of the intermediates abroad has created difficulties in applying the reaction.[3] We have established the applicability of numerous other systems, and are led to publish these in the hope that they may provide a wider selection of reagents and solvents.

Lithium borohydride is readily soluble in both ethyl ether and tetrahydrofuran. Olefin and lithium borohydride in either solvent may be treated with (1) hydrogen chloride, (2) boron trifluoride or trichloride etherates, or (3) aluminum chloride to achieve hydroboration.

A solution of 18.8 g. (200 mmoles) of norbornene and 1.98 g. (90 mmoles) of lithium borohydride in 100 ml. ether at 0° was treated over a period of 1 hour with 17 g. (0.120 mole) of boron trifluoride etherate. After a second hour at 0°, water was added to destroy residual hydride, alkali added, and the product carefully oxidized with 21 ml. of 30% hydrogen peroxide. There was obtained 15.9 g. of norborneol, m.p. 123–124°, 70% yield.

Sodium borohydride is essentially insoluble in ethyl ether or tetrahydrofuran. However, treatment of a suspension of sodium borohydride in tetrahydrofuran with hydrogen chloride results in the formation of a solution of diborane in the solvent. Addition of the olefin to this solution results in ready hydroboration.

To a well-stirred suspension of 3.0 g. (80 mmoles) of sodium borohydride and 100 ml. tetrahydrofuran at 0° was added over a period of 2 hours 45 ml. of 1.5 *M* hydrogen chloride (67 mmoles) in tetrahydrofuran. To the resulting solution of diborane was added 22.4 g. (200 mmoles) of 1-octene. The product was oxidized and isolated as usual: 21 g. of 1-octanol, 80%, b.p. 98–100° at 23 mm., $n^{20}D$ 1.4295.

In diglyme solution, sodium borohydride and an olefin may be treated with hydrogen chloride, benzyl chloride, boron halide,[1] or aluminum chloride[1] to achieve hydroboration. In this solvent, sodium hydride and boron trifluoride etherate can also be utilized.[4]

Potassium borohydride is insoluble in these solvents. However, in two hours at room temperature an equimolar stirred suspension of potassium borohydride and lithium chloride in tetrahydrofuran undergoes metathesis to form a solution of lithium borohydride[5] (80% yield). The solution may be utilized as described above.

Finally, lithium aluminum hydride can be utilized in ethyl ether with boron trifluoride etherate[3] or with boron trichloride etherate.[6] Alternatively, it is possible to utilize an equimolar mixture of borate ester and aluminum chloride as a substitute for boron trichloride.

To a solution of 100 mmoles of 1-octene, 30 mmoles of lithium aluminum hydride and 40 mmoles of methyl borate in 50 ml. of ether at 0° was added a solution of 40 mmoles of aluminum chloride in 30 ml. of ether. After 1 hour, Vapor Phase Chromatography examination showed 90% conversion of olefin to organoborane.

Amine-boranes also can serve as hydride in the presence of Lewis acids, but the procedures are less convenient than those already described.

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(3) Dr. Franz Sondheimer of the Weizmann Institute of Science, Rehovoth, Israel has communicated that he has utilized the action of boron trifluoride on a mixture of olefin and lithium aluminum hydride to overcome this difficulty. This useful modification of the hydroboration reaction by Dr. Sondheimer and his co-workers will be published shortly.

(4) Unpublished research of Dr. B. C. Subba Rao.

(5) R. Paul and N. Joseph, *Bull. soc. chim.*, 550 (1952).

(6) A. E. Finholt, A. C. Bond, Jr., and H. I. Schlesinger, THIS JOURNAL, **69**, 1199 (1947).

STEROIDS. CXXIX.[1] A NEW GENERAL ROUTE TO FLUORINATED STEROIDS

Sir:

