such substitutions of different reacting species, we should like to stress that the appearance of discrepancies may be due, wholly or at least partially, to the misuse of the results of quantum-mechanical calculations by the aforementioned authors.

In the first place, electronic charges calculated for the isolated, unreacting molecules should not be used without care for the interpretation of their chemical reactivity. This reactivity depends on the properties of the molecule in the activated complex. Information about these properties, although rarely complete, may be reached, *e.g.*, through calculations of localization energies. While, in some cases, predictions based on the results of charge distribution in the ground state correlate with those obtained from the localization energies, this is in no way a general rule. We have already discussed the significance of this situation for the particular case of purine.[2,3] It also may be useful to add that the same observation concerns properties other than chemical reactivity, in particular the basicity which Jones and Robins[4] have also proposed to correlate recently in the case of purines with the electron density on the nitrogen atoms. Fundamental studies of this problem[5,6] show that the basicity of the nitrogens, in particular in a polyazaheterocyclic compound like purine, depend on a more complex set of factors than the electronic charges of the nitrogen atoms.

In the second place, the calculations to which Sutcliffe and Robins refer are those concerning the purine molecule, while the experimental results with which they are correlated refer to 2,6,8-trichloropurine. Now, it cannot, of course, be assumed without proof or at least without caution that the distribution of the indices responsible for nucleophilic reactivity in a 2,6,8-trisubstituted purine parallels exactly the distribution of the same indices in purine itself. No calculations are available, unfortunately, for 2,6,8-trichloropurine, but an illustration of the fact that this may not be the case is offered by the calculations available for 2,6,8-trihydroxypurine (the enol form of uric acid).[7] The calculations of localization energies predict that the most reactive center towards nucleophilic substitution in this molecule should be carbon 6, while in purine itself equal reactivity was found from that point of view for carbons 6 and 8.

In conclusion, while it is, of course, true that a careful examination of the actual species undergoing the reaction is a most important factor to be considered, it is not less important that the correlation with quantum-mechanical calculations refer to the proper or at least very closely related structure and that the theoretical indices (taken into account) be appropriate for the phenomenon investigated.

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[2] B. Pullman, *J. Chem. Soc.*, 1621 (1959).

[3] B. Pullman, *Tetrahedron Letters*, **4**, 231 (1963).

[4] J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963).

[5] T. Nakajima and A. Pullman, *J. chim. phys.*, 793 (1958).

[6] A. Pullman, "Electronic Aspects of Biochemistry," Proceedings of an International Symposium, Ravello, September, 1963, Academic Press, New York, N. Y.

[7] B. Pullman and A. Pullman, "Quantum Biochemistry," Wiley's Interscience Division, Inc., New York, N. Y., 1963, p. 227.

The Effect of an α-Bromine on the Dienone–Phenol Rearrangement

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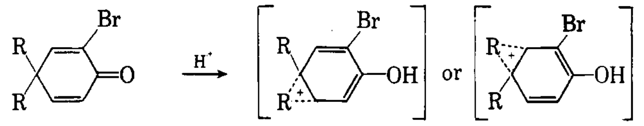
Kirk and Petrow have reported that substitution of a chlorine in the 2- and/or 4-position of $\Delta^{1,4}$-dien- and $\Delta^{1,4,6}$-trien-3-keto steroids results in a marked decrease in the facility with which they undergo the dienone–phenol rearrangement.[2] Likewise, Inhoffen and coworkers found that the rearrangement of the methyl ester of 2,4-dibromo-3-keto-12α-acetoxy-$\Delta^{1,4,6}$-cholatrienic acid was sluggish as compared to the unbrominated substance.[3] The availability of 2-bromo-4,4-diphenylcyclohexa-2,5-dienone (I) and 2-bromo-4,4-dimethylcyclohexa-2,5-dienone (II)[4] offered an opportunity to study the influence of an α-bromine atom on the dienone–phenol rearrangement unencumbered by subsequent reactions which often complicate such rearrangements in steroids.[5]

