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α-(PROXIMAL)-AZOXYALKYL CARBANIONS -- NEW SYNTHESES OF A PROXIMAL α,β-UNSATURATED AZOXYALKENE

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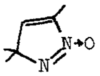
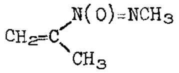
The "cross-conjugated", or proximal[1], α,β-unsaturated azoxyalkene unit appears in the natural products elaiomycin[2] and LL-BH872α[3], but synthetic routes to this function are limited. Thus, 1 was prepared by Zn reduction of the HCl adduct of pernitrosomesityl oxide[4], and 2 and 3 were obtained from peracid oxidations of unsymmetrical azoalkenes[5]. The regioselectivity of the latter method is unpredictable; distal α,β-unsaturated azoxyalkenes were obtained from closely related azoalkenes[5].

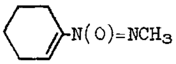


1



$CH_2{=}C(CH_3)N(O){=}NCH_3$

2



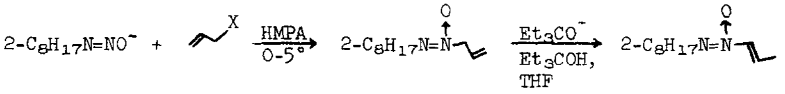
3

$C_6H_5CH{=}C[N(O){=}NOCH_3]_2$

4

Synthesis of 4[6], by the base catalyzed condensation of benzaldehyde with "bis methoxazonyl methane" [7], suggested to us that monofunctional, proximal, azoxyalkyl carbanions might be readily obtainable and synthetically useful. The isoelectronic relation of $CH_3N(O){=}NR$ to nitromethane (p$K_a \sim 11$)[8] supports this concept, and the present communication demonstrates its fruitfulness and potential utility.

Octane 2-diazotate was alkylated[9] with allyl iodide (or bromide), affording β,γ-unsaturated azoxyalkene, 5 (bp., 88°/3 Torr) in 17% distilled yield[10], eq. (1). Gc purified



(1)

5 6

(10% SF-96, 160°) 5[11] showed ir bands at 1642 (C=C) and 1493 cm^{-1} (azoxy); uv absorption at 224 nm (ϵ=6900, EtOH); and nmr signals at δ6.1 (1H, broad m, vinyl), 5.47 (1H, crude d, J=4, vinyl), 5.21 (1H, narrow m, vinyl), 4.63 (2H, d, J=6, allylic), 3.98 (1H, m, α-distal carbinyl), 1.25 (alkyl), 1.03 (3H, d, J=6, α-CH_3), and 0.88 (terminal CH_3)[12].

β,γ-Azoxyalkene 5 could be smoothly isomerized to its α,β-unsaturated isomer, 6 (spectra described below), using the highly hindered base, potassium triethylcarboxide (0.02M) in triethylcarbinol-THF, eq. (1). The α-azoxyalkyl-α-vinyl carbanion, 7, is a presumptive intermediate.** Treatment of 5 with refluxing methoxide/methanol+ gave 70% of azoxyether 8:

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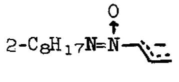
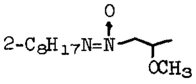
** For simplicity, resonance involving the azoxy function is not shown.

\+ Conditions: 10 mg $NaOCH_3$ in 20 ml of CH_3OH, 12 hrs reflux.

ir, 1497 and 1299 cm^{-1}(azoxy); uv, 223 nm (ϵ=6600, EtOH); nmr, δ4.00 (4H, m, proximal and distal α protons, proton α to OCH_3), 3.32 (3H, s, OCH_3), and other signals expected from the 2-octyl moiety[11]. Formation of **8** suggests prior isomerization of **5** to **6**, followed by a methoxide catalyzed Michael addition of methanol, occurring via the proximal α-azoxyalkyl anion, **9**[13**].