A recent publication[2] describing the conversion of a $\Delta^{9(11)}$-steroid into its 9α-bromo-11β-fluoro analog by the use of N-bromoacetamide and anhydrous hydrogen fluoride prompts us to record the synthesis of a number of mono fluoro-bromo steroids by the addition of Br-F to a *wide variety of unsaturated steroids*. The method involves addition of 1.1 molar equivalents of N-bromoacetamide to a solution of the steroid in methylene dichloride–tetrahydrofuran containing a large excess of anhydrous hydrogen fluoride (25–100 mols) at −80°. After 1 hour at −80° the reaction mixtures were kept at 0° for 2 to 16 hours. This novel fluorination procedure represents by far the best route to the biologically important 6α-fluoro steroid hormones.[3] Δ^5-Pregnene-3β,17α-diol-20-one 17-acetate (I) afforded 5α-bromo-6β-fluoropregnane-3β,17α-diol-20-one 17-acetate (II)[4] m.p. 290–292° (all mps. uncorr.), $[\alpha]_D$ +5° (all rotns. in $CHCl_3$). Oxidation of II in acetone solution with 8*N* chromic acid in aqueous sulfuric acid gave the corresponding C-3-ketone (III)[4] m.p. 171–173°, $[\alpha]_D$ +17°, converted into 6β-fluoro-17α-acetoxyprogesterone (IV)[4] m.p. 207–208°, $[\alpha]_D$ −18° λ_{max}^{EtOH} 232–234 mμ ε 13,000, by sodium acetate in methanol. Either III or IV with hydrogen chloride in acetic acid[3a,b] gave 6α-fluoro-17α-acetoxyprogesterone (V).[1,3b,c] Similarly Δ^5-pregnene-3β-ol-20-one and Δ^5-pregnene-3β,17α,21-triol-20-one 17,21-diacetate gave the 6β- and thence the 6α-fluoro analogs of progesterone[3a,c] and compound "S" diacetate.[5] Previous approaches[1,3,5] to 6α-fluoro-Δ^4-3-ketones have always been *via* 5α,6α-epoxides obtained by peracid treatment. Such an approach is often precluded with poly-unsaturated steroids; thus, $\Delta^{5,9(11)16}$-pregnatriene-3β-ol 20-one[6] led to a complex mixture from which the 5α,6α-monoepoxide could be isolated only in poor yield. *A much higher degree of selectivity* was obtained

(1) Part CXXVIII, A. Bowers, L. C. Ibáñez and H. J. Ringold, THIS JOURNAL, in press.

(2) C. H. Robinson, L. Finckenor, E. P. Oliveto and D. Gould, *ibid.*, **81**, 2191 (1959).

(3) (a) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958); (b) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 4423 (1958); (c) J. A. Hogg, *et al.*, *Chemistry and Industry*, 1002 (1958); (d) A. Bowers, E. Denot, M. B. Sánchez and H. J. Ringold, *Tetrahedron*, in press.

(4) All new compounds gave satisfactory results upon elemental analysis.

(5) A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron*, in press.

(6) A. Bowers, M. B. Sánchez, E. Denot, F. Neumann and C. Djerassi, manuscript in preparation.

with the Br–F reaction as was shown when 16α,17α-oxido-$\Delta^{5,9(11)}$-pregnadiene-3β-ol-20-one[7] afforded 5α - bromo - 6β - fluoro - 16α,17α - oxido - $\Delta^{9(11)}$ - pregnene - 3β - ol - 20 - one (VI),[4] m.p. 195–197° $[\alpha]_D$ +13° and thence 6β-fluoro-16α,17α - oxido - $\Delta^{4,9(11)}$ - pregnadiene - 3,20 - dione (VII)[4] m.p. 195–197° $[\alpha]_D$ +54°, λ_{max}^{EtOH} 232 mμ ε 11,200. The transformation of VII into 6α,9α-difluoro-16α-hydrocortisone[5] (and its Δ^1-analog) will be described in a detailed paper.

Similarly addition of Br–F to $\Delta^{4,6}$-pregnadiene-17α,21-diol-3,20-dione diacetate (VIII) (m.p. 210–212°, $[\alpha]_D$ +20°, λ_{max}^{EtOH} 284 mμ ε 27,500) afforded 6β - fluoro - 7α - bromo - Δ^4 - pregnene - 17α,21 - diol-3,20 dione diacetate (IX),[4] m.p. 120–122°, $[\alpha]_D$ +7°, λ_{max}^{EtOH} 234–236 mμ, ε 10,500; Δ^{16}-allopregnene-3β-ol-11,20-dione acetate (X) gave a 16,17-bromo-fluoro compound probably 16β-fluoro-17α - bromoallopregnane - 3β - ol - 11,20 - dione acetate (XI),[4] m.p. 209–211° $[\alpha]_D$ −4°. Chromous chloride treatment of XI gave X; $\Delta^{4,9(11)}$-pregnadiene - 17α,21 - diol - 3,20 - dione 21-acetate (XII) gave 9α-bromo-11β-fluoro-Δ^4-pregnene - 17α,21 - diol - 3,20 - dione 21 - acetate (XIII),[4] m.p. 210–212° +139°, λ_{max}^{EtOH} 241 mμ ε 15,500, (A., 0.3).[9,10] Chromous chloride treatment of XIII gave XII.

(7) A. Bowers, L. C. Ibáñez, H. J. Ringold and C. Djerassi, forthcoming publication.

(8) J. S. Mills, A. Bowers, C. Casas Campillo, C. Djerassi and H. J. Ringold, THIS JOURNAL, **81**, 1264 (1959).

(9) A = Anti-inflammatory assays by cotton pellet, subcutaneous route, hydrocortisone = 1. Assays by Endocrine Laboratories, Madison, Wisconsin.

