TABLE I

PRODUCTS OF REACTION OF ALLYLIC ALCOHOLS WITH THIONYL CHLORIDE

| Alcohol | Reaction conditions | Product composition |
|---|---|---|
| $CH_3CHClCH{=}CH_2$ | $SOCl_2$, no solvent | 33% $CH_3CHClCH{=}CH_2$<br>67% $CH_3CH{=}CHCH_2Cl$ |
| $CH_3CH{=}CHCH_2OH$ | $SOCl_2$, no solvent | 71% $CH_3CHClCH{=}CH_2$<br>29% $CH_3CH{=}CCHCH_2Cl$ |
| $CH_3CH{=}CHCH_2OH$ | $SOCl_2$ in $Et_2O$ | 99% $CH_3CHClCH{=}CH_2$ |
| $CH_3CHOHCH{=}CH_2$ | $SOCl_2$ in $Et_2O$ | 100% $CH_3CH{=}CHCH_2Cl$ |
| (−)trans-<br>$CH_3CH{=}CHCHOHCH_3$ | $SOCl_2$ in $Et_2O$ | 100% (−) *trans*-<br>$CH_3CH{=}CHCHClCH_3$ |
| $C_6H_5CH{=}CHCH_2OH$ | 0.1 *M* ROH + 0.1 *M* $SOCl_2$ in $Et_2O$ | 100% $C_6H_5CHClCH{=}CH_2$ |
| $C_6H_5CH{=}CHCH_2OH$ | 1 *M* ROH + 1 *M* $SOCl_2$ in $Et_2O$ | 60% $C_6H_5CHClCH{=}CH_2$<br>40% $C_6H_5CH{=}CHCH_2Cl$ |

show $\alpha$-phenylallyl chloride is the product. This thermodynamically less stable secondary chloride is rearranged only very slowly in the reaction solution.

Our present evidence is still insufficient to decide whether the SNi′ mechanism[2] involves a one-stage concerted process or ionization to an intimate, rigidly oriented carbonium chlorosulfinate ion pair,[5] followed by internal return[6] of the chloride component of the chlorosulfinate anion to give rearranged chloride. It is very clear that the SNi′ mechanisms does not involve a carbonium chloride ion pair of the type employed by Cram[7] in his preferred mechanism for the action of thionyl chloride on the 3-phenyl-2-butanols. A carbonium chloride ion pair in the $\alpha,\gamma$-dimethylallyl system would lead to a *trans*-chloride which is 100% racemic instead of the inverted chloride actually observed. Further, a carbonium chloride ion pair would not lead to the specific structural results obtained with the butenols and cinnamyl alcohol.

The dominant role of the SNi′ reaction is sometimes difficult to preserve. In the case of cinnamyl alcohol, even the use of 1 *M* concentrations of reactants changes the polarity of the medium and results in the product ion of a mixture of 60% cinnamyl chloride and 40% $\alpha$-phenylallyl chloride from the reaction itself since $\alpha$-phenylallyl chloride is stable under the conditions used.

(5) E. Kosower, Ph.D. Thesis, U.C.L.A., 1952, page 97.

(6) W. G. Young, S. Winstein and H. L. Goering, THIS JOURNAL, **73**, 1958 (1951).

(7) D. J. Cram, *ibid.*, **75**, 332 (1953).

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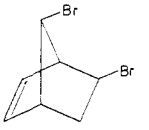
RECEIVED APRIL 28, 1955

## 7-NORBORNENYL AND 7-NORBORNYL CATIONS

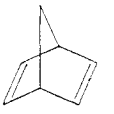
*Sir:*

We wish to record the synthesis of *anti*-7-norbornenol (I) and 7-*nor*borneol (II), and *a ratio of 10*[11] *in the solvolytic reactivities of the corresponding toluenesulfonates.*

*anti*-7-Norbornenol, m.p. 117–118°, was obtained: (i) as its acetate by reaction of ethylene with acetoxycyclopentadiene,[1] generated *in situ* from acetoxydicyclopentadiene, at 190°, and (ii) by selective hydrolysis of the unsaturated dibromide (III), one of the products of addition of bromine to bicycloheptadiene (IV), followed by zinc debromination of the resulting bromohydrin.



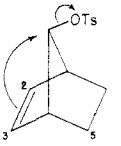

III



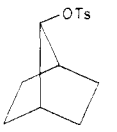
IV

7-Norborneol, m.p. 150–151°, was obtained by catalytic hydrogenation of *anti*-7-norbornenol (I).

