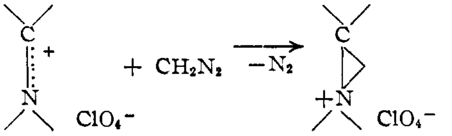
A NEW SYNTHESIS OF AZIRIDINIUM SALTS. 2,2-PENTAMETHYLENE-1,1-TETRAMETHYLENEAZIRIDINIUM PERCHLORATE, A PROTOTYPE[1]

Sir:

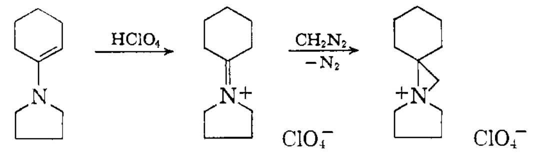
In a reaction patterned after the nucleophilic attack of diazomethane on the ketone carbonyl, we have found that similar attack on a ternary iminium perchlorate (I) can give the corresponding



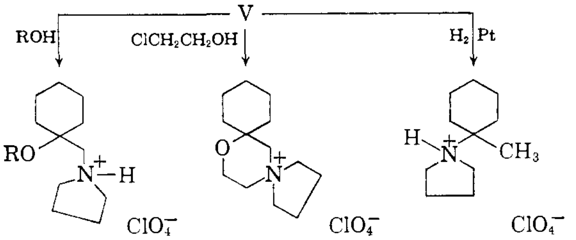
I II

aziridinium perchlorate (II) in high yield. The aziridinium cation has been recognized as the key intermediate in chemical reactions of nitrogen mustards, β-haloethyl-*tert*-amines,[2–10] and as their pharmacologically active species,[2,11–14] but thus far has been trapped only in the form of unwieldy salts.[3,12,14–16] The combination of the aziridinium cation and perchlorate anion proves to be most favorable for isolation and for study of the chemistry of the three-membered ring. The iminium perchlorate (I) precursor is readily available by acidification of the corresponding enamine, and the iminium salts are known to undergo nucleophilic attack with a variety of reagents.[17]

1-N-Pyrrolidylcyclohexene (III) was treated with perchloric acid in ethanol to give N-cyclohexylidenepyrrolidinium perchlorate (IV), m.p. 226.5–228° dec., $\nu_{\max}^{\text{Nujol}}$ 1665 cm.$^{-1}$ (Calcd. for $C_{10}H_{18}ClNO_4$: C, 47.71; H, 7.21; N, 5.57. Found: C, 47.94; H, 7.26; N, 5.69).[18] Compound IV reacted rapidly with diazomethane in methanol-ether solution at 0°, indicated by evolution of nitrogen and decolorization of the solution. The reaction mixture, when concentrated at 0° *in vacuo*, deposited crystalline 2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate (V) in 88% yield, m.p. 132–133° (Calcd. for $C_{11}H_{20}ClNO_4$: C, 49.70; H, 7.61; N, 5.32. Found: C, 49.71; H, 7.52; N, 5.40). The presence of the new three-membered ring, suggested by chemical analogy, analysis and the absence of infrared absorption corresponding to $\geqslant N^+H$ and $>C{=}^+N<$, was established by titration with thiosulfate,[9] which indicated a relatively stable aziridinium ring, and by the n.m.r. spectrum (V compared with IV), especially the new singlet peak at a τ value of 7.02.[19] Representative chemical reactions of V also supported the structural requirement of the aziridinium ring and confirmed the total structure. For example, treatment of V with refluxing methanol for 20 minutes gave N-(1-methoxycyclohexylmethyl)-pyrrolidine perchlorate (VIa), m.p. 120–121°, yield 82%, $\gamma_{\max}^{\text{Nujol}}$ 3125 cm.$^{-1}$ (Calcd. for $C_{12}H_{24}ClNO_5$: C, 48.40; H, 8.12; N, 4.70; OCH_3, 10.42. Found: C, 48.41; H, 8.07; N, 4.63; OCH_3, 10.46). Compound VIa was prepared unequivocally by the route described. Methyl 1-hydroxycyclohexanecarboxylate[20] in pure hexane was treated with sodium hydride, then by methyl iodide to give methyl 1-methoxycyclohexanecarboxylate, b.p. 92–93° (14–15 mm.), $n^{24}D$ 1.4501, which was converted with ammonia under pressure to 1-methoxycyclohexanecarboxamide, m.p. 155–156°. Reduction with lithium aluminum hydride in ether yielded (1-methoxycyclohexyl)-methylamine, isolated as the hydrochloride, m.p. 151–152° (Calcd. for $C_8H_{18}ClNO$: C, 53.47; H, 10.09; N, 7.79. Found: C, 53.06; H, 10.11; N, 7.78). Alkylation of the amine with 1,4-dibromobutane, following recorded



III IV V



VI VII VIII

VIa, R = CH_3
b, R = C_2H_5

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[1] This investigation was supported by a research grant (USPHS-RG5829) from the National Institutes of Health, U. S. Public Health Service.