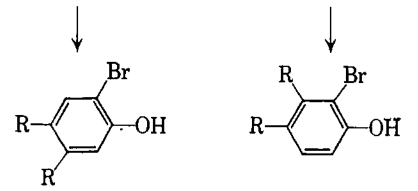
Acid-catalyzed rearrangements of either I or II in acetic anhydride led to two isomeric products. In both instances the major product was the 2-bromo-4,5-disubstituted phenyl acetate, the minor component being the 2-bromo-3,4-disubstituted phenyl acetate. The preference was about 2 to 1 in the dimethyl series but only about 1.2 to 1 in the diphenyl series.

The major product formed in a dienone–phenol rearrangement can generally be accounted for by considering the relative stabilities of the transition states for the possible modes of rearrangement. Of the two possible transition states A and B, A will be favored in that the positive charge is further removed from the electrophilic carbon atom bearing the bromine than is true for B. Steric factors also favor transition state A, but this effect cannot be a deciding factor, since a larger amount of the more sterically crowded product is



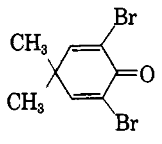
I, R = phenyl
II, R = methyl

(transition state A) (transition state B)



(as the acetate)
III, R = phenyl
V, R = methyl

(as the acetate)
IV, R = phenyl
VI, R = methyl



VII

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[1] Allied Chemical Corp. Fellow, 1960–1961; Eastman Kodak Co. Fellow, 1961–1962.

[2] D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 877 (1959).

[3] H. H. Inhoffen and W. Becker, *Ber.*, **86**, 116 (1953); see also H. H. Inhoffen, H. Jahnke, and P. Nehring, *ibid.*, **87**, 1154 (1954).

[4] F. G. Bordwell and K. M. Wellman *J. Org. Chem.*, **28**, 2544 (1963).

[5] R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950); C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, and St. Kaufmann, *ibid.*, 4540; E. J. Bailey, J. Elks, J. F. Oughton, and L. Stevenson, *J. Chem. Soc.*, 4535 (1961).