The first order rate constants ($k_1$) for acetolysis of the corresponding *p*-toluenesulfonates in acetic acid (0.1 *M* in potassium acetate, containing 1% $Ac_2O$), and other pertinent data, are




V




VI

| | | |
|---|---|---|
| m.p. 60.5–61.0° | | m.p. 54.7–55.7° |
| | $k_1(205°)$ | $8.40 \times 10^{-5}$ sec.$^{-1}$ |
| 23.3 ± 0.3 kcal./mole | $\Delta H^{\ddagger}$ | 35.7 ± 0.6 kcal./mole |
| 5.7 ± 2.0 e.u. | $\Delta S^{\ddagger}$ | −3.5 ± 1.7 e.u. |
| $9.04 \times 10^{-4}$ sec.$^{-1}$ | $k_1(25°)$ | $6.36 \times 10^{-10}$ sec.$^{-1}$ |

The striking situation brought to light by the new measurements is emphasized by the following reactivities at 25°

| *p*-TOLUENESULFONATE | |
|---|---|
| *anti*-7-Norbornenyl | $10^4$ |
| *exo*-5-Norbornenyl[2] | $10^3$ |
| Cyclohexyl[2] | 1 |
| *endo*-5-Norbornenyl[2] | $10^{-1}$ |
| 7-Norbornyl[3] | $10^{-7}$ |

It is clear that the geometry of the norbornyl system is uniquely unfavorable for stabilization of a cationic center at C.7.

We attribute the high reactivity of the *anti*-7-norbornenyl derivatives to powerful anchimeric assistance to ionization at C.7, involving the 2,3 $\pi$-electron cloud (V, *arrow*). It will be noted that a homoallylic system[4] is present, which is geometrically unique in that a vacant orbital on C.7 can overlap the *p* orbital systems of the double bond

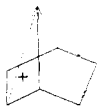
(1) Dissertations (Harvard): P. Wilder, Jr. (1950), R. E. Vanelli (1950), C. J. Norton (1955).

(2) S. Winstein, H. M. Walborsky and K. Schreiber, THIS JOURNAL, **72**, 5795 (1950); H. L. Schmid and K. Schreiber, unpublished work.

(3) Qualitative mention of low reactivity for 7-norbornyl chloride and *syn*-7-norbornenyl chloride has been made by J. D. Roberts, F. O. Johnson and R. A. Carbon, *ibid.*, **76**, 5695 (1954).

(4) M. Simonetta and S. Winstein, *ibid.*, **76**, 18 (1954).

symmetrically. The 7-norbornenyl cation may be represented by (VI). It reacts with solvent



VI

stereospecifically; complete retention of configuration was observed in the hydrolysis of the dibromide (III) to the alcohol, and in the acetolysis of 7-norbornenyl toluenesulfonate (V).

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RECEIVED JULY 13, 1955

## MICROBIOLOGICAL TRANSFORMATION OF STEROIDS. I. $\Delta^{1,4}$-DIENE-3-KETOSTEROIDS

*Sir:*

It has become a problem of importance[1,2] to devise efficient techniques for the introduction of $\Delta^1$-unsaturation in cortisone (I)[3] and cortisol (II) since it has been shown that $\Delta^{1,4}$-pregnadiene-17$\alpha$,21-diol-3,11,20-trione (III) and $\Delta^{1,4}$-pregnadiene-11$\beta$,17$\alpha$,21-triol-3,20-dione (IV) are considerably more potent anti-inflammatory agents than the natural corticosteroids. We wish to report that I may be converted to III and II may be converted to IV by the action of *Corynebacterium simplex* (A.T.C.C. 6946). Either I or II, dissolved in methanol, was added to shake flasks containing a 24-hour culture of *C. simplex* in a nutrient medium of 0.1% Difco yeast extract buffered at *p*H 7. The mixture was shaken at 28° for 3–24 hours. Extraction of the resultant broth with chloroform, followed by evaporation to a residue and crystallization from acetone, afforded excellent yields of III or IV, respectively. Compounds III and IV, obtained in this way, were identical in every respect with samples prepared by purely chemical means.[4] By similar microbiological procedures we have also prepared $\Delta^{1,4}$-pregnadiene-17$\alpha$,21-diol-3,20-dione (V) [m.p. 246–249° dec., $[\alpha]^{25}D$ + 76° ($CHCl_3$), $\lambda_{max}^{methanol}$ 244 m$\mu$ ($\epsilon$ = 15,900), $\lambda_{max}^{Nujol}$ 3.05 $\mu$ (OH), 5.80 $\mu$ (20-carbonyl), 6.0, 6.16 and 6.22 $\mu$ ($\Delta^{1,4}$-diene-3-one),[5] found: C, 73.56; H, 8.40], $\Delta^{1,4}$-pregnadiene-11$\beta$,21-diol-3,20-dione (VI) [m.p. 227.5–230.5° dec., $[\alpha]^{25}D$ +173° (methanol), $\lambda_{max}^{methanol}$ 243 m$\mu$ ($\epsilon$ = 14,300), $\lambda_{max}^{Nujol}$ 2.88 and 2.97 $\mu$ (OH), 5.88 $\mu$ (20-carbonyl), 6.07, 6.20 and 6.25 $\mu$ ($\Delta^{1,4}$-diene-3-one), found: C, 73.49; H, 8.12], $\Delta^{1,4}$-pregnadiene-21-ol-3,20-dione 21-acetate (VII)[6] (m.p. 202–204°, $[\alpha]^{25}D$ +143° (chloroform), +152° (ethanol) $\lambda_{max}^{methanol}$ 243 m$\mu$ ($\epsilon$ = 15,800, $\lambda_{max}^{Nujol}$ 2.93 $\mu$ (OH), 5.72 and 5.80 $\mu$ (20-carbonyl, 21-acetate interaction), 6.01, 6.16 and 6.23 $\mu$ ($\Delta^{1,4}$-diene-3-one) 8.06 $\mu$ (C-O-C of acetate), found: C, 74.46; H, 8.24], and 9$\alpha$-fluoro-$\Delta^{1,4}$-pregnadiene-11$\beta$,17$\alpha$,21-triol-3,20-dione (IX) [m.p. 265–269° dec., $[\alpha]^{25}D$ +111° (ethanol), $\lambda_{max}^{methanol}$ 239 m$\mu$ ($\epsilon$ = 14,800), found: C, 64.22; H, 7.51. Calcd. for $C_{21}H_{27}O_5F \cdot CH_4O$: C, 64.37; H, 7.61].

