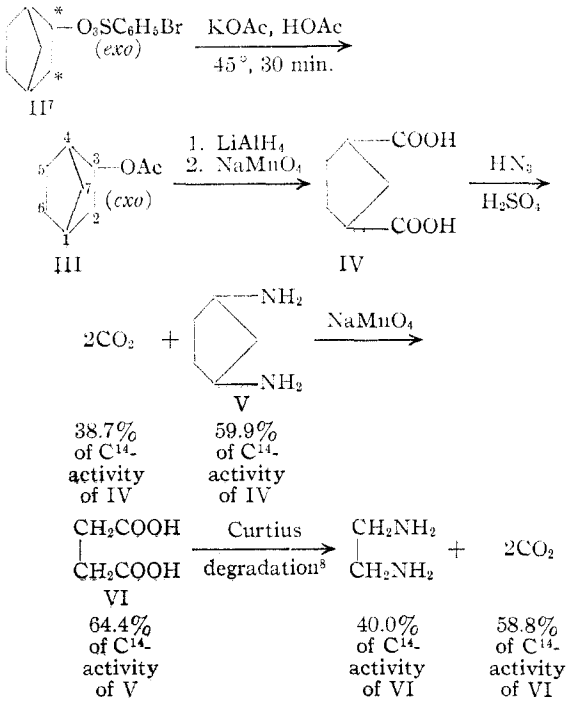
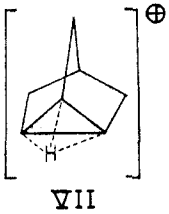
metry.[3] Actually, the reaction results in a more drastic shuffling of carbon atoms than can be accounted for solely on the basis of I or a combination of the customary 1,2-shifts of hydrogen or carbon not involving a 1-norbornyl cation. The finding that substantial C^{14}-activity was located in the 5,6-positions of the norbornyl acetate (III) is particularly significant.

An outline of the experimental results follows.



The C^{14}-activity distribution in III is calculated to be as follows: 2,3-positions, 40%; 1,4-positions, 23%; 5,6-positions, 16%; and 7-position, 21%.

An attractive interpretation of the present results is that the formation of I from II precedes, or possibly is competitive with the formation of a nonclassical cation with a three-fold symmetry axis such as a "nortricyclonium" ion (VII). Preliminary results indicate that the relative importance of VII, or the equivalent, increases slightly in formic acid and decreases markedly in acetone–water.



VII

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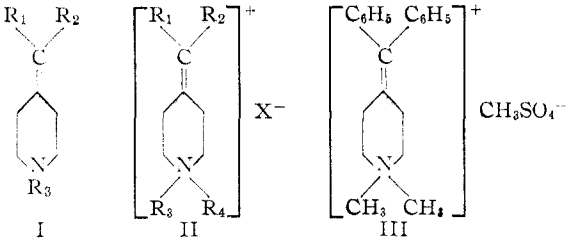
(7) The synthesis of II starting from barium carbide-C^{14} (obtained from Tracerlab, Inc., on allocation from the U. S. Atomic Energy Commission) will be described in detail later.

(8) A. A. Benson and J. A. Bassham, THIS JOURNAL, **70**, 3939 (1948).

A NEW CLASS OF PARASYMPATHETIC BLOCKING AGENTS

Sir:

Pharmacological investigation of a series of compounds of formulas I and II, wherein R_1 is aryl or substituted aryl, R_2 is alkyl, cycloalkyl, cycloalkenyl, aryl or aralkyl, R_3 is alkyl, R_4 is alkyl or



aralkyl and X is halogen or methyl sulfate, disclosed that the quaternary salts of formula II exhibit pronounced parasympathetic blocking activity, parenterally and orally effective in reducing gastric secretion and motility, in several species. On the basis of its high activity and low toxicity in animals,[1] N,N-dimethyl-4-piperidylidene-1,1-diphenylmethane methyl sulfate (III) was selected for further study. Preliminary clinical trials indicate that III is a highly specific parasympathetic blocking agent. Surprisingly, the mydriasis and dryness of the mouth, characteristic of atropine, have not been observed with III given in therapeutic dosages.

The substituted piperidines I were synthesized by two procedures, the preparation of III illustrating these processes. Methyl-N-methyl isonipecotate and an excess of phenylmagnesium bromide gave N-methyl-4-piperidyl-diphenylcarbinol, m.p. 133–134°; hydrochloride, m.p. 290–291° (*Anal.* Calcd. for $C_{19}H_{24}NOCl$: Cl, 11.16. Found: Cl, 11.53). Heating the carbinol with 60% sulfuric acid gave N-methyl-4-piperidylidene-1,1-diphenylmethane, b. p. 145–150° (1 mm.) (*Anal.* Calcd. for $C_{19}H_{21}N$: C, 86.67; H, 8.04; N, 5.32. Found: C, 86.50; H, 8.30; N, 5.54). Quaternization with dimethyl sulfate in benzene yielded III, m.p. 194–195° (*Anal.* Calcd. for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.98; N, 3.59. Found: C, 65.07; H, 7.05; N, 3.36). In the alternate synthesis, N-methyl-4-piperidyl diphenylcarbinol was obtained as follows: N-Methyl isonipecotic acid hydrochloride was converted to the acid chloride hydrochloride, which, with benzene and aluminum chloride, yielded 4-benzoyl-N-methylpiperidine, b.p. 130–135° (2 mm.) (*Anal.* Calcd. for $C_{13}H_{17}NO$: N, 6.89. Found: N, 6.75). This ketone, with an excess of phenylmagnesium bromide, gave the tertiary carbinol. For the compounds of formula I wherein R_1 and R_2 are the same, the ester procedure was the method of choice, whereas the ketone synthesis was the route when R_1 and R_2 are different.

Complete experimental details for the compounds of formulas I and II as well as the corresponding compounds derived from nicotinic, picolinic and other heterocyclic acids will be published at a later date.

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(1) S. Margolin, M. Doyle, J. Giblin, A. Makovsky, M. T. Spoerlein, I. Stephen, G. Belloff and R. T. Tislow, to be published.