7



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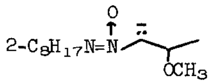
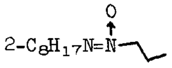


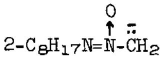
9

Pure **6**, or mixtures of **5** and **6**, also gave **8** upon treatment with CH_3O^-/CH_3OH.

Hexane solutions of **5** or **6** could be hydrogenated (25°, 1 atm.) to 2-octyl-<u>NNO</u>-1-azoxypropane, **10**, over 5% Rh/Al_2O_3[14]. Authentic **10** was prepared by the alkylation[9] of octane 2-diazotate with <u>n</u>-propyl iodide: ir, 1493 and 1309 cm^{-1}(azoxy); uv, 223 nm (ϵ=6400,EtOH); and characteristic nmr signals at δ4.02 (2H, t, J=7, proximal methylene), superimposed on a broad 1H multiplet (distal carbinyl proton)[11].

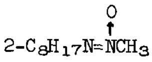


10



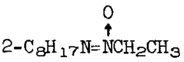
$2\text{-}C_8H_{17}N{=}\overset{\overset{O}{\uparrow}}{N}\text{-}\overset{\therefore}{C}H_2$

11



$2\text{-}C_8H_{17}N{=}\overset{\overset{O}{\uparrow}}{N}CH_3$

12



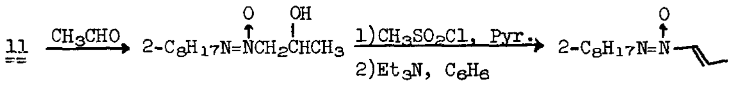
$2\text{-}C_8H_{17}N{=}\overset{\overset{O}{\uparrow}}{N}CH_2CH_3$

13

The apparent ease of access to α-azoxyalkyl carbanions **7** and **9** suggested that we attempt the generation of the proximal α-azoxymethyl anion, **11**.** Alkylation[9] of octane 2-diazotate with CH_3I gave 2-octyl-<u>NNO</u>-azoxymethane, **12**, in 40% distilled yield (bp., 71-74°/0.25 Torr): ir, 1504 and 1321 cm^{-1}(azoxy); uv, 223 nm (ϵ=7000, EtOH); and characteristic nmr signals at δ3.94 (3H, s, proximal CH_3), superimposed on a broad 1H m at δ3.90 (distal carbinyl proton)[11]. Addition of **12** to 1 equiv. of $LiN[Si(CH_3)_3]_2$ in THF at 0° gave, after 50 min., an orange-brown solution of carbanion **11**. Quenching with excess C_2H_5I (8 hrs., 25°) afforded **10**, in addition to some unreacted **12**, and a long retention time, possibly dialkylated product. (Gc employed the SF-96 column at 145°.)

Similarly, reaction of **11** with CH_3I gave the known[9,15] 2-octyl-<u>NNO</u>-azoxyethane, **13**, in 60% yield; 40% of **12** was recovered. When this experiment was repeated using **12** (α_D^{30}-6.88°, neat, 1 dm.) prepared from octane 2-diazotate of 45% optical purity, we obtained **13** (α_D^{30}-7.27°, neat, 1 dm). Corrected for precursor optical purity, this rotation corresponds to -16.2°. Since optically pure **13** has α_D^{30} $|16.9|$ ±0.2° (neat, 1 dm.)[15], little racemization (removal of the distal carbinyl proton) attended the sequence **12**→ **11** →**13**.

Finally, anion **11** was employed in a straightforward synthesis of **6**, eq. (2). Azoxyalkane **12** (4.5 g, 26.1 mmol) was converted to **11** with $LiN[Si(CH_3)_3]_2$ in THF, and the



14 **6** (2)

anion was quenched with excess acetaldehyde (30 seconds) to afford 6.1 g of crude azoxyalcohol, **14**. Methanesulfonyl chloride in pyridine (25°, 8 hrs.) gave **14**-OMs, which afforded 3.7 g

(18.7 mmol) of 2-octyl-*NNO*-*trans*-1-azoxypropene, **6**, upon reflux with triethylamine in benzene[16]. The yield was 70%, based on **12**.