(1) J. J. Bunim, M. M. Pechet and A. J. Bollet, *J. Am. Med. Assoc.*, **157**, 311 (1955).

(2) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(3) E. Vischer, C. Meystre and A. Wettstein, *Helv. Chim. Acta*, **38**, 855 (1955), have reported the preparation of III and V by the action of *Fusarium solani* on cortisone and Reichstein's Compound S, respectively, and the preparation of VI and VII by the action of *Calonectria decora* on corticosterone and desoxycorticosterone (followed by acetylation in the latter case).

(4) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, THIS JOURNAL, in press.

(5) J. Fried, R. W. Thoma and A. Klingsberg, *ibid.*, **75**, 5764 (1953).

In addition to the recently noted, enhanced glucocorticoid activity of the 21-acetate of IX[7] we wish to report that IX and its 21-acetate possess intense mineralocorticoid action,[8] of the order of the parent fluorinated steroid, 9$\alpha$-fluoro-4-pregnene-11$\beta$,17$\alpha$,21-triol-3,20-dione.[9]

In subsequent reports we will describe in greater detail the chemistry and microbiology of these and related transformations, and the biochemical studies of the previously undescribed $\Delta^1$-unsaturated derivatives of the known natural and synthetic steroid hormones.

(6) *Cf.* R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini, *ibid.*, **77**, 661 (1955).

(7) R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *ibid.*, **77**, 3166 (1955).

(8) M. R. Cook, Jr., and F. Elmadjian, *J. Am. Pharm. Assoc.*, Sci. Ed.; XLII, **329** (1953).

(9) J. Fried and E. F. Sabo, THIS JOURNAL, **76**, 1455 (1954).

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RECEIVED JULY 14, 1955

## ISOLATION FROM URINE AND SYNTHESIS OF TETRAHYDROCORTISONE GLUCURONOSIDE

*Sir:*

It is generally agreed that 3$\alpha$,17$\alpha$,21-trihydroxypregnane-11,20-dione (tetrahydrocortisone) is the most abundant adrenocortical steroid metabolite excreted by man, and that it is present in urine largely as a glucuronoside. Because of the general interest in this conjugate and the recent evidence that its synthesis can be accomplished *in vitro*[1] we wish to report its recovery from urine in a relatively pure state and the synthesis and characterization of its tetraacetyl methyl ester.

Eight 250-mg. doses of free tetrahydrocortisone in aqueous alcohol were given orally to a man at half hourly intervals. The urine which was collected during this period and the twelve-hour interval that followed was acidified and extracted with butanol. The butanol extract was washed with water, neutralized with aqueous sodium carbonate and concentrated *in vacuo*. The crude product which separated weighed 2.92 g. and contained 1.45 g. of the desired sodium glucuronosidate as determined by analysis based on the method of Porter and Silber.[2] Four hundred milligrams of

(1) K. J. Isselbacher and J. Axelrod, THIS JOURNAL, **77**, 1070 (1955).

(2) C. C. Porter and R. H. Silber, *J. Biol. Chem.*, **185**, 201 (1950).