in β-N-acetylglucosaminidase levels was reported for the synovial fluid of patients suffering from severe rheumatoid arthritis.[5]

We envisaged that 11β,17-dihydroxy-3,20-dione-1,4-pregnadien-21-yl 2-acetamido-2-deoxy-β-D-glucopyranoside (I) should show antiinflammatory activity only after cleavage by β-N-acetylglucosaminidase, because cortisol 21-methyl and hexadecyl ethers possess substantially no systemic cortisone-like activity.[6] Lack of systemic activity of I, in conjunction with preferential enzymatic cleavage at the inflamed site, should cause I to be an effective but relatively nontoxic antiinflammatory agent.

The Koenigs–Knorr condensation of prednisolone (II) with 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride led to 11β,17-dihydroxy-3,20-dione-1,4-pregnadien-21-yl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (III), m.p. 246–248°; $[\alpha]^{25}D$ +36° (*c* 1, $CHCl_3$); λ_{max}^{MeOH} 243 mμ (log ε 4.17). *Anal.* Found: C, 60.98; H, 7.02. Methanolysis afforded I, m.p. 183–184°; $[\alpha]^{25}D$ +66° (*c* 1, MeOH); λ_{max}^{MeOH} 243 mμ (log ε 4.19). *Anal.* Found: C, 62.13; H, 7.47; N, 2.28. Incubation of I with β-N-acetylglucosaminidase[7] gave the theoretical amount of II. As expected, the addition of 2-acetamido-2-deoxy-D-gluconolactone inhibited the enzymatic hydrolysis.[8] Unlike prednisolone phosphate, I was not rapidly converted into prednisolone after parenteral injection into a rat or dog. When plasma levels of II were determined after intravenous administration of I, the blood levels of II never reached more than one-fifth those obtained after the subcutaneous injection of an equimolar amount of prednisolone 21-phosphate. Incubation of tritiated I[9] with sera and joint fluids of two arthritic patients[10] resulted in more enzymatic hydrolysis per unit volume in the joint fluids than in the sera and this difference was particularly striking (17-fold) in a severely ill patient.[11]

Compound I was tested in the rat in the granuloma inhibition assay after subcutaneous administration. It showed eight-tenths of the antiinflammatory potency of an equimolar dose of II. Indices for undesired effects were, however, considerably smaller (two-tenths that of II for body weight loss, three-tenths that of II for thymus involution, and four-tenths that of II for ACTH inhibition). A very striking separation of an undesired effect was observed in a standard ulcerogenic assay[12] in the rat, where I had <5% the ulcerogenicity of an equimolar quantity of II. The high order of antiinflammatory activity is particularly impressive because of the low plasma levels of II reported above. Whether these favorable results can be duplicated in man cannot be ascertained without prolonged clinical studies.

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
RAHWAY, NEW JERSEY
RALPH HIRSCHMANN
ROBERT G. STRACHAN
P. BUCHSCHACHER
L. H. SARETT

MERCK INSTITUTE FOR THERAPEUTIC RESEARCH
RAHWAY, NEW JERSEY
S. L. STEELMAN
R. SILBER

RECEIVED JULY 31, 1964

(5) N. G. C. Hendry and A. J. Carr, *Nature*, **199**, 392 (1963). These findings (ref. 4, 5) are consistent also with concepts of C. de Duve ("Subcellular Particles," T. Hayashi, Ed., Ronald Press Co., New York, N. Y., 1959).

(6) L. Velluz, G. Amiard, R. Heymes, and B. Goffinet, *Compt. rend.*, **250**, 371 (1960); W. S. Allen and M. J. Weiss, *J. Org. Chem.*, **26**, 4156 (1961); also unpublished results from these laboratories.

(7) Kindly supplied by Dr. Karl Meyer, College of Physicians and Surgeons, Columbia University.

(8) J. Findlay, G. A. Levvy, and C. A. March, *Biochem. J.*, **69**, 467 (1958).

(9) Prepared from labeled prednisolone kindly supplied by Dr. G. E. Arth of these laboratories.

(10) The fluids were kindly supplied by Dr. John Calabro, College of Medicine, Seton Hall University.

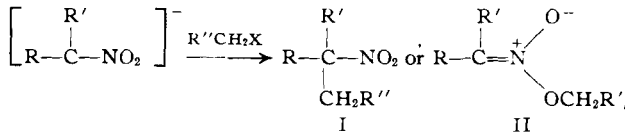
(11) We are indebted to Dr. C. Rosenblum, Mrs. B. C. Christensen, and Mr. A. Gerber for the radiochemical determinations.

(12) S. L. Steelman and E. R. Morgan, "Inflammation and Diseases of Connective Tissues," L. C. Mills and J. H. Moyer, Ed., W. B. Saunders Co., Philadelphia, Pa., 1961, p. 349.

