (obtained by dehydrating the propanol **2***a* with HCl–acetic acid) (4 g, 3 h, room) and NCBr (1.7 g) in $CHCl_3$ (20 ml) gave 3-bromo-2-methyl-1,1-diphenylprop-1-ene (3.5 g), b.p. 118°/0.05 mm, m.p. 45–47°, λ_{max} 252 mμ, ε 13 200 in ethanol; p.m.r. characteristics in $CDCl_3$: multiplet 2.8 (10 aryl protons), singlets 5.97 (2-methylene protons) and 8.08 τ (*t*-methyl).

Anal. Calcd. for $C_{16}H_{15}Br$: C, 66.9; H, 5.3; Br, 28.5. Found: C, 66.9; H, 5.1; Br, 28.55.

Reaction of β-4-chloro-1-methyl-4-phenylpiperidine with KCN.

A mixture of the 4-chloropiperidine (6), (1.8 g), freshly liberated from the hydrochloride salt, KCN (0.6 g), ethanol (15 ml), and water (2.8 ml) was heated under reflux for 11 h. The product was concentrated, diluted with water, and extracted with ether. The ether (dried, Na_2SO_4) was evaporated and the residue (1.7 g) acidified with ethanol–HCl when the cyanomethylamino-alkene **7** hydrochloride (0.6 g) m.p. 125.5–126.5° after recrystallization, separated; ν_{max} 2245 cm^{-1} (CN, base, band obscured in the salt), λ_{max} 231 mμ, ε 7600 in ethanol; p.m.r. characteristics in $CDCl_3$; quartet 4.2 *J* 7 Hz (base 4.4, vinylic proton), broad singlet 4.72 (base 6.62, NCH_2CN), singlet 7.08 (base 7.78, NMe), and doublet 8.4 *J* 7 (base 8.45, τ MeCH=).

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.1; H, 7.6; N, 11.2. Found: C, 67.6; H, 7.6; N, 11.6.

β-Prodinol hydrochloride (0.2 g), m.p. 214–214.5°, was isolated from the mother liquors.

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.5; H, 8.3; N, 5.8. Found: C, 64.3; H, 8.25; N, 6.1. The p.m.r. spectrum of the total reaction product (base in $CDCl_3$) had signals characteristic of β-prodinol (3-Me doublet at 9.23) (7) and the tetrahydropyridine **9** (vinylic band at 4.17 and Me doublet at 9.02 τ) (13).

Acknowledgments

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1. A. F. Casy and M. M. A. Hassan. Tetrahedron, **23**, 4075 (1967).
2. A. Pohland and H. R. Sullivan. J. Am. Chem. Soc. **75**, 4458 (1953); H. R. Sullivan, J. R. Beck, and A. Pohland. J. Org. Chem. **28**, 2381 (1963).
3. A. F. Casy, J. L. Myers, and P. Pocha. Tetrahedron, **22**, 1001 (1966).
4. C. A. Grob, H. R. Kiefer, H. Lutz, and H. Wilkens. Tetrahedron Letters, 2901 (1964).
5. A. F. Casy. J. Chem. Soc. 5057 (1961).
6. A. F. Casy. Tetrahedron, **22**, 2711 (1966).
7. S. Archer, T. R. Lewis, and B. Zenitz. J. Am. Chem. Soc. **80**, 958 (1958).
8. P. Pocha. Ph.D. Thesis, University of London. 1966.
9. A. F. Casy and P. Pocha. J. Chem. Soc. B. 1160 (1966).
10. A. Ziering and J. Lee. J. Org. Chem. **12**, 911 (1947).
11. C. J. Schmidle and R. C. Mansfield. J. Am. Chem. Soc. **77**, 5698 (1955).
12. A. Jung and M. Brini. Bull. Soc. Chim. (France), 693 (1964).
13. A. F. Casy, A. H. Beckett, M. A. Iorio, and H. Z. Youssef. Tetrahedron, **21**, 3387 (1965).