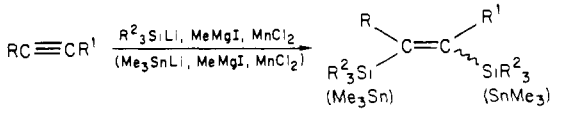
**Table I.** Disilylation or Distannylation of Acetylenes with Si–Mn or Sn–Mn Reagent



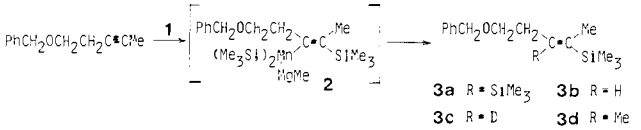

| acetylene $RC{\equiv}CR^1$ | reagent $R^2_3SiLi$ | product yield, % | product $Z/E$ |
|---|---|---|---|
| $HC{\equiv}CSiMe_3$ | $Me_3SiLi$ | 72 | |
| $C_4H_9C{\equiv}CH$ | $Me_3SiLi$ | 66 | 33/67 |
| $PhC{\equiv}CH$ | $Me_3SiLi$ | 65 | 50/50 |
| $C_4H_9C{\equiv}CSiMe_3$ | $Me_3SiLi$ | 80 | |
| $PhCH_2OCH_2CH_2C{\equiv}CH$ | $PhMe_2SiLi$[a] | 51 | 42/58 |
| $PhCH_2OCH_2CH_2C{\equiv}CD$ | $PhMe_2SiLi$ | 55 | 42/58[b] |
| $PhCH_2OCH_2CH_2C{\equiv}CSiMe_3$ | $Me_3SiLi$ | 59 | |
| $THPOCH_2CH_2C{\equiv}CH$ | $Me_3SiLi$ | 63 | 65/35 |
| $THPOCH_2CH_2C{\equiv}CH$ | $PhMe_2SiLi$ | 70 | 65/35 |
| $THPOCH_2CH_2C{\equiv}CSiMe_3$ | $Me_3SiLi$ | 83 | |
| $HOCH_2CH_2C{\equiv}CSiMe_3$ | $Me_3SiLi$[c] | 58 | |
| $C_{10}H_{21}C{\equiv}CH$ | $Me_3SnLi$[d] | 56 | 100/0 |
| $C_{10}H_{21}C{\equiv}CD$ | $Me_3SnLi$ | 55 | 100/0[b] |
| $THPOCH_2CH_2C{\equiv}CH$ | $Me_3SnLi$ | 54 | 100/0 |
| $THPOCH_2CH_2C{\equiv}CH$ | $Bu_3SnLi$[d] | 48 | 90/10 |
| $PhCH_2OCH_2CH_2C{\equiv}CH$ | $Me_3SnLi$ | 52 | 90/10 |

[a] See ref 6. [b] Deuterium remained completely, thus reagents do not cause the acetylenic proton–metal exchange. [c] Three millimoles of manganese reagent and 1 mmol of substrate were employed. [d] See ref 7.

of tetrahydropyranyl ether of 4-(trimethylsilyl)-3-butyn-1-ol (0.23 g, 1.0 mmol) in THF (3 mL) was added and the resulting mixture was stirred for 3 h at 0 °C. The mixture was diluted with ether and poured into saturated $NH_4Cl$. Purification by preparative TLC on silica gel gave tetrahydropyranyl ether of 3,4,4-tris(trimethylsilyl)-3-buten-1-ol (0.31 g) in 83% yield as a colorless oil: bp 150 °C (1.0 torr, bath temperature); IR (neat) 1440, 1350, 1260, 1250, 1200, 1140, 1120, 1030, 840 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.19 (s, 9 H), 0.22 (s, 9 H), 0.23 (s, 9 H), 1.5–1.9 (m, 6 H), 2.89 (t, $J$ = 8 Hz, 2 H), 3.36 (dt, $J$ = 8, 10 Hz, 1 H), 3.5–3.6 (m, 1 H), 3.66 (dt, $J$ = 8, 10 Hz, 1 H), 3.8–3.9 (m, 1 H), 4.61 (t, $J$ = 3 Hz, 1 H); MS, $m/z$ 372 ($M^+$, 1), 270 (64), 197 (43), 155 (48), 85 (100), 73 (99). Found: C, 58.02; H, 11.06%. Calcd for $C_{18}H_{40}O_2Si_3$: C, 58.00; H, 10.82%.