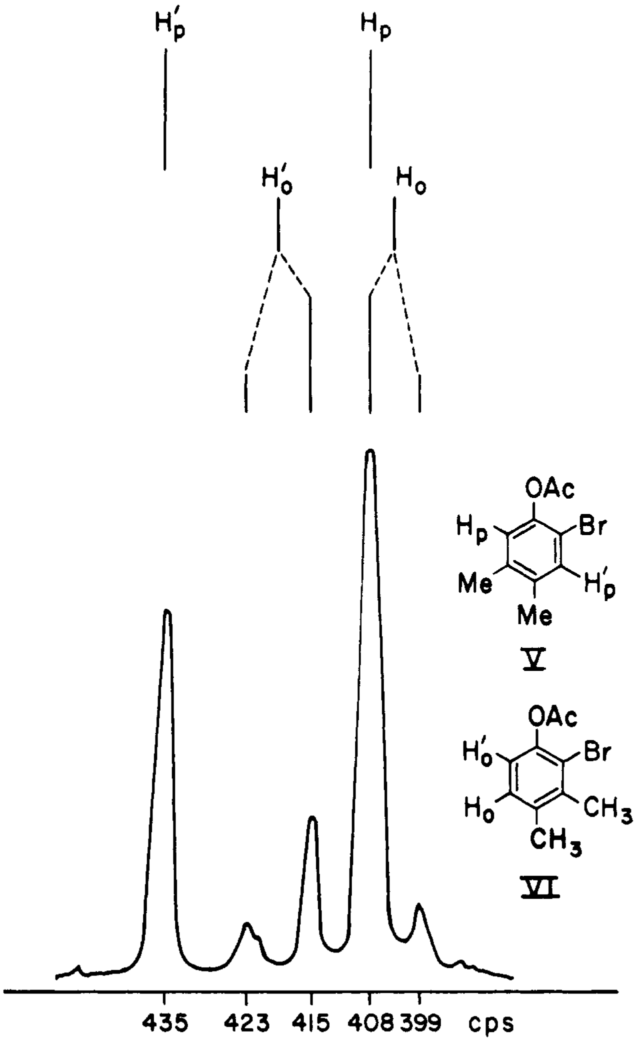

Fig. 1.—The partial 60-Mc. n.m.r. spectrum of the 2-bromo-4,4-dimethylcyclohexa-2,5-dienone rearrangement product.

formed in the diphenyl case than in the dimethyl case. Apparently, the ability of the phenyl group to delocalize the positive charge stabilizes both transition states A and B, thereby making the reaction less selective in the diphenyl series.

The capacity of an α-bromine to destabilize a transition state such as B is further indicated by the failure of 2,6-dibromo-4,4-dimethylcyclohexa-2,5-dienone (VII) to rearrange except under forcing conditions. Here methyl migration in either direction will require a transition state comparable to B. The expected product, 2,6-dibromo-3,4-dimethylphenyl acetate, is formed only on heating VII with *p*-toluenesulfonic acid in acetic anhydride for 37.5 hr.; even then, a small amount (11%) of starting dibromodienone remains. (Of course, the lower basicity of VII also causes a slower reaction.)

The structural assignments to 2-bromo-3,4-diphenyl- and 2-bromo-4,5-diphenyl acetates (III and IV) are based on their common conversion to 3,4-diphenyl acetate and on their proton magnetic resonance (p.m.r.) spectra. One of the two phenolic ring protons was masked in each spectrum by the phenyl protons at about 7.1 p.p.m. In III a singlet aromatic proton (relative area of one) was observed at 7.59 p.p.m. as would be expected for weakly coupled *para* protons,[6] whereas in IV an unsymmetrical doublet at 7.40 p.p.m. (relative area of one) with a first-order coupling constant of 8.5 c.p.s. was observed, as would be expected for one of two *ortho* protons in the phenolic ring.

It is of interest to note that IV was catalytically debrominated only very slowly and could be recovered essentially unchanged when treated under conditions where III was readily debrominated. It seems likely that the slower rate for IV is a consequence of greater hindrance to adsorption of the bromine atom on the palladium catalyst.

In the dimethyl series, gas–liquid chromatography (g.l.c.) of the rearrangement product showed only two components. 2-Bromo-4,5-dimethylphenyl acetate (V) was identified as the major product by introducing an authentic sample and noting which peak was enhanced. The presence of V was confirmed by isolation of the corresponding phenol from the hydrolysis mixture. A second phenol isolated from the hydrolysate afforded 2,6-dibromo-3,4-dimethylphenol on monobromination, thereby verifying the structure of the second monobromide as the phenol of VI. P.m.r. spectra were used to support the g.l.c. analyses and structural assignments (see Experimental).

Experimental[8]

Dienone–Phenol Rearrangement of 2-Bromo-4,4-diphenylcyclohexa-2,5-dienone (I).—A solution of 1.402 g. (0.00431 mole) of I,[4] 0.147 g. of *p*-toluenesulfonic acid monohydrate, and 30 ml. of acetic anhydride was heated at reflux for 1.75 hr. and then poured into water. Solid sodium bicarbonate was added to destroy the excess acetic anhydride, and the hydrolysis mixture was extracted with 600 ml. of ether. A solid suspended at the water–ether interface was separated and dissolved in 200 ml. of benzene. The combined benzene–ether fractions were dried and concentrated to an oily solid. The solid was washed thoroughly with about 20 ml. of ether to give 0.6003 g. (0.00166 mole, 38%) of **2-bromo-3,4-diphenylphenyl acetate (IV)**, m.p. 208–211°. One recrystallization from chloroform raised the melting point to 214°. An analytial sample melted at 214.5°; λ_{max}^{KBr} 5.68, 8.27, 10.7 μ.

Anal. Calcd. for $C_{20}H_{15}BrO_2$: C, 65.41; H, 4.18. Found: C, 65.22; H, 4.27.

The ethereal mother liquors were concentrated to an oil which was adsorbed onto a silica gel column (3 × 65 cm., eluted with 10% ether–hexane). The first fraction (250 ml.) was blank. The second fraction (1400 ml.) gave 0.7458 g. (0.00203 mole, 47%) of **2-bromo-4,5-diphenylphenyl acetate (III)** as thin plates, m.p. 102–103°, after one crystallization from hexane. Further recrystallization raised the melting point to 103–104°; λ_{max}^{KBr} 5.65–5.69 (limits of the broad carbonyl band at its peak), 6.78, 7.30, 8.30–8.40 (broad), 11.08 μ.

Anal. Calcd. for $C_{20}H_{15}BrO_2$: C, 65.41; H, 4.18. Found: C, 64.99; H, 4.22.

The third fraction (500 ml.) gave 0.0090 g. (1%) of IV, m.p. 208–210°, m.m.p. 208–211°.

Debromination of III and IV.—A 62.2-mg. (0.17 mmole) sample of III was stirred with 0.204 g. of 10% palladium–carbon in 5 ml. of acetic acid for 10 hr. under 45 lb. of hydrogen pressure. The mixture was diluted with 50 ml. of ether, filtered through diatomaceous earth, and the filtrate poured into about 100 ml. of water. Solid sodium bicarbonate was added, and the

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(6) *para* protons are known to have small coupling constants of the order of 0–1 c.p.s., whereas, *ortho* protons have coupling constants of about 7–10 c.p.s.[7]

(7) See H. Conroy, "Advances in Organic Chemistry," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1960, p. 309; and L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 85.

(8) Microanalyses were by Miss Hilda Beck and Micro-tech Laboratories, Skokie, Ill. P.m.r. spectra were recorded by Mr. Larry Shadle on a Varian high resolution spectrometer operated at 60 Mc. using either carbon tetrachloride or chloroform as a solvent. Chemical shifts were measured relative to tetramethylsilane (δ 0); a positive value signifies a downfield shift from the reference.

ethereal layer was separated and dried. Concentration gave 47.5 mg. of material melting at 100–115°. Two recrystallizations from hexane gave 18.7 mg. (0.064 mmole) of 3,4-diphenylphenyl acetate, m.p. 126–128°, identified by mixture melting point and infrared spectral comparison with an authentic sample prepared in 86% yield (m.p. 129.5–130.5°, lit.[9] m.p. 130.0–131.5°) according to the method of Zimmerman and Schuster.[9]

In a similar manner, 91.7 mg. of IV in 5 ml. of acetic acid with 0.2 g. of 10% palladium–carbon was stirred for 1 week under 40–45-lb. of hydrogen pressure. The same processing gave 58.9 mg. of ether-insoluble starting material and 17.2 mg. (m.p. 105–115°) of ether-soluble material. Infrared analysis of the ether-soluble material indicated it was mainly 3,4-diphenylphenyl acetate. Crystallization from hexane gave 7.7 mg., m.p. 124–127°, m.m.p. 125–127°.

Dienone–Phenol Rearrangement of 2-Bromo-4,4-dimethylcyclohexa-2,5-dienone (II). **A. Gas–Liquid Chromatography and Proton Magnetic Resonance Analyses.**—A solution of 1.506 g. (0.00749 mole) of II[4] and 0.705 g. of *p*-toluenesulfonic acid monohydrate in 45 ml. of acetic anhydride was heated at reflux for 2.5 hr. Processing in the usual manner gave 1.719 g. (0.00707 mole) of a liquid. G.l.c. analysis[10] showed only two components (partially resolved) with areas in the ratio of 1.98:1.00. V was identified as the major component by introducing an authentic sample, prepared according to Wegand, *et al.*,[11] and noting which peak was enhanced.

