Regioselective Functionalization in the Oxymercuration of β,γ-Unsaturated Urethanes. Synthesis of γ-Ketourethanes

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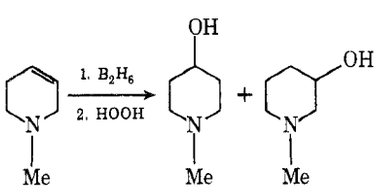
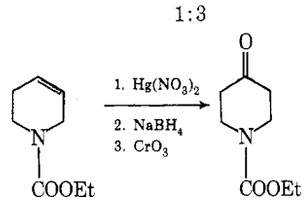
A specific directing effect on the regiochemistry of oxymercuration has been exerted by a proximate urethane functionality during the oxymercuration of selected β,γ-unsaturated urethanes. This effect has been utilized in the synthesis of γ-ketourethanes by reduction of initially formed oxymercurials with sodium borohydride followed by chromic acid oxidation. A mixture of products arising from spontaneous demercuration of an allylic mercurial has been obtained following oxymercuration of a dienic urethane.

The oxymercuration reaction, combined with *in situ* reduction of the oxymercuric intermediate, provides a convenient mild method to achieve Markovnikov hydration of a carbon–carbon double bond.[1] Additionally, for those cases where the rules of Markovnikov addition are not applicable, the synthetic utility of oxymercuration is often enhanced by the ability of proximate Lewis base groups to exert specific directing effects in promoting regioselective additions.[2] We here report a study of the utilization of such a directing effect in the synthesis of cyclic and bicyclic γ-ketourethanes from β,γ-unsaturated urethanes. Involved is a synthetic sequence of regioselective mercuric nitrate oxymercuration, sodium borohydride demercuration, and chromic acid oxidation.[3] Hereafter, the sequence of reactions will be referred to as ketofunctionalization.

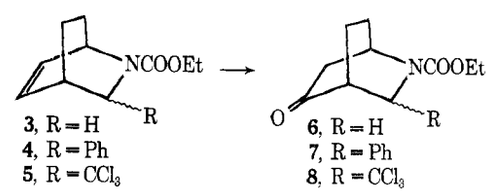
A study of the syntheses of hydroxypiperidines by the hydroboration of β,γ-unsaturated tetrahydropyridines followed by oxidation indicated a 3:1 preference for formation of 3-piperidinols.[4] The result probably reflects an electronic attraction between the boron and nitrogen atoms. By contrast, the mercuric nitrate ketofunctionalization sequence using *N*-carbethoxy-1,2,3,6-tetrahydropyridine (**1**) has been found to afford regiospecifically *N*-carbethoxy-4-ketopiperidine (**2**), which can be converted to *N*-methyl-4-hydroxypiperidine by lithium aluminum hydride reduction.





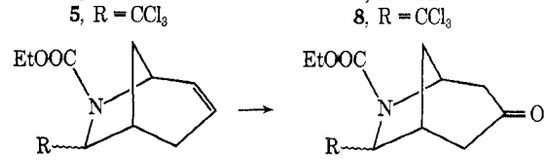
1 **2**

Introduction of bridging atoms did not change the regioselectivity of functionalization. *N*-Carbethoxydioscorone (**6**) was obtained[5] regiospecifically from 2-azabicyclo[2.2.2]oct-5-ene (**3**). This route to dioscorone from **3** offers a distinct advantage over two previous nonregiospecific synthetic approaches, one of which involved a hydroboration–oxidation route[6] and a second which utilized an epoxidation, reductive ring opening, oxidation sequence.[7] The introduction of a 3-phenyl substituent did not hinder the course of the reaction, and **4**, R = 80% *exo*-phenyl, afforded **7**, R = 80% phenyl. However, the mixture **5**, R = 75% *endo*-trichloromethyl, was unreactive toward the oxymercuration conditions. It is likely for **5** that, when the trichloromethyl group is endo, the urethane functionality is for steric reasons not in the endo configuration required for coordination of a cationic mercury species with both the olefinic bond and the urethane. Although plausible, this argument fails to account for failure of the remaining *exo*-trichloromethyl isomer to oxymercurate.



