Nuclear magnetic resonance spectroscopy. 13C-15N coupling constants as a conformational probe? [3]

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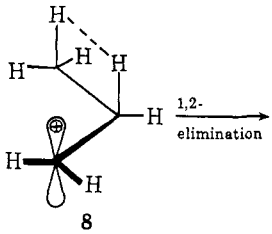
gest the allyl ion as the ionic product. The activation energy (46 kcal/mole) given in Table I is computed relative to the 2-propyl cation (ΔH_f = 192 kcal/mol).[14] Since the kinetic energy release in H_2 loss is 8 kcal/mol, the maximum possible energy content of the $C_3H_5^+$ ion is 230 kcal/mol. Calculations[15] of the heats of formation (otherwise unavailable) of cyclopropyl (257 kcal/mol), 2-propenyl (233 kcal/mol), and 1-propenyl (249 kcal/mol) exclude all product structures except allyl (experimental ΔH_f = 226 kcal/mol[16]) and possibly 2-propenyl. The allyl ion is certainly the best candidate, and even this most stable structure on the $C_3H_7^+$ manifold allows only 4 kcal/mol of internal energy of the products.

Calculations of energies of $C_3H_7^+$ cations[17] indicate that the presence of 46 kcal/mol of internal energy in excess of the heat of formation of 2-propyl will allow interconversion among at least seven plausible geometries of $C_3H_7^+$, all of which either cannot be generated or appear unlikely to be generated, in a smooth transition *via* 1,1-addition of H_2 to the allyl ion. It is therefore suggested that the forward reaction is represented *via* concerted 1,2- or 1,3-elimination from the 1-propyl or 2-propyl cation, respectively (**8** → **9** or **10** → **9**).



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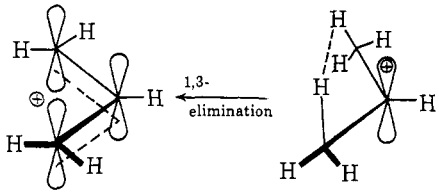
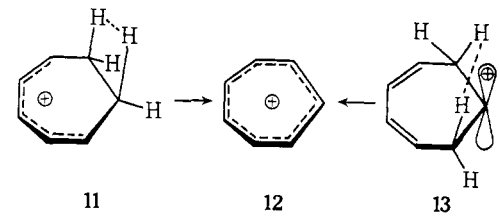


9 **10**

These suggestions, based on energetic considerations, are in accord with the concepts outlined in this and the preceding communication,[1] since both **8** → **9** and **10** → **9** represent concerted symmetry-forbidden reactions which should occur with release of kinetic energy, as observed (Figure 1d).

Since reaction 5 occurs with a large release of kinetic energy (Figure 1e, 20 kcal/mol), we formulate this reaction as the symmetry-forbidden loss of H_2 from a dihydrotropylium cation *via* either 1,2- or 1,3-elimination (**11** → **12**, or **13** → **12**). The same flat-topped metastable peak is observed irrespective of whether the $C_7H_9^+$ ion is generated *via* fragmentation of benzyl methyl ether,[10] protonation of cycloheptatriene in a chemical ionization source, or *via* protonation of toluene.[18]

It is striking that, in comparing the behavior of the



11 **12** **13**

homologs $C_2H_5^+$ and $C_3H_7^+$ or $C_6H_7^+$ and $C_7H_9^+$, no significant kinetic energy release occurs in H_2 loss where vinylium ion structures are forced upon the products, but kinetic energy release occurs where 1,2- or 1,3 elimination can give rise to π-delocalized cations (allyl or tropylium).

The 1,1-eliminations of hydrogen considered in this paper are "four-electron" reactions, in contrast to processes where the reverse bimolecular reaction involves the addition of molecular hydrogen to a cation in a "two-electron" reaction. Reactions of the latter type are also symmetry-allowed and accordingly may occur through the most probable channel without a large and relatively specific release of translational energy. In line with expectations, the most probable channel for the reaction $H_3^+ \rightarrow H^+ + H_2$ results in minimum kinetic energy release and maximum vibrational excitation of H_2.[19] The kinetic energy released in the reaction $CH_5^+ \rightarrow CH_3^+ + H_2$ does not appear to have been reported, but if this reaction occurs slowly enough for the observation of a metastable peak, then the peak shape is expected to indicate that this symmetry-allowed process occurs without a large release of kinetic energy.