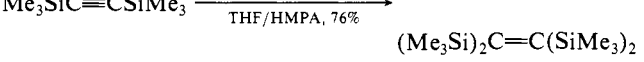
For other examples see Table I. The reaction proceeded smoothly with silylacetylenes as well as terminal acetylenes. Terminal acetylenes gave mixtures of $E$ and $Z$ isomers of disilylated products. MeMgI is essential for the formation of disilylated products, although its role is not clear. Without MeMgI, monosilylated products were obtained predominantly after aqueous workup. For instance, treatment of 4-(benzyloxy)-1-butyne with $3Me_3SiLi$–$MnCl_2$ gave a mixture of 4-(benzyloxy)-2-(trimethylsilyl)-1-butene, 4-(benzyloxy)-1-(trimethylsilyl)-1-butene, and disilylated product in 1:1:1 ratio (65% combined yield). The reaction has been extended to distannylation of acetylenes. See Table I.

Treatment of 5-(benzyloxy)-2-pentyne with the reagent $(Me_3Si)_3MnMgMe$ (**1**) at 0 °C for 20 min and 25 °C for 3 h gave 2,3-bis(trimethylsilyl)-2-alkene **3a** in 78% yield. Meanwhile, the




addition of $H_2O$ (or $D_2O$, MeI) to the reaction mixture after stirring at 0 °C for 20 min without warming up to room temperature gave monosilylated product **3b** (71%) (or **3c** (71%), **3d** (70%)) along with the disilylated product **3a** (13–20%).[8] Thus, the formation of disilylated product may be explained as follows: (1) Addition of the reagent **1** to triple bond in cis fashion[9] giving silylated alkenylmanganese **2** and (2) reductive elimination of manganese affording disilylated olefin.

It is worth noting that the reaction can be successfully applied to the synthesis of highly strained tetrakis(trimethylsilyl)ethene which is not readily available by known methods.[10]




(5) A solution of $Li_2MnCl_4$ in THF could be used instead of $MnCl_2$.
(6) A stock solution in THF was used. Gilman, H.; Lichtemwalter, G. D. *J. Am. Chem. Soc.* **1958**, *80*, 607.
(7) Prepared from $SnCl_2$ and 3 equiv of alkyllithium. Hibino, J.; Matsubara, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 2151.
(8) In the case of terminal acetylenes and silylacetylenes in Table I, the intermediary alkenylmanganese could not be trapped by the electrophiles such as $D_2O$ and MeI.
(9) The cis addition of Si–Mn component was confirmed as follows. Monosilylated alkene, 5-(benzyloxy)-2-(dimethylphenylsilyl)-2-pentene was prepared from $(PhMe_2Si)_3MnMgMe$ and 5-(benzyloxy)-2-pentyne according to the generation of **3b**. Protodesilylation with $n$-$Bu_4NF$ (Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 2877) gave 5-(benzyloxy)-2-pentene. The examination of the $^1H$ NMR spectra proved that the olefin had $Z$ configuration (>95%, $J$ = 11 Hz).
(10) Sakurai, H.; Nakadaira, Y.; Kira, M.; Tobita, H. *Tetrahedron Lett.* **1980**, *21*, 3077. Chung, C.; Lagow, R. J. *J. Chem. Soc., Chem. Commun.* **1972**, 1078.

## Palladium-Catalyzed Annelation onto *N,N*-Dialkylanilines by Tetrahydrofuran. Stereospecific Formation of Heterotricyclic Compounds via Cation Radical Intermediates

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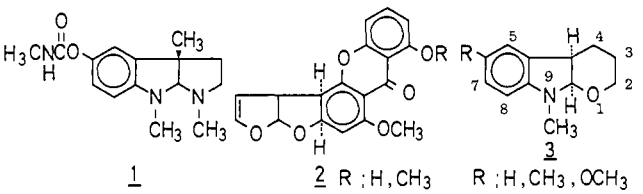
The natural compounds with cis-[2,3-*b*]-fused N,N- or O,O-diheterobicyclic structures, such as physostigmin (**1**) and strig-




matocystins (**2**), are interesting due to their pharmacology[2] and synthetically challenging structures. We now report a facile method to obtain a new class of heterotricyclic compounds **3** containing cis-[2,3-*b*]-fused N,O-diheterobicyclic structure by palladium(II)-assisted annelation onto *N,N*-dialkylanilines by tetrahydrofuran. The reactions may be explained in terms of a formation of *N,N*-dialkylaniline cation radicals.

