derived for the mechanism

$$CoA_4SO_3(X) \underset{k_2^X}{\overset{k_1^X}{\rightleftharpoons}} CoA_4SO_3^+ + X \quad (4)$$

$$CoA_4SO_3^+ + Y \xrightarrow{k_2^Y} CoA_4SO_3(Y) \quad (5)$$

The following reactions exhibited the full rate law described by eq 3 when the concentrations were varied from 0.025 to 0.05 M SCN^- and 0.08 to 0.32 M NH_3 in the case of reaction 6, and from 9×10^{-3} to 1.9×10^{-2} M NO_2^- and 0.15 to 0.45 M NH_3 in the case of reaction 7.

$$CoA_4SO_3(SCN) + A \longrightarrow CoA_5SO_3^+ + SCN^- \quad (6)$$

$$CoA_4SO_3(NO_2) + A \longrightarrow CoA_5SO_3^+ + NO_2^- \quad (7)$$

The kinetic data yielded the values $k_1^{SCN^-} = 1.75$ sec^{-1}, $k_2^{SCN^-}/k_2^A = 30$, $k_1^{NO_2^-} = 0.46$ sec^{-1}, and $k_2^{NO_2^-}/k_2^A = 70$.

Reaction 8, examined over the concentration ranges 0.03 to 0.7 M NH_3 and 1.3×10^{-5} to 2.0×10^{-4}

$$CoA_4SO_3(OH) + A \longrightarrow CoA_5SO_3^+ + OH^- \quad (8)$$

M OH^-, exhibited a rate law which at the higher OH^- concentrations approached the limiting form described by eq 3 and yielded the values $k_1^{OH^-} = 7$ sec^{-1} and $k_2^{OH^-}/k_2^A = 8 \times 10^3$. At lower OH^- concentrations an additional contribution from a path involving $CoA_4(OH_2)SO_3^+$ was indicated.

In the case of the other reactions only a limiting form of the rate law described in eq 3 was observed owing to domination of one or other of the terms in the denominator. Thus, the series of reactions

$$CoA_5SO_3^+ + Y^- \longrightarrow CoA_4SO_3(Y) + A \quad (9)$$

(where $Y^- = OH^-$, CN^-, NO_2^-, and SCN^-), when the concentrations of Y^- and A were such that the reactions proceeded in the direction indicated (typically in the ranges 0.01 to 0.1 M A and 0.01 to 0.4 M Y^-), all exhibited the same limiting first-order rate law $-d \ln [CoA_5SO_3^+]/dt = k_1^A = (1.2 \pm 0.1) \times 10^{-2}$ sec^{-1} (independent of Y^-) in agreement with eq 3, when $k_2^Y[Y] >> k_2^X[X]$. The equilibrium constants for reactions 6 and 8, computed from the above kinetic data, were in excellent agreement with the spectrophotometrically measured values of 4.9 and 7×10^{-2}, respectively.

Reaction 10, examined over the concentration range 0.05 M A, 0.1 to 0.4 M OH^-, and 5.0×10^{-3} to $4.0 \times$

$$CoA_4SO_3(OH) + CN^- \longrightarrow CoA_4SO_3(CN) + OH^- \quad (10)$$

10^{-2} M CN^-, exhibited the rate law $-d[CoA_4SO_3(OH)]/dt = k'[CoA_4SO_3(OH)][CN^-]/[OH^-]$, consistent with the limiting form of eq 3 when $k_2^{OH^-}[OH^-] >> k_2^{CN^-}[CN^-]$ and yielding $k' = k_1^{OH^-}k_2^{CN^-}/k_2^{OH^-} = 3.8 \times 10^{-2}$ sec^{-1}.

We conclude that all of these reactions proceed through limiting SN1 mechanisms (eq 4 and 5) involving the common intermediate $CoA_4SO_3^+$. From the kinetic data the following values have been obtained for the dissociation constants (k_1^X) of the various complexes $CoA_4SO_3(X)$ and the relative reactivities (k_2^X) of various nucleophiles (X) toward $CoA_4SO_3^+$.

X	NH_3	NO_2^-	SCN^-	CN^-	OH^-
k_1^X, sec^{-1}	1.2×10^{-2}	0.46	1.75	..	7
k_2^X/k_2^A	1	70	30	43	8×10^3

For comparison, the corresponding values obtained by Wilmarth, *et al.*,[3] for the relative reactivities of some of the same nucleophiles toward $Co(CN)_5^{2-}$ are $k_2^{SCN^-}/k_2^A = 2.3$ and $k_2^{OH^-}/k_2^A = 1.1 \times 10^4$.

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A Unique Reversal of Stereospecificity in the Addition of Phenyllithium *vs.* Phenylmagnesium Bromide to 1,2-Dicyclohexylethanedione-C[14]

Sir:

As part of a continuing study by isotope dilution techniques of the quantitative stereochemistry of the addition of organometallic reagents to α-diketones and ketols,[1,2] both phenyllithium and phenylmagnesium bromide, respectively, were added in excess to carbon-14 labeled 1,2-dicyclohexylethanedione. Phenyllithium gave exclusively the *dl*-racemic glycol, 1,2-diphenyl-1,2-dicyclohexylethanediol (57.6% yield, ether solution, 11-hr reaction time); less than 0.25% of the *meso* form, well within the limits of the technique, was found. Phenylmagnesium bromide produced solely the *meso* glycol (14.8% yield, ether solution, 5 days reaction time); similarly, less than 0.25% of the racemate form was observed. Substitution of phenylmagnesium iodide gave rise to less than 0.5% of glycol in 8 days reaction time. The results of the quantitative studies were reflected in macro runs, utilized in the case of the phenyllithium to prepare dilution materials. The *meso* glycol was prepared, in turn, by careful seeding of the crude glycolic product isolated from the zinc–sulfuric acid reduction in aqueous ethanol of phenyl cyclohexyl ketone.[3] Assignment of diastereoisomeric identity rested on infrared[4] and nmr[5] spectroscopic data. The synthesis of the labeled diketone has been described.[2]

A simple reversal of predominant diastereoisomer formed has been reported previously for these reagents on two occasions;[1,6] there do not appear to be any previous reports of a stereospecific reversal of behavior. The present extreme case further emphasizes the puzzle.

(1) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Am. Chem. Soc.*, **82**, 3913 (1960).

(2) J. H. Stocker, *J. Org. Chem.*, **29**, 3593 (1964).

(3) These glycols have been reported twice in the literature. Prepared similarly to the metal–acid procedure above by O. Neunhoeffer and F. Nerdel [*Ann.*, **526**, 47 (1936)], they were separated by fractional crystallization and reported to melt at 160 and 198°, respectively. They were subsequently prepared by Y. Yukawa and T. Hanabusa [*J. Chem. Soc. Japan, Pure Chem. Section*, **82**, 1724 (1961)], similarly separated, and reported to melt at 167–171 and 194–197°, respectively. The glycols employed as dilution materials in the present study showed melting points of 179–180 and 208–209°, respectively. They were analytically pure and both rearranged under the influence of strong acid by phenyl migration to the same ketone.

(4) See, *e.g.*, W. A. Mosher and N. D. Heindel, *J. Org. Chem.*, **28**, 2154 (1963), and references cited therein.

(5) The hydroxylic proton resonance of the *meso*-glycol appears at higher field strength than that of the racemic isomer. This appears to be a general phenomenon. (Private communication from B. M. Benjamin, Oak Ridge National Laboratory.) See also J. Wieman, G. Dana, Sa-Le-Thi-Thuan, M. Brami, and M. Delépine, *Compt. Rend.*, **258**, 3724 (1964).

(6) J. Yoshimura, Y. Ohgo, and T. Sato, *J. Am. Chem. Soc.*, **86**, 3958 (1964). These authors were investigating substitution rather than addition reactions and the situations are probably not analogous.

Discussion pertinent to this problem appeared in previous papers.[1,2,7] We are continuing our investigation in this particular system as well as other systems in an effort to clarify the situation.

Acknowledgment. Financial support of the above research under AEC Contract No. AT-40-1-2833 is gratefully acknowledged.

(7) A useful model for the phenyllithium addition can be formulated by constructing a Dreiding-type molecule of the intermediate ketol and noting that equatorial–equatorial hydrogen interaction of the two cyclohexyl rings forces the phenyl group into a position maximally blocking approach of a second, incoming phenyl from that side. Thus, the racemate form, quite possibly stereospecifically, would be predicted. This, of course, offers an explanation only of the stereospecificity as distinguished from stereoselectivity of the one reaction and leaves the problem of stereospecific reversal unanswered.

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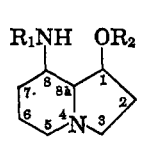
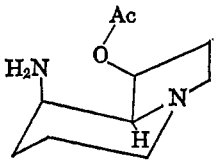
Slaframine. Structural Studies of a Parasympathomimetic Alkaloid of Fungal Origin

Sir:

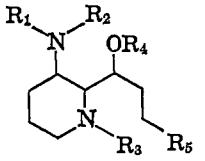
Excessive salivation in dairy cattle fed certain legume forages is due to infestation of such forages by *Rhizoctonia leguminicola*.[1] We describe here recent results[2] with an alkaloid from this fungus characterized earlier as its crystalline picrate[3] and Mayer's salt.[4] We now assign structure I to this alkaloid, for which we propose the name slaframine (*slafra*, to slaver). *In vitro* experiments show that this compound is not a cholinesterase inhibitor, nor does it stimulate cholinergic fibers directly; rather, it appears to hypersensitize smooth muscle preparations to acetylcholine. Its action can be reversed both *in vivo* and *in vitro* by atropine.[5]



I, R_1=H, R_2=Ac
II, R_1=R_2=H
III, R_1=R_2=Ac



Ia



IV, R_1=R_4=Ac, R_2=H, R_3=CN, R_5=Br.
V, R_1=C_2H_5, R_2=R_3=R_4=R_5=H
VI, R_1=C_2H_5, R_2=R_3=CH_3; R_4=R_5=H
VII, R_1=C_2H_5, R_2=R_3=R_4=Ac, R_5=H

Slaframine ($C_{10}H_{18}N_2O_2$)[6a] was isolated[4] from the mycelium of *R. leguminicola* as its amorphous hygroscopic dihydrochloride[6a,b] [NH_2, 4.99 (Van Slyke)] and characterized as its crystalline dipicrate, mp 183–184°,[2] $C_{10}H_{18}N_2O_2 \cdot 2C_6H_3N_3O_7$.[6b]

Slaframine hydrochloride contains a secondary acetate group (nmr in D_2O: three-proton singlet at τ 7.85, one-proton multiplet at τ 4.45). Exposure of slaframine or impure "salivation factor" to mild alkali (*e.g.*, pH >10 for several hours at 25°) results in loss of physiological activity, and treatment of slaframine for 2 min with boiling 1 *N* sodium hydroxide yields crystalline Dragendorff-positive[7] deacetylslaframine (II, $C_8H_{16}N_2O$),[6a] which is devoid of biological activity. In the nmr spectrum (D_2O) of the hydrochloride of this compound, the secondary carbinol proton appears at τ 5.40.

A primary amino group in slaframine is indicated by a purple ninhydrin test and by Van Slyke analysis on the hydrochloride. Treatment of slaframine free base with acetic anhydride at 95° gave crystalline N-acetylslaframine (III, $C_{12}H_{20}N_2O_3$),[6a,b] mp 140–142°, $[\alpha]^{25}D$ −15.9° (*c* 5, EtOH), whose infrared spectrum ($CHCl_3$) contains bands at 3420 (amide N–H stretch), 1665, and 1510 cm^{-1} (amide I and II bands, respectively).

Slaframine, with neither C=C nor C=N (infrared) and no nmr methyl signal other than that of the acetyl group, must be a bicyclic tertiary amine since the remaining basic nitrogen (bridgehead) is not acetylatable and gives positive citric acid–acetic anhydride[8] and positive Dragendorff's[7] tests.

Treatment of N-acetylslaframine with cyanogen bromide gave the ring-opened product IV, $C_{13}H_{20}BrN_3O_3$[6b] (N—C≡N band at 2210 cm^{-1}), which when treated with sodium iodide followed by lithium aluminum hydride gave V ($C_{10}H_{22}N_2O$).[6a,b]

The latter was methylated with formaldehyde–formic acid to give VI ($C_{12}H_{26}N_2O$)[6a,b] and was also acetylated with acetic anhydride to give VII ($C_{16}H_{28}N_2O_4$).[6a,b]

The nmr spectrum of V shows, in addition to the expected N-ethyl group (N–CH_2CH_3, τ 6.79 m, 8.90 t), a C–CH_2CH_3 group (τ 8.45 m, 9.00 t), established as part of a –$CHOHCH_2CH_3$ group by the loss of 59 mass units (C_3H_7O) from the parent ions of V and VI and the loss of 101 mass units from the parent ion of VII, a fragmentation not found for slaframine and its derivatives II and III. Thus, the partial formula >N–CH_2CH_2CHOH– is established for I.

The similar mass spectra of slaframine and deacetylslaframine (II) show major peaks independent of the oxygen atom for losses of 56 and 43 mass units. The peak at M − 43 (due to loss of C_3H_7) shifts on deuterium exchange of slaframine hydrochloride (NH_2); that at M − 56 (due to loss of C_3H_6N) does not. The former indicates a –$CH_2CH_2CH_2$– unit, the latter suggests the unit –$CH(NH_2)CH_2CH_2$–; the two are then combined as –$CH(NH_2)CH_2CH_2CH_2$–, and the structure

(1) E. B. Smalley, R. E. Nichols, M. H. Crump, and J. N. Henning, *Phytopathology*, 52, 753 (1962).
(2) Taken in part from the Ph.D. Thesis of S. D. A. University of Illinois, 1965.
(3) D. P. Rainey, E. B. Smalley, M. H. Crump, and F. M. Strong, *Nature*, 205, 203 (1965).
(4) S. D. Aust and H. P. Broquist, *ibid.*, 205, 204 (1965).
(5) J. H. Byers and H. P. Broquist, *J. Dairy Sci.*, 44, 1179 (1961).
(6) (a) Mass spectra, obtained on an Atlas CH_4 mass spectrometer by the direct inlet technique, employing a TO4 ion source and vacuum lock, were in agreement with the formula cited. Salts of slaframine (hydrochloride, citrate, oxalate, and chloroacetate) dissociate in the ion source, giving essentially the same spectrum as that of the free base. (b) Elemental analyses agree with the formula given.
(7) H. M. Bregoff, E. Roberts, and C. C. Delwiche, *J. Biol. Chem.*, 205, 565 (1953).
(8) F. Feigl, "Spot Tests in Organic Analysis," 5th ed, Elsevier Publishing Co., New York, N. Y., 1956, p 270.