as described previously.[11] The apparatus consisted of a 100-ml. three-necked flask with stirrer, dropping funnel, and gas-exit tube connected through a drying tube to a Dry Ice condenser with receiver, and finally to a Dry Ice-cooled trap. Diethylcarbitol (dried over sodium) (20 ml.) and 0.97 g. (0.025 mole) of lithium aluminum hydride were stirred and heated to 70°, and a solution of 7.07 g. (0.031 mole) of isoprene-*x*-^{14}C dibromide in 6 ml. of dry diethylcarbitol was added over a period of 65 minutes, the reaction being quite vigorous. After an additional 20 minutes, 10 ml. of water was added cautiously, the evolved hydrogen driving the last traces of trimethylethylene-*x*-^{14}C into the receiver. The product (1.99 g., 92%) had an infrared spectrum identical to the spectrum of authentic trimethylethylene, b.p. 37.6–38.5° (738 mm.), prepared by heating *t*-amyl chloride with water.

2-Methyl-2,3-butanediol-*x*-^{14}-C.—The procedure was as described previously.[12] From the treatment of 1.99 g. (0.028 mole) of 2-methyl-2-butene-*x*-^{14}C with performic acid followed by saponification was obtained, after distillation through a 23-cm. column packed with a tantalum wire coil, 1.21 g. (42%) of 2-methyl-2,3-butanediol-*x*-^{14}C, b.p. 89.5–89.7° (22.2 mm.).

Degradation of 2-Methyl-2,3-butanediol-*x*-^{14}C to II, III, IV, V and VI.—The procedures were as described previously.[12] The 2,4-dinitrophenylhydrazone of 3-methyl-2-butanone-*x*-^{14}C (II) after three recrystallizations from methanol–water had m.p. 122.9–123.5°. The iodoform-^{14}C samples (III and VI) after three recrystallizations from methanol–water had m.p. 118.2–119.5 dec. The dimethone derivative of acetaldehyde-*x*-^{14}C (IV) after 3 recrystallizations from cyclohexane had m.p. 142.9–143.5°. Ether extraction of the crude dinitrophenylhydrazone of acetone-^{14}C (V) was necessary to separate the unreacted 2,4-dinitrophenylhydrazine (insoluble in ether). The dinitrophenylhydrazone of V was then recrystallized three times from methanol–water to give material of m.p. 124.4–125.1°.

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[11] L. W. Trevoy and W. G. Brown, This Journal, **71**, 1675 (1949).

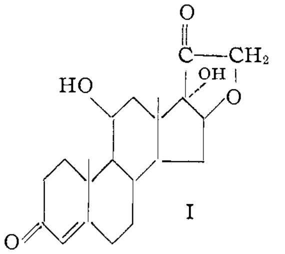
[12] J. D. Roberts, R. E. McMahon and J. S. Hine, *ibid.*, **72**, 4237 (1950).

COMMUNICATIONS TO THE EDITOR

STEROIDAL CYCLIC KETALS. XXI.[1] THE PREPARATION OF 16β,21-EPOXIDO-STEROIDS

Sir:

We wish to report the synthesis of a steroid which has been tentatively assigned the structure 11β,17α-dihydroxy-3,20-dioxo-4-pregnen-16β,21-epoxide (I).



I

This represents, in essence, the first synthesis of a steroid possessing the pentacyclic skeleton of a perhydro-furocyclopentenophenanthrene, the basic structure of the pseudosapogenins.[2] Moreover, this ring system with a β-tetrahydrofuranone moiety as in I has been employed in a hypothetical structure of diginin[3,4] and its aglycone, diginigenin.[4]

Acetylation of 3,20-bis-ethylenedioxy-5,16-pregnadiene-11β,21-diol (II)[5] in pyridine afforded its 21-acetate III, m.p. 167–168°,[6] [α]D −32°[6] (*Anal.* Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.72; H, 8.38) which on hydroxylation with osmium tetroxide was converted into 21-acetoxy - 3,20 - bis - ethylenedioxy - 5 - pregnene-11β,16α,17α-triol (IV). The latter, m.p. 189–192°, [α]D −19° (*Anal.* Calcd. for $C_{27}H_{40}O_9$: C, 63.76; H, 7.93. Found: C, 63.59; H, 8.21), was also obtained by selective acetylation of 3,20-bis - ethylenedioxy - 5 - pregnene - 11β,16α,17α,21-tetrol (V).[1] Mesylation afforded 21-acetoxy-3,20-bis - ethylenedioxy - 16α - methanesulfonyloxy - 5-pregnene-11β,17α-diol (VI), m.p. 169–171° (*Anal.* Calcd. for $C_{28}H_{42}O_{11}S$: S, 5.60. Found: S, 6.38).

Compound VI in 5% alcoholic potassium hydroxide was refluxed for 4 hours, and a 1:4 displacement reaction[7] (the derived anion at C-21 displaced by way of the β-face the 16α-mesyloxy group) occurred to afford in 79% yield 3,20-bis-ethylenedioxy - 11β,17α - dihydroxy - 5 pregnene-16β,21-epoxide (VII), m.p. 232–234°, [α]D −81°, $\nu_{\max}^{\text{KBr}}$ 3620, 1682, 1160 and 1105 cm.$^{-1}$ (*Anal.* Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.14; H, 7.82). Compound VII was also obtained by reduction with lithium aluminum hydride[8] of 3,20-bis-ethylenedioxy-17α-hydroxy-11-oxo-5-pregnene-16β,21-epoxide (VIII), m.p. 230.5–232.5°, [α]D −76°, $\nu_{\max}^{\text{KBr}}$ 3620, 1722, 1680, 1090 and 1060 cm.$^{-1}$ (*Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.61; H, 8.00), similarly prepared by a displacement reaction.

Acid hydrolysis (8% v./v. sulfuric acid in methanol, 16 hours reflux) of VII gave 11β,17α-dihydroxy - 3,20 - dioxo - 4 - pregnen - 16β,21 - epoxide (I), m.p. 235–237°, $\lambda_{\max.}^{\text{abs. alc.}}$ 241 mμ (ε 15,900), [α]D +8°, $\nu_{\max}^{\text{KBr}}$ 3790, 3508 (hydroxyl, doublet), 1780 (20-carbonyl), 1662 (3-carbonyl), 1631 (Δ^4) and 1066 cm.$^{-1}$ (strong C–O) (*Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.72;

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[1] Paper XX, W. S. Allen and S. Bernstein, This Journal, **78**, 1909 (1956).

[2] R. E. Marker, *et al.*, *ibid.*, **64**, 1655 (1942).

[3] W. Karrer, E. C. Barell Festschrift, Basel, 1936, p. 238, isolated diginin from the leaves of *Digitalis purpurea*.

[4] C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **23**, 975 (1940); **25**, 1611 (1942); C. W. Shoppee, *ibid.*, **27**, 246, 426 (1944).

[5] W. S. Allen and S. Bernstein, This Journal, **77**, 1028 (1955).

[6] M.p.'s are uncorrected. Rotations are for chloroform solution at 24–25°.

[7] S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 9; and S. Peat, "Advances in Carbohydrate Chemistry," Vol. 2, Academic Press, Inc., Publ., New York, N. Y., 1946, p. 56.

[8] When this reduction was attempted with sodium borohydride in tetrahydrofuran and 5% sodium hydroxide (overnight reflux) the product was principally starting material.

H, 7.96), positive legal test.[4,9] Treatment of I with acetic anhydride–pyridine at room temperature yielded only starting material. The compound formed a mono-2,4-dinitrophenylhydrazone at C-3, m.p. 256° d., $\lambda_{\max}^{1\%\ \text{chloroform-abs. alc.}}$ 257 (ϵ 17,300) and 387–388 mμ (ϵ 29,000) (*Anal.* Calcd. for $C_{27}H_{32}N_4O_8$: C, 59.99; H, 5.97; N, 10.37. Found: C, 59.71; H, 6.15; N, 10.25).

A detailed report of this work will be forthcoming in this JOURNAL.

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(9) W. D. Paist, E. R. Blout, F. C. Uhle and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941).

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RECEIVED APRIL 6, 1956

INDISCRIMINATE REACTION OF METHYLENE WITH THE CARBON-HYDROGEN BOND

Sir:

Methylene shows essentially no discriminatory power in its reaction with the carbon–hydrogen bonds[1] in the saturated hydrocarbons, *n*-pentane and 2,3-dimethylbutane and in the olefin, cyclohexene. When diazomethane is irradiated with these hydrocarbons either at −75° or at 15°, the distribution of products resulting from insertion of the carbene into a carbon–hydrogen bond is very close to statistical. For example, diazomethane may react with *n*-pentane at carbon atoms 1, 2 or 3 to give *n*-hexane, 2-methylpentane and 3-methylpentane in the statistical ratio 6:4:2 or 50:33.3:16.7, respectively; in fact, these three products are formed at −75° in the ratio 48:35:17; and at 15° in the ratio 49:34:17.

2,3-Dimethylbutane which contains primary and tertiary hydrogen in the ratio of 12:2 or 85.7:14.3 reacts with diazomethane to give 2,3-dimethylpentane and 2,2,3-trimethylbutane in the ratio 83:17. It is possible that the small difference between the statistical and actual values lies outside the experimental error but higher resolution in the form of considerably refined techniques would be required to decide.

In cyclohexene there are three types of carbon–hydrogen bonds of widely differing chemical characteristics: the "vinyl" hydrogen atoms at carbon atoms 1 and 2, the "allylic" hydrogens at C_3 and C_6 and the "aliphatic" hydrogens at C_4 and C_5. Reaction with methylene can occur in principle at each type of carbon–hydrogen bond to give 1-methylcyclohexene, 3-methylcyclohexene and 4-methylcyclohexene, respectively, in the statistical ratio of 2:4:4. Reaction can also occur by addition to the double bond to give norcarane. In fact, these four products are formed at −75° in the ration 10:25:25:40 and at 15° in the ratio 11:26:26:37. Here again one product, 1-methylcyclohexene, appears to be formed in amount differing slightly from the statistical, but the estimated error of 10% is too large to justify further comment at this time.

Finally diazomethane reacts with cyclopentane to give methylcyclopentane unaccompanied (less than 0.1%) by cyclohexane. Within much increased limits, one concludes that methylene does not react with the carbon–carbon bond.

Within a few per cent. it is clear that methylene fails to distinguish between different types of carbon–hydrogen bonds, reacting at random with 1°, 2° and 3° aliphatic C–H bonds as well as with "allylic" and "vinyl" types. Even more surprising is the fact that the reaction cross-section of the double bond is only about three times that of a hydrogen atom. One might reasonably have expected an overwhelming preference similar to that shown by dichlorocarbene.[2] Methylene must be classed as the most indiscriminate reagent known in organic chemistry.

The experiments were carried out in the usual way by irradiating very dilute solutions of diazomethane in the hydrocarbon with sun-lamps, removing most of the solvent by fractional distillation in a 50-plate column and analyzing the product by gas–liquid partition chromatography using a Perkin–Elmer Model 154 Vapor Fractometer and by infrared spectroscopy. In all cases but one, samples of pure product were isolated from the Fractometer and identified by comparing their infrared spectra with those of authentic samples (neat, 0.1-mm. cell). In the cyclohexene reaction where the Fractometer would not resolve 3- and 4-methylcyclohexene but easily separated this mixture from the other components, analysis was made infrared spectroscopically comparing with known mixtures of the authentic olefins.

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(1) The photochemical decomposition of diazomethane was first investigated by H. Meerwein, H. Rathjen and H. Werner, *Ber.*, **75**, 1610 (1942), in ether where ethyl *n*-propyl and ethyl isopropyl ether were formed. Although the latter product appears to be formed by direct reaction of a carbon–hydrogen bond, the presence of the oxygen atom and the possibility it affords for initial "ylid" formation [see R. Huisgen, *Angew. Chem.*, **67**, 439 (1955)] makes the mechanism ambiguous. The direct reaction of carbethoxy carbene with saturated hydrocarbons has been reported by W. von E. Doering and L. H. Knox, 119th Meeting of the American Chemical Society, Boston, Mass., April 2, 1951 "Abstracts of Papers," p. 2M, and THIS JOURNAL, in press.

(2) W. von E. Doering and A. K. Hoffmann, THIS JOURNAL, **76**, 6162 (1954).

(3) Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut.

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RECEIVED JUNE 4, 1956

SYNTHESIS OF APOGOSSYPOL HEXAMETHYL ETHER

Sir:

Apogossypol hexamethyl ether, the primary degradation product of gossypol (I), has been formulated as 2,2′-bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (II) by Adams[1] as a result of his extensive and thorough studies. The Adams structures however, have been criticized recently by three separate groups of investigators.[2,3,4] The present

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(1) R. Adams, R. C. Morris, T. A. Geissman, D. J. Butterbaugh and E. C. Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

(2) D. A. Shirley and W. L. Dean, *ibid.*, **77**, 6077 (1955).

(3) R. T. O'Connor, P. Haar, E. F. DuPre, L. E. Brown and C. H. Pominski, *ibid.*, **76**, 2368 (1954).

(4) C. H. Boatner, "Pigments of Cottonseed and Cottonseed Products," Edited by A. E. Bailey, Interscience Publishers, Inc., New York, N. Y., 1948, Chap. VI, pp. 215–262.