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ON THE BIOGENESIS OF GLIOTOXIN. SYNTHESIS OF 3-(β-AMINOETHYL)BENZENE OXIDE.

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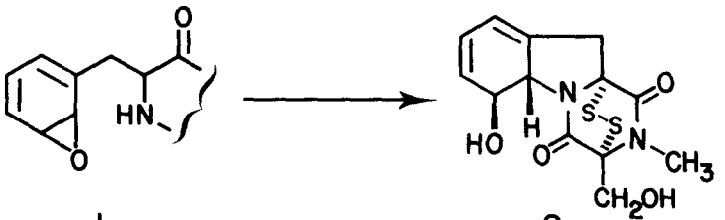
Abstract: The synthesis of 3-(β-aminoethyl)benzene oxide (7) is described. The failure of 7 to ring close (7→8) is attributed to the low "nucleophilic susceptibility" of the arene oxide.

In an elegant scheme Neuss and coworkers in 1968 postulated[1,2] the intermediacy of a 3-(β-aminoethyl)benzene oxide (e.g., 1) derived from phenylalanine during the fungal biogenesis of gliotoxin. Thus, it was suggested, the stereochemistry of the dihydroarene moiety of gliotoxin (2) is established by intramolecular displacement at carbon with Walden inversion in the arene oxide intermediate (1→2). Herein we report the synthesis of arene oxide 7 (Scheme), a model for the putative gliotoxin precursor, and detail our initial attempts to achieve biogenetic-type cyclization of 7.



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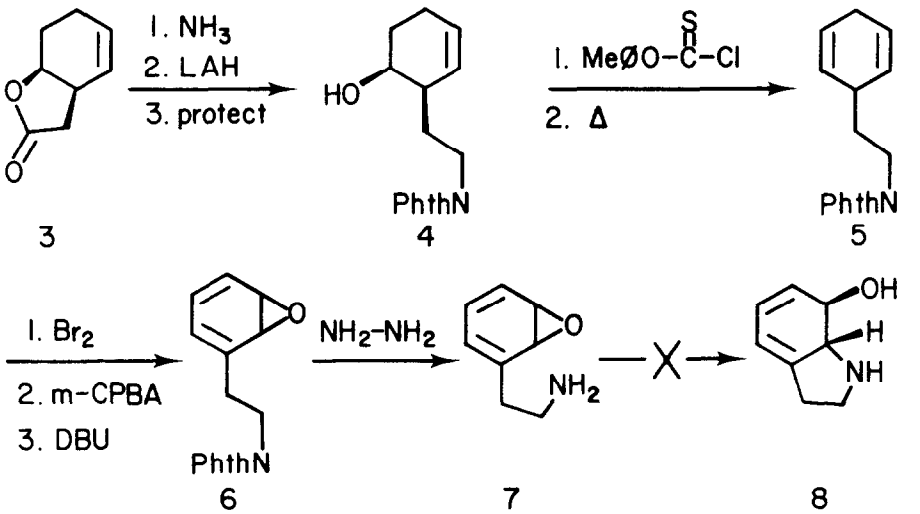
As starting material for the synthesis of 7 we utilize the known[3] lactone 3 Aminolysis,[4] reduction[5] and protection[6] gives protected amino alcohol 4[7] (overall 74%). Regiospecific generation of the 1,4-cyclohexadiene 5[8] is achieved by pyrolytic syn-elimination of the p-tolylthionocarbonate derivative[9] of alcohol 4 (overall 65%). Bromination,[10] epoxidation[11] and dehydrobromination[12] produces phthaloyl-protected aminoarene oxide 6 (overall 38%). Deprotection of 6 is effected by four equivalents of NH_2NH_2 in CH_2Cl_2, cleanly giving 3-(β-aminoethyl)benzene oxide (7)[13] as a pale yellow oil after high-vacuum transfer (61%).