In arene oxidation by metal salts, a recent monograph[3] noted that free cation radicals are formed with hard metal ions such

(1) Physical Institute, College of Liberal Arts.
(2) (a) Glasby, J. S. "Encyclopedia of the Alkaloids"; Plenum Press: New York, 1975; Vols. I, II. (b) Shibata, S. "Bioactive Natural Products" (in Japanese); Ishiyaku Press: Tokyo, 1979; pp 397–402. (c) Natori, S. *Yakugaku Zasshi* **1983**, *103*, 1109. Udagawa, S.; Muroi, T.; Sekita, S.; Yoshihira, K.; Natori, S.; Ueda, M.; *Can. J. Microbiol.* **1979**, *25*, 170. Sekita, S.; Yoshihira, K.; Natori, S.; Udagawa, S.; Muroi, T.; Sugiyama, Y.; Kurata, H.; Umeda, M.; *Ibid.* **1981**, *27*, 766.
(3) Shelden, R. A.; Kochi, J. K. "Metal-Catalyzed Oxidation of Organic Compounds"; Academic Press: New York, 1981; pp 130–133.

0002-7863/85/1507-6417$01.50/0 

**Table I.** Reactions of *N,N*-Dialkylanilines (**4**) with THF by Palladium(II) Compounds[a]

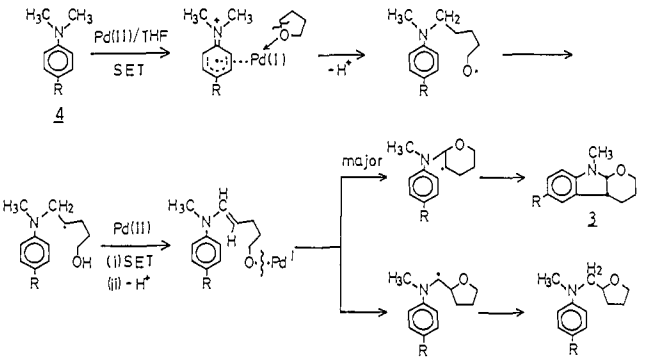
| Run | Reactants | | | Temp. Time | Conv. of 4 (%) | Products[b] (%)[c] |
|---|---|---|---|---|---|---|
| 1. | 4a | THF | $Pd(OAc)_2$ AcOH | 50°C 19 h | (83.4) | 3a (14.0) 6a (15.7) 7a (36.7) |
| 2. | 4b | THF | $Pd(OAc)_2$ AcOH - Benzene | 50° 5 h | (79.0) | 3b (69.6) 8b (trace) |
| 3. | 4b | THF | $Pd(OAc)_2$ AcOH | 40° 23 h | (71.3) | 3b (12.4) 5b (2.6) 6b (8.0) |
| 4. | 4b | THF | AcOPd AcOH | 80° 10 h | (59.9) | 3b (47.2) 8b (trace) 8b (trace) |
| 5. | 4c | THF | $Pd(OAc)_2$ AcOH | 50° 6 h | (39.7) | 3c (19.2) 9c (6.9) |
| 6. | 4c | THF | AcOPd AcOH - Benzene | 80° 27 h | (54.1) | 3c (56.6) |
| 7. | 4d | THF | $Pd(OAc)_2$ AcOH | 50° 7 h | (58.4) | 3d (6.8) 6d (6.3) 9d (4.4) |
| 8. | 4e | THF | $Pd(OAc)_2$ AcOH | 50° 4 h | (55.3) | 3b (5.2) 3e (14.4) |

[a] The reactions were carried out by using $^1/_2$ equiv of Pd(II) compounds and a mixed solvent of THF/AcOH (1:1) or THF/AcOH/benzene (2:1:1). [b] All spectral data of isolated products supported the presented structures. [c] Isolated yields of products were based on used Pd(II) compounds.