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Nuclear Magnetic Resonance Spectroscopy. $^{13}C-^{15}N$ Coupling Constants as a Conformational Probe?[1]

Sir:

There have been several attempts to explain the variation in $^{13}C-^{15}N$ coupling constants with the stereochemical orientation of the carbons with respect to the nitrogen lone pairs.[2,3] Most of the substances in-

(1) Supported by the National Science Foundation and by the Public Health Service, Research Grant No. GM-11072, from the Division of General Medical Sciences.

(2) For two recent reviews on coupling constants involving ^{14}N and ^{15}N, see (a) R. L. Lichter in "Determination of Organic Structure by Physical Methods," Vol. 4, J. J. Zuckermann and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1972, p 195; (b) T. Axenrod in "Nitrogen NMR," M. Witanowski and G. A. Webb, Ed., Plenum Press, New York, N. Y., 1973, p 261.

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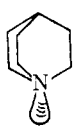
(18) See also J. H. Beynon, W. E. Baitinger, and J. W. Amy, *Int. J. Mass Spectrom. Ion Phys.*, **3**, 55 (1969).

vestigated so far, however, have the possibility of averaging of coupling constants due to bond rotation and/or nitrogen inversion. The only relatively rigid substances looked at have had aromatic[3b,c] nitrogen, and, with these, other effects are expected to play a role.

We have initiated a study of $^{13}C-^{15}N$ coupling constants of azabicyclic compounds, where some of the limitations of previous work could be overcome, and we present here a comparison of ^{15}N-labeled quinuclidine (**1**) and 1-propylamine (**2**). With **1**, the C_α, C_β,



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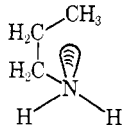


2

and C_γ carbon atoms are essentially in fixed positions, while with **2**, these carbons are involved in rapid conformational equilibration and, of course, there is also rapid nitrogen inversion.

To synthesize quinuclidine[4] with a ^{15}N label, Prelog's procedure[5,6] has the advantage of introducing the nitrogen in the very last step. We have therefore prepared quinuclidine-^{15}N by the directions described for the Prelog synthesis by Lukes.[6] 1-Propylamine-^{15}N was synthesized by the Gabriel synthesis[7] following Smith and Emerson.[8] The $^{13}C-^{15}N$ coupling constants were measured on our "Brukarian" DFS-60 spectrometer,[9] using $CDCl_3$ as solvent both for the free bases and their hydrochlorides, and as internal field-frequency lock at a probe temperature of 30°. The smallest possible sweep width (600 Hz) was chosen to allow an acquistion time of 6.6 sec, yielding a final spectral resolution of 0.15 Hz/point after a 8 K Fourier transform. All spectra were taken at least three times. The deviations in subsequent runs were a maximum of ±0.1 Hz. Care was taken in preparing the samples to exclude water.[10] The results for the free bases and their hydrochlorides are given in Table I.

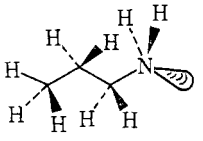
Table I. $^{15}N-^{13}C$ Coupling Constants, in Hz

	Quinuclidine	Quinuclidine·HCl	1-Propylamine	1-Propylamine·HCl
C_α	2.1	4.8	3.9	4.4
C_β	<0.2	<0.2	1.2	<0.2
C_γ	2.8	6.7	1.4	1.3

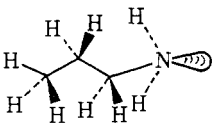
Comparison of the couplings for quinuclidine and 1-propylamine shows that $^2J_{NC}$ is larger for 1-propylamine than for quinuclidine and $^3J_{NC}$ in quinuclidine is even larger than $^1J_{NC}$, whereas $^3J_{NC}$ is comparable with $^2J_{NC}$ in propylamine and considerably less than $^1J_{NC}$. The results indicate that there is a considerable directional effect on J_{NC} for these compounds. Assuming the nitrogen lone pair is in something like an sp^3 orbital, the dihedral angle between this orbital and the $C_\alpha-C_\beta$ bond in quinuclidine can be assumed to be 180°, whereas this is only true for one particular rotational conformation of 1-propylamine as regards the C_α–N bond. The fact that on protonation of the nitrogen of 1-propylamine $^2J_{NC}$ becomes undetectable supports this assumption, because now, there is no preferred conformation about the C_α–N bond.