The aromatic proton region in the p.m.r. spectrum (see Fig. 1) of the oil showed a singlet for each *para* proton in V and a partially hidden quartet corresponding to the AB system of *ortho* protons in VI with a first-order coupling constant of 8 c.p.s. Areas under proton signals H_p' and H_o', corresponding to one proton in each molecule, were in the ratio of 1.95:1.00, respectively, in excellent agreement with the ratio obtained by g.l.c. A pure sample of V had singlet aromatic proton signals at 6.80 and 7.25 p.p.m.

B. Hydrolysis and Isolation.—A solution of 1.010 g. (5.00 mmoles) of the bromodienone II and 0.507 g. of *p*-toluenesulfonic acid monohydrate dissolved in 30 ml. of acetic anhydride was refluxed for 10 hr. The dark reaction mixture was poured into 250 ml. of water and shaken for several minutes to hydrolyze most of the acetic anhydride. The aqueous mixture was extracted with two 250-ml. portions of ether, and the combined extracts were washed with dilute sodium bicarbonate, dried, and concentrated to give about 2 ml. of liquid. The liquid was dissolved in 30 ml. of 5% methanolic sodium hydroxide and refluxed for 1 hr. After neutralizing the excess base with acetic acid, the solution was concentrated almost to dryness. The residue was taken up in an ether–water mixture, the ethereal layer separated, and the water fraction washed with ether. The combined organic extracts were dried and concentrated to yield an oil (0.8267 g.) which solidified on standing. Attempts to obtain the pure phenol from this material by recrystallization or sublimation were unsuccessful. The material was chromatographed on a 2 × 45 cm. column packed with silica gel and eluted with 6% ether–hexane. Fractions 1 (250 ml.) and 7 (125 ml.) were blank. Fractions 2 (100 ml.) and 3 (40 ml.) were combined to yield 0.0742 g. (0.37 mmole) of an oil which appeared to be a phenol (presumably 2-bromo-3,4-dimethylphenol) from its infrared spectrum [$\lambda_{\max}^{CS_2}$ 280 mμ (sharp), 6.20 μ] and monobromination product (following). The oily phenol could not be caused to solidify[12] and definitely was not V (by infrared analysis). Fraction 4 (125 ml., 0.1513 g., 0.75 mmole) appeared, by rough infrared analysis, to be a mixture of approximately equal amounts of the phenols of V and VI. Fraction 5 (250 ml.) yielded 0.2654 g. (1.26 mmole, m.p. 60–70°) of 2-bromo-4,5-dimethylphenol. One recrystallization gave pure phenol (m.p. 77°), identified by infrared comparison and mixture melting point with an authentic sample prepared according to Heiken[14]; $\lambda_{\max}^{KBr}$ 2.94, 6.19, 11.5, 12.8, 13.6 μ.

Twenty milligrams (0.1 mmole) of the oily phenol in 1 ml. of acetic acid was treated with 25 mg. (0.16 mmole) of bromine in 0.4 ml. acetic acid and the solution allowed to stand in the dark at 25° for 30 min. After pouring into water, neutralizing the acid with sodium bicarbonate, and extracting with ether, 22.8 mg. (0.082 mmole) of an oil was obtained, which solidified to oily needles when seeded with 2,6-dibromo-3,4-dimethylphenol (see below). Recrystallization afforded the dibromophenol as needles, m.p. 33–34°, further identified by infrared analysis.

