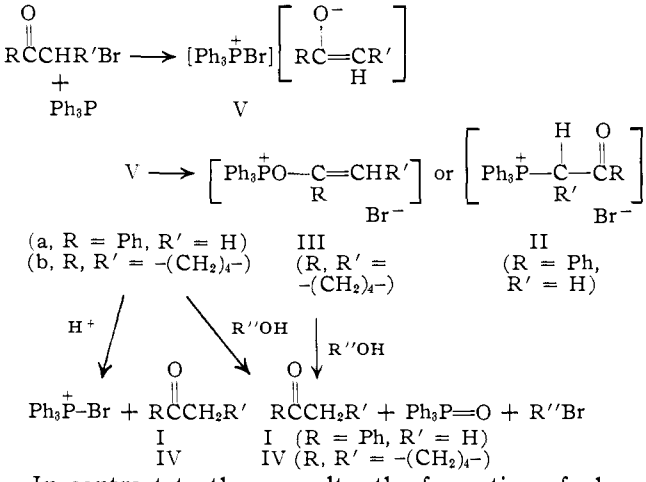
TABLE I
THE REACTION OF PHENACYL BROMIDE WITH TRIPHENