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., $\lambda_{max}^{1\%\ chloroform-abs.\ alc.}$ 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.

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

MEDICINAL CHEMICAL RESEARCH SECTION
RESEARCH DIVISION
AMERICAN CYANAMID COMPANY   WILLIAM S. ALLEN
LEDERLE LABORATORIES   SEYMOUR BERNSTEIN
PEARL RIVER, NEW YORK
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,

(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.

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.

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

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

HICKRILL CHEMICAL   W. von E. DOERING[3]
RESEARCH FOUNDATION   R. G. BUTTERY
KATONAH, NEW YORK   R. G. LAUGHLIN
   N. CHAUDHURI
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

(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.

communication reports an unambiguous synthesis of apogossypol hexamethyl ether, identical in all respects with that obtained from I (natural product m.p. 277–278°; synthetic product m.p. 277–279°; mixed m.p. 277–278°; infrared spectra indistinguishable),[5] which establishes conclusively the correctness of the original Adams formulation. Compound II was synthesized by the oxidative coupling of 5-isopropyl-6,7-dimethoxy-3-methyl-1-naphthol (III) m.p. 129–130°, found; C, 73.76; H, 7.78)[6] with ferric chloride in dioxane as the solvent and subsequent methylation of the resulting 2,2' - bi - 1 - (5 - isopropyl - 6,7 - dimethoxy - 3-methyl)-naphthol (m.p. 271–275°, found: C, 74.21; H, 7.39). Consideration of models demonstrates that no coupling in the 4-position of III can occur due to steric hindrance.

Compound III was prepared in the following manner: formylation of 3-isopropyl-1,2-dimethoxybenzene[7,8] gave 2-isopropyl-3,4-dimethoxybenzaldehyde (IV), b.p. 98–102° (0.13 mm.) (2,4-dinitrophenylhydrazone, m.p. 190–192°, found: C, 55.79; H, 5.58). Oxidation of IV gave 2-isopropyl-3,4-dimethoxybenzoic acid as shown by comparison with an authentic sample.[9] The Stobbe reaction of IV and diethyl succinate with subsequent ring closure (sodium acetate and acetic anhydride) and saponification in the conventional manner gave 1-hydroxy-5-isopropyl-6,7-dimethoxy-3-naphthoic acid (m.p. 226–227°, found: C, 66.32; H, 6.34). Reduction with lithium aluminum hydride gave 3-hydroxymethyl-5-isopropyl-6,7-dimethoxy-1-naphthol (m.p. 207–209°, found: C, 69.71; H, 7.20). Hydrogenolysis with palladium on charcoal in methanol with a trace of hydrochloric acid gave III.

The interest and encouragement of Professor R. B. Turner is gratefully acknowledged.

(5) Perkin–Elmer Model 21 Spectrophotometer, 0.11-mm. cells, solvent chloroform, concn. 7%.

(6) All analyses by Huffman Microanalytical Laboratories, Wheatridge, Colorado.

(7) R. Adams, M. Hunt and R. C. Morris, THIS JOURNAL, 60, 2972 (1938).

(8) J. D. Edwards, Jr., and J. L. Cashaw, J. Org. Chem., 20, 847 (1955).

(9) R. Adams and B. R. Baker, THIS JOURNAL, 61, 1138 (1939).

RESEARCH LABORATORIES   J. D. EDWARDS, JR.
VETERANS ADMINISTRATION HOSPITAL   J. L. CASHAW
HOUSTON, TEXAS
                RECEIVED MAY 21, 1956

NUCLEAR MAGNETIC RESONANCE STERIC SHIFTS IN –CH GROUPS

Sir:

Sterically interfering hydrogen atoms in the 4–5 position of phenanthrene and many similar molecules shows up strongly in high resolution nuclear magnetic resonance experiments. Since the work of Arnold, et al.,[1] on the steric effects of methylene groups in hydrindene and tetralin with α-substituents in the aromatic ring shows clearly that the interaction is much greater when both rings are six-membered than when one of them is five-membered, it is of interest to investigate the effect

(1) R. T. Arnold, V. J. Webers and R. M. Dodson, THIS JOURNAL, 74, 368 (1952).

of ring size on the nuclear magnetic resonance signals. Accordingly, the proton signals from a number of polycyclic compounds have been examined (Table I). The shifts are measured relative to the main peak due to the rest of the aromatic hydrogens. Usually the distance of the two peaks from a standard marker (cyclohexane or decalin when the latter was used as solvent) were measured. The strong interaction found in benzophenanthrene is considerably weakened by the change in angle introduced by the 5-membered ring in dibenzofluorene, and the initially weaker phenanthrene interaction is similarly much reduced in fluorene and completely removed in fluoranthene, where the hydrogen atoms are even farther apart.

TABLE I

	H–H distance A	Shift, cycles
3,4-Benzophenanthrene	0.53	68
1,2,5,6-Dibenzanthracene	1.71	45
1,2,5,6-Dibenzfluorene	1.73	40
Phenanthrene	1.76	42
Fluorene	2.72	12 uncertain
Fluoranthene	2.95	0 uncertain

A fairly simple relation exists between the nuclear magnetic resonance shift and the hydrogen–hydrogen distance. However, since the H–H distances are calculated on the basis of a planar molecule and the H–H repulsion must distort the molecule somewhat out of plane, these values are not the true equilibrium H–H distances. Allowance for this fact would increase the small H–H distances proportionally more than the large ones.

A consideration of other molecules with interacting protons shows some interesting effects. Perylene with two sterically interfering pairs each tending to twist the molecule out of plane about the central pair of bonds shows a shift of only 25 cycles, about half that observed for phenanthrene. The doubled torque has clearly effected an increased twist, so that the protons in each pair are considerably farther apart than in phenanthrene. Chrysene also has two interacting pairs, but now the torque is across a 3-bond rather than a two-bond system. Correspondingly we find a shift intermediate between that of phenanthrene and perylene (35 cycles). A more detailed examination of this kind of structural effect will be published shortly.

One is easily convinced from the molecular models that the 4–5 proton repulsion in phenanthrene puts the maximum strain on the C_9–C_{10} bond. The anomalously high "K region" reactivity which is greater than predicted by molecular orbital theory based on a planar molecule is no doubt due to this fact. A study of the shifts in carcinogenic hydrocarbons is also in progress.

It has been pointed out to the author[2] that the closeness of the proton to two aromatic rings rather than one may result in the kind of shift observed. An investigation of the relative importance of the two factors is under way.

The work reported here was done using a Varian Associates Model V4300 spectrometer working at

(2) W. G. Schneider, H. J. Bernstein and J. A. Pople, private communication.