3, R = H
4, R = Ph
5, R = CCl_3

6, R = H
7, R = Ph
8, R = CCl_3

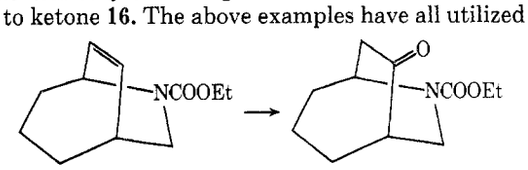


9, R = H
10, R = Ph
11, R = CCl_3

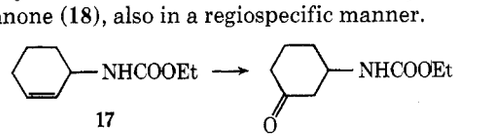
12, R = H
13, R = Ph
14, R = CCl_3

Actinobolamine,[8] reported as a degradation product of actinobolin, has a substituted 6-azabicyclo[3.2.1]octan-3-one skeleton (**12**). Ketofunctionalization of 7-azabicyclo[3.2.1]oct-5-ene (**9**) afforded **12**. The *N*-methyl[9] and *N*-benzyl[10] derivatives of **12** have been synthesized previously from 3,4,5-trimethoxybenzoic acid. Similarly, **10**, R = 85% *exo*-phenyl, afforded **13**, R = 85% *exo*-phenyl. An *exo*-trichloromethyl group did not deter reaction in this ring system and **11** afforded **14** in 75% yield.

The trimethylene bridged urethane **15** was functionalized to ketone **16**. The above examples have all utilized urethanes of secondary amines; however, the urethane of a primary allylic amine **17** afforded *N*-carbethoxy-3-aminocyclohexanone (**18**), also in a regiospecific manner.



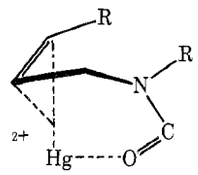
15 **16**



17 **18**

In the regiospecific additions of HgX and OH to the various β,γ-unsaturated urethanes, the urethane functionality, although exerting an obvious directing effect, remains unchanged at the end of the reactions. It is likely that the

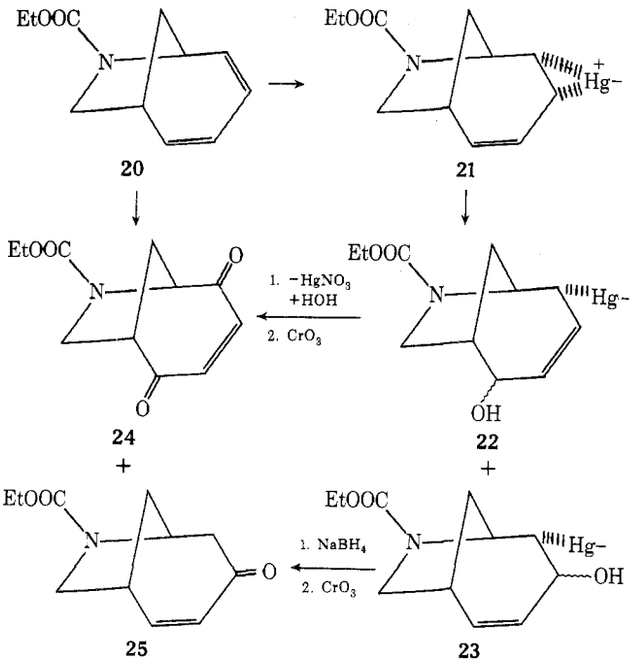
Lewis base group in the urethane, most probably the carbonyl oxygen,[11] is assisting by the formation of an intermediate nonsymmetrically disposed olefin–mercury complex **19** in which the mercuric salt is further complexed with the



19

Lewis base group.[12] Ultimately, reaction of this unsymmetrical complex with external nucleophile is most likely at the more weakly coordinated γ position, since a six-membered ring structure involving coordination of organomercurial with urethane can be maintained. Alternatively, the inductive effect of the nitrogen atom may favor attack at the γ position of a mercurinium ion by external nucleophile.

The ketofunctionalization procedure was also investigated for the bicyclic dienic urethane **20.** Two products, the diketone **24** and the monoketone **25,** were obtained. The formation of both products is explicable in terms of initial mercuration of the olefinic carbon nearest the urethane functionality to give **21.** Nucleophilic attack on the nonsymmetrical mercury complexed species **21** can occur at either of two allylic sites to form **22** and **23.** The allylic mercurial **22** under the reaction conditions can solvolyze with loss of mercury and nitrate ion to form an allylic cation,[13] which following attack by solvent leads to a diol which is oxidized to **24.** The mercurial **23,** following sodium borohydride demercuration, is oxidized to conjugated ketone **25.**



Experimental Section

The nmr spectra were determined on a Varian Associates XL-100-15 spectrometer, operated at 40°. Deuteriochloroform was used as solvent with 2% tetramethylsilane as internal standard (see Table I). Structural assignments were confirmed with the aid of decoupling experiments.

Analysis were performed by Micro-analysis, Inc., Wilmington, Del.

