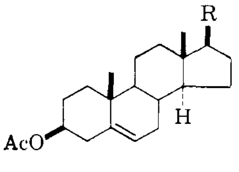
A CONVENIENT SYNTHESIS OF 19-NORSTEROIDS

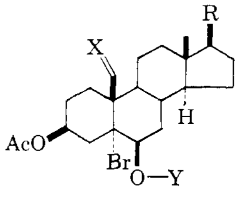
Sir:

The medical importance of 19-norsteroids is well known.[1] We wish to report a general conversion of readily available 3β-acetoxy-$\Delta^{5,6}$-steroids of the type (I) into the corresponding 19-nor compounds of the type (V) by the application of nitrite photolysis.[2]

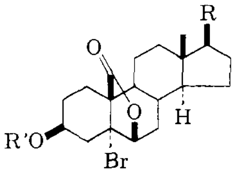
Treatment of (Ia, Ib and Ic) with hypobromous acid[3] gave the bromohydrins (IIa[3], Y = H, X = H_2), m.p. 172–174°; (IIb, Y = H, X = H_2) m.p. 171–172°, $[\alpha]^{26}\mathrm{D}$ +1.9° (all rotations in 1% $CHCl_3$ solutions); (IIc, Y = H, X = H_2), m.p. 171–174°, $[\alpha]^{25.5}$ +7°. These bromohydrins were nitrosated using nitrosyl chloride and pyridine. Photolysis of the resulting nitrites (IIa, IIb and IIc, Y = NO, X = H_2) in toluene at 0° with a 500-watt Hanovia lamp gave the nitroso dimers which were rearranged to the oximes (IIa, X = NOH, Y = H), m.p. 176–180°, $[\alpha]^{21}\mathrm{D}$ −35°; (IIb, X = NOH, Y = H) m.p. 178.5–180°, $[\alpha]^{26}\mathrm{D}$ −11°; and (IIc, X = NOH, Y = H) m.p. 173–178°, $[\alpha]^{26}\mathrm{D}$ −5.4°, respectively.

The 19-oximes with nitrous acid[2] gave the corresponding aldehydes (in hemiacetal form) which, without purification were oxidized with chromic acid in acetone to the lactones (IIIa, R′ = Ac), m.p. 170–172°, $[\alpha]^{22}\mathrm{D}$ −16.2°; (IIIb, R′ = Ac), m.p. 221–229°, $[\alpha]^{27}\mathrm{D}$ −13° and (IIIc, R′ = Ac) m.p. 153–157° and 161–164°, $[\alpha]^{22.5}\mathrm{D}$ +13°. The lactone (IIIb, R′ = Ac) with peracetic acid enlarged the ring D to furnish the D-homodilactone (VI, R′ = Ac) m.p. 268–272°, $[\alpha]^{25.5}\mathrm{D}$ −58.4°. The 3β-acetate in these lactones was removed with HCl in dioxane and water to yield the lactone alcohols (IIIa, R′ = H), m.p. 173.5–178.5°, $[\alpha]^{25.5}\mathrm{D}$ −17.9°; (IIIb, R′ = H), m.p. 221–232°, $[\alpha]^{25.5}\mathrm{D}$ +10°; (IIIc, R′ = H), m.p. 210–214°, $[\alpha]^{23}\mathrm{D}$ +18° and (VI, R′ = H), m.p. 244–247°, $[\alpha]^{26}\mathrm{D}$ −66.1°. Oxidation with chromic acid in acetone and treatment with hot pyridine or $HCl/CHCl_3$ yielded the conjugated ketones (IVa), m.p. 179–184°, $[\alpha]^{26}\mathrm{D}$ −102°, $\lambda_{\max}^{\mathrm{MeOH}}$ 238 mμ (ϵ = 12,500); (IVb) m.p. 291–293°, $[\alpha]^{23.5}\mathrm{D}$ −86°, $\lambda_{\max.}^{\mathrm{MeOH}}$ 235 mμ (ϵ = 12,000); (IVc) m.p. 236–239°, $[\alpha]^{23.5}\mathrm{D}$ −246°; $\lambda_{\max}^{\mathrm{MeOH}}$ 237 mμ (ϵ = 12,700); and (VII) m.p. 293.5–298.5°, $[\alpha]^{21.5}\mathrm{D}$ −191°, $\lambda_{\max}^{\mathrm{MeOH}}$ 233 mμ (ϵ = 16,200). The conjugated ketones (IVa, IVb, IVc, and VII) with zinc and acetic acid for fifteen minutes at reflux temperature, followed by mild acid treatment, gave 19-norcholestenone (Va) as a low-melting solid, $[\alpha]^{26}\mathrm{D}$ +44.2°, $\lambda_{\mathrm{mox}}^{\mathrm{MeOH}}$ 240 mμ (ϵ = 14,000); 19-norandrostendione (Vb), m.p. 164–169°, $[\alpha]^{27}\mathrm{D}$ +136°, $\lambda_{\max}^{\mathrm{MeOH}}$ 241 mμ (ϵ = 17,000); 19-norprogesterone (Vc), m.p. 143–146°, $[\alpha]^{25}\mathrm{D}$ +142°, $\lambda_{\max}^{\mathrm{MeOH}}$ 240 mμ (ϵ = 17,000) 19-nortestolactone (VIII), m.p. 195–199°, $[\alpha]^{26}\mathrm{D}$ −16.9°, $\lambda_{\max}^{\mathrm{MeOH}}$ 238 mμ (ϵ = 17,000). The constants for (Vb, Vc and VIII) are in good agreement with the literature.[4,5,6]

