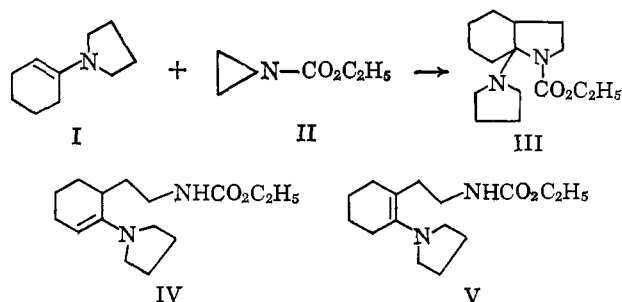


A New Heterocyclic Synthesis. Enamine Cycloaddition with N-Carbethoxyaziridine

Sir:

As part of a program concerning the reactivity and utility of small ring compounds in the synthesis of medium ring systems, we have examined the reaction of N-carbethoxyaziridine¹ with the pyrrolidine enamine of cyclohexanone.² This report is concerned with the first demonstration of the formal cycloaddition of an enamine with an N-acylaziridine.

Amines are known to participate in a facile nucleophilic ring opening of N-carbethoxyaziridine³ at room temperature, resulting in the formation of a product derived from alkylation of the amine nitrogen. However the reaction of an enamine, to proceed by carbon alkylation, is sluggish at best, even in refluxing ethanol or benzene solutions. At elevated temperatures a reaction does occur. Thus a xylene solution of equivalent amounts of 1-(1-pyrrolidinyl)cyclohexene (I) and N-carbethoxyaziridine (II) provides after refluxing for 14 hr. in an atmosphere of nitrogen a 42% yield of a 1:1 addition product, b.p. 105–113° (0.15 mm.), to which we assign an octahydroindole structure (III).



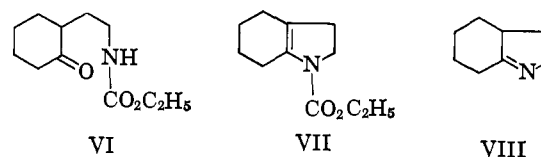
Alternative structures IV and V are not supported by the infrared spectrum, which possesses no absorptions characteristic of N—H or C=C groups. The p.m.r. spectrum is in accord with the proposed structure (III). A molecular weight determination gave a value of 265 (theoretical, 266).⁴ The combustion analysis of this unstable amine gave slightly low values for carbon. *Anal.* Calcd. for C₁₅H₂₆N₂O₂: C, 67.65; H, 9.85; N, 10.52. Found: C, 66.96; H, 9.68; N, 10.29. However, treatment of the octahydroindole compound (III) with aqueous-alcoholic 2,4-dinitrophenylhydrazine solution induced the formation and precipitation of a yellow derivative, m.p. 161–164° (*Anal.* Calcd. for C₁₇H₂N₅O₆: C, 51.90; H, 5.89; N, 17.80. Found: C, 51.89; H, 6.07; N, 17.71), of the keto urethan VI, the hydrolysis product of III.

The best conditions for performing the cycloaddition consisted of refluxing a solution of 0.05 mole of enamine and 0.10 mole of N-carbethoxyaziridine in 40 ml. of *p*-xylene for 4 hr. under nitrogen, the product being

- (1) H. Bestian, *Ann.*, **566**, 210 (1956).
- (2) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
- (3) G. E. Ham, *J. Org. Chem.*, **29**, 3052 (1964), and references therein.
- (4) Molecular weights were determined in benzene by a Mechrolab Model 301 vapor pressure osmometer.

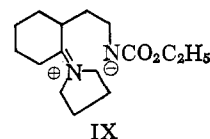
isolated in 65% yield upon removal of the solvent and distillation at reduced pressure.

A convenient elimination of the elements of pyrrolidine was achieved by distillation of the crude reaction product from a small amount of *p*-toluenesulfonic acid, this giving rise to the hexahydroindole compound VII



in 44% yield, b.p. 93–95° (0.15 mm.). *Anal.* Calcd. for C₁₁H₁₇NO₂: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.57; H, 8.90; N, 6.99. This hexahydroindole (VII) was converted to the salt of the known hexahydroindole⁵ (VIII) with methanolic hydrogen chloride.

