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

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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]

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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

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

activity coefficients

$$\frac{\bar{\bar{m}}_6}{\bar{\bar{m}}_7} \times \frac{m_7}{m_6} = 1 + \epsilon = \left(\frac{\bar{\gamma}_7}{\bar{\gamma}_6} \times \frac{\gamma_6}{\gamma_7}\right) \qquad (1)$$

where the bar marks the stronger solution. Equation 1 takes account of the fact that the solutions are mixtures of two electrolytes, utilizing Brφnsted's rule. The ratio of the activity coefficients in the dilute solution equals about unity. Hence

$$\ln (1 + \epsilon) \simeq \epsilon \simeq (\ln \bar{\gamma}_7 - \ln \bar{\gamma}_6) \qquad (2)$$

Glueckauf[2] has shown that the hydration parameters which largely determine the trends of the activity coefficients are a function of the Pauling radius of the cation. Equally—without making use of the hydration concept—the activity coefficients of the aqueous solutions of alkali salts of the same halogen can be directly expressed as functions of the Pauling radii (r, in ångström). The activity coefficients of all alkali chlorides at 25° for $m > 1$ are adequately expressed by the equation[3]

$$\ln \gamma = 0.60\sqrt[3]{\bar{m}} + km \qquad (3)$$

where

$$k = 0.270\,((1/r) - 0.38) \qquad (4)$$

The differences of the Pauling radii for Li^6 and Li^7 are known from Thewlis' measurement[4] of the lattice constants of Li^6F and Li^7F. These data give

$$(r)_{Li^6} - (r)_{Li^7} = 0.0004 \pm 0.00007 \text{ ångström} \qquad (5)$$

From equations 2, 3, 4, 5 follows

$$\epsilon = \left(\frac{\partial \ln \gamma}{\partial r}\right)_m \times \Delta r = \frac{0.270\,\bar{m}}{(r_{Li})^2} \times (r_6 - r_7) = 3 \times 10^{-4}\bar{m} \qquad (6)$$

where $r_{Li} = 0.60$ Å.

TABLE I

% DVB	Approx. exchanger molality ($\bar{m}$)	10^3 ϵ observed (ref. 1)	10^3 ϵ calculated for LiCl solutions ($\bar{m}$) from eqn. 6
4	3	1.0	0.9
8	5.5	1.6	1.7
12	7.5	2.7	2.3
16	9	3.7	2.7
24	12.5	3.8	3.8

Table I shows the agreement between the separation factors ϵ observed,[1] when the isotopes were separated on various exchanger types of different crosslinking (divinyl benzene content) by elution with dilute hydrochloric acid solution, and those calculated for the equilibria between a dilute and a concentrated lithium chloride solution of the same molal concentration as the exchanger.

Equation 6 can be used also for the reverse process of calculating the differences in ionic radius from observed isotopic separation factors, *e.g.*, for the case of the isotopes Na^{22} and Na^{24}.[5] On Dowex 50 ($\bar{m} \sim 6$) this gave $\epsilon = 1.4 \times 10^{-4}$ at 25°. Hence from eq. 6

$$r_{22} - r_{24} = \frac{\epsilon (r_{Na})^2}{0.270\bar{m}} = \frac{1.4 \times 10^{-4} \times 0.95^2}{0.27 \times 6} \simeq 8 \times 10^{-5} \text{ ångström}$$

The radii of two adjoining Na-isotopes would thus differ by only a tenth of the difference between the Li-isotopes, this being the square of the inverse ratio of the masses. If this principle applies generally, the outlook for enriching isotopes of higher mass by pure ion exchange is very dim indeed. One would expect for the exchange on Dowex 50

$$K^{39}\text{–}K^{41} \quad \Delta r = 2 \times 10^{-5}\text{Å. and } \epsilon = 1.8 \times 10^{-5}$$

and for

$$Rb^{85}\text{–}Rb^{87} \quad \Delta r = 5 \times 10^{-6}\text{Å. and } \epsilon = 3.5 \times 10^{-6}$$

ATOMIC ENERGY RESEARCH ESTABLISHMENT
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π-CYCLOPENTADIENYL-π-CYCLOHEPTATRIENYL VANADIUM

Sir:

The chemical literature contains several examples of the preparation of cyclopentadienyl-metal carbonyl compounds by heating together a metal carbonyl and cyclopentadiene or dicyclopentadiene.[1] However, when molybdenum hexacarbonyl or iron pentacarbonyl is heated with cycloheptatriene, there is no loss of hydrogen to form tropylium compounds. Instead the complexes $C_7H_8Mo(CO)_3$[2] and $C_7H_8Fe(CO)_2$[3] are produced. The only tropylium sandwich compound so far reported is the ionic compound $[C_7H_7Mo(CO)_3]BF_4$, prepared by a different method.[4]

Using a different approach to tropylium-sandwich chemistry, the reaction between cyclopentadienyl vanadium tetracarbonyl[5] and cycloheptatriene was investigated. A mixture of $C_5H_5V(CO)_4$ (0.01 mole) and 30 ml. of commercial cycloheptatriene was refluxed under nitrogen at 120° for 9 hours. After removal of excess cycloheptatriene a black residue remained. Sublimation at 80° yielded oily material which was discarded. Further sublimation at 100° afforded 0.82 g. (yield 40%) of purple crystals, $C_5H_5VC_7H_7$, sparingly soluble in organic solvents to give purple solutions which in air begin to deposit a brown precipitate after a few minutes.

Anal. Calcd. for $C_{12}H_{12}V$: C, 69.6; H, 5.8; V, 24.6; mol. wt., 207. Found: C, 69.7, 69.8; H, 5.8, 5.8; V, 24.6; mol. wt., 229 (cryoscopic in benzene).

The analytical results are in less accord with a composition $C_5H_5VC_7H_8$ (C, 69.2; H, 6.25) than for $C_5H_5VC_7H_7$. However, a clearer demonstration of the nature of the new vanadium compound is provided by its magnetic properties. It is paramagnetic with $\lambda_{mole}^{298°} = 1055 \times 10^{-6}$ cm.^{3}-mole^{-1}, corresponding to 1.69 B.M., which is equivalent to one unpaired electron. This confirms the composition as $C_5H_5VC_7H_7$ rather than

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(1) For a recent review of compounds wherein an aromatic ring system and carbon monoxide groups are simultaneously bonded to metal atoms, see E. O. Fischer and H. P. Fritz, "Advances in Inorganic and Radiochemistry" (Eds. H. J. Emeléus and A. G. Sharpe) **1**, 55 (1959), Academic Press, Inc., New York, N. Y.

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