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A Stable α-Lactam Derived from Adamantane

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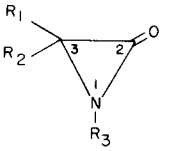
Sir:

Only three α-lactams [I (1), II (2), III (3)] have thus far been isolated in a pure form and characterized, and, of these, only one (III) survives temperatures significantly above room temperature or attack by nucleophiles, such as methanol, above 0°. We now report the isolation of another α-lactam (IV) which is unusually stable, and is of potential interest in medicine (4).



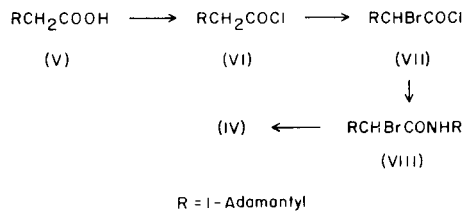
(I) $R_1 = R_2 = Me$, $R_3 = t\text{-Bu}$

(II) $R_1 = C_6H_5$, $R_2 = H$, $R_3 = t\text{-Bu}$

(III) $R_1 = R_3 = t\text{-Bu}$, $R_2 = H$

(IV) $R_1 = R_3 = 1\text{-Adamantyl}$, $R_2 = H$

Reaction of 1-adamantaneacetic acid (V) with thionyl chloride yielded the acid chloride (VI), which was refluxed with one molar equivalent of bromine in carbon tetrachloride to afford VII. Treatment of VII with two molar equivalents of 1-aminoadamantane produced the bromoamide (VIII) (5), m.p. 202-204° (from *n*-heptane), in 90% overall yield from V without purification of intermediate compounds. Reaction of VIII with potassium *t*-butoxide in ether at 0° afforded IV [ν max (chloroform) 1830 cm^{-1}; the n.m.r. spectrum at 60 Mc./sec. in carbon tetrachloride exhibits a singlet at τ 7.30, 1 H, and a complex multiplet at τ 7.67-8.60, 30 H], m.p.~180° (sealed tube) (6), in 72% yield.



The unusual stability of IV is illustrated by several observations. Compound IV is stable in presence of potassium *t*-butoxide at 0°; in fact, the use of 100% excess of this base leads to the complete conversion of VIII to IV. The purification of IV can be effected by crystallization from boiling *n*-heptane, and the lactam ring survives sublimation at 105-110° under high vacuum (about 0.025 mm.). In boiling xylene, the presence of IV can be detected up to 3.5 hours. In boiling methanol, complete decomposition of IV occurs only after 30 hours.

The low susceptibility of III to nucleophilic attack (in boiling methanol, complete decomposition required 87 hours) was attributed (3) to steric hindrance by the two *t*-butyl groups (atoms 1 and 3 of the aziridinone ring are of the neopentyl type, and attack at C-2 is hindered on account of a "six number" (7) of eighteen). The 1-adamantyl substituent may be regarded as a *t*-butyl group in which the three methyl groups are "tied back" to a cyclohexane ring. Since Newman (7) considers the "tying back" of alkyl groups to lead to a considerable decrease in steric hindrance (by a factor of 24 when only two alkyl chains are "tied back"), the similarity of the stability of IV to that of III rather than that of I or II is unexpected.

Similar α-lactams as well as other small-ring derivatives of adamantane are being actively studied by us.

Acknowledgment.

Awards of a Graduate Traineeship to A. E. D. by the National Science Foundation, and an Undergraduate Fellowship for Summer, 1967, to A. E. C. by the Cancer Association of Greater New Orleans, as well as partial support by the Research Council of Louisiana State University in New Orleans, are gratefully acknowledged.

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(2) H. E. Baumgarten, *ibid.*, 84, 4975 (1962).

(3) J. C. Sheehan and J. H. Beeson, *ibid.*, 89, 362 (1967).

(4) 1-Aminoadamantane and its derivatives have marked antiviral properties.

(5) Satisfactory analyses were obtained for all new compounds. The spectra of VIII are in agreement with the assigned structure.

(6) The melting point and melting range depend on the rate of heating.

(7) M. S. Newman, *J. Am. Chem. Soc.*, 72, 4783 (1950).

Received October 11, 1967

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