The magnitude of $^3J_{NC}$ in quinuclidine could be the result of a smaller average C_γ–N distance than for 1-propylamine or through assumption of a through-space interaction between C_γ and the back lobe of the electron pair orbital.[11] This latter explanation does not appear to accord with the fact that the *ratio* of $^1J_{NC}/^3J_{NC}$ for quinuclidine and its hydrochloride is almost the same, and for quinuclidine hydrochloride the back-lobe interaction should be less important. Because the ratio of $^1J_{NC}/^3J_{NC}$ for 1-propylamine and its hydrochloride is not very different, there seems no pronounced directional effect on three-bond carbon–nitrogen couplings. That the coupling information can be transmitted by three equivalent pathways in quinuclidine to C_γ provides perhaps an explanation for the magnitude of the ^{15}N to $^{13}C_\gamma$ couplings for this substance. To test these qualitative considerations, we have calculated the $^{13}C-^{15}N$ coupling constants using the INDO approach of Pople and Beveridge[12] taking only the Fermi contact contribution into consideration. Although the absolute values of the coupling constants obtained by this treatment are off by a factor of 3–5 on the average, the overall experimental trends are generally well reproduced. For quinuclidine, $^1J_{NC}$ and $^3J_{NC}$ are predicted to be of the same order of magnitude, and $^2J_{NC}$ is predicted to be very small and of opposite sign. For quinuclidine hydrochloride, $^3J_{NC}$ is predicted to be somewhat larger than $^1J_{NC}$.

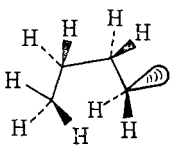
The calculations for 1-propylamine were made with three different conformations: fully staggered (**2a**), staggered, but with a dihedral angle of 60° between the lone-pair orbital and the $C_\alpha-C_\beta$ (**2b**), and in a conformation with the three carbon atoms and the positions they would have in quinuclidine (**2c**). Both in the fully



2a



2b



2c

staggered conformation **2a** and the quinuclidine conformation **2c**, the value of $^2J_{NC}$ is predicted to be much too small. However, in conformation **2b**, $^2J_{NC}$ is suggested to be even larger than $^1J_{NC}$ and $^3J_{NC}$. These results indicate that some intermediate position could

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well be the true conformation. Further work of this kind could well give more insight into the conformational dependence of $^{13}C-^{15}N$ coupling constants and, hence, the conformation of alkylamines in solution.

(13) Deutsche Forschungsgemeinschaft Postdoctoral Fellow, 1973–1974.

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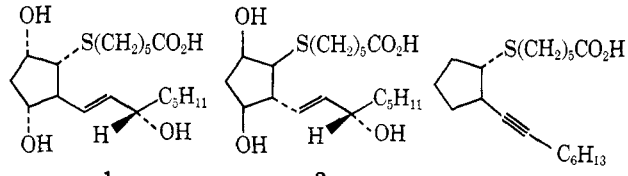
Stereospecific Synthesis of 7-Thiaprostaglandins

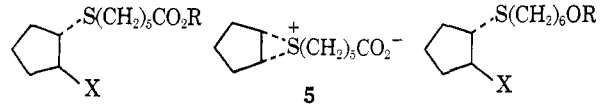
Sir:

It has been amply demonstrated that 7-oxa derivatives of the prostaglandins[1-3] may function as either prostaglandin agonists or antagonists[4] depending on the degree of hydroxyl substitution.[5] It was felt that replacement of the ether oxygen by sulfur might have interesting biological consequences, in light of experiences, among others, in the steroid field,[6] and when considering the well-known equivalence of oxybiotin and biotin in the nutrition of most biotin-requiring species.[7]