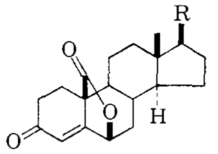




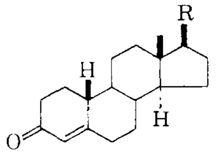
I, a, b, and c
II, a, b and c
a, R = cholesterol sidechain
b, R = 17-ketone
c, R = CH_3-CO



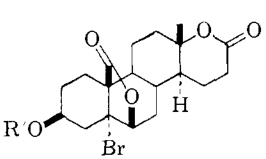
III, a, b and c



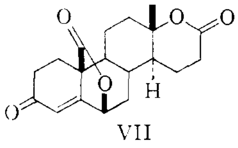
IV, a, b and c



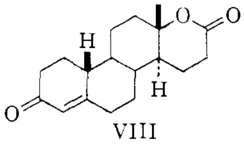
V, a, b and c



VI



VII



VIII

Acknowledgment.—We express our thanks to Dr. M. M. Pechet for his continued interest and encouragement and to Mrs. C. B. Pantuck, and the Misses A. Scott and L. T. Gendron for their able assistance throughout the course of this work. We thank Dr. L. E. Geller for preliminary experiments.

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(2) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *ibid.*, **83**, 4076 (1961).

(3) Y. Ueno, *J. Pharm. Soc. Japan*, **72**, 1622 (1952).

(4) H. Hagiwara, S. Noguchi and M. Nishikawa, *Chem. and Pharm. Bull. Japan*, **8**, 84 (1960).

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CONFIGURATIONAL STABILITY OF SULFONYL CARBANIONS GENERATED BY DECARBOXYLATION REACTION[1]

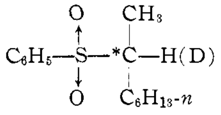
Sir:

Through a comparison of the rates of base-catalyzed racemization and isotopic exchange of I, it was concluded in a former study[2] that the sulfonyl carbanion was capable of maintaining configurational stability to a degree that varied widely with solvent. Thus $k_{\mathrm{exchange}}/k_{\mathrm{racemization}}$ ranged between 10 and about 2000. Another study revealed that sulfoxide and phosphine oxide groups in II and III

(1) This work was supported by a grant from the National Science Foundation.

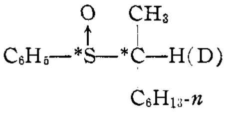
(2) D. J. Cram, D. A. Scott and W. D. Nielsen, *J. Am. Chem. Soc.*, **83**, 3696 (1961).

respectively did not impart any special stereochemical properties to their corresponding anions.[3] The current study was initiated to determine whether the configurational stability of the sulfonyl carbanion was independent of leaving group.



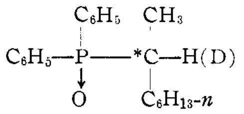
$$\mathrm{C_6H_5{-}\underset{\underset{O}{\downarrow}}{\overset{\overset{O}{\uparrow}}{S}}{-}{}^{*}\underset{\underset{C_6H_{13}\text{-}\mathit{n}}{|}}{\overset{\overset{CH_3}{|}}{C}}{-}H(D)}$$

I



$$\mathrm{C_6H_5{-}{}^{*}\overset{\overset{O}{\uparrow}}{S}{-}{}^{*}\underset{\underset{C_6H_{13}\text{-}\mathit{n}}{|}}{\overset{\overset{CH_3}{|}}{C}}{-}H(D)}$$

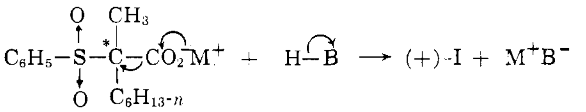
II



$$\mathrm{C_6H_5{-}\underset{\underset{O}{\downarrow}}{\overset{\overset{C_6H_5}{|}}{P}}{-\!\!-}{}^{*}\underset{\underset{C_6H_{13}\text{-}\mathit{n}}{|}}{\overset{\overset{CH_3}{|}}{C}}{-}H(D)}$$

III

Acid IV was prepared by successive alkylations of ethyl benzene-sulfonylacetate[4] with *n*-hexyl bromide followed by methyl iodide, and hydrolysis of the resulting ester.[5] This acid (m.p. 97–98°) was resolved through its quinine salt to maximum rotation, $[\alpha]^{29}_{546} + 15.6^\circ$ (*c* 8, CHCl$_3$). The optically active acid is an oil.



