104 kcal.[10] suggests that the energetics of hydrogen abstraction by the benzophenone triplet and the *t*-butoxy radical must be very similar.

We are extending our experiments to other substrates and triplet states of other ketones and find, for example, that the acetophenone triplet shows similar but significantly different selectivities.

(10) P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959).
(11) National Science Foundation Cooperative Fellow, 1963–1964.

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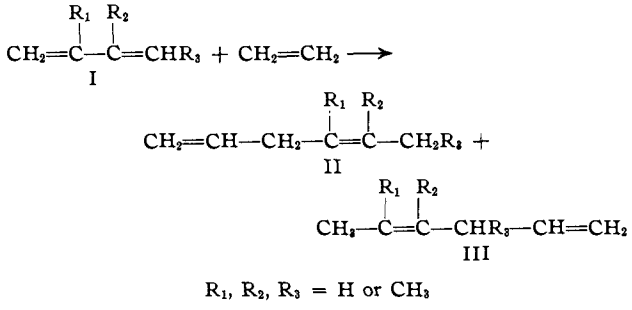
Stereospecific Synthesis of 1,4-Dienes

Sir:

We wish to report the novel synthesis of 1,4-dienes II and III by the reaction of 1,3-dienes I with ethylene in the presence of a catalyst consisting of iron compounds and organoaluminum compounds. This reaction affords either of the possible geometrical isomers of the 1,4-dienes selectively.



R_1, R_2, R_3 = H or CH_3

In a typical example, 25 ml. of toluene, 0.003 mole of iron(III) acetylacetonate, 0.012 mole of triethylaluminum, and 0.6 mole of 1,3-butadiene were placed in a stainless steel autoclave (100 ml.). The resulting mixture was stirred for 1.5 hr. at 30° under ethylene pressure (40 kg./cm.^{2}). After the usual work-up, the reaction products were separated by preparative gas chromatography. 1-*cis*-4-Hexadiene, b.p. 66.5°, n^{20}D 1.4147, was obtained in 35% yield and identified by comparison of its infrared spectrum and gas chromatographic retention time with an authentic sample.[1] In addition, small amounts of 2,4-hexadiene and 1,3-hexadiene were obtained.

For 1,3-pentadiene and isoprene, there are two possible sites of addition. The reaction of 1,3-pentadiene with ethylene at 50° afforded 3-methyl-1-*cis*-4-hexadiene, b.p. 83°, n^{20}D 1.4169, and 1-*cis*-4-heptadiene, b.p. 93°, n^{20}D 1.4209, in a ratio of 7:3, *i.e.*, ethylene adds more easily to the 4- position of 1,3-pentadiene than to the 1- position. The terminal double bond of the former compound was reduced by addition of an equivalent amount of diisobutylaluminum hydride, followed by hydrolysis to give 4-methyl-*cis*-2-hexene. The absence of the *trans* isomer[2] was confirmed by gas chromatographic analysis. The latter compound was identified by comparing it with an authentic sample.[1] 1-*trans*-3-Pentadiene reacts faster than the *cis* isomer. The unreacted 1,3-pentadiene was found to be rich in the *cis* isomer.

The reaction of isoprene with ethylene at 20° gave 4-methyl-1,4-hexadiene (one geometrical isomer), b.p. 88–89°, n^{20}D 1.4248, and 5-methyl-1,4-hexadiene, b.p. 88–89°, n^{20}D 1.4256, in a ratio of 6:4. As the reaction temperature was raised, the ratio approached 1:1. The terminal double bonds of 4-methyl- and 5-methyl-1,4-hexadiene were reduced by diisobutylaluminum hydride to afford one geometrical isomer of 3-methyl-2-hexene and 2-methyl-2-hexene,[3] respectively. A mixture of geometrical isomers of 3-methyl-2-hexene was prepared by the Wittig reaction of 2-pentanone with ethylidenetriphenylphosphorane. The isomers were separated by gas chromatography using a squalane column (4 m.) at 60°. The infrared spectrum and gas chromatographic retention time of the first eluted component were identical with those of the reduction product of 4-methyl-1,4-hexadiene. Investigation of its geometry is underway.

In a similar way, the reaction of 2,3-dimethyl-1,3-butadiene with ethylene gave 4,5-dimethyl-1,4-hexadiene, b.p. 119–120°, n^{20}D 1.4408.

The steric course and orientation of the reaction are being investigated. A detailed description of these reactions will be published later.

(1) Mixtures of *cis* and *trans* isomers of 1,4-hexadiene and 1,4-heptadiene were prepared by the known method [B. H. Shoemaker and C. E. Boord, *J. Am. Chem. Soc.*, **53**, 1505 (1931)]. The *cis* isomers of both 1,4-dienes were separated by gas chromatography using a silver nitrate–benzyl cyanide column (2.5 m.).
(2) F. J. Soday and C. E. Boord, *ibid.*, **55**, 3293 (1933).
(3) M. D. Sutherland, *ibid.*, **75**, 5944 (1953).

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An Approach to an Improved Antiinflammatory Steroid. The Synthesis of 11β,17-Dihydroxy-3,20-dione-1,4-pregnadien-21-yl 2-Acetamido-2-deoxy-β-D-glucopyranoside[1]

Sir:

When cortisone is used in the treatment of inflammation, a number of effects also occur which are undesirable in this therapy, such as negative nitrogen balance, osteoporosis, adrenal atrophy, formation of ulcers, and retention of sodium chloride. Numerous synthetic steroids have been prepared[2] in an attempt to obtain a therapeutically active drug which will not cause these side effects. However, mineralocorticoid activity is the only effect, undesired in antiinflammatory therapy, which has been dissociated.

It seemed possible to reduce all of these side effects if an inactive steroid could be prepared which is preferentially converted into an active drug at the site of its therapeutic action.

Connective tissue has an active metabolism of hyaluronic acid.[3] An indication of higher activity of β-D-glucuronidase in the synovial fluid of joints from patients with rheumatoid arthritis than in liver was given by Bollet.[4] Very recently a striking increase

(1) The authors are indebted to Drs. G. Boxer and K. Meyer for many stimulating discussions.
(2) L. H. Sarett, A. A. Patchett, and S. L. Steelman, *Fortschr. Arzneimittelforsch.*, **5**, 11 (1963).
(3) See, *e.g.*, E. Buddecke, *Angew. Chem.*, **72**, 663 (1960).
(4) A. J. Bollet, J. F. Goodwin, and A. K. Brown, *J. Clin. Invest.*, **38**, 451 (1959).

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.

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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.

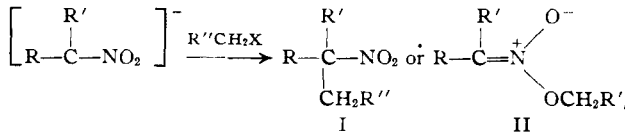
(11) We are indebted to Dr. C. Rosenblum, Mrs. B. C. Christensen, and Mr. A. Gerber for the radiochemical determinations.

(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 **11** is not isolated; instead the carbonyl compound and oxime are obtained, *i.e.*, **11** → RR'C=NOH + R''CHO.