by the color of the ferric chloride test, and by the abnormally low frequency of the carbonyl absorption in the infrared absorption spectrum (1740 cm.$^{-1}$ in chloroform) as contrasted to the characteristic γ-lactone carbonyl absorption (1765 cm.$^{-1}$ in chloroform) observed for the methyl ether.[2]

Synthesis was effected through the pyridine–piperidine catalysed condensation of 3-methoxyphthalic anhydride with malonic acid, hydrolysis of the resulting 3-methylene-7-methoxyphthalide to 2-acetyl-6-methoxybenzoic acid, and reduction of this intermediate to 7-methoxy-3-methylphthalide by sodium amalgam. This product, which was obtained in low yield, is identical with that derived from terramycin as indicated by melting points, mixed melting point, and the identity of their infrared absorption spectra. Several alternative synthetic routes yielded 4-hydroxy-3-methylphthalide rather than the desired product.

(2) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

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RECEIVED SEPTEMBER 7, 1951

DEGRADATION OF SOLASODINE

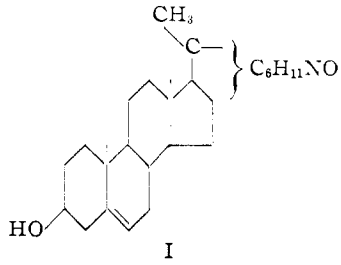
Sir:

In view of the present acute interest in new sources for steroids we wish to report the degradation of solasodine to a pregnane derivative.

To solasodine, the aglycone of the alkaloidal glycoside solasonine obtainable from a number of *Solanum* species[1] has been assigned a steroidal structural formula mainly, because it yielded Diels' hydrocarbon[2,3] in the selenium dehydrogenation.

By treatment of solasodine (m.p. 197–201°[4] $[\alpha]^{20}D$ −98.5°, *c*, 0.396, methanol; calcd. for $C_{27}H_{43}NO_2$: C, 78.40; H, 1048; N, 3.39. Found: C, 78.17; H, 10.29; N, 3.45, acetate, m.p. 191–193°) with acetic anhydride, oxidation of the reaction product with chromic acid anhydride in acetic acid, and subsequent hydrolysis with methanolic potassium hydroxide, we obtained a semi-crystalline mass which was chromatographed, acetylated and again chromatographed twice over alumina (previously washed with ethyl acetate). We eventually isolated 3β-acetoxy-$\Delta^{5,16}$-pregnadiene-20-one (of m.p. 172–174°, $[\alpha]^{20}D$ −24.5 ± 4°, *c*, 0.449, ethanol, calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.38; H, 9.39) and 3β-acetoxy-16α-methoxy-Δ^5-pregnen-20-one of m.p. 157–159°. The identity of these compounds was established by determination of the mixture-melting points, and the comparison of the infrared spectra[5] with authentic samples. A small amount of a third compound not as yet identified (m.p. 198–200.5°, $\lambda_{max.}$ 240, 280) could also be isolated. In addition, a considerable amount of acidic products was formed in the oxidation.

The isolation of the above pregnane derivatives establishes the partial structural formula I for solasodine. One point of attachment of the nitrogen-containing portion is fixed at C-20. The other point is probably at position 16.



I

(1) Henry, "The Plant Alkaloids," 4th ed., The Blakiston Company, Philadelphia, Pa., 1949, p. 666.

(2) Rochelmeyer, *Arch. Pharm.*, **274**, 543 (1936).

(3) See also Rochelmeyer, *ibid.*, **275**, 336 (1937); **277**, 329 (1939); Rochelmeyer, Stützel and Chen, *ibid.*, **282**, 92 (1944); Briggs, *et al.*, *J. Chem. Soc.*, 1, 3, 12 (1942); 3013, 3020 (1950).

(4) All melting points reported were taken on the Kofler block and are uncorrected.

(5) By Mrs. Phyllis B. Humphries, of this Laboratory.