While this reaction represents a formal cycloaddition to an aziridine single bond, it seems reasonable that the zwitterionic material (IX) would be formed as an intermediate in the reaction course and cyclize spontaneously to the neutral indole derivative.



We intend to explore and extend this novel type of reaction further and clarify the stereochemistry of the ring fusion in bicyclic cases such as the one cited here.

(5) F. C. King, D. M. Bovey, K. G. Mason, and R. L. St.D. Whitehead, *J. Chem. Soc.*, 250 (1953).

(6) To whom inquiries may be addressed at the Section of Organic Chemistry, The Squibb Institute for Medical Research, New Brunswick, N. J. 08903.

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Long-Range Interactions in Semidiones Derived from Bicyclo[2.2.1]heptanes and Bicyclo[2.2.2]octanes¹

Sir:

The e.s.r. spectra of acyclic or monocyclic semidiones (RC(O·)=C(O⁻)R) involve predominant hyperfine splitting by hydrogen atoms α to the dicarbonyl system.^{2–5} This splitting is a function of the dihedral angle ($a^H \propto \cos^2 \theta$) between the carbon-hydrogen bond and the carbonyl carbon p_z orbital.² Hydrogen atoms β to the dicarbonyl system interact only weakly

(1) Application of E.s.r. Spectroscopy to Problems of Structure and Conformation. V. This work was supported by grants from the National Science Foundation and the Petroleum Research Fund.

- (2) G. A. Russell and E. T. Strom, *J. Am. Chem. Soc.*, **86**, 744 (1964).
- (3) G. A. Russell and E. R. Talaty, *ibid.*, **86**, 5345 (1964).
- (4) G. A. Russell and E. R. Talaty, *Science*, **148**, 1217 (1965).
- (5) E. T. Strom, G. A. Russell, and R. D. Stephens, *J. Phys. Chem.*, **69**, 2131 (1965).

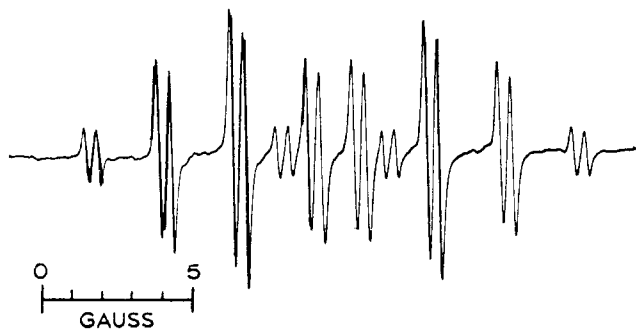
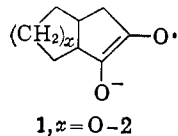


Figure 1. First derivative e.s.r. spectrum of bicyclo[2.2.2]heptane-2,3-semidione at 25° in dimethyl sulfoxide solution prepared by reduction of bicyclo[2.2.2]heptane-2,3-dione (0.05 *M*) by propiophenone (0.05 *M*) in the presence of potassium *t*-butoxide (0.10 *M*).

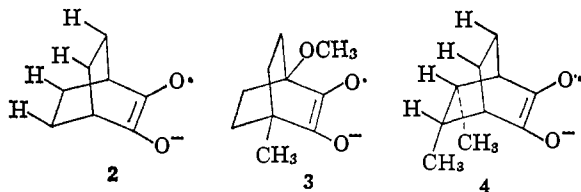
with hyperfine splitting constants (h.f.s.c.) considerably less than 0.5 gauss.⁵

Semidiones derived from decalones^{3,4} and the bicyclic semidiones of structure 1⁶ do not display any unusually strong h.f.s. by β -hydrogen atoms. It



was thus surprising to observe extremely strong splittings by certain β -hydrogen atoms in bicyclic semidiones with 1,3- and 1,4-ring fusions.

