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°, $\lambda_{max}^{EtOH}$ 232 mμ ε 11,200. The transformation of VII into 6α,9α-difluoro-16α-hydrocortisone[5] (and its $\Delta^1$-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°, $\lambda_{max}^{EtOH}$ 284 mμ ε 27,500) afforded 6β - fluoro - 7α - bromo - $\Delta^4$ - pregnene - 17α,21 - diol-3,20 dione diacetate (IX),[4] m.p. 120–122°, $[\alpha]_D$ +7°, $\lambda_{max}^{EtOH}$ 234–236 mμ, ε 10,500; $\Delta^{16}$-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-$\Delta^4$-pregnene - 17α,21 - diol - 3,20 - dione 21 - acetate (XIII),[4] m.p. 210–212° +139°, $\lambda_{max}^{EtOH}$ 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° $\lambda_{max}^{EtOH}$ 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 $\Delta^1$ analog[8], m.p. 244–247°, $[\alpha]_D$ +170°, $\lambda_{max}^{EtOH}$ 238 mμ, ε 14,500, were prepared. In contrast to the findings of the Schering workers[8] 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 | Di-glyme Yield, % | Pro-cedure $n^{20}D$ | Tri-glyme Yield, % | Pro-cedure $n^{20}D$ | 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).

The hydroboration product from 2-hexene prepared as described above, was heated under reflux for three hours (isomerization procedure). The reaction mixture was then treated with 300 mmoles of propionic acid and handled as above. There was obtained 14.7 g. of *n*-hexane, 85% yield.

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## SOME NEW COMPOUNDS HAVING THE HEXAGONAL BARIUM TITANATE STRUCTURE

*Sir:*

The structure of hexagonal barium titanate was determined by Burbank and Evans[1] using a single crystal prepared by the method of Matthias.[2] The procedure, which involves heating the reactants in a platinum crucible, has been repeated in this laboratory to obtain the amber colored crystals. These crystals did not become colorless upon heating for several days in air at 1200°. It seemed likely that the presence of platinum was needed to stabilize this hexagonal structure, especially since the isotypic phase $Ba(Ti_{0.75}Pt_{0.25})O_3$ has been reported by Blattner.[3] The possibility that stabilization could be promoted by other foreign ions has been under investigation here for some time.

It has been found, using X-ray powder patterns as the criterion, that the hexagonal structure was adopted in presence of platinum, iridium, rhodium, ruthenium, cobalt, iron, manganese, chromium, vanadium and even trivalent titanium. The phases were prepared according to the formula $BaM_xTi_{1-x}O_{3-z}$. Mixtures of barium oxide, titanium dioxide, and the added metal oxide were ground together in an agate mortar and heated in air except those containing $Mn_2O_3$, $Cr_2O_3$ and $V_2O_3$. These mixtures were heated in evacuated sealed silica capsules. X-Ray powder diffraction photographs showed that the patterns of the phases given agreed closely with that of hexagonal barium titanate. Only a slight difference in spacing and intensities of reflections were observed.

| | | |
|---|---|---|
| $BaPt_{0.10}Ti_{0.90}O_{3-z}$ | $BaIr_{0.25}Ti_{0.75}O_{3-z}$ | $BaIr_{0.50}Ti_{0.50}O_{3-z}$ |
| $BaRh_{0.25}Ti_{0.75}O_{3-z}$ | $BaRu_{0.25}Ti_{0.75}O_{3-z}$ | $BaRu_{0.50}Ti_{0.50}O_{3-z}$ |
| $BaCo_{0.25}Ti_{0.75}O_{3-z}$ | $BaFe_{0.25}Ti_{0.75}O_{3-z}$ | $BaFe_{0.50}Ti_{0.50}O_{3-z}$ |
| $BaFe_{0.75}Ti_{0.25}O_{3-z}$ | $BaV_{0.50}Ti_{0.50}O_{3-z}$ | $BaV_{0.75}Ti_{0.25}O_{3-z}$ |
| $BaV_{0.80}Ti_{0.20}O_{3-z}$ | | |

Chemical analyses of these phases have not yet been made. The formulas are derived from starting compositions and from the absence of any evidence for heterogeneity obtained by X-ray and microscopic examination. When the proportion of foreign ion was smaller than the lowest figure shown in the formulas, the pattern of tetragonal barium titanate could be detected in the photographs. Iridium, ruthenium, iron and vanadium in proportions larger than the highest given in the formulas caused the introduction of extraneous lines in the X-ray diffraction photographs. The limiting compositions of the phases have not yet been determined. The data suggest, however, that these metal ions are incorporated in the lattice of the hexagonal barium titanate.

Magnetic susceptibility measurements have been made on the phases of $BaIr_{0.25}Ti_{0.75}O_{3-z}$, $BaCo_{0.25}Ti_{0.75}O_{3-z}$, and $BeFe_{0.25}Ti_{0.75}O_{3-z}$. While these measurements have been made only at one temperature, they appear to indicate one, two and four unpaired electrons per atom of iridium, cobalt and iron, respectively.

Work is now in progress to determine the permissible range of composition of the phases prepared.

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## ISOLATION OF ALDOSTERONE FROM INCUBATES OF ADRENALS OF THE AMERICAN BULLFROG AND STIMULATION OF ITS PRODUCTION BY MAMMALIAN ADRENOCORTICOTROPIN[1,2]

*Sir:*

We wish to report that aldosterone was the most abundant steroid found in incubates of adrenals from the American bullfrog, *Rana catesbeiana*, under the stimulation of bovine adrenocorticotropin. Corticosterone was the second major steroid found in the incubates, with the ratio of aldosterone to corticosterone, 3.6 to 1. No cortisol could be detected, although previous studies have disclosed only cortisol and corticosterone as the major steroids secreted by the adrenals of both mammals[3] and cold-blooded animals.[4,5] The salt metabolism of the frog has been shown to be under the regulation of both the adrenals and the anterior pituitary,[6] and it is possible that aldosterone may be the adrenal hormone responsible for this regulation.

Adrenal tissue (1218 mg. fresh weight) excised from 37 female bullfrogs (total body weight 13.13 kg.) just prior to their breeding season were cut up into small pieces in isotonic Krebs–Ringer bicarbonate solution containing glucose (200 mg. per 100 cc.). which has been flushed with mixture of 5% $CO_2$–95% $O_2$ (final *p*H, 7.4). After incubation for 30 minutes at 25–26° the medium was discarded and incubation was continued for 2 hours with a new volume of medium containing bovine adrenocorticotropin[7] (1.09 I.U. per 100 mg. of tissue). This medium then was extracted with dichloromethane and ethyl acetate. The extract was fractionated by partitioning between ethyl

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(3) H. Blattner, H. Gränicher, W. Kanzig and W. Merz, *Helv. Phys. Acta*, **21**, 341 (1948).

(1) Paper XVIII of the adrenocorticotropin (ACTH) series; for Paper XVII, see C. H. Li, *Bull. Soc. Chim. Biol.*, **40**, 1757 (1958).
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