

TABLE I
 PHYSICAL CONSTANTS OF FLUORINATED STEROID KETONES

	Compound	M.p., °C.	[α] _D ²⁰	$\lambda_{\text{C=O}}^{\text{KBr}}$	Found:		
					Carbon, %	Hydrogen, %	Fluorine, %
I	2 α -Fluorocholestan-3-one ¹	173-174	+ 60°	5.78 μ	80.20	11.19	4.71
II	2 α -Fluoroandrostane-3,17-dione	204-205	+133	5.78	74.28	8.86	5.99
III	2 α -Fluorodihydrotestosterone acetate	195-196	+ 59	5.80	71.93	8.84	5.38
IV	2 α -Fluorodihydrotestosterone	187-188	+ 62	5.79	73.91	9.33	6.10
V	6 β -Fluoro-4-cholesten-3-one	103-104	+ 10	5.95	80.26	10.78	4.61
VI	6 α -Fluoro-4-cholesten-3-one ⁷	117-118.5	+102	5.97	80.60	10.77	4.58
VII	6 α -Fluoroprogesterone ^{7,9}	144-145	+191	5.98
VIII	21,21-Difluoro-3 β -hydroxy-5-pregnen-20-one	135-136	+ 54	5.81	71.29	3.48	10.73
IX	21,21,21-Trifluoro-3 β -hydroxy-5-pregnen-20-one	179-181	+ 56	5.74	67.89	8.03	15.69
X	21,21-Difluoroprogesterone	147-147.5	+203	5.81	71.77	8.61	11.03
XI	21,21,21-Trifluoroprogesterone	159-160	+212	5.74	68.22	7.67	15.55

In contrast to enamines which yield 4,4-difluoro-3-keto- Δ^5 -steroids,⁶ enol ethers of Δ^4 -3-ketosteroids are fluorinated at position 6. Thus, 3-ethoxy-3,5-cholestadiene with perchloryl fluoride in pyridine three minutes at -20° gave the 6 β -fluoro derivative, V, isomerized by hydrogen chloride in chloroform-ethanol to the known⁷ 6 α -isomer, VI. Similarly, 3-ethoxy-3,5-pregnadien-20-one gave a mixture⁸ of 6 β - and 6 α -fluoroprogesterones^{7,9} isomerized by acid to yield VII, identical with authentic 6 α -fluoroprogesterone.¹⁰

Certain ketones already bearing α -fluoro-substituents can be fluorinated further without intermediate conversion to enol ether derivatives. Thus VIII, prepared from perchloryl fluoride and sodio-21-ethoxyalyl-3 β -hydroxy-5-pregnen-20-one in ethanol containing one extra equivalent of sodium ethoxide, as its acetate ester (m.p. 127.5-129°) was treated with FClO₃ for 90 minutes at room temperature in pyridine containing *t*-butyl alcohol and sodium *t*-butoxide to produce 21,21,21-trifluoro-3 β -acetoxy-5-pregnen-20-one (m.p. 155-156°) saponified by methanolic potash to yield IX. Oxidation of VIII by Djerassi's procedure¹¹ gave X, whereas Oppenauer oxidation of IX furnished XI.

In contrast to the enhanced biological activity of 21-fluoroprogesterone,¹² X and XI are progestationally inactive at 0.25 mg.¹³ Preliminary tests of II at 0.2 mg. and III at 0.1 mg. in castrate male rats¹³ indicate that fluorination has abolished androgenic activity, although III is strongly anabolic in young female rats and markedly inhibits rat mammary cancer induced by feeding methylcholanthrene.¹⁴ Thus 2 α -fluorination may well accomplish our long-standing objective of

eliminating primary hormonal activity by a molecular change so subtle that secondary actions including antitumor effects are retained.¹⁵

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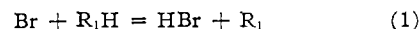
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THE REACTIONS OF BROMINE ATOMS AND THE STRENGTHS OF C-H BONDS

Sir:

Reactions of type (1) are important both because



of their intrinsic interest and because Kistiakowsky and Van Artsdalen¹ have shown how the strength of C-H bonds in alkanes can be deduced from measurements of the activation energies, E_1 . The strengths are given by

$$D(\text{C-H}) = D(\text{H-Br}) + E_1 - E_{-1}$$

We have determined relative values of E_1 for a number of hydrocarbons by a competitive method previously employed to study the reactions of fluorine and chlorine atoms.² Absolute values of the Arrhenius parameters have been obtained by relating the rate constant for ethane to that for methyl bromide¹

$$\log k/\text{mole}^{-1} \text{ cm.}^3 \text{ sec.}^{-1} = 13.73 - (16050/2.3RT)$$

A mixture of two reactants together with bromine was irradiated in a Pyrex reaction vessel. The concentration of the less reactive compounds was usually about four times that of the more reactive. The products were analyzed by gas chromatography after the excess bromine had been removed. The relative rates of formation of the alkyl bromides, from which the relative rate con-

(6) R. L. Morgan and E. V. Jensen, to be published.

(7) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(8) Characterized by papergram analysis carried out by Mr. L. M. Reineke, The Upjohn Co.

(9) J. A. Hogg, *et al.*, *Chem. and Ind.*, 1002 (1958).

(10) Kindly supplied by Dr. J. C. Babcock.

(11) C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(12) P. Tannhauser, R. J. Pratt and E. V. Jensen, *THIS JOURNAL*, **78**, 2658 (1956); Ch. R. Engel and R. L. Noble, *Endocrinology*, **61**, 318 (1957).

(13) Subcutaneous assay by F. L. Schmidt, S. C. Lyster and W. E. Dulin, The Upjohn Co.

(14) Subcutaneous assay by Dr. C. Huggins, University of Chicago.

(1) G. B. Kistiakowsky and E. R. Van Artsdalen, *J. Chem. Phys.*, **12**, 469 (1944); H. C. Anderson and E. R. Van Artsdalen, *ibid.*, p. 479; B. H. Eckstein, H. A. Scheraga and E. R. Van Artsdalen, *ibid.*, **22**, 28 (1954); E. I. Hormats and E. R. Van Artsdalen, *ibid.*, **19**, 775 (1951).

(2) J. H. Knox and R. L. Nelson, *Trans. Faraday Soc.*, **55**, 937 (1959); G. C. Fettes and A. F. Trotman-Dickenson, to be published.

stants were calculated, were independent of the irradiation time, the concentration of bromine and the addition of considerable quantities of hydrogen bromide.

The results obtained were

Reactant 1	Reactant 2	Temp., °C.	$E_1 - E_2$, kcal. mole ⁻¹	A_1/A_2
CH ₃ Br	C ₂ H ₆	58-199	2.654 ± 0.088	0.73
C ₂ H ₆	<i>s</i> -C ₃ H ₈	12-145	3.247 ± .051	1.52
<i>s</i> -C ₃ H ₈	<i>t</i> -iso-C ₄ H ₁₀	34-148	2.640 ± .065	2.56
<i>s</i> - <i>n</i> -C ₄ H ₁₀	<i>t</i> -iso-C ₄ H ₁₀	-12- 98	2.716 ± .030	8.26

The activation energies for attack by bromine atoms are therefore

Alkyl group	E_1	kcal. mole ⁻¹ E_{-1}	$D(\text{C-H})(25^\circ)$
Methyl	18.3	1.8	102.5 ^{1,4}
Ethyl	13.4	(2.5)	96.9
<i>s</i> -Propyl	10.2	(3.1)	93.1
<i>s</i> -Butyl	10.2	(3.1)	93.2
<i>t</i> -Butyl	7.5	(3.6)	90.0

The values of the activation energies and A factors do not present any of the difficulties associated with the earlier determinations.³ The A factors agree closely with those that can be calculated from transition state theory.

Bond strengths cannot be obtained directly from these results because E_{-1} is only known for methane. However, the difference between $D(\text{CH}_3\text{-H})$ and $D((\text{CH}_3)_3\text{C-H})$ is known with reasonable accuracy from electron impact measurements to be 12.5 kcal. mole⁻¹.⁵ Hence if we assume that the Polanyi relation between heats and activation energies of reaction holds, then $\alpha \approx 0.86$ and the intermediate bond strengths given in the fourth column are found. These strengths correspond to the values of E_{-1} in column 3.

We are presently extending the measurements of E_1 to include other alkanes and hope to obtain direct information on E_{-1} so that the derived bond strengths may be more certain.

