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_3Br	C_2H_6	58–199	2.654 ± 0.088	0.73
C_2H_6	s-C_3H_8	12–145	3.247 ± .051	1.52
s-C_3H_8	t-isoC$_4H_{10}$	34–148	2.640 ± .065	2.56
s-n-C_4H_{10}	t-isoC$_4H_{10}$	−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(C–H)(25°)
Methyl	18.3	1.8	102.5[1,4]
Ethyl	13.4	(2.5)	96.9
s-Propyl	10.2	(3.1)	93.1
s-Butyl	10.2	(3.1)	93.2
t-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 $D(CH_3\text{–H})$ and $D((CH_3)_3C\text{–H})$ 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).

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RECEIVED JULY 13, 1959

ETHYL BICYCLO[1.1.0]BUTANE-1-CARBOXYLATE[1]

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 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 tosylate[2] with lithium bromide. On treatment with sodium triphenylmethide in ether solution, it gave II, $C_7H_{10}O_2$, 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

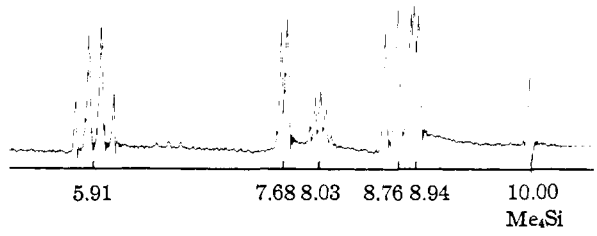
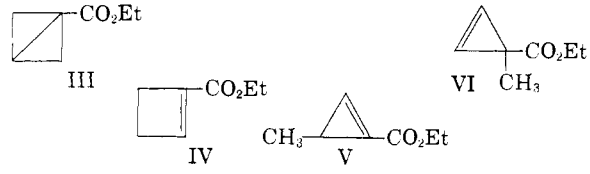


Fig. 1.—Nuclear magnetic resonance spectrum of ethyl bicyclo[1.1.0]butane-1-carboxylate.

band at τ[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 $-CH_2-\underset{|}{CH}-CH_2-$, 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-

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

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

(3) $\tau = 10.00 - \delta^{\text{int.}}_{Me_4Si}$.

bon–carbon bond cleavage to ethyl 1-methylcyclopropanecarboxylate, which then is reduced to the observed product

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RECEIVED AUGUST 10, 1959

STEROIDS. CXXXII.[1] 2-FLUORO AND 21,21-DIFLUORO STEROIDS

Sir:

The fluorination of active methylene compounds with perchloryl fluoride has been demonstrated recently.[2] Subsequently, Gabbard and Jensen[3] utilized this reagent in the steroid series, preparing 2α-fluorocholestanone from cholestanone pyrrolidyl enamine while Kissman, Small and Weiss[4] prepared 2α-fluorohydrocortisone from 2-methoxalylhydrocortisone 20-ketal.

We have prepared a number of 2α-fluoro steroids in the potentially important androstane series by reaction of the sodio salt of the appropriate 2-hydroxymethylene-3-keto steroid with perchloryl fluoride followed by alkaline cleavage of the resultant 2-aldehydo-2-fluoro compounds.[5] Thus, 2-hydroxymethylene-testosterone,[6] -androstan-17β-ol-3-one (m.p. 125–130°, $[\alpha]$D + 60° (all rot. in $CHCl_3$), λ_{max}^{EtOH} 282 mμ, log ϵ 3.94), -17α-methyltestosterone,[7] and 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one,[7] in benzene solution, were reacted successively with sodium methoxide and perchloryl fluoride. Treatment of the reaction products with potassium acetate in boiling methanol gave 2α-fluorotestosterone (I) (m.p. 140–141°, $[\alpha]$D + 131°, λ_{max}^{EtOH} 242 mμ, log ϵ 4.15, λ_{max}^{KBr} 5.90 μ. Found for $C_{19}H_{27}FO_2$: C, 74.27; H, 8.85; F, 5.97); 2α-fluoroandrostan-17β-ol-3-one[8] (II) (m.p. 183–185°, $[\alpha]$D + 63°, λ_{max}^{EtOH} 283 mμ, log ϵ 1.44, λ_{max}^{KBr} 5.75 μ. Found for $C_{21}H_{31}FO_3.C_3H_6O$: C, 70.96; H, 8.91; F, 4.81); II acetate (m.p. 190–193°, $[\alpha]$D + 56°); 2α-fluoro-17α-methyltestosterone (III) (m.p. 168–169°, $[\alpha]$D + 116°, λ_{max}^{EtOH} 242 mμ, log ϵ 4.22, λ_{max}^{KBr} 5.90 μ. Found for $C_{20}H_{29}FO_2$: C, 75.30; H, 8.63; F, 5.80); 2α-fluoro-17α-methylandrostan-17β-ol-3-one (IV) (m.p. 193–194°, $[\alpha]$D + 46°, λ_{max}^{EtOH} 283 mμ, log ϵ 1.52, λ_{max}^{KBr} 5.75 μ. Found for $C_{20}H_{31}FO_2$: C, 74.49; H, 9.69; F, 5.89). The assignment of the 2α-fluoro configuration rests on the shift in the infrared and lack of shift in the ultraviolet of the carbonyl maximum[9] as well as on rotatory dispersion data.[10]