Gas chromatograph analyses (vpc) and collections were performed on a Varian Aerograph A-90-P3 instrument (thermal conductivity detector), using a 2 m × 0.25 in., 20% DC550 on 45/60 Chromosorb W column.

Table I
Nmr Spectra[a,b]

Compd[d]	Registry no.	Spectrum
2	29976-53-2	2.30 (4 H, t, J = 4.2 Hz), 3.60 (4 H, t)
6	37778-51-1	4.53 (1 H, m), 3.68 (1 H, dd), 3.52 (1 H, dd, J = 2, 11.5 Hz), 2.61 (1 H, dd, J = 19, 2.2 Hz), 2.27 (1 H, dd), 2.50 (1 H, m), 1.95 (4 H, m)
7	52003-25-5	4.82 (1 H, br), 5.12 (1 H, d, J = 3 Hz), 2.52–2.92 (2 H, m), 2.35 (1 H, dd, J = 2, 18 Hz), 1.82–2.0 (4 H, m)
12	52003-26-6	4.38 (1 H, br), 3.94–3.22 (2 H, m), 3.20–2.46 (4, H, m), 2.34 (1 H, dd, J = 2, 17 Hz), 1.84–2.22 (2 H, m)
13	52003-27-7	4.96 (0.15, *endo*-phenyl isomer, d, J = 5.0 Hz), 4.74 (0.85 H, *exo*-phenyl isomer, s), 4.52 (1 H, br), 3.20–2.32 (3 H, m), 2.76 (1, H, m), 2.36 (1 H, dd, J = 3, 17 Hz), 2.14–1.52 (2 H, m, J = 12 Hz)[c]
14	52003-28-8	4.48 (1 H, br), 4.55 (1 H, s), 3.30–2.76 (3 H, m), 2.74–2.52 (2 H, m), 2.37 (1 H, dd, J = 12.5, 2 Hz), 1.86 (1 H, m, J = 14 Hz)[c]
16	52003-29-9	4.60 (1 H, br), 3.84–3.40 (2 H, m, J = 12 Hz),[c] 2.86–2.18 (3 H, m, J = 18 Hz),[c] 2.12–1.40 (6 H, m)
18	38031-97-9	5.22 (1 H, br), 3.92 (1 H, br), 2.74 (1 H, dd, J = 14 Hz),[c] 2.60–2.24 (3 H, m), 2.24–1.46 (4 H, m)
24	52003-30-2	6.36 (2 H, s), 4.60 (1 H, br), 3.94–3.72 (2 H, m), 3.41 (1 H, br), 2.74–2.28 (2 H, m)
25	52003-31-3	6.26 (1 H, m, J = 13 Hz),[c] 5.82 (1 H, m, J = 13 Hz),[c] 4.38 (1 H, br), 3.72–3.54 (2 H, m), 3.40–2.84 (2 H, m), 2.60–2.40 (3 H, m)

[a] Reported in δ as parts per million from TMS in $CDCl_3$ solution: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. [b] Chemical shifts of OCH_2CH_3 are not listed. [c] Additional small couplings were noted. [d] Satisfactory elemental analyses were reported for all new compounds listed in the table.

General Procedure for Ketofunctionalization of β,γ-Unsaturated Urethanes. The procedure of Brown and Geoghegan[1] was used for the synthesis of alcohols from representative olefins. Mercuric nitrate in 50:50 tetrahydrofuran–water was substituted for mercuric acetate. Alcohols were oxidized in acetone solution using chromic acid according to established procedure.[14] Reaction conditions and yields of products are given in Table II. No traces of the isomeric β-amino ketones were observed in the expanded spin-decoupled spectra of **2, 6, 7, 12, 13, 14, 16,** or **18.** Gc spectra of **2, 6, 12, 14,** and **18** confirmed the isomeric purity. The β-keto derivative isomeric with **2** has been shown to be stable to the oxidation procedure used in this study and to the thermal gc conditions.[6] Because of the structural similarity of the molecules used in this study, it is thus unlikely that β-keto isomers were formed and then decomposed at some point in the synthetic sequence. Reported product yields represent recovered yields and were not optimized.