Reaction of bicyclo[2.2.2]octan-2-one with a trace of oxygen in dimethyl-*d*₆ sulfoxide containing potassium *t*-butoxide, reduction of bicyclo[2.2.2]octane-2,3-dione by the propiophenone enolate anion in DMSO, or treatment of 3-bromobicyclo[2.2.2]octan-2-one with potassium *t*-butoxide in DMSO⁷ produces a radical anion stable for hours at 25–30°. Up to 5% of the dione can be converted to radical anion. The e.s.r. spectrum is a 1:4:6:4:1 quintet, $a^H = 2.09$ gauss. This radical anion is assigned structure 2 and the hyperfine splitting is believed to be due to the four hydrogen atoms *exo* to the dicarbonyl system since a similar quintet ($a^H = 2.14$ gauss) is observed for 3, produced by oxidation of the monoketone,⁸ while oxidation of *endo,endo*-5,6-dimethylbicyclo[2.2.2]octan-2-one, m.p. 67.5–68.5°,⁹ in DMSO or DMSO-*d*₆ yields a radical anion (4) with hyperfine splitting by two pairs of hydrogen atoms, $a^H = 2.12$ and 1.34 gauss. The *exo* or *anti* splitting by hydrogen atoms in a W-



plan or zigzag arrangement¹⁰ with the carbonyl carbon

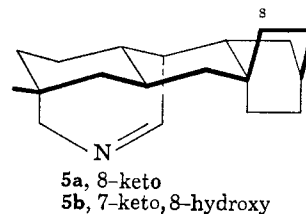
(6) Unpublished results of Dr. R. Horrocks.

(7) G. A. Russell, R. D. Stephens, and E. R. Talaty, *Tetrahedron Letters*, 1139 (1965); this process apparently involves the disproportionation of an intermediate α -hydroxy ketone.

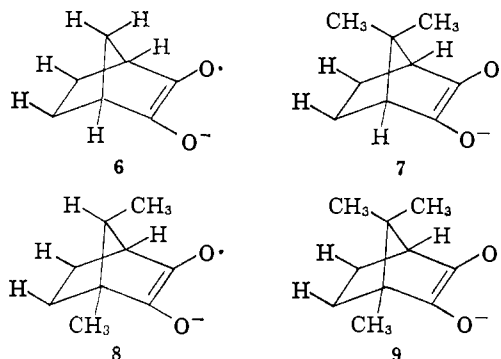
(8) K. Morita, M. Nishimura, and Z. Suzuki, *J. Org. Chem.*, 30, 533 (1965).

(9) Prepared from *endo,endo*-bicyclo[2.2.2]octene-2,3-dicarboxylic anhydride.

p_z orbital is consistent with the quartet splitting, $a^H = 2.20$ gauss, observed for the semidione prepared by oxidizing the atisine derivatives (5)¹¹ in DMSO-*d*₆ (5a) or DMSO (5b).¹²



Bicyclo[2.2.1]heptane-2,3-semidione (6), prepared by reduction of the dione,¹³ shows a more complex e.s.r. spectrum (Figure 1) involving doublet (6.54 gauss), quintet (2.43 gauss), and doublet (0.41 gauss) h.f.s. These splittings are assigned to the *anti*-7-H, C-1, C-4, *exo*-C-5, *exo*-C-6, and *syn*-7-H, respectively. These



assignments are based on the e.s.r. spectra observed for the oxidation products of apocamphor (7), β -santenone (8), and camphor (9).² Under low resolution 7, 8, and 9 give quintet, quintet, and quartet splittings, respectively. The only combination of hydrogen atoms that would predict such major splitting and also be consistent with the spectra of 6 and 4 would be nearly magnetically equivalent hydrogen atoms at C-1, C-4, *exo*-C-5, *exo*-C-6, and *anti*-C-7. Under higher resolution differences in these hydrogen atoms can be observed ($a^H_{\text{bridgehead}} = 2.07$ (7), 2.55 (8), 2.08 (9)¹⁴; $a^H_{\text{exo}} = 2.90$ (7), 2.55 (8), 3.01 (9); $a^H_{\text{anti}} = 3.05$ (8) in addition to smaller splittings (0.15–0.55 gauss) by methyl groups (one in 7, two in 8 and 9) and by the *endo* hydrogen atoms in 7 and 9 ($a^H = 0.26$ (triplet) and 0.22 (doublet) gauss, respectively).¹⁵

(10) For examples of W-plan splitting in n.m.r. see J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, 83, 2769 (1961); C. W. Jefford, B. Waegell, and K. Ramey, *ibid.*, 87, 2191 (1965); M. Barfield, *J. Chem. Phys.*, 41, 3825 (1964), and references cited therein.

(11) D. Dvornik and O. E. Edwards, *Can. J. Chem.*, 42, 137 (1964).

(12) E.s.r. spectroscopy thus provides a convenient method for assigning structure to substituted bicyclo[2.2.2]octanones. The 5-methyl group in 1,5-dimethyl-4-methoxybicyclo[2.2.2]octan-2-one³ is assigned the *syn* structure on the basis of the semidione whose e.s.r. spectrum shows a quartet ($a^H = 2.10$ gauss) and a doublet ($a^H = 0.93$ gauss) splitting.

(13) K. Alder, H. K. Schäfer, H. Esser, H. Krieger, and R. Reubke, *Ann.*, 593, 23 (1955).

(14) Hyperfine splitting by α -hydrogen atoms is a function of the dihedral angle.² This manifestation of Bredt's rule illustrates a stereoelectronic restriction to hyperconjugation. Apparently hyperconjugation is not completely restricted for bridgehead hydrogens in the 2,2,1 system where $\theta > 90^\circ$ as it is in the symmetrical 2,2,2 system ($\theta = 90^\circ$).

(15) Apparently *endo* splitting is much more important in the presence of the *anti*-7-methyl group. The methyl splittings are tentatively assigned to the *anti*-7-methyl in 7 ($a^H_{\text{CH}_3} = 0.53$ gauss) and to the *anti*-7-methyl and 1-methyl in 9 ($a^H_{\text{CH}_3} = 0.55, 0.15$ gauss). In 8 both methyls have $a^H_{\text{CH}_3} = 0.18$ gauss.

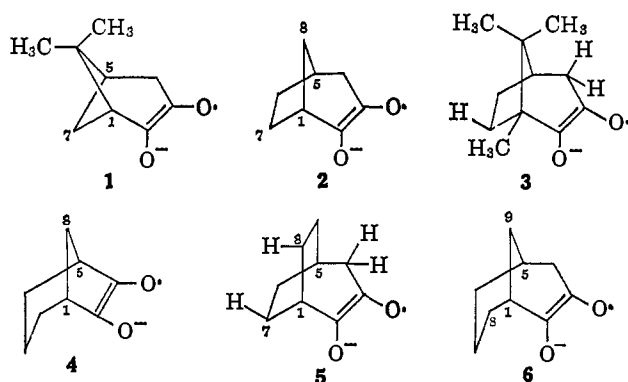
Acknowledgment. We wish to thank Professor H. Walborsky for a sample of bicyclo[2.2.2]octan-2-ol, Professor P. Yates for bicyclo[2.2.2]octane-2,3-dione, Dr. K. Morita for 1-methyl-4-methoxybicyclo[2.2.2]octan-2-one and its 5-methyl derivatives, Dr. O. Edwards for the atisine derivatives **5**, and Professor H. C. Brown for a sample of apocamphor.

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 Received July 13, 1965

Long-Range Interactions in Semidiones in the Bicyclo[3.1.1]heptane, Bicyclo[3.2.1]octane, Bicyclo-[3.2.2]nonane, and Bicyclo[3.3.1]nonane Systems¹

Sir:

Semidiones **1-6** have been prepared by oxidation of the corresponding monoketones in dimethyl sulfoxide solution containing potassium *t*-butoxide.



Extensive long-range interactions are observed in all the radical anions. In view of our observations on the bicyclo[2.2.2]octane-2,3-semidione,² most of the major interactions can be assigned to carbon-hydrogen bonds α to the dicarbonyl system or β to the dicarbonyl system and in a zigzag arrangement with the carbonyl carbon p_z orbital.

Analysis of the hyperfine splitting in semidiones is simplified by the fact that in DMSO- d_6 the α -hydrogen atoms are replaced by deuterium atoms with a resultant change in the e.s.r. spectrum ($a^H/a^D \cong 7$). However, in bicyclic compounds such as **1**, **2**, or **4** such exchange at the bridgehead position is prohibited.

The hyperfine splittings observed for **1-6** are given in Table I together with an assignment of certain of the hyperfine splitting constants to specific hydrogen atoms.

The spectra observed for **3** (Figure 1) and **5** (Figure 2) are easily interpreted. For **5** two pairs of equivalent hydrogen atoms are indicated. The magnetic equivalence of a pair of hydrogen atoms at C-4 and a pair at C-7 and C-8 can be explained by dynamic interconversion between two asymmetric twist conforma-

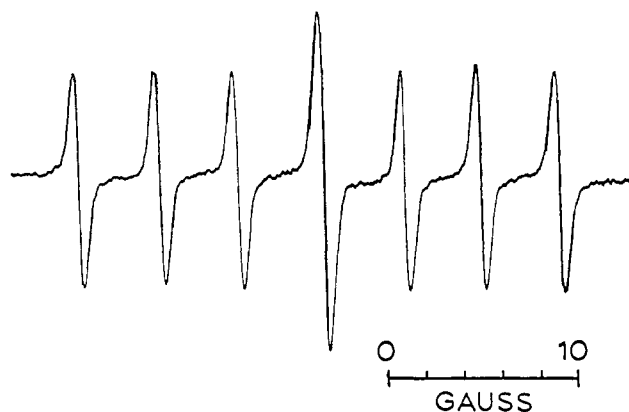


Figure 1. First derivative e.s.r. spectrum of semidione **3** prepared by reaction of a trace of oxygen with homocamphor (0.05 *M*) in dimethyl sulfoxide containing potassium *t*-butoxide (0.10 *M*) at 25°.

tions,³ but the lack of bridgehead splitting is surprising since time averaging cannot affect this nearly orthogonal dihedral angle.

Table I. Hyperfine Splitting Constants for Bicyclic Semidiones^a

Semi-dione	H.f.s.c., gauss	Assignment of H
1	9.46 (doublet) ^b	C-4
	9.04 (doublet) ^b	C-4
	3.88 (doublet)	<i>anti</i> -C-7
	0.42 (sextet)	C-1, <i>syn</i> -C-7, methyl
2	13.5 (doublet) ^b	C-4
	8.69 (doublet) ^b	C-4
	3.45 (doublet)	C-1 or <i>exo</i> -C-7 or <i>anti</i> -C-8
	2.13 (doublet)	C-1 or <i>exo</i> -C-7 or <i>anti</i> -C-8
	1.42 (doublet)	C-1 or <i>exo</i> -C-7 or <i>anti</i> -C-8
	0.28 (triplet)	<i>endo</i> -C-7 and <i>syn</i> -C-8
3	12.5 (doublet) ^b	C-4
	8.4 (doublet) ^b	C-4
	4.1 (doublet)	<i>exo</i> -C-7
	0.53 (sextet)	<i>exo</i> -C-2,4; <i>anti</i> -C-8; C-1,4; <i>endo</i> -C-2,4; <i>syn</i> -C-8
5	10.5 (triplet) ^b	C-4
	2.2 (triplet)	<i>anti</i> -C-7,8
6	12.74 (doublet) ^b	C-4
	6.93 (doublet) ^b	C-4
	3.35 (doublet)	<i>exo</i> -C-8 or <i>anti</i> -C-9
	1.96 (doublet)	<i>exo</i> -C-8 or <i>anti</i> -C-9
	0.56 (doublet)	C-1

^a In DMSO at 25°. ^b Exchangeable in DMSO- d_6 .

A considerable amount of work is required before unique hyperfine splitting constants can be rigorously assigned to all the hydrogen atoms involved. Our preliminary data are being presented at this time because the extension of this work to the assignment of structure of derivatives of **1-6**, of synthetic or natural origin, is obvious and in certain cases a unique struc-

(1) Application of E.s.r. Spectroscopy to Problems of Structure and Conformation. VI. This work was supported by grants from the National Science Foundation and the Petroleum Research Fund.

(2) G. A. Russell and K. Y. Chang, *J. Am. Chem. Soc.*, **87**, 4381 (1965).

(3) C. W. Jefford, J. Mahajan, B. Waegell, and K. Ramey, private communications.