the same as those recently reported by Moodie, Connor, and Stewart.[1] The ions with all rings similarly deuterated gave the following results: 3,5-*d*, two peaks, intensity 1:2, low intensity at low field; 3,4,5-*d*, one peak with weak trace at low field; 2,4,6-*d*, with traces of undeuterated material, one intense peak, with one weak triplet at low fields, and a weak doublet at high fields very close to the intense peak. We have assigned the low field peaks, in agreement with the work of Moodie, Connor, and Stewart,[1] as belonging to the *para*-protons. The group at highest fields must be due to the *ortho*- protons, and the intermediate absorption, close to the *ortho*- peak, arises from *meta*-protons.

The identity of the three rings is established as follows: The 3,5-*d* spectrum may correspond either to two kinds of rings, with essentially no chemical shift within each kind, or to two kinds of positions, with all three rings equivalent. The single strong peak in the 3,4,5-*d* species shows that the *ortho*- positions of all three rings are equivalent, and so therefore must the other positions be also.

The apparent conflict between these results, which establish ring equivalence and those of Newman and Deno[2] which base nonequivalence on the ultraviolet spectrum, may be resolved by reinterpretation of the origin of the ultraviolet bands. Historically, the virtual identity of the spectra of triarylcarbonium ions with those of related fuchsones has been interpreted as evidence in support of quinoid structure in one (or more) rings. Reconsideration of the nature of the trityl cation chromophore suggests that it should be attributed instead *to the ion as a whole*. Its ground and first excited electronic energy levels, respectively, can be characterized as the totally symmetric (A) and doubly degenerate (E) combinations of one quinoid and two benzenoid structures. The A↔E transition is allowed and is probably the source of the intense color in triphenylcarbonium and other di- and triarylcarbonium ions as well.[3] With only one ring (phenylcarbonium), no such combinations can exist, so no low-frequency absorption takes place.

The shift of the aromatic protons relative to an external water peak is approximately −100 c.p.s., in agreement with Moodie *et al.* The chemical shifts, from audio modulation at 60 mc., give $\delta_{ortho\text{-}para}$ ~31 c.p.s. and $\delta_{meta\text{-}para}$ ~21 c.p.s. Tentative spin coupling values are $J_{ortho\text{-}meta}$ ~1.8 c.p.s. and $J_{meta\text{-}para}$ ~3.0 c.p.s. No *ortho-para* coupling was detected.

The results show that negative charge density is greatest on the *ortho*- positions, slightly less on the *meta*s, and considerably less still on the *para*-positions. This is in excellent agreement with the predictions of self-consistent molecular orbital theory, as carried out by Pople[4]; his calculations give the following charge densities: *ortho*-, 0.95; *meta*-, 0.94, and *para*-, 0.81.[5]

Acknowledgment. The authors would like to express their appreciation to Dr. E. D. Becker of the National Institutes of Health for taking the 60-mc. spectra.

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(1) R. B. Moodie, T. M. Connor, and Ross Stewart, *Canad. J. Chem.*, **37**, 1402 (1959).

(2) M. S. Newman and N. C. Deno, *J. Am. Chem. Soc.*, **73**, 3644 (1951).

(3) One of us (RSB) is indebted to Professor W. T. Simpson, The University of Washington, Seattle, for helpful and enlightening discussion of this problem.

(4) J. A. Pople, *J. Phys. Chem.*, **61**, 6 (1957).

(5) Note added in proof: At the suggestion of Professor Newman, we have examined the proton resonance spectrum of tri-*O*-tolyl carbonium ion at 40 mc., under the same conditions as triphenylcarbonium ion. Steric blocking by the methyl groups effectively prohibits coplanarity of the rings. The magnetic resonance spectrum shows a single sharp methyl peak, thus indicating that even in this extreme case the three rings are equivalent on a time scale of 0.1 sec., and suggests that the molecule is propeller-shaped [*cf.* N. C. Deno, P. T. Groves, and G. Saines, *J. Am. Chem. Soc.*, **81**, 5790 (1959)].

16,16-Dimethylprednisone Acetate

Sir:

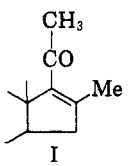
In view of the enhanced anti-inflammatory activity and elimination of sodium retention brought about by introduction of a 16α-methyl[1] or 16β-methyl[2] group into cortical steroids we undertook the synthesis of a suitable 16,16-dimethyl steroid. In the present communication we describe the preparation of 16,16-dimethylprednisone acetate (IV).

The conjugate addition of methylmagnesium iodide[3] to 3α-acetoxy-16-methyl-16-pregnene-11,-20-dione (I)[2a,b] in the presence of cuprous chloride

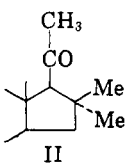
(1) (a) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958). (b) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958).

(2) (a) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958). (b) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4428 (1958). (c) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M Pechet, *J. Am. Chem. Soc.*, **80**, 6627 (1958).

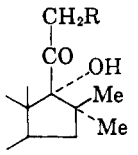
(3) M. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941); R. E. Marker and H. M. Crooks [*J. Am. Chem. Soc.*, **64**, 1280 (1942)] prepared 16α-alkylpregnan-20-ones by conjugate addition of Grignard reagents to 16-unsubstituted-16-pregnene-20-ones.



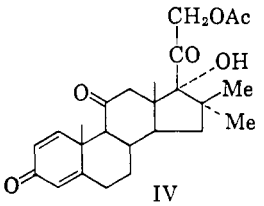
I



II



IIIa. R = H
IIIb. R = OAc



IV

followed by acetylation proceeded in part by 1:4 addition to give 3α-acetoxy-16,16-dimethylpregnane-11,20-dione (II) m.p. 212–217°; $[\alpha]_D^{Chf}$ +77°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.58; H, 9.51 Found: C, 74.80; H, 9.35. Introduction of the 17α-hydroxyl group was achieved by a modification[4] of the method of Hogg and Nathan[5] to give 3α,17α-dihydroxy-16,16-dimethylpregnane-11,20-dione (IIIa) m.p. 177–182°; λ_{max}^{Chf} 2.75, 2.92, 5.87 μ. *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.40; H, 9.57. Found: C, 73.29; H, 9.44. As a consequence of the high degree of steric hindrance in the vicinity of C-17 and C-20, IIIa was inordinately sensitive to base catalyzed D-homoannulation and conventional alkaline hydrolysis of the intermediate peracid product could not be employed. A new procedure, to be reported subsequently, involving the use of ethylenediamine was developed. Bromination of IIIa at C-21 followed by acetoxylation led to 21-acetoxy-16,16-dimethylpregnane-3α,17α-diol-11,20-dione (IIIb) m.p. 206–208°; λ_{max}^{Chf} 2.72, 2.9 (broad), 5.74, 5.76, 5.85, 8.1 μ.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.90; H, 8.53. Oxidation of IIIb at C-3 by sodium dichromate in aqueous acetic acid led to 21-acetoxy-16,16-dimethylpregnane-17α-ol-3,11,20-trione, m.p. 203–206°; $[\alpha]_D^{Chf}$ +114°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.59; H, 8.48. Dibromination of the 3,11,20-trione followed by dehydrobromination in dimethylformamide-dimethylaniline[6] led to 16,16-dimethylprednisone acetate (IV), m.p. 231–235°; $[\alpha]_D^{Chf}$ +210°; λ_{max}^{MeOH} 238 mμ (14,200); λ_{max}^{Chf} 2.85, 5.73, 5.76, 5.84, 6.00, 6.14, 6.19 sh., 8.06, 11.20 μ.

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.08; H, 7.53. Found: C, 70.02; H, 7.42.

In the rat systemic granuloma and mouse liver glycogen assays compound IV showed respectively no activity and *ca.* one-tenth the activity of hydrocortisone.[7]

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(4) Procedure of M. Sletzinger of these laboratories. We are grateful to Dr. Sletzinger for informing us of his procedure in advance of publication and for several helpful discussions.

(5) J. A. Hogg and A. H. Nathan, U. S Patents 2,740,782, 2,740,783 (1956).

(6) Procedure of J. Day, R. Erickson and R. Pettebone, U. S. Patent 2,873,284 (1959).

(7) We are grateful to Dr. R. H. Silber of the Merck Institute for therapeutic research for the biological assays.

Potential Anticancer Agents.[1] XXIX. Inversion of a Ring Carbon of a Glycoside

Sir:

The low reactivity of secondary sugar sulfonates toward S_N2 displacement by nucleophiles has placed a severe restriction on an otherwise potentially useful reaction for the synthesis of rare sugars. Few nucleophiles are powerful enough to effect this displacement unaided by a neighboring group. Thus, sodium iodide generally fails to react with "isolated" secondary tosylates, and sodium hydroxide or sodium methoxide, when they do react, bring about simple hydrolysis of the sulfonate with retention of configuration.[2]

A useful reaction for the synthesis of amino sugars involves the displacement of an "isolated" secondary tosylate by ammonia, or better, by hydrazine.[3] This reaction, as illustrated by the synthesis of 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-D-allofuranose from 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-D-glucofuranose, proceeds with inversion of configuration.[4] A recent report from these laboratories[5] described the use of sodium benzoate in refluxing *N*,*N*-dimethylformamide to effect the displacement of a side-chain secondary tosylate by benzoate with inversion of configuration. Of paramount interest was the determination whether the use of this reagent could be extended to cover the broad range of sterically more hindered and much less reactive ring sulfonates.

We wish to report the successful displacement of a pyranoside ring tosylate by sodium benzoate to give the sugar benzoate with inverted configuration on the ring carbon.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Org. Chem.*, **25**, in press (1960).

(2) R. S. Tipson, *Advances in Carbohydrate Chemistry*, **8**, 107 (1953).

(3) K. Freudenberg and F. Brauns, *Ber.*, **55**, 3233 (1922).

(4) R. U. Lemieux and P. Chu, *J. Am. Chem. Soc.*, **80**, 4745 (1958).

(5) E. J. Reist, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5775 (1958).