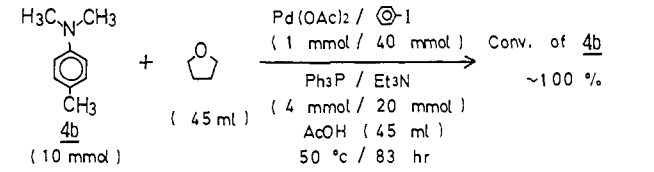
as Co(III), Mn(III), and Ce(IV) owing to relative low stability of aryl-metal bonds, while with soft metal ions such as Pb(IV), Tl(III), and Pd(II), only several electron-rich arenes in trifluoroacetic acid are oxidized to discrete cation radical intermediates. However, in case of Pd(II), only a few speculative examples of discrete cation radicals in the reactions of palladium(II) salts with organic substrates have appeared.[4] Furthermore, most of these cation radical intermediates have been generally trapped by external nucleophiles or metal species, so that only formal nucleophilic or electrophilic substitution products have been isolated.[5] It has been already suggested the oxidation of *N,N*-dimethylanilines with palladium(II) salts involves cation radical intermediates, which result in a new type of reactions.[4c,6] We herein describe the generation of discrete arene cation radical species in the reaction of arylamines with palladium(II) compounds under gentle oxidation conditions (e.g., in acetic acid at room temperature) and their transformation to interesting oxidation products involving novel carbon–carbon bond formation.

Treatment of *N,N*-dimethyl-*o*-toluidine (**4b**) with tetrahydrofuran and palladium(II) acetate in acetic acid and benzene (1:1) at 50 °C for 5 h under nitrogen gave, after filtration of the metallic palladium that was formed, workup, and column chromatography,

Scheme I. Probable Reaction Mechanism




6,9-dimethyl-3,4,4a,9a-tetrahydro-2*H*-pyrano[2,3-*b*]indole (**3b**) in a yield of 69.6%, along with recovery of **4b** (21%). The




compound **3b**[7] shows no carbonyl absorption in its IR and a doublet ($J$ = 4.0 Hz, 1H) at $\delta$ 4.53 in its $H^1$ NMR. The doublet signal assigned to the C-9a proton of **3b** was decoupled to a singlet by irradiating multiplet signals near $\delta$ 2.4, which may be assigned to a proton on C-4a. The small coupling constant ($J_{4a\text{-}9a}$ = 4.0 Hz) may be attributed to the existence of cis-fused tetrahydropyran ring.[8]

The results of reactions of various *N,N*-dialkylanilines with tetrahydrofuran by palladium(II) compounds are summarized in Table I, together with other isolated products. As can be seen in Table I, the use of [*o*-[(dimethylamino)methyl]phenyl]palladium(II) acetate in place of palladium(II) diacetate and benzene as one of solvents improved the yields of the adducts **3**. The reaction of *N*-ethyl-*N*-methyl-*p*-toluidine (**4e**) with tetrahydrofuran gave **3b** in a yield of 5.2% in addition to 14.4% of the corresponding 9-ethyl derivative **3e**. The former might have originated from **4b** which could be formed in situ by palladium-catalyzed disproportionation of **4e**.[10]

Palladium-catalyzed synthesis of **3** was preliminarily examined under a few different conditions. In the presence of silver(I) acetate as a reoxidant of zero-valent palladium along with catalytic amount of palladium(II) acetate, **4b** gave **3b** in a yield of 295%, on the basis of used palladium(II) acetate, together with 164.4% of **6b** and 12.5% of **5b**. A similar reaction of **4b** that used iodobenzene as a reoxidant[11] also gave 120% of **3b** together with 30.2%

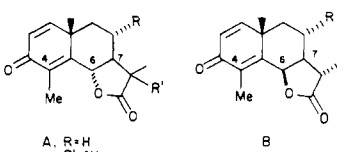
(4) (a) Davidson, J. M.; Triggs, C.; *J. Chem. Soc. A* **1968**, 1324, 1331. (b) Reference 3, pp 198–200. (c) Sakakibara, T.; Kotobuki, J.; Dogomori, Y. *Chem. Lett.* **1977**, 25. Sakakibara, T.; Dogomori, Y.; Tsuzuki, T. *Bull Chem. Soc. Jpn.* **1979**, *52*, 3592.