We wish to report a stereospecific synthesis of *nat*-7-thia-$PGF_{1\alpha}$ (**1**), *ent*-15-epi-7-thia-$PGF_{1\alpha}$ (**2**), and *rac*-7-thia-13-prostynoic acid (**3**),[8] in which the trans geometry of the two side chains is established by substitution reactions involving episulfonium intermediates. The elaboration of the basic skeletal structure is exemplified by the synthesis of **3**, which is compatible with the additional functionality required for **1** and **2**. Reaction of cyclopentene oxide with methyl 6-mercaptohexanoate[9] in the presence of sodium methoxide in methanol at 25° for 5 hr produced the trans hydroxy ester **4** (98%), which was hydrolyzed to the oily acid **4a**[10] (98%) with 2% KOH in methanol at 25°. Treatment of **4a** with methanesulfonyl chloride in pyridine at 0° for 1 hr afforded the trans chloro acid **4b** in 82% yield, evidently formed by attack of chloride ion



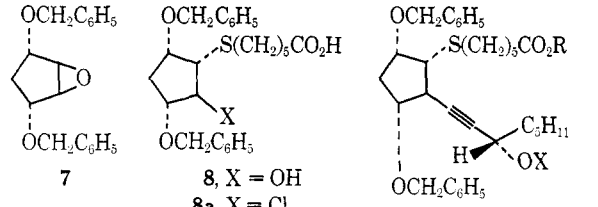
1 **2** **3**
3a, tetrahydro



4, R = CH_3; X = OH
4a, R = H; X = OH
4b, R = H; X = Cl
4c, R = H; X = Br

5

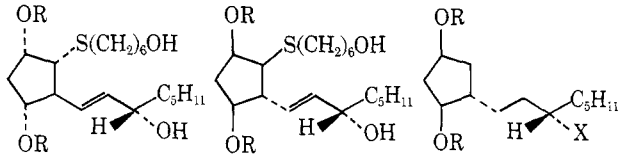
6, X = OH; R = H
6a, X = OH; R = trityl
6b, X = Cl; R = trityl



7

8, X = OH
8a, X = Cl
8b, X = Br

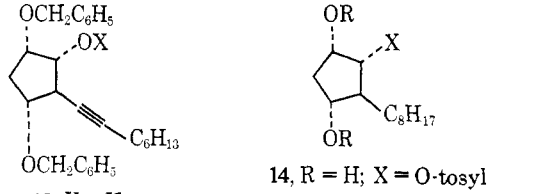
9, R = H; X = *t*-butyl
9a, R = CH_3; X = H



10, R = $CH_2C_6H_5$
10a, R = H

11, R = $CH_2C_6H_5$
11a, R = H

12, X = H; R = H
12a, X = OH; R = H
12b, X = H; R = CH_3CO



13, X = H
13a, X = tosyl

14, R = H; X = O-tosyl
14a, R = H; X = H
14b, R = CH_3CO; X = H

on the expected mesylate (**4a**, X = OSO_2CH_3) *via* the episulfonium intermediate **5**.[11]

Evidence for the formation of such a symmetrical intermediate was obtained as follows. 2-(1′-Hydroxyhexyl-6′-thio)cyclopentanol (**6**), prepared by a sequence of reactions analogous to that employed for **4**, was resolved *via* the diurethane obtained with (+)-α-phenethylamine isocyanate in boiling toluene for 24 hr and crystallization from ethyl acetate–hexane, mp 87–88°, $[\alpha]_D$ −62° (*c* 1.6).[12]

Reduction with LAH in THF gave (−)-**6** of unknown absolute configuration, $[\alpha]_D$ −21° (*c* 2.9), which was converted to the monotrityl ether **6a** with trityl chloride (1.2 equiv) in pyridine, $[\alpha]_D$ −10° (*c* 0.65). Reaction with methanesulfonyl chloride in pyridine at 0° for 1 hr gave the chloro thioether **6b** devoid of significant optical activity ($[\alpha]_D$ +1°, (*c* 1.1), indicating that racemization had taken place, most probably

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(8) Resolution of this acid was not attempted since (+)- and (−)-7-oxa-13-prostynoic acids possessed equal biological activity. *Cf.* ref 5.
(9) Prepared in 90% yield from 6-bromohexanoic acid and thiourea in DMSO (H. L. Pan and T. L. Fletcher, *Chem. Ind. (London)*, 546 (1968)), followed by methylation.
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(12) All rotations in chloroform at 25° unless indicated otherwise.