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[17] N. J. Leonard and A. S. Hay, THIS JOURNAL, **78**, 1984 (1956).

[18] A. G. Cook, Ph.D. Thesis, University of Illinois, 1959. The authors have prepared others in the series of iminium salts, *e.g.*: N-cyclopentylidenepyrrolidinium perchlorate, m.p. 219–220° dec., $\nu_{\max}^{\text{Nujol}}$ 1705 cm.$^{-}$; N-cycloheptylidenepyrrolidinium perchlorate, m.p. 234–235° dec., $\nu_{\max}^{\text{Nujol}}$ 1655 cm.$^{-}$; N-cycloöctylidenepyrrolidinium perchlorate, m.p. 140–141°, $\nu_{\max}^{\text{Nujol}}$ 1649 cm.$^{-1}$ (*cf.* G. Opitz, H. Hellmann and H. W. Schubert, *Ann.*, **623**, 112, 117 (1959); M. E. Kuehne, THIS JOURNAL, **81**, 5400 (1959); Z. Eckstein, A. Sacha and W. Sobótka, *Bull. de l'Acad. Polonaise des Sciences, Série des chim., geol. et géogr.*, **7**, 295 (1959)).

[19] The n.m.r. spectra of IV and V, 25% solutions in sulfur dioxide, were obtained at 60 mc. with a Varian Associates Model V-4300B spectrometer equipped with a superstabilizer. The chemical shifts were determined using tetramethylsilane as an internal standard, obtaining side bands by the application of an audiofrequency signal from an external source.

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cyclization procedures,[21,22] furnished authentic N - (1 - methoxycyclohexylmethyl) - pyrrolidine in 52% yield, b.p. 130–131° (14 mm.), $n^{25}\text{D}$ 1.4806 perchlorate identical with the product (VIa) from V by m.p., mixture m.p., infrared spectrum and paper chromatography. Ethanolysis of 2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate (V) by the same procedure yielded (55%) N-(1-ethoxycyclohexylmethyl)-pyrrolidine perchlorate (VIb), m.p. 93–94° (Calcd. for $C_{13}H_{26}ClNO_5$: C, 50.07; H, 8.41; N, 4.49. Found: C, 50.15; H, 8.65; N, 4.44). By reaction of V with ethylenechlorohydrin, and then treatment of the product with sodium hydroxide in water, extraction with ether, and refluxing of the ether extract for 24 hours, the hygroscopic 2,2-pentamethylene-4,4-tetramethylenemorpholinium chloride was obtained and was converted to the perchlorate (VII), m.p. 190–191°, yield 45% (Calcd. for $C_{13}H_{24}ClNO_5$: C, 50.42; H, 7.81; N, 4.52. Found: C, 50.50; H, 7.71; N, 4.48).

By contrast to the alcoholysis of V, the catalytic reduction with platinum oxide in methanol produces major cleavage (70%) at the bond between the quaternary nitrogen and the methylene carbon, giving rise to N-(1-methylcyclohexyl)-pyrrolidine perchlorate (VIII), m.p. 122–123° (Calcd. for $C_{11}H_{22}ClNO_4$: C, 49.33; H, 8.29; N, 5.23. Found: C, 49.45, H, 8.37, N, 5.23), identical with the salt of the compound obtained from methylmagnesium iodide and IV.

In summary, a new route to aziridinium salts has been provided; three-membered rings varying in degree of substitution and reactivity now become readily available; and the chemistry of aziridinium compounds can be studied systematically, with the attendant benefit of wide synthetic utility. Subsequent publications will present these features with detailed examples.