Azoxyalkene **6** was nearly pure after simple distillation (bulb-to-bulb, 110°/2 Torr.); gc on the SF-96 column at 160° afforded pure material[11]: ir, 1664 (C=C), 1462, 1311 (azoxy), and 943 cm^{-1} (*trans*-olefin); uv, 232 nm (ϵ=7500, EtOH); nmr, δ6.87 (2H, m, vinyl), 4.10 (1H, m, distal carbinyl), 1.88 (3H, crude d, J=6, with fine structure, allylic CH_3), 1.33 (envelope, CH_2), 1.10 (d, J=7, $CH\underline{H_3}$), 0.88 ("t", $CH_2\underline{CH_3}$). Some chemistry of **6** is described above.

The present work greatly widens the scope of azoxyalkane chemistry: the accessibility of α-azoxyalkyl anions, together with the preexisting general synthesis of unsymmetrical azoxyalkanes[9] and the photochemical interconversion of azoxyalkane O-position isomers[17], opens the way to the synthesis of many new *additionally functionalized* azoxyalkanes and azoxyalkenes. We are vigorously exploring extensions of this work[18].

Acknowledgments - We thank the National Institutes of Health and the National Science Foundation for financial support.

References and Notes

(1) In $R_1N(O){=}NR_2$, we refer to R_1, or any subfunction of R_1, as *proximal*, and to R_2, or any subfunction of R_2, as *distal*. The reference point is the *N*-oxide.

(2) C. L. Stevens, B. T. Gillis, and T. H. Haskell, *J. Amer. Chem. Soc.*, **81**, 1435 (1959), and earlier references cited there.

(3) W. J. McGahren and M. P. Kunstmann, *J. Org. Chem.*, **37**, 902 (1972), and earlier references cited there.

(4) J. P. Freeman, *ibid.*, **27**, 1309 (1962).

(5) B. T. Gillis and J. D. Hagarty, *ibid.*, **32**, 95 (1967).

(6) R. B. Woodward and C. Wintner, *Tetrahedron Letters*, 2689 (1969).

(7) $CH_2[N(O){=}NOCH_3]_2$.

(8) R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).

(9) R. A. Moss, M. J. Landon, K. M. Luchter, and A. Mamantov, *ibid.*, **94**, 4392 (1972).

(10) About 20% of a product presumed to be $(CH_2{=}CHCH_2)_2C(CH{=}CH_2)N(O){=}N\text{-}2\text{-}C_8H_{17}$ was also formed.

(11) A satisfactory microanalysis (C,H,N) was obtained.

(12) Spectroscopic parameters for azoxyalkanes appear in ref. (9).

(13) Treatment of **5** with *t*-$C_4H_9O^-$/*t*-C_4H_9OH afforded the *t*-butyl analog of **8**. This new ether pyrolytically eliminated *t*-BuOH at 190°, giving a 50:50 mixture of **5** and **6**.

(14) W. J. McGahren and M. P. Kunstmann, *J. Amer. Chem. Soc.*, **91**, 2808 (1969).

(15) R. A. Moss and G. M. Love, *ibid*., **95**, 3070 (1973).

(16) Conversion of the mesylate to **6** was also achieved with $KOC(C_2H_5)_3$ in $HOC(C_2H_5)_3$ (25°, 8 hrs.).

(17) J. Swigert and K. G. Taylor, *J. Amer. Chem. Soc*., **93**, 7337 (1971); K. G. Taylor and T. Riehl, *ibid*., **94**, 250 (1972).

(18) This report is "Alkane Diazotates, XV". For Part XIV, see R. A. Moss, P. E. Schueler, and T.B.K. Lee, *Tetrahedron Letters*, 2509 (1973).