Radical Anions as Intermediates in Substitution Reactions. Carbon Alkylation of Nitroparaffin Salts

Sir:

Nitroparaffin salts normally undergo oxygen alkylation on treatment with alkyl halides.[1] However, instances are known in which the result is carbon alkylation. Thus, when *p*-nitrobenzyl chloride is treated with a salt of 2-nitropropane an 83–95% yield of the carbon alkylate is obtained.[1,2] With *o*-nitrobenzyl chloride a 37–46% yield of the carbon alkylate is isolated. Significantly, *m*-nitrobenzyl chloride gives no carbon alkylate.[1b,3]



In 1961 it was established that the uniqueness of the *p*-nitrobenzyl system depends not only on the *p*-nitro group but also on the leaving group; the more easily displaced the leaving group the less carbon alkylate is produced.[2] For example, *p*-nitrobenzyl chloride gives 92% carbon alkylation while *p*-nitrobenzyl iodide gives an 86% yield of the oxygen alkylate. In contrast, the unsubstituted benzyl system shows no leaving-group effect; the reactions of benzyl chloride, bromide, iodide, or tosylate with the lithium salt of 2-nitropropane all give 82–84% yields of benzaldehyde. It was proposed[2] that oxygen alkylation, the usual mode of reaction of a nitroparaffin anion, derives simply from nucleophilic displacement by the oxygen of the anion on the benzylic carbon but that in the *p*-nitrobenzyl series, with a difficultly displaced leaving group, a second mode of attack by the nitroparaffin anion has a chance to compete and it is this second process which is productive of carbon alkylation. The studies described herein not only provide strong support for this view but, in addition, they provide a basis for understanding the carbon-alkylation process.

When the rates at which the various *p*-nitrobenzyl halides react with the lithium salt of 2-nitropropane in DMF are broken down into their carbon and oxygen components a striking fact emerges. On passing from the chloride to the bromide to the iodide the rate of oxygen alkylation increases by a factor of 900; in sharp contrast, the rate of carbon alkylation only increases by a factor of 6 (Table I). This large spread in the rate of oxygen alkylation is significant for two reasons. It parallels very closely the rate increase

(1) (a) L. Weisler and R. W. Helmkamp, *J. Am. Chem. Soc.*, **67**, 1167 (1945); (b) H. B. Hass and M. L. Bender, *ibid.*, **71**, 1767, 3482 (1949).

(2) N. Kornblum, P. Pink, and K. V. Yorka, *ibid.*, **83**, 2779 (1961).

(3) Actually II is not isolated; instead the carbonyl compound and oxime are obtained, *i.e.*, II → RR'C=NOH + R''CHO.

on going from the chloride to the bromide to the iodide in the *m*-nitrobenzyl system–a system which gives only oxygen alkylation. Furthermore, a large spread in rate on going from a chloride to a bromide to an iodide is to be expected for an SN2 displacement in a dipolar aprotic solvent such as DMF.[4]

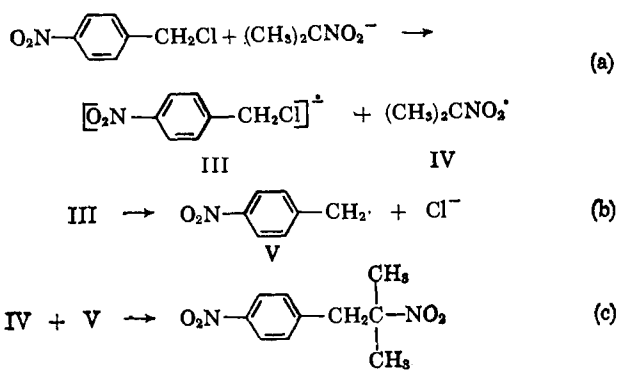
TABLE I

RATES AND PRODUCTS IN THE ALKYLATION OF THE LITHIUM SALT OF 2-NITROPROPANE WITH NITROBENZYL HALIDES[a]

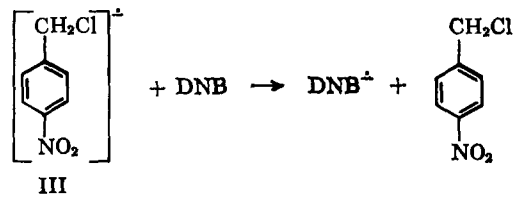
	para					*meta*
	% yield		Rates[b]			Rate[c]
Halide	C-Alkylate	O-Alkylate	k_{total}	k_{carbon}	k_{oxygen}	k_{total}
Cl	92	6	0.024	0.022	0.002	0.0013
Br	17	57	0.34	0.058	0.28	0.28
I[d]	7	86	1.9	0.13	1.8	1.4

[a] In DMF at 0°. [b] k_{total} in M^{-1} sec.$^{-1}$ as measured by rate of halide ion production; $k_{carbon} = k_{total} \times$ % C-alkylate; $k_{oxygen} = k_{total} - k_{carbon}$. [c] k_{total} in M^{-1} sec.$^{-1}$ as in *b*; here $k_{total} = k_{oxygen}$. [d] All iodide rate data extrapolated from −23°

We propose that carbon alkylation, in contrast to oxygen alkylation, is a radical anion process.