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RECEIVED NOVEMBER 7, 1960

A NEW REARRANGEMENT: CATALYTIC ISOMERIZATION OF *m*-DIOXANES TO β-ALKOXY ALDEHYDES

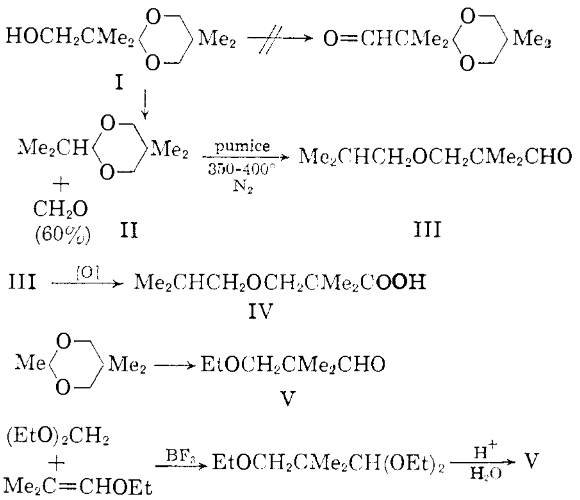
Sir:

2-(Hydroxy-*t*-butyl)-5,5-dimethyl-*m*-dioxane (I) was vaporized through a silver–copper on pumice catalyst[1] in the presence of air at 350° to oxidize the hydroxymethyl group to aldehyde. The expected product was not formed, and I instead was dealdolized to formaldehyde and the known[2] 2-isopropyl-5,5-dimethyl-*m*-dioxane (II). A new compound, isobutoxypivalaldehyde (III) (b.p. 80° (30 mm.), $n^{25}\text{D}$ 1.4078), was a significant component of the pyrolyzate. Under the same conditions, pure II was isomerized to III in 56% conversion (90% yield). Use of pumice without metallic additives in a nitrogen atmosphere gave identical results with II, and at higher temperatures conversion became more nearly complete.

The structure of III was demonstrated by analysis (Calcd. for $C_9H_{18}O_2$: C, 68.4; H, 11.4. Found: C, 68.5; H, 11.5), by conversion to the 2,4-dinitrophenylhydrazone (m.p. 124°) (*Anal.* Calcd. for $C_{15}H_{22}N_4O_5$: C, 53.2; H, 6.6; N, 16.5. Found: C, 53.2; H, 6.6; N, 16.4) and the semicarbazone (m.p. 134°) (*Anal.* Calcd. for $C_{10}H_{21}N_3O_3$: C, 55.8; H, 9.8; N, 19.5. Found: C, 56.3; H, 9.7; N, 19.3), and by permanganate or air oxidation to isobutoxypivalic acid (IV) (b.p. 84° (0.7 mm.), $n^{25}\text{D}$ 1.4207) (isobutoxypivalamide, m.p. 36°). The acid IV and its amide were identical to independently synthesized samples.

Ethyl hydroxypivalate was alkylated with methallyl chloride[3] in the presence of sodium hydride to generate ethyl methallyloxypivalate (b.p. 94° (16 mm.), $n^{25}\text{D}$ 1.4268. *Anal.* Calcd. for $C_{11}H_{20}O_3$: C, 66.0; H, 10.0. Found: C, 65.9; H, 10.2). Reduction of the double bond and hydrolysis yielded IV (b.p. 78° (0.9 mm.), $n^{25}\text{D}$ 1.4200. *Anal.* Calcd. for $C_9H_{18}O_3$: C, 62.1; H, 10.3; neut. equiv., 174. Found: C, 62.2; H, 10.3; neut. equiv., 173). Its amide was prepared, m.p. 37°, mixture m.p. with above amide 36–37° (*Anal.* Calcd. for $C_9H_{19}NO_2$: N, 8.1. Found: N, 8.0).

2,5,5 - Trimethyl - *m* - dioxane (b.p. 130°, $n^{25}\text{D}$ 1.4134. *Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.6; H, 10.8) was converted by pumice at 390° to 66% of ethoxypivalaldehyde (V) (b.p. 146°, $n^{25}\text{D}$ 1.4037. *Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.0; H, 10.3), which yielded a 2,4-dinitrophenylhydrazone, m.p. 128° (*Anal.* Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.32; H, 5.85; N, 18.06. Found: C, 50.4; H, 5.9; N, 18.0). The aldehyde V was synthesized independently by the boron trifluoride-catalyzed addition of diethyl formal to ethyl isobutenyl ether,[4] which formed 1,1,3-triethoxy-2,2-dimethylpropane (b.p. 100° (33 mm.), $n^{25}\text{D}$ 1.4100. *Anal.* Calcd. for $C_{11}H_{24}O_3$: C, 64.66; H, 11.84.



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[3] Use of isobutyl iodide in the procedure of L. Marcilly, *Bull. soc. chim. France*, [3] **31**, 119 (1904), for preparing ethoxypivalic acid led to isobutylene by dehydroiodination.

[4] See for example K. C. Brannock, *J. Org. Chem.*, **25**, 258 (1960).