Dienone–Phenol Rearrangement of 2,6-Dibromo-4,4-dimethylcyclohexa-2,5-dienone (VII).—A solution containing 0.9509 g. (0.0034 mole) of VII[4] and 0.4971 g. of *p*-toluenesulfonic acid monohydrate in 30 ml. of acetic anhydride was heated at reflux for 37.5 hr. Processing as above gave 0.5920 g. of a partially solid material. Fractional crystallization gave 0.1093 g. (0.38 mmole, 11%) of starting material (m.p. 142–144°), further identified by its infrared spectrum. The mother liquors from the crystallization were concentrated and adsorbed onto a chromatographic column (2 × 40 cm.) which had been packed with silica gel and eluted with 8% ether–hexane; 250-ml. fractions were collected. Fractions 1 and 2 gave 0.3417 g. of 2,6-dibromo-3,4-dimethylphenyl acetate containing a small amount of VII as an impurity. Several recrystallizations from petroleum ether (b.p. 40–50°) gave 0.2373 g. (0.74 mmole, 22%) of pure **2,6-dibromo-3,4-dimethylphenyl acetate**, m.p. 57–58°. It was identified by mixture melting point and infrared comparison with an authentic sample (m.p. 57–58°, $\lambda_{\max}^{KBr}$ 5.60, 8.35, 9.68 μ) prepared by acetylation of 2,6-dibromo-3,4-dimethylphenol.[15]

Anal. Calcd. for $C_{10}H_{10}Br_2O_2$: C, 37.30; H, 3.13. Found: C, 37.47; H, 3.06.

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[9] H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **84**, 4527 (1962).

[10] G.l.c. analyses were made on an F & M Model 300 chromatograph using a 15-ft. column packed with 8% 550 silicon oil on 60–80-mesh Chrom P, programmed over 140–190°.

[11] F. Wegand, K. Vogelback and K. Zimmerman, *Ber.*, **80**, 391 (1947).

[12] Hunsberger, *et al.*,[13] have reported that 2-bromo-3,4-dimethylphenol exists as an oil.

[13] I. M. Hunsberger, D. Lednicer, H. S. Gutowsky, D. L. Bunker, and P. Taussig, *J. Am. Chem. Soc.*, **77**, 2466 (1955).

[14] K. Heiken, *Angew. Chem.*, **52**, 236 (1939).

[15] E. von Auwers, *Ann.*, **344**, 171 (1906).

The Structure of Carolic Acid

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Carolic acid,[1] a metabolite of *Penicillium charlesii* G. Smith, possesses the molecular formula $C_9H_{10}O_4$. Consideration of the reactions of the acid in aqueous solution led Clutterbuck,[2] *et al.*, to suggest that the compound resembled the α-acyltetronic acids and could best be represented as a hydrated form (I). It was postulated that the crystalline compound was derived from the hydrated form by loss of water and might possess structure II. Clutterbuck, *et al.*,[2] found that in dry anisole, carolic acid contained no active hydrogen, whereas in pyridine one active hydrogen atom was shown to be present; in order to explain this observation they postulated that the —$COCH_2$— group of the seven-membered ring in II may undergo enolization to —C(OH)=CH— in pyridine. Duncanson[3] has commented that the infrared spectrum of carolic acid under anhydrous conditions suggests that the structure is more closely related to those of the alkyl ethers of the tetronic acids than to the tetronic acids themselves.

A study of the n.m.r. spectrum[4] of carolic acid now confirms its formulation as II. Unlike those of typical acyltetronic acids[5] the spectrum shows no absorption

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[1] P. W. Clutterbuck, W. N. Haworth, H. Raistrick, G. Smith, and M. Stacey, *Biochem. J.*, **28**, 94 (1934).

[2] P. W. Clutterbuck, H. Raistrick, and F. Reuter, *ibid.*, **29**, 300 (1935).

[3] L. A. Duncanson, *J. Chem. Soc.*, 1207 (1953).

[4] Measured on Varian A-60 spectrometer in deuteriochloroform solution with tetramethylsilane as internal standard (δ = 0.00 p.p.m.).

[5] L. J. Haynes and J. R. Plimmer, unpublished observations.