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.

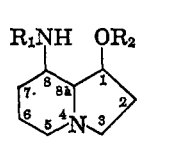
(7) A useful model for the phenyllithium addition can be formulated by constructing a Dreiding-type molecule of the intermediate ketol and noting that equatorial–equatorial hydrogen interaction of the two cyclohexyl rings forces the phenyl group into a position maximally blocking approach of a second, 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.

Jack H. Stocker
Department of Chemistry
Louisiana State University in New Orleans
New Orleans, Louisiana 70122
Received March 26, 1966

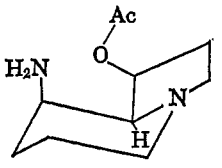
Slaframine. Structural Studies of a Parasympathomimetic Alkaloid of Fungal Origin

Sir:

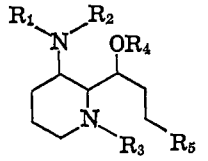
Excessive salivation in dairy cattle fed certain legume forages is due to infestation of such forages by *Rhizoctonia leguminicola*.[1] We describe here recent results[2] with an alkaloid from this fungus characterized earlier as its crystalline picrate[3] and Mayer's salt.[4] We now assign structure 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

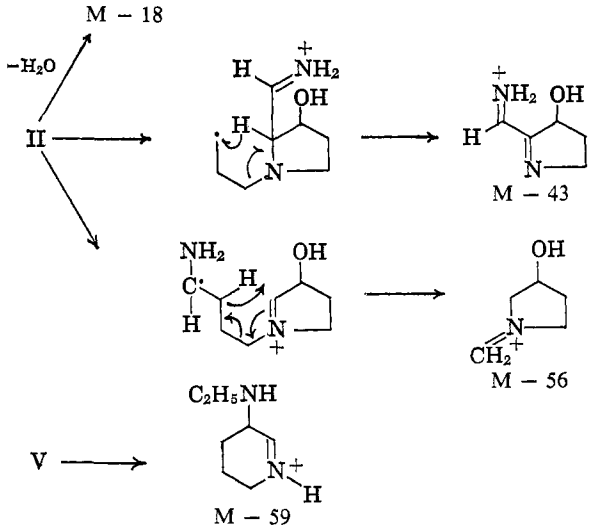
(1) E. B. Smalley, R. E. Nichols, M. H. Crump, and J. N. Henning, *Phytopathology*, **52**, 753 (1962).
(2) Taken in part from the Ph.D. Thesis of S. D. A. University of Illinois, 1965.
(3) D. P. Rainey, E. B. Smalley, M. H. Crump, and F. M. Strong, *Nature*, **205**, 203 (1965).
(4) S. D. Aust and H. 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.

of slaframine is assigned as I, 1-acetoxy-8-aminooctahydroindolizine. The von Braun opening of the pyrrolidine ring in preference to the piperidine ring is in accord with results on known octahydroindolizines.[9]

The fragmentation pathways referred to above are summarized in Scheme I for the unacetylated compounds II and V.

Scheme I



Stereochemistry of the molecule remains to be assigned but is suggested to be that of Ia from the low frequency (1700 cm^{-1}) of the ketone formed on chromic acid oxidation of N-acetyldeacetylslaframine and the instability of slaframine free base.

Acknowledgment. This work was supported in part by Public Health Service Grant No. AI-04769 from the National Institute of Allergy and Infectious Diseases.

(9) E. Ochiai and K. Tsuda, *Ber.*, 67, 1011 (1934).

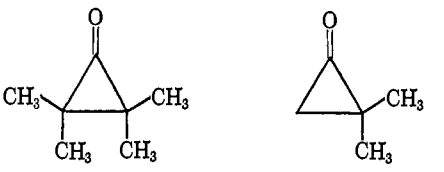
Steven D. Aust, Harry P. Broquist
Department of Dairy Science
Kenneth L. Rinehart, Jr.
Department of Chemistry and Chemical Engineering
University of Illinois, Urbana, Illinois
Received March 26, 1966

Cyclopropanones. III. 2,2-Dimethylcyclopropanone

Sir:

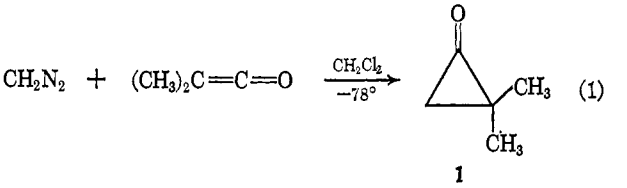
The synthesis and properties of tetramethylcyclopropanone (**1**) have been reported recently.[1-3] The yield of **1** as prepared by photolysis of 2,2,4,4-tetramethylcyclobutane-1,3-dione was low because of secondary photolyses. Furthermore, **1** is apparently sensitive to oxygen[4] and its handling requires special precautions. We are therefore prompted to report a convenient, high yield synthesis and characterization of 2,2-dimethylcyclopropanone (**2**), the first example of an unsymmetrically substituted dialkylcyclopropanone.

(1) N. J. Turro and W. B. Hammond, *J. Am. Chem. Soc.*, 87, 3258 (1965).
(2) N. J. Turro, W. B. Hammond, and P. A. Leermakers, *ibid.*, 87, 2774 (1965).
(3) N. J. Turro and W. B. Hammond, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 8S.
(4) The reaction of **1** with oxygen is more complicated than originally thought[2] and will be reported in detail in a future publication. Attempts to prepare **1** as a pure liquid inevitably afforded dimers of **1**. The dimerization, however, may be a catalyzed process.



1 **2**

Preparation and Physical Properties of 2. Slow addition of 20 ml of a cold (−78°) methylene chloride solution of diazomethane[5] (16 mmoles) to dimethylketene[6] (30 mmoles in 5 ml of methylene chloride) affords **2** in >93% yield, based on diazomethane.[7]

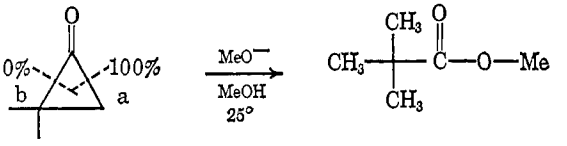


1

Compound **2** shows: infrared bands at $\lambda_{max}^{CH_2Cl_2}$ (cm^{-1}) 3050 (C–H stretch, cyclopropane), 1815 (C=O stretch, strained), 1380–1387 (doublet, *gem*-dimethyl group); nmr,[8] singlets at 1.40 (two protons) and 1.20 ppm (six protons); ultraviolet spectrum, $\lambda_{max}^{CH_2Cl_2}$ 3400 A ($\epsilon \sim 40$).

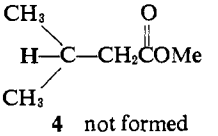
Reactions of 2. The reactions of **2** are of interest for a number of reasons including a comparison of relative reactivity with **1** and the possible effect of asymmetry of **2** in determining the direction of attack on unsymmetrical substrates.[9]

Treatment of **2** with NaOMe–MeOH leads to a >70% yield of methyl trimethylacetate (**3**). No methyl isopropylacetate (**4**) could be detected[10] by vpc anal-



2 **3**

ysis. This result is consistent with formation of the



4 not formed

most stable carbanion by exclusive bond cleavage of bond a (eq 2) after attack of base on the cyclopropanone. Such a preference is predicted from results of Favorskii rearrangement of unsymmetrical α-halo ketones.[11]

The reaction of **2** with methanol is extremely rapid[12]

(5) G. L. Closs and J. J. Coyle, *J. Am. Chem. Soc.*, 87, 4270 (1965).
(6) W. E. Hanford and J. C. Sauer, *Org. Reactions*, 3, 136 (1946).
(7) Vigorous evolution of nitrogen occurs even at this low temperature. The excess dimethylketene is easily separated from **2** by bulb-to-bulb distillation at ~−60°.
(8) All spectra reported were taken on a Varian A-60 instrument with tetramethylsilane as an external standard. Compound **1** shows a sharp singlet at 1.09 ppm in CH_2Cl_2.
(9) The problem of interconversion of stereoisomeric cyclopropanones is also under investigation.
(10) The Favorskii rearrangement of 3-methyl-3-chloro-2-butanone and methoxide also leads to **3** as the sole rearrangement product, but in poorer yield due to *side reactions of the α-haloketone.*[11]
(11) For a discussion of this point see A. S. Kende, *Org. Reactions*, 11, 261 (1960).
(12) Methanol reacts at least ten times faster with **2** than with dimethylketene.