We are much indebted to Imperial Chemical Industries, General Chemicals Division, for a grant in support of this work.

(3) A. F. Trotman-Dickenson, "Gas Kinetics," Butterworths, London, 1955, p. 193; D. J. Wilson and H. S. Johnston, *THIS JOURNAL*, **79**, 29 (1957).

(4) L. H. Long, *Proc. Roy. Soc. (London)*, **A198**, 62 (1949).

(5) D. P. Stevenson, *Disc. Faraday Soc.*, **10**, 35 (1951).

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ETHYL BICYCLO[1.1.0]BUTANE-1-CARBOXYLATE¹

Sir:

In trying to achieve an understanding of the role of ring strain in determining the physical and chemical properties of cyclic compounds, the study of compounds more highly strained than cyclopropane is of importance. One of the more interesting of these compounds is bicyclo[1.1.0]butane, of which no authentic derivative has been reported. We wish to record the synthesis of a

(1) This work was supported by the Office of Ordnance Research, U. S. Army.

compound of this type, ethyl bicyclo[1.1.0]butane-1-carboxylate.

Ethyl 3-bromocyclobutane-1-carboxylate, I, was prepared by the reaction of 3-carbethoxycyclobutanol-1 tosylate² with lithium bromide. On treatment with sodium triphenylmethide in ether solution, it gave II, C₇H₁₀O₂, b.p. 56-58° at 15 mm. (*Anal.*, Calcd: C, 66.6; H, 8.0; mol. wt., 126. Found: C, 66.3; H, 8.2; mol. wt., 126). The ester, II, polymerized on standing, and the polymerization was retarded by *t*-butylcatchol. On catalytic hydrogenation using a platinum catalyst, it absorbed two equiv. of hydrogen giving ethyl 2-methylbutyrate. II must have structure III or be one of the double bond isomers of IV, V or VI. The latter are incompatible with the n.m.r. spectrum (Fig. 1) in that there is no vinyl proton

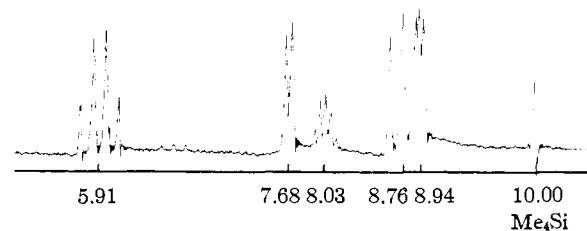
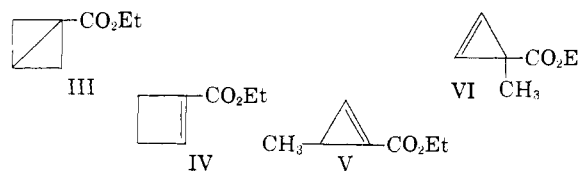


Fig. 1.—Nuclear magnetic resonance spectrum of ethyl bicyclo[1.1.0]butane-1-carboxylate.

band at $\tau^3 = 4-5$, and there is no unsplit methyl band.



The triplet at 8.76 is due to the methyl of the ester group, and the methylene appears as a quadruplet at 5.91. The remaining bands are a pentuplet at 8.03 (one proton) and two doublets, one at 7.68 and the other at 8.94 (two protons each). The spin-spin coupling is the same for all of these latter bands indicating that the structural unit must be $-\text{CH}_2-\text{CH}-\text{CH}_2$, in which each of the carbons is attached to another carbon, the latter not bearing any protons. Since there can be only one additional carbon, it is apparent that all three carbons must be connected to that one. Thus, structure III is uniquely capable of accommodating the observed spectrum. One of the doublets arises from the two *endo*-hydrogens, and the other from the two *exo*-hydrogens.

The polymerization, which is presumably a radical chain process since it is inhibited by *t*-butylcatechol, suggests that the central carbon-carbon bond dissociation energy has become so low that it has acquired pseudo-olefinic character. The hydrogenation probably involves initial car-

(2) M. Avram, C. D. Nenitzescu and M. Maxim, *Ber.*, **90**, 1424 (1957).

(3) $\tau = 10.00 - \delta_{\text{Me}_4\text{Si}}$.