We have failed repeatedly in achieving the biogenetic-type cyclization 7→8. Arene oxide 7 is stable in $CDCl_3$ and CH_2Cl_2 (Al_2O_3 treated), but aromatizes[14] readily in MeOH and in alkaline H_2O or when treated with Woelm-200 basic alumina in Et_2O.[15] The difficulty in achieving the conversion 7→8

apparently is not due to a lack of mutual reactivity of the amine and epoxide functionalities, rather the failure of 7 to ring close is due to its greater propensity to aromatize. Protic conditions which should facilitate ring closure also accelerate the arene oxide to phenol rearrangement. Thus the "nucleophilic susceptibility"[16] of 7 is low; the epoxide is not opened even by intramolecular amine attack.[17]

Scheme (Phth = phthaloyl)



The in vitro reactivity of our model arene oxide 7 does not match the reactivity of the putative gliotoxin biogenetic precursor.[1,2] A similar dilemma is posed by the enzyme epoxide hydratase[18] which mediates the addition of H_2O to arene oxides of low "nucleophilic susceptibility" -- similar additions have been achieved in the laboratory only recently by use of alumina catalysis.[15]

We continue to study the reactivity of 7. In particular, we seek means of functional group activation of the amino group for intramolecular nucleophilic addition.

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References and Notes

1. (a) N. Neuss, R. Nagarajan, B.B. Molloy, and L.L. Huckstep, Tetrahedron Lett., 4467 (1968); (b) N. Neuss, L.D. Boeck, D.R. Brannon, J.C. Cline, D. C. DeLong, M. Gorman, L.L. Huckstep, D.H. Lively, J. Mabe, M.M. Marsh, B.B. Molloy, R. Nagarajan, J.D. Nelson,and W.M. Stark, Antimicrob. Agents Chemother., 213 (1968).

2. Review of the biogenesis of gliotoxin and related metabolites: C. Leigh and A. Taylor, Chapter 11 of "Mycotoxins", ed. I.F.H. Purchase, Elsevier, Amsterdam (1974).
3. (a) K. Kondo, M. Matsumoto and F. Mori, Angew. Chem., Int. Ed. Engl., 14, 103 (1975); (b) E.J. Corey and T. Ravindranithan, Tetrahedron Lett., 4753 (1971).
4. Liquid NH_3, ambient temperature/sealed tube. The amide product displays satisfactory ^1H NMR and IR; exact mass, Calcd. for $C_8H_{13}NO_2$, 155.09462, found, 155.09453; Anal., Calcd. C, 61.91; H, 8.44; N, 9.02; O, 20.61; found C, 61.71; H, 8.50; N, 8.92; 0, 20.32; mp 129.5-130.5°C (uncorrected).
5. $LiAlH_4$/THF. The amino alcohol product displays satisfactory ^1H NMR and IR; exact mass, Calcd. for $C_8H_{15}NO$, 141.11536, found, 141.11672; bp 72-74°C, 0.03 mmHg.
6. $PhthNCO_2Et/ClCH_2CHCl_2$, reflux; see G.H.L. Nefkens, Nature, 185, 309 (1960).
7. Compound 4, isolated as an oil, displays satisfactory ^1H NMR and IR; exact mass, Calcd. for $C_{16}H_{17}NO_3$, 271.12084, found, 271.12219.
8. Compound 5 displays satisfactory ^1H NMR and IR; exact mass, Calcd. for $C_{16}H_{15}NO_2$, 253.11027, found, 253.11098.
9. The p-tolylthionocarbonate displays satisfactory ^1H NMR and IR; exact mass, parent minus p-$CH_3ØOC(S)O$-, Calcd. for $C_{16}H_{16}NO_2$, 254.11810, found, 254.11711; p-$CH_3ØOC(S)OH^+$, Calcd. for $C_8H_8O_2S$, 168.02450, found 168.02570; Anal., Calcd. C, 68.39; H, 5.50; N, 3.32; 0, 15.18; S, 7.61; found C, 68.25; H, 5.24; N, 3.37; O, 15.38; S, 7.34; mp 115.5°C (uncorrected). Thionocarbonate pyrolysis performed in diglyme at 162°C/4 hrs; see H. Gerlach, T.T. Huong and W. Müller, J. Chem. Soc., Chem. Commun., 1215 (1972).
10. Br_2/CH_2Cl_2 at -78°C; the oily mixture of diastereomeric dibromides was not separated; the mixture displays satisfactory ^1H NMR and IR; exact mass, parent minus ^{81}Br, Calcd. for $C_{16}H_{15}{}^{79}BrNO_2$, 332.02861, found 332.03054.
11. Achieved with m-CPBA/CH_2Cl_2 at reflux. The mixture of diastereomeric dibromoepoxides displays satisfactory ^1H NMR and IR; exact mass, parent minus ^{79}Br, Calcd. for $C_{16}H_{15}{}^{81}BrNO_3$, 350.02148, found, 350.02242. Silica gel chromatography (10% Et_2O in CH_2Cl_2) separates the mixture into two components. Only the slower eluting fraction (mp 131-132°C, uncorrected) can be transformed efficiently into arene oxide 6. Fractional crystallization of the material melting 131-132°C gives an analytically pure sample, mp 146.5-147.5°C (uncorrected). Anal., Calcd. C, 44.79; H, 3.52; N, 3.26; Br, 37.24; O, 11.19; found C, 44.57; H, 3.33; N, 3.15; Br, 37.15; O, 11.02.
12. Effected by 1.3 equivalents of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in THF, O°C to ambient temperature. The arene oxide 6, isolated as a waxy yellow solid, displays satisfactory ^1H NMR and IR.
13. Arene oxide 7 displays ^1H NMR (d_6 benzene) δ(TMS) 1.09 (br s, NH_2); 2.28 (1/2 A_2B_2, allylic CH_2); 2.88 (1/2 A_2B_2,CH_2-N); 4.47 (mult, 2H); 6.11 (mult,