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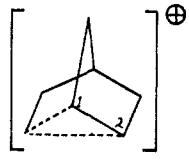
RECEIVED AUGUST 27, 1951

THE NATURE OF THE INTERMEDIATE IN THE SOLVOLYSIS OF NORBORNYL DERIVATIVES[1,2]

Sir:

It has been suggested[3] on the basis of solvolysis rate and stereochemical considerations that the solvolysis of *exo*- and *endo*-norbornyl *p*-bromobenzenesulfonates in acetic acid proceeds by a bridged "non-classical" carbonium ion having a structure (I) like that proposed[4] for the cationic intermediate involved in the rearrangement of camphene hydrochloride to isobornyl chloride. The desirability of tracer experiments to confirm structure I has been pointed out earlier[5] and, as part of



I

an investigation of the mechanisms of reaction of norbornyl derivatives, solvolysis reactions of *exo*- and *endo*-norbornyl-2,3-C_2^{14} *p*-bromobenzenesulfonates are being studied in several solvents.

Solvolysis of the *exo*-isomer (II) in acetic acid via intermediate I would be expected to yield equal[6] parts of *exo*-norbornyl-2,3-C_2^{14} and *exo*-norbornyl-1,7-C_2^{14} acetates since positions 1 and 2 must become equivalent if I is to have a plane of sym-

(1) Supported by the program of research of the U. S. Atomic Energy Commission under Contract AT(30-1)-905.

(2) Presented at the Symposium on Reaction Mechanisms at the 75th Anniversary Meeting of the American Chemical Society, September 7, 1951.

(3) S. Winstein and D. S. Trifan, THIS JOURNAL, **71**, 2953 (1949); S. Winstein and D. S. Trifan, Abstracts of April, 1951, Meeting of the American Chemical Society, 53M, 54M.

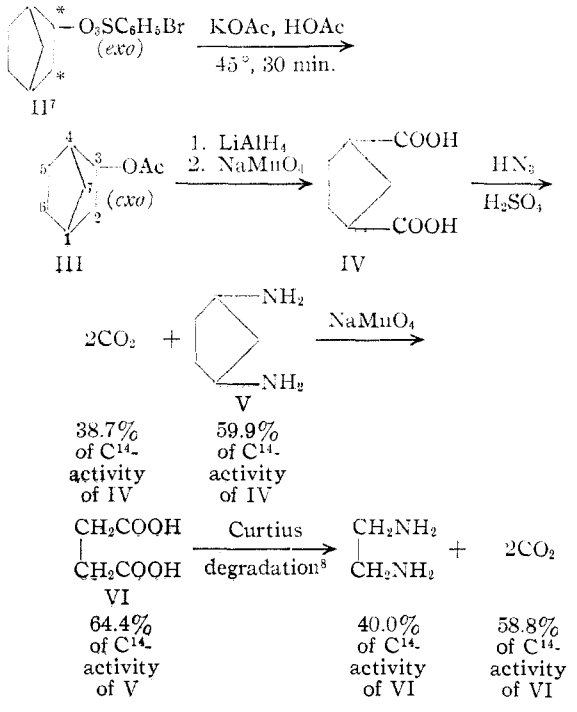
(4) T. P. Nevell, E. de Salas and C. L. Wilson, *J. Chem. Soc.*, 1188 (1939).

(5) J. D. Roberts, R. E. McMahon and J. S. Hine, THIS JOURNAL, **72**, 4237 (1950).

(6) Neglecting differences in reaction rate between C^{12} and C^{14} atoms (isotope effect).

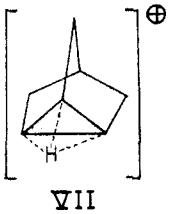
metry.[3] Actually, the reaction results in a more drastic shuffling of carbon atoms than can be accounted for solely on the basis of I or a combination of the customary 1,2-shifts of hydrogen or carbon not involving a 1-norbornyl cation. The finding that substantial C^{14}-activity was located in the 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 non-classical 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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RECEIVED AUGUST 20, 1951

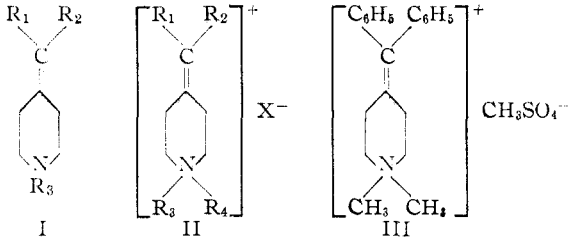
(7) The synthesis of II starting from barium carbide-C^{14} (obtained from Tracerlab, Inc., on allocation from the U. S. Atomic Energy Commission) will be described in detail later.

(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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RECEIVED AUGUST 1, 1951

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