(5) (a) Hanotier, J.; Hanotier-Bridoux, H.; de Radzitzky, P. *J. Chem. Soc., Perkin Trans. 2* **1973**, *381*, 1035. (b) Kochi, J. K.; Tang, R. T.; Bernath, T. *J. Am. Chem. Soc.* **1973**, *95*, 7114. (c) Norman, R. O. C.; Thomas, C. B.; Willson, J. S. *J. Chem. Soc. B* **1971**, 518. (d) Kurz, M. E.; Hage, G. W. *J. Org. Chem.* **1977**, *42*, 4080. (e) Taylor, E. C.; Mckillop, A. *Acc. Chem. Res.* **1970**, *3*, 338; *Chem. Ber.* **1972**, *8*, 4. (f) Elson, I. H.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 5061.

(6) (a) Sakakibara, T.; Matsuyama, H. *Chem. Lett.* **1980**, 1331. (b) Sakakibara, T.; Hamakawa, T. *Chem. Lett.* **1982**, 1823.

(7) **3b** was characterized as follows: IR ($cm^{-1}$) 2935, 2855, 2815, 1620, 1510, 1450, 1295, 1205, 1100, 1060, 1000, 800; $H^1$ NMR ($Me_4Si$, $CDCl_3$) $\delta$ 7.20–6.43 (m, 3 H, Ar H), 4.53 (d, 1 H, 9a-H, $J$ = 4.0 Hz), 4.08–3.64 (m, 2 H, 2-H), 3.33–1.57 (m, 5 H, 3-, 4-, 4a-H), 2.82 (s, 3 H, N–$CH_3$), 2.23 (s, 3 H, Ar $CH_3$); $C^{13}$ NMR ($Me_4Si$, $CDCl_3$) $\delta$ 145.1 (s), 131.4 (d), 129.5 (d), 126.6 (s), 122.0 (s), 111.9 (d), 75.8 (d), 65.2 (t), 52.9 (t), 39.3 (q), 36.2 (d), 30.1 (t), 20.1 (q); mass spectrum, $m/e$ 203 ($M^+$), 172, 160, 158. 10 M mass: $M^+$ obsd 203.1372, calcd for $C_{13}H_{17}NO$ 203.1310.

(8) The stereochemical study with molecular models showed that cis-fused and trans-fused structures of **3** have the dihedral angles of 45° and 170° between 4a-H and 9a-H, respectively, and hence the Karplus formula gives $J_{4a\text{-}9a}$ = 3.97 Hz for cis and 8.93 Hz for trans. Natural $\alpha$-santonin (A) and

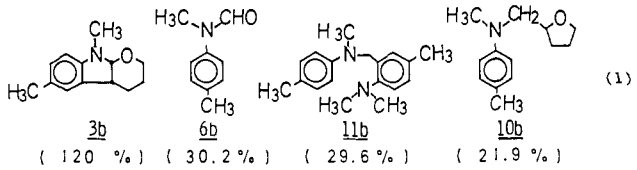



$\alpha$-episantonin (B) give $J_{6,7}$ = 9.0 Hz and $J_{6,7}$ = 4.6 Hz, respectively.[9]

(9) Pinhey, J. T.; Sternhell, S. *Tetrahedron Lett.* **1963**, 275.

(10) Concerning to palladium-catalyzed amine exchange reaction of tertiary amine, see: Murahashi, S.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348.

of **6b** and 29.6% of **11b** (eq 1). In the latter reaction, *N*-




(1)

methyl-*N*-(tetrahydrofurfuryl)-*p*-toluidine (**10b**) was isolated in a yield of 21.9%, which was identical with authentic material prepared by an alternative method[12] by IR, NMR, and TLC. The compound **10b** may be noteworthy in relation to the formation of **3b**.