$$\mathrm{C_6H_5{-}\underset{\underset{O}{\downarrow}}{\overset{\overset{O}{\uparrow}}{S}}{-}\underset{\underset{C_6H_{13}\text{-}\mathit{n}}{|}}{\overset{\overset{CH_3}{|}}{{}^{*}C}}{-}CO_2^{-}M^{+} + H{-}B \longrightarrow (+)\text{-}I + M^{+}B^{-}}$$

(+)-IV

Decarboxylations of (+)-IV were performed at 90° in *tert*-butyl alcohol, methanol, ethylene glycol, water and dimethyl sulfoxide. The substrate concentrations were 0.20 *M* in all solvents except water, in which the concentration was 0.04 *M*. Enough dry potassium carbonate was added in all runs to give solutions 0.17 *M* in potassium ion, except in the case of water, in which the final solution was 0.034 *M*. In an additional run in dimethyl sulfoxide, tetramethylammonium hydroxide was substituted for the carbonate (concentrations were the same as when potassium carbonate was used). Product was isolated as described previously[2] in yields from 10–99%, depending on how long the reaction was allowed to go. Control experiments demonstrated the product ((+)-I)[2] to be optically stable under conditions of its formation and, further, that acid IV did not decarboxylate in the absence of base. In all runs, product of 97 ± 3% optical purity[2] was obtained, the smallest observed rotation being $[\alpha]^{26}_{546} + 0.65^\circ$ (*l* 1 dm., *c* 5, CHCl$_3$). The reaction occurred under all conditions with stereospecificities experimentally indistinguishable from one another and from 100%.[6] These results coupled with those obtained previously[2] leave little doubt that this reaction occurs with high retention, and that the sulfonyl carbanion possesses considerable configurational stability. In fact, in methanol and dimethyl sulfoxide as solvents, the decarboxylations occurred with greater stereospecificity than the isotope exchange reactions.[2]

The present results have a bearing on the unresolved problem of the type of hybridization at carbon in sulfonyl carbanions. In the exchange reaction,[2] the leaving group and attacking electrophile differed only isotopically. Thus the bond-making and breaking processes should involve essentially the same transition states. Application of the principle of microscopic reversibility indicates the two processes should be the exact reverse of one another, except for isotope effects. In the decarboxylation reaction, the two processes are quite different, and therefore the stereospecificity of the reaction in no way depends on a reversible process. If the carbanion is hybridized sp^2-p, and depends for its asymmetry on rotamer stability, the proton would have to attack on the same side of the flat carbanion from which the carbon dioxide molecule left. This adds one more condition to use of an sp^2-p-rotamer stability explanation[2] for the configurational stability of the sulfonyl anion.

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RECEIVED FEBRUARY 23, 1962

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[3] D. J. Cram, D. Partos, S. Pine and H. Jager, *J. Am. Chem. Soc.*, in press (1962).

[4] W. C. Ashley and R. L. Shriner, *ibid.*, **83**, 4410 (1932).

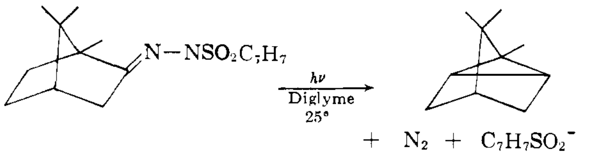
[5] All intermediates and the final compound gave carbon and hydrogen analyses that differed from theory by less than 0.30%.

[6] In an earlier study, J. E. Taylor and F. H. Verhoek [*ibid.*, **81**, 4537 (1959)] observed that the anion of optically active 2-methyl-2-benzenesulfonylbutyric acid decarboxylated at high temperatures to give optically active 2-butyl phenyl sulfone of undetermined optical purity.

PHOTOCHEMICAL TRANSFORMATIONS. XII. THE DECOMPOSITION OF SULFONYLHYDRAZONE SALTS[1,2]

Sir:

It has been established by Powell and Whiting[3] and Friedman and Schechter[4] that *p*-toluenesulfonylhydrazones of aliphatic aldehydes and ketones react at elevated temperatures (130–180°) with bases in aprotic solvents to give diazo compounds and in protic solvents to yield diazonium ions. The diazo and diazonium species formed at the high temperatures immediately decompose *via* carbenoid and cationoid routes, respectively. It has now been found that the potassium salt of a *p*-toluenesulfonylhydrazone upon irradiation with ultraviolet light at *room temperature* yields products similar to those in the thermal reaction.



At room temperature, a solution of camphor *p*-toluenesulfonylhydrazone (I) in 0.1 *N* methanolic potassium hydroxide is stable for many hours in the dark, but such a solution upon exposure to a quartz 500-watt Hanovia high pressure mercury lamp is transformed rapidly into a mixture of hydrocarbons and ethers. The composition of the hydrocarbon

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[1] For Paper XI, see W. G. Dauben and R. L. Cargill, *J. Org. Chem.*, in press.

[2] This work was supported, in part, by Grant No. A-709, U. S. Public Health Service.

[3] J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).

[4] L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959).