This mechanism is supported by the following facts. (1) The lack of sensitivity of the rate of carbon alkylation to the leaving group strongly suggests that here we do not deal with an SN2 displacement. (2) In step a of the proposed mechanism it is postulated that the anion derived from 2-nitropropane transfers one electron to a nitroaromatic system. Actually, direct evidence for this view has been obtained. A solution of the lithium salt of 2-nitropropane in DMF converts nitrobenzene into its radical anion as shown by the production of a well resolved ten-line e.p.r. spectrum.[5] *p*-Nitrobenzyl methyl ether also gives an e.p.r. spectrum when treated with a DMF solution of the lithium salt of 2-nitropropane; and, most directly, a study of the reaction of *p*-nitrobenzyl chloride with the lithium salt of 2-nitropropane in DMF at −50° reveals an unambiguous, albeit unresolved, resonance of about 30-gauss width. (3) Radical anions derived from nitroaromatics are long-lived radicals.[6] Furthermore, electron transfer from nitroaromatic radical anions to nitroaromatics is often very rapid.[7] Consequently, it appeared possible that an easily reduced nitroaromatic such as a dinitrobenzene (DNB) might be able to take an electron away from the radical anion (III) before loss of chloride occurred (b) and, thereby, prevent carbon alkylation.



The net effect of such interception would be to retard carbon alkylation without affecting oxygen alkylation and, hence, the proportion of oxygen alkylate should rise even as that of carbon alkylate falls. As can be seen from Table II, carbon alkylation is, indeed, suppressed by aromatic nitro compounds. It is especially noteworthy that the efficiency with which the nitroaromatics suppress carbon alkylation completely parallels the ease with which they undergo one-electron reduction.[8] It is also significant that with much less than a stoichiometric amount of *p*-DNB the major product is the oxygen alkylate.

TABLE II

THE INFLUENCE OF NITROAROMATICS ON THE REACTION OF *p*-NITROBENZYL CHLORIDE WITH THE LITHIUM SALT OF 2-NITROPROPANE[a]

Added nitroaromatic (mmoles)	% yield	
	C-Alkylate	O-Alkylate
None	92	6
$PhNO_2$ (40)	84	7
m-DNB (10)	61	29
m-DNB (20)	40	48
p-DNB (2)	29	57
p-DNB (10)	2	72

[a] In DMF at 0° using 10 mmoles of chloride and 21 mmoles of lithium salt.

It will be seen that a radical anion such as III has the special property that by loss of a stable anion it is readily transformed into the corresponding free radical V. Extension of these ideas to the reactions of other nucleophiles is in progress.

Acknowledgment.—This work was supported by a grant from the Explosives Department of the Du Pont Company to whom our sincere thanks are due.

(4) A. J. Parker, *J. Chem. Soc.*, 1332 (1961).

(5) G. A. Russell, E. G. Janzen, and E. T. Strom [*J. Am. Chem. Soc.*, **86**, 1807 (1964)] have very recently shown that the nitrobenzene radical anion is formed on treating nitrobenzene with nitroparaffin salts in *t*-butyl alcohol–DMSO. Although our spectrum is less well resolved than theirs there is no doubt that it is produced by the same radical anion.

(6) D. H. Geske and A. H. Maki, *ibid.*, **82**, 2671 (1960); L. H. Piette, P. Ludwig, and R. N. Adams, *ibid.*, **84**, 4212 (1962); P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.*, **39**, 609 (1963).

(7) S. I. Weissman, *Z. Elektrochem.*, **64**, 47 (1960); R. L. Ward, *J. Chem. Phys.*, **32**, 410 (1960); M. T. Jones and S. I. Weissman, *J. Am. Chem. Soc.*, **84**, 4269 (1962).

(8) A. H. Maki and D. H. Geske, *ibid.*, **83**, 1852 (1961).

(9) National Science Foundation Cooperative Graduate Fellow.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

ROBERT C. KERBER[9]
GRANT W. URRY
NATHAN KORNBLUM

RECEIVED JULY 31, 1964

A New Insertion Reaction of Cationic Oxygen

Sir:

It has been reported that 1,3,3-trimethylcyclohexyl hydroperoxide (I, X = OH), when treated with *p*-nitrobenzenesulfonyl chloride in pyridine, forms the bicyclic ether II in 5–10% yield.[1] It was suggested that the reaction proceeds by decomposition of an intermediate persulfonate *via* an ion-paired transition state involving C–H insertion of cationic oxygen. We

(1) E. J. Corey and R. W. White, *J. Am. Chem. Soc.*, **80**, 6686 (1958).