The intermediates of heterotricycle formation were investigated by absorption spectrum measurement and ESR method. Mixing of *N*,*N*-dimethyl-*p*-anisidine (**4c**) and *N*,*N*-dimethylbenzylamine–palladium(II) $\sigma$-complex in benzene containing a small amount of acetic acid gave a pale green solution ($\lambda_{max}$ 604 nm), which was ESR active and showed a fairly resolved signal (*g* value 2.0043). The signal gradually diminished at room temperature. The ESR spectrum consisted of 11 lines, showing high spin density on nitrogen, *N*-methyls, and ortho carbons of **4c**. The result is almost identical with the spin distribution of *N*,*N*-dimethyl-*p*-anisidine radical cation which was generated in acetonitrile by anodic oxidation of **4c**.[13] This may support an initial single electron transfer process in the palladium(II) oxidation of **4**.

In the absence of THF, the major products were cyclodimers; e.g., **4b** gave **5b** in a yield of 52.4%.[6] Therefore, the origin of the 9a carbon of **3** may be the *N*-methyl carbon of **4** and hence the formation of **3** must involve three new bond formations, i.e., *N*-methyl C–THF $\alpha$-C, *N*-methyl C–O, and aromatic C–THF $\alpha$-C bonds. The most probable mechanism is shown in Scheme I, which consists of double SET processes, 1,5-radical rearrangement, and double intramolecular radical cyclizations. The first cyclization with oxygen radical might preferentially give tetrahydropyranyl radicals,[14] which could form cis-fused products stereospecifically.[15]

**Acknowledgment.** We are grateful to Prof. Tsunao Hase for helpful discussion and mass analyses. Partial financial support from the Ministry of Education, Science, and Culture, Japanese Goverment (Grant-in-aid 59550582), is acknowledged.

**Registry No. 3a**, 98526-33-1; **3b**, 98526-34-2; **3c**, 98526-35-3; **3d**, 98526-36-4; **3e**, 98526-37-5; **4a**, 121-69-7; **4b**, 99-97-8; **4c**, 701-56-4; **4d**, 770-03-6; **4e**, 35113-87-2; **5b**, 7137-79-3; **6a**, 93-61-8; **6b**, 2739-04-0; **6d**, 65772-53-4; **7a**, 101-61-1; **8b**, 73172-84-6; **9c**, 5961-59-1; **9d**, 38036-47-4; **10b**, 98526-38-6; **11b**, 23970-61-8; THF, 109-99-9; $Pd(OAc)_2$, 3375-31-3; [*o*-[(dimethylamino)methyl]phenyl]palladium(II) acetate, 40243-08-1; silver(I) acetate, 563-63-3; iodobenzene, 591-50-4; *N*-methyl-*p*-toluidine, 623-08-5; tetrahydrofurfuryl bromide, 1192-30-9; 1,8-bis(dimethylamino)naphthalene, 20734-58-1.

**Supplementary Material Available:** Figures for $C^{13}$ NMR and mass fragmentation pattern of the compounds **3** and ESR spectrum of the radical cation intermediate (1 page). Ordering information is given on any current masthead page.

(11) Arylpalladium(II) $\sigma$-complexes are formed by the oxidative addition of aryl halides to Pd(0); cf.: Patel, B. A.; Ziegler, C. B.; Cortese, N. A.; Plevyak, J. E.; Zebovitz, T. c.; Terpko, M.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3903. Cortese, N. A.; Ziegler, C. B., Jr.; Hornjez, B. J.; Heck, R. F. *Ibid.* **1978**, *43*, 2952.

(12) **10b** was prepared by the reaction of *N*-methyl-*p*-toluidine with tetrahydrofurfuryl bromide in the presence of 1,8-bis(dimethylamino)-naphthalene: 40% yield, bp 127 °C (7 mmHg).

(13) Seo, E. T.; Nelson, R. F.; Fritsch, J. M.; Marcoux, L. S.; Leedy, D. W.; Adams, R. F. *J. Am. Chem. Soc.* **1966**, *88*, 3498.

(14) Intramolecular radical cyclization onto $\omega$-olefins have been known preferentially to give five-membered rings.[15] In Pd-mediated cyclization, we have the precedence that the six-membered ring formation is preferred to the corresponding five-membered ring formation; e.g.: Semmelhack, M. F.; Bodurow, C. *Ibid.* **1984**, *106*, 1496. However, further model studies of intramolecular cyclizations of oxygen-centered radicals on an enamine functionality would be necessary to elucidate regioselectivity.

