known origin occur in the spectra with intensities equal to a few per cent of the ether fragment, and one cannot discount the possibility that the small apparent difference in total *vs.* ether ^{18}O enrichment is due to an unknown fragment or impurity in the spectrum. It would require further very careful work to more unambiguously establish whether or not the small apparent peroxy ^{18}O incorporation is real.[15]

In any case, our principal conclusions seem well founded. The mass spectral results show that nearly all of the aldehydic oxygen is incorporated at the ether site in the final ozonide; this supports a zwitterion pathway. The upper limit for processes that produce peroxy ^{18}O incorporation, such as the aldehyde interchange pathway, is about 10% in our runs.[16] These results indicate therefore that such an alternative pathway for the formation of methyl isopropyl ozonide from diisopropylethylene is considerably less important than previously supposed.[8] The reason that our results differ from those reported earlier by Story, *et al.*,[8] is not clear. Reaction conditions were similar in both studies. We have, in fact, employed lower reaction temperatures than those used previously, and a nonzwitterion pathway should become more important as the reaction temperature is decreased.[11] The notable difference is that our analysis dealt with the ozonides themselves while the previous study determined the ^{18}O enrichment in alcohols derived from the ozonides; this latter procedure is therefore less direct.[17]

Acknowledgment. This work was partially supported by a grant (GP 38750X) from the National Science Foundation. Assistance from Margaret Lathrop Johnson in the mass spectral analyses is appreciated.

(14) M. Bertrand, J. Carles, S. Fliszár, and Y. Rousseau, *Org. Mass Spectrom.*, **9**, 297 (1974).

(15) For example, if a small correction (7%) is made to the *m/e* 100 fragment based on the small peak observed at 98 (loss of H_2O_2), the values for percent ether ^{18}O enrichment become 53.2, 54.1, 52.8, 55.1, and 50.7%. A difference between total and ether ^{18}O enrichment is then no longer clearly apparent for four runs. We have been reluctant to prefer these values since it is not entirely certain that the small mass 98 peak originates from ozonides. Further work is necessary on this point.

(16) The figure of 10% is estimated from the last run in Table I. Extrapolation of that run to 100% ^{18}O enrichment in the ozonide leads to about 90% ^{18}O ether enrichment.

(17) C. E. Bishop and P. R. Story, *J. Amer. Chem. Soc.*, **90**, 1905 (1968).

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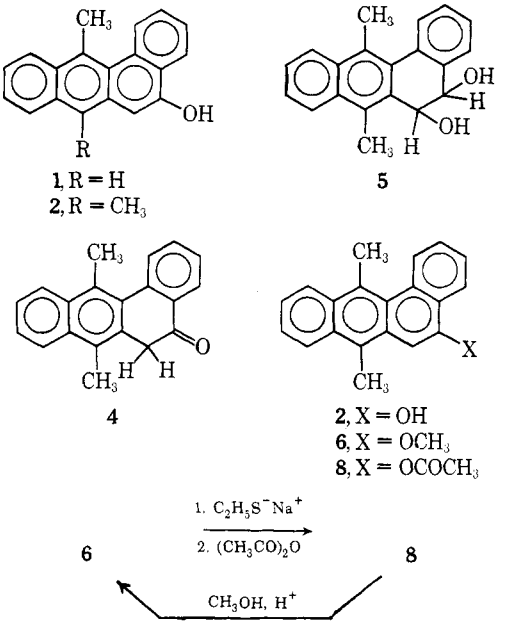
A New Hypothesis Concerning the Reactive Species in Carcinogenesis by 7,12-Dimethylbenz[*a*]anthracene. The 5-Hydroxy-7,12-dimethylbenz[*a*]anthracene–7,12-Dimethylbenz[*a*]anthracen-5(6*H*)-one Equilibrium

Sir:

Previous attempts[1,2] to isolate and characterize 5-hydroxy-12-methylbenz[*a*]anthracene (**1**) and 5-hydroxy-7,12-dimethylbenz[*a*]anthracene (**2**) have failed to yield either **1** or **2**, although the presence of **1** and **2** was inferred because of conversions of crude reaction products into the corresponding amino derivatives by the Bucherer reaction.[1] The formation of **2** on mild acid hydrolysis of 5,6-dihydro-7,12-dimethylbenz[*a*]anthracene 5,6-epoxide (**3**) was claimed,[3] but no melting point or other analytical data on this compound were reported.

In our attempts to prepare **2** we have found that the compound exists as a mixture of 7,12-dimethylbenz[*a*]-anthracen-5(6*H*)-one (**4**) and the phenolic tautomer **2**. On vacuum sublimation of *cis*-5,6-dihydro-7,12-dimethylbenz[*a*]anthracen-5,6-diol[4] (**5**) from acidic alumina we obtained a solid sublimate[5] whose nmr and ir spectra indicated that a mixture (*ca.* 1:1) of ketonic and phenolic substances was at hand.[6] This material (*m/e* 272.1205; calcd 272.1201) gives a red 2,4-DNPH derivative,[5] mp 229–230° dec, in a sealed capillary, on recrystallization from dioxane. In order to tell whether the 5-keto or 6-keto isomer (or a mixture of the two) was present we synthesized 5-methoxy-7,12-dimethylbenz[*a*]anthracene (**6**) (nmr, $CDCl_3$, $(CH_3)_4Si$, δ 2.78 (s, 3 H, 7-CH_3), 3.13 (s, 3 H, 12-CH_3), 3.90 (s, 3 H, OCH_3), 6.93 (s, 1 H, 6-H)), by a method somewhat better than that described,[1] and 6-methoxy-7,12-dimethylbenz[*a*]anthracene[7] (**7**), mp 140–141° (δ 3.13 (s, 6 H, 7- and 12-CH_3), 3.83, 3 H, OCH_3), 6.59 (s, 1 H, 5-H)), and cleaved each by heating with sodium ethylmercaptide in dimethylformamide.[8] The resulting deep red solutions of sodium salts were treated *in situ* with acetic anhydride to yield 5-acetoxy-7,12-dimethylbenz-[*a*]anthracene (**8**),[5] mp 149–150° (nmr 2.40 (s, 3 H,



(3) S. H. Goh and R. G. Harvey, *J. Amer. Chem. Soc.*, **95**, 242 (1973).

(4) R. Criegee, B. Marchand, and H. Wannowius, *Justus Liebigs Ann. Chem.*, **550**, 99 (1942); J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948).

(5) All new compounds gave C and H analyses, ir, mass spectra, and nmr data consistent with the postulated structure.

(6) The distinguishing features of the nmr ($CDCl_3$, $(CH_3)_4Si$ standard) were a broad singlet at δ 5.38 (rel intensity 19) attributed to OH and a singlet at δ 3.62 (rel intensity, 46) attributed to the methylene adjacent to the carbonyl group. The band at 5.38 disappeared within 1 min when D_2O was added. In one experiment the band at 3.62 disappeared in 40 min when the solution was shaken with D_2O–K_2CO_3 solution. The peak at 3.62 reappeared when H_2O was added. In CCl_4 the peaks are at δ 6.17 and 3.67 with relative intensities of 8.6 and 21.2, respectively. In the ir spectrum in $CHCl_3$, bands at 2.97 μ (OH) and at 5.94 (CO) are noted (3.02 and 5.99 in a KBr pellet).

(7) A description of this work will soon be published.

(8) G. I. Fentrill and R. W. Mirrington, *Tetrahedron Lett.*, 1327 (1970).

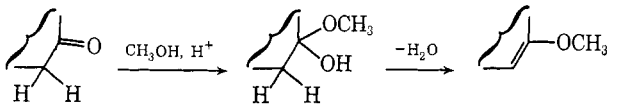
(1) W. M. Smith, Jr., E. F. Pratt, and H. J. Creech, *J. Amer. Chem. Soc.*, **73**, 319 (1951).

(2) Unpublished results in the Ph.D. Thesis of C. C. Davis, Ohio State University, 1966.

$COCH_3$), 2.87 (s, 3 H, 7-CH_3), 3.17 (s, 3 H, 12-CH_3)), and 6-acetoxy-7,12-dimethylbenz[*a*]anthracene (**9**), mp 138–139° (nmr 2.30 (s, 3 H, $COCH_3$), 3.02 (s, 3 H, 7-CH_3), 3.18 (s, 3 H, 12-CH_3), 7.12 (s, 1 H, 5-H)), respectively. We had hoped to prepare the pure hydroxy compounds corresponding to **8** and **9** by acid-catalyzed methanolysis of **8** and **9**. However, on standing with methanol containing hydrogen chloride at room temperature, *the methoxy compounds, 6 and 7, were obtained in almost quantitative yields!* As far as we know this represents unparalleled behavior for phenolic acetates.

Since methanolysis surely produces methyl acetate and the phenolic tautomer first, we have two cases in which a phenol is converted into its methyl ether by mild treatment with methanolic HCl. Neither 1- or 2-naphthol exhibits this behavior. Our interpretation of these unexpected results is that the benzanthracene phenols rapidly tautomerize to the ketonic tautomers which add methanol to form hemiketals. The latter lose water to yield the methyl ethers, **6** and **7**,[9] as shown (only for the 5-substituted case) in Scheme I. Similarly, both the material obtained on sublima-

Scheme I



tion of **5** over acid alumina and the dihydrodiol, **4**, were converted into **6** in high yield by methanolic HCl.

The tendency for **2** and the 6-hydroxy isomer to exist in the keto form may be explained by the steric strain due mainly to the 12-methyl group.[10] This strain is relieved more in the keto form than in the phenol form. The question as to whether similar equilibria exist in other derivatives of benz[*a*]anthracene is under investigation.

The fact that the keto form, **4**, is so reactive may be of significance in the metabolic processes by which 7,12-dimethylbenz[*a*]anthracene, DMBA, induces cancer. From evidence we have adduced, it seems probable that carcinogenic metabolism involves the 5-position in 7-methylbenz[*a*]anthracene and DMBA.[11] Current hypotheses suggest that **3** has a role in carcinogenesis.[12] *We suggest that the reactive intermediate in the case of DMBA may be the ketonic substance* **4** which in principle could readily be formed from an epoxide precursor or some alternate intermediate. The reason why DMBA is more active as a carcinogen than 7-methylbenz[*a*]anthracene may be related to the increased steric strain in DMBA which causes **2** to have a much larger ketonic component than 5-hydroxy-7-methylbenz[*a*]anthracene. Further studies to test the above hypothesis are under way. The carcinogenic activity of hydroxy (part keto?) derivatives of 7-methylbenz[*a*]anthracene and of 12-methylbenz[*a*]anthracene are to be assayed.[13]

Acknowledgment. This work was supported by Research Grant CA-0734 from the National Institutes of Health.

(9) A somewhat related example of the formation of an aryl ether from a ketone is supplied by the conversion of 1,2-dihydrobenz[*de*]-anthracen-3-one to 3-ethoxy-7*H*-benz[*de*]anthracene, on heating in ethanol. See D. W. Cameron, D. G. I. Kingston, and P. E. Schutz, *J. Chem. Soc. C*, 2113 (1967).

(10) A discussion of the steric effect of the 12-methyl group on carcinogenic activity has been presented by M. S. Newman and R. F. Cunico, *J. Med. Chem.*, **15**, 323 (1972).

(11) M. S. Newman and R. F. Cunico, *J. Med. Chem.*, **15**, 323 (1972), and references therein.

(12) E. Boyland, *Biochem. Soc. Symp.*, **5**, 40 (1950); D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, **90**, 6525 (1968).

(13) We hope to be able to supply samples of these materials and of **2** and **4** to interested investigators in the near future.

(14) Postdoctoral Research Associate.

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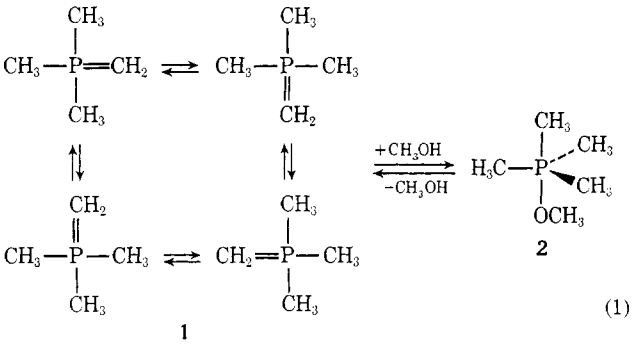
A Carbon-13 and Phosphorus-31 Study of Tetramethylmethoxyphosphorane

Sir:

The title compound (**2**) has recently been prepared[1] from salt-free trimethylmethylenephosphorane (**1**)[2] and methanol (eq 1). It was assigned a trigonal bipyramidal molecular structure on the basis of analytical and spectral data.[3] One of the most interesting implications of this geometry is the appearance of one of the methyl groups in an *axial* position. This proposal rested primarily on the strong shielding of the phosphorus nucleus, which is characteristic of pentacoordinate phosphorus (δ_p −88 ppm, *i.e.*, upfield of the H_3PO_4 standard), and on the low temperature proton nmr spectrum.[3] However, the overall pmr behavior of compound **2** is extremely complex due to facile exchange of protons between the methoxyphosphorane and the various ylidic species,[3,4] as well as the methanol, and the corresponding scrambling of the methoxy groups (eq 1). Ambiguities arising from these dynamic phenomena[5] should be greatly reduced in the ^{13}C nmr spectra, and it was therefore felt desirable to support the proposed structure by additional, more detailed nmr studies and to further characterize the state of



(1)

(1) H. Schmidbaur and H. Stühler, *Angew. Chem.*, **84**, 166 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 145 (1972).

(2) H. Schmidbaur and W. Tronich, *Chem. Ber.*, **101**, 595 (1968).

(3) H. Schmidbaur, H. Stühler, and W. Buchner, *Chem. Ber.*, **106**, 1238 (1973).

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(5) The mechanism of the proton exchange of ylids has been under continuing experimental[4,6,7] and theoretical study,[8] but no final conclusion has been reached as yet.

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(7) H. Schmidbaur, W. Buchner, and D. Scheutzow, *Chem. Ber.*, **106**, 1251 (1973).

(8) R. Hoffmann, D. B. Boyd, and S. Z. Goldberg, *J. Amer. Chem. Soc.*, **92**, 3929 (1970); D. B. Boyd and R. Hoffmann *ibid.*, **93**, 1064 (1971).