2α-Fluoro-17α-ethynyltestosterone (V) (m.p. 243–245°, $[\alpha]$D + 65°, λ_{max} 242 mμ, log ϵ 4.28, λ_{max}^{KBr} 3.00, 5.90 μ. Found for $C_{21}H_{27}FO_2$: C, 76.47; H, 8.28; F, 5.39) was prepared by condensing 17α-ethynyltestosterone with ethyl formate and treating the crude 2-hydroxymethylene compound as described above.

Since sodio malonic ester is difluorinated by perchloryl fluoride even in the absence of excess base[2] it appeared that 21,21-difluorination, leading to a hitherto unknown class of steroids, would be feasible. The sodio salt of 21-ethoxalyl-Δ^5-pregnen-3β-ol-20-one[11] in absolute ethanol or benzene and in the presence of excess sodium methoxide was treated with perchloryl fluoride and then methanolic potassium acetate yielding 21,21-difluoro-Δ^5-pregnen-3β-ol-20-one (m.p. 133–135°, $[\alpha]$D + 54°, λ_{max}^{KBr} 5.75 μ. Found for $C_{21}H_{30}F_2O_2$: C, 71.05; H, 8.88; F, 10.28). Oppenauer oxidation gave 21,21-difluoroprogesterone (VI) (m.p. 140–143°, $[\alpha]$D + 204°, λ_{max}^{EtOH} 241 mμ, log ϵ 4.22, λ_{max}^{KBr} 5.75, 6.00 μ. Found for $C_{21}H_{28}F_2O_2$: C, 72.54; H, 8.10; F, 10.14).

In preliminary seven day assays[12] in the castrate rat, I and II exhibited 20% and 50% of the androgenic potency of testosterone with myotrophic activity about 50% of the standard while compound III, orally administered in the same assay was 25% as androgenic as methyltestosterone. Both I and II were potent gonadotrophin inhibitors in a 10-day parabiotic rat assay.[12] VI was considerably less active than progesterone in the Clauberg assay[12] in sharp contrast to the activity of 21-monofluoroprogesterone.[13]

(1) Steroids CXXXI, J. Zderic and D. Chávez Limón, THIS JOURNAL, in press (1959).

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(3) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).

(4) H. Kissman, A. M. Small and M. J. Weiss, THIS JOURNAL, **81**, 1262 (1959).

(5) A number of the fluoro hormone analogs reported in this paper have been prepared by E. V. Jensen and co-workers through alternate routes. Their results are published simultaneously p. 5259.

(6) F. Weisenborn, D. Remy and T. L. Jacobs, THIS JOURNAL, **76**, 552 (1954).

(7) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *ibid.*, **81**, 427 (1959).

(8) Dr. E. V. Jensen kindly compared our product with samples prepared through the enamine and enol ether (see ref. 5) routes and found them to be identical.

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(11) H. Ruschig, *Ber.*, **88**, 878 (1955).

(12) Assays by The Endocrine Laboratories, Madison, Wisconsin.

(13) P. Tannhauser, R. J. Pratt and E. V. Jensen, THIS JOURNAL, **78**, 2658 (1956).

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ISOTOPE SEPARATION BY ION EXCHANGE

Sir:

The sign, magnitude and trend of the separation factors observed by Lee and Begun[1] provide another example of the close analogy between ion exchange resins and concentrated aqueous solution, because the observed values are very nearly those which would be expected from an equilibrium between a dilute aqueous solution and a concentrated aqueous solution of a molality corresponding to that of the exchangers concerned.

For two aqueous solutions, *e.g.*, of LiCl, the separation factor $k = 1 + \epsilon$ is given by the ratio of

(1) D. A. Lee and G. M. Begun, THIS JOURNAL, **81**, 2332 (1959).