(15) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

# Thiolate Additions to Bicyclomycin and Analogues: A Structurally Novel Latent Michael-Acceptor System

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*Received May 28, 1985*

Seven years after the isolation and structure elucidation of bicyclomycin (**1**), Iseki and co-workers[1] reported the regiospecific addition of sodium methane thiolate to the C-5 *exo*-methylene moiety of this structurally unique antibiotic affording the sulfide **3**. Iseki[2] has shown that bicyclomycin irreversibly forms covalent bonds to inner-membrane proteins (BBP's) of *E. coli* that were shown to be distinct from the penicillin-binding proteins; the function of the BBP's are presently unknown. It has been suggested[1] that "...the terminal olefinic group reacts with the sulfhydryl groups of the inner-membrane proteins and covalent bonds are formed. Thus the olefinic double bond seems to be the reactive site or functional site of bicyclomycin..." The chemical mechanism by which bicyclomycin undergoes simple thiolate additions and the intriguing connection between sulfide-forming capacity and BBP-covalent modification (i.e., antimicrobial activity) remains to be established.

We recently proposed[3] two distinct, yet related, possible chemical mechanisms by which **1** could irreversibly undergo alkylation at the C-5 *exo*-methylene. One mechanism[3] (shown) suggests that bicyclomycin may act as a "latent" $\alpha,\beta$-unsaturated pyruvamide **2** which should undergo facile Michael-type addition at the C-5 exomethylene (**1** → **2** → **3**, Scheme I).

We have examined the thiolate addition reaction to semisynthetic[4] and totally synthetic[5] bicyclomycin systems in detail and report herein several fundamentally interesting and unexpected observations in this context that are relevant to the mechanism of action of bicyclomycin.

All thiolate reactions were carried out in homogeneous solutions of 0.2 M $NaSCH_3$ in 3:1 $THF/H_2O$ (pH 12.5) at 25 °C. The acetonide derivative **13**[6] was used as a reactivity standard, which underwent clean thiolate addition analagous to **1**. Not surprisingly, the 6-deoxy derivatives **7**–**9**[3,5] were totally unreactive under these conditions. Surprisingly, the C-6 oxygenated derivatives **10**–**12**[3,5] were equally unreactive. Even more curious was the observation that the *N*,*N*′-dialkylated derivatives of the control, **14**[5] and **15**[5] proved to be completely unreactive to thiolate addition. From these simple observations, it can be hypothesized that free N–H amides *and* a C-1′ hydroxyalkyl residue play a subtle yet critical role in facilitating thiolate addition. The hydroxymethyl derivative **16**[4] was prepared and found to cleanly afford the sulfide **17**; thus, compound **16** represents the *minimal* structural requirements for sulfide formation at C-5; this notion is further supported by the following. Conversion of **16** to the *N*,*N*′-dimethyl derivative **18** and the silyl ether **19** afforded, in both cases, an unreactive substrate consistent with the behavior of **10**–**15**. Of the two monomethyl derivatives compound **20** proved unreactive, but compound **21** furnished the adduct **22**. Thus, it is clear that the amide adjacent to the C-6 hydroxyl must be unsubstituted (–N-

(1) Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiot.* **1979**, *32*, 402 and references cited therein concerning isolation and structural elucidation.

(2) (a) Tanaka, N.; Iseki, M.; Miyoshi, T.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1976**, *29*, 155. (b) Someya, A.; Iseki, M.; Tanaka, N. *Ibid.* **1978**, *31*, 712.

(3) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Med. Chem.* **1985**, *28*, 733.

(4) Muller, B. W.; Zak, O.; Kump, W.; Tosch, W.; Wacker, O. *J. Antibiot.* **1979**, *32*, 689.

(5) (a) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1984**, *106*, 5748. (b) *Ibid.* **1985**, *107*, 3253.

(6) Kamiya, T.; Maeno, S.; Kitaura, Y. Belgium Patent 847 475.

(7) All new compounds displayed satisfactory spectroscopic and analytical data in accord with the assigned structures.

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