3H); IR (neat) 3375, 3300, 3050, 3020, 2935, 2860, 1638, 1607, 1570, 1420, 1240, 1070, 1030, 943, 845, 825, 771, 750, 703 cm^{-1}; UV (n-BuOH) λ_{max} 271, $\varepsilon = 3.0 \times 10^3$; exact mass, Calcd. for $C_8H_{11}NO$, 137.08406, found 137.08418. Arene oxide 7 was derivatized by Diels Alder reaction with bis(trichloroethyl)azodicarboxylate (see W.H. Rastetter, J. Amer. Chem. Soc., 98, 6350 (1976)); the crystalline adduct melts 136.5-137.5°C (uncorrected). Anal., Calcd. C, 40.76; H, 2.64; N, 6.48; Cl, 32.82; O, 17.28; found C, 41.01; H, 2.75; N, 6.38; Cl, 32.53; O, 17.47.

14. Arene oxide 7 aromatizes to the corresponding o-phenol (o-tyramine), mp 112.5-114°C (uncorrected); lit. mp 113-115°C, Beilstein, H 13, 624; I, 233; III, 1624.
15. G.A. Posner and D.Z. Rogers, J. Amer. Chem. Soc., 99, 8208 and 8214 (1977).
16. See P.Y. Bruice, T.C. Bruice, H. Yagi and D.M. Jerina, ibid, 98, 2973 (1976).
17. Approach vector analysis suggests that 1,2- rather than 1,4-addition of the amine to the epoxide is favored; see J.E. Baldwin, J. Chem. Soc., Chem. Commun., 734 (1976).
18. See G.C. DuBois, F. Appella, W. Levin, A.Y.H. Lu and D.M. Jerina, J. Biol. Chem., 253, 2932 (1978) and R.P. Hanzlik, M. Edelman, W.J. Michaely, and G. Scott, J. Amer. Chem. Soc., 98, 1952 (1976) and references therein.

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