(10) As part of our structure-activity studies 9α,11β-dichloro Compound "S" 21-acetate, m.p. 236–238°, $[\alpha]_D$ +192° λ_{max}^{EtOH} 240 mμ, ε 16,050 (a compound reported by S. K. Figdor, Abstracts, p. 66-P, Amer. Chem. Soc. Meeting, Chicago, Ill., Sept., 1958) and the corresponding Δ^1 analog[2], m.p. 244–247°, $[\alpha]_D$ +170°, λ_{max}^{EtOH} 238 mμ, ε 14,500, were prepared. In contrast to the findings of the Schering workers[2] and in agreement with Figdor's report we found only low-anti-inflammatory activity[9] for these compounds; *i.e.*, 0.5A.[9] for the $\Delta^{1,4}$-9α-11β-dichloro compound whereas ref. 2 reports 8.5 × prednisolone.

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A CONVENIENT NON-CATALYTIC CONVERSION OF OLEFINIC DERIVATIVES INTO SATURATED COMPOUNDS THROUGH HYDROBORATION AND PROTONOLYSIS

Sir:

The ready conversion of unsaturated derivatives into organoboranes through the hydroboration reaction[1] makes these compounds available as intermediates for organic synthesis.

Although the organoboranes are relatively stable to hydrolysis by water, they are susceptible to attack by acetic acid,[2] $(C_2H_5)_3B + CH_3CO_2H \rightarrow (C_2H_5)_2BOCOCH_3 + C_2H_6$. A detailed study of the action of carboxylic acids on organoboranes has revealed that two of the three groups can be removed by excess acid at room temperature, and all three groups can generally be removed by refluxing the organoborane in diglyme solution with a slight excess of propionic acid for 2 to 3 hours.

Consequently, hydroboration of olefins in diglyme, and then refluxing with propionic acid, offers a convenient non-catalytic procedure for the hydrogenation of double-bonds.

$$3RCH{=}CH_2 \xrightarrow{NaBH_4,\ BF_3} (RCH_2CH_2)_3B \xrightarrow{C_2H_5CO_2H} 3RCH_2CH_3$$

Use of the solvent triglyme, b.p. 216°, with caprylic acid, permits completion of the protonation stage in 0.5 to 1.0 hour.

Secondary alkyl groups appear to undergo protonolysis less readily than primary. Consequently, in hydrogenating internal olefins, it is preferable that the boron be transferred to the terminal position by heating under reflux[1] prior to addition of the acid.

Since olefins containing active sulfur, chlorine and nitrogen substituents readily undergo hydroboration,[1,3] this procedure opens up the possibility of hydrogenating olefinic derivatives containing such labile groups. To test this possibility we examined the reduction of allylmethylsulfide. In diglyme only two of the three groups were removed and the yield of isolated product was 47%; in triglyme all three groups are removed and the isolated yield was 72%. The results are summarized in Table I. We are continuing our exploration of the scope of the reaction.

TABLE I

CONVERSION OF OLEFINS INTO SATURATED DERIVATIVES

Olefin	Diglyme Yield, %	Procedure $n^{20}D$	Triglyme Yield, %	Procedure $n^{20}D$	Lit. $n^{20}D$ of product
1-Hexene	91	1.3747	90	1.3751	1.3748
1-Octene	95	1.3970	90	1.3976	1.3975
Cyclohexene	76	1.4266	84	1.4257	1.4262
2,4,4-Trimethyl-1-pentene	82	1.3910			1.3914
Styrene	88	1.4954	84	1.4950	1.4959
2-Hexene	85	1.3745			1.3748
2-Heptene			90	1.3888	1.3876
2,4,4-Trimethyl-2-pentene	77	1.3920	85	1.3918	1.3914
Allyl methyl sulfide	47	1.4432	72	1.4447	1.4444

Some typical procedures are given: To a stirred solution of 200 mmoles of 1-hexene and 55 mmoles of sodium borohydride in 55 ml. of diglyme under nitrogen was added 75 mmoles of boron trifluoride etherate in 25 ml. of diglyme over a period of 1.5 hours. To the reaction mixture was added 300 mmoles of propionic acid and the reaction mixture was brought up to the boiling point and maintained there over a period of two hours as ethyl ether and the product distilled. The product was washed with bicarbonate solution, water, dried and distilled through a Todd micro column. There was obtained 15.6 g. of *n*-hexane, b.p. 68–69° at 738 mm., 91% yield.

(1) H. C. Brown and B. C. Subba Rao, THIS JOURNAL, **78**, 5694 (1956); *J. Org. Chem.*, **22**, 1136 (1957).

(2) H. Meerwein, G. Hinz, H. Majert and H. Sönke, *J. prakt. Chem.*, **147**, 251 (1936); J. Goubeau, R. Epple, D., D. Ulmschneider and H. Lehmann, *Angew. Chem.*, **67**, 710 (1955).

(3) M. F. Hawthorne and J. A. Dupont, THIS JOURNAL, **80**, 5830 (1958).