***N*-Carbethoxy-3-trichloromethyl-2-azabicyclo[2.2.2]oct-5-ene (5).** A solution of *N*-carbethoxytrichloromethylimine[20] (4.4 g, 20 mmol), cyclohexa-1,3-diene (1.6 g, 20 mmol) and boron trifluoride etherate (0.5 ml) in CCl_4 (200 ml) was stirred at 30° for 72 hr. Acid was removed by washing with water and aqueous sodium bicarbonate. Removal of solvent, extraction of the residue with *n*-heptane, and removal of solvent afforded 4.27 g (71%) of oil, bp 132–134° (0.05 mm). Nmr ($CDCl_3$) indicated 75 ± 3% *endo*-trichloromethyl isomer, δ 4.70 (d, H_{3x}, $J_{3,4}$ = 2.8 Hz), and 25 ± 3% exo isomer, δ 4.32 (dd, H_{3n}, $J_{3n,4}$ = 3.2, $J_{3n,8a}$ = 1.4 Hz).

Anal. Calcd for $C_{11}H_{14}NO_2Cl_3$: C, 44.22; H, 4.71; N, 4.71. Found: C, 44.30: H, 4.93: N, 4.74.

***N*-Carbethoxy-6-trichloromethyl-7-azabicyclo[3.2.1]oct-**

Table II
Results Realized for the Conversion of Representative β,γ-Unsaturated Urethanes into γ-Ketourethanes by the Solvomercuration–Demercuration[a]–Oxidation[b] Procedure Utilizing Mercuric Nitrate

Olefin	Registry no.	g (mmol)	Reaction time, hr	Product ketone	Yield, %	Molecular distillation pot temp, °C (pressure, mm)
1[c]	52003-32-4	1.55 (10)	5.0	**2**	80[d]	160 (0.05)
3[e]	3693-69-4	1.81 (10)	0.2	**6**	87[f]	*g*
4[h]	3693-55-8	0.50 (1.9)	72	**7**	86	179–190 (0.05)
5[i]	52003-33-5	0.50 (1.7)	48	**8**[t]	0	
9[j]	42793-16-8	0.50 (2.6)	48	**12**	79[k]	100–120 (0.1)
10[j]	52003-34-6	0.50 (1.9)	72	**13**	85	160–200 (0.05)
11[l]	52003-35-7	0.38 (1.3)	1.0	**14**	75	110–150 (0.05)
15[m]	40792-14-1	0.50 (2.5)	24	**16**	57	150–180 (0.1)
17[n]	1541-28-2	1.0 (6.2)	24	**18**	57[o]	120–125 (0.07)
20[p]	40792-18-5	1.0 (5.2)	168	24,[q] 25[r]	42[s]	

[a] Reference 1. [b] Reference 14. [c] Prepared from 1,2,3,6-tetrahydropyridine (Aldrich) and ethyl chloroformate. [d] 99% purity by vpc analysis. [e] Reference 6. [f] 2% unreacted starting material by vpc. [g] See ref 5 and 6. [h] 80% *exo*-phenyl, ref 6 and 15. [i] 75 ± 3% *endo*-CCl_3. [j] Reference 16. [k] 10% unreacted **9**. [l] 100% *exo*-CCl_3, mp 93–95° ($CHCl_3$). [m] Reference 17. [n] Reference 18. [o] Contains 10% unreacted **17**, vpc (190°) retention time 3 min, and 90% **18**, vpc retention time 9.5 min. [p] Reference 19. [q] Uv (95% EtOH) λ_{max} 270 mμ (log ε 3.8), 223 (4.2). [r] Uv (95% EtOH) λ_{max} 225 mμ (log ε 4.0). [s] Vpc (200°), **20** retention time (4.5 min, 40%), **24** (retention time 17.6 min, 29%), **25** (retention time 13 min, 23%). [t] Registry no., 52003-36-8.

2-ene (11). Trichloro adduct **5** (1.2 g, 0.4 mmol) and trifluorosulfonic acid (5 drops) in 70 ml of benzene was stirred for 48 hr at 30°. After washing with water to remove acid, drying over $MgSO_4$, and removal of solvent, 1.04 g (87%) of rearranged[16] *exo*-trichloromethyl adduct **11** was formed: mp 84–86°; vpc (2 m × 0.25 in., 5% DC550 on Chromosorb W, 190°, 27 min); ir (CCl_4) 1710 cm^{-1}; nmr ($CDCl_3$) δ 6.25 (1 H, m), 5.58 (1 H, m), 4.58 (1 H, s), 4.38 (1 H, m), 4.20 (2 H, q, J = 7 Hz), 2.90 (2 H, m), 2.45 (2 H, m), 1.83 (1 H, m), 1.25 (3 H, t, J = 7 Hz).

Anal. Calcd for $C_{11}H_{14}NO_2Cl_3$: C, 44.22; H, 4.71; N, 4.71. Found: C, 44.50; H, 4.81; N, 4.59.

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Registry No.—*N*-Carbethoxytrichloromethylimine, 16723-30-1; cyclohexa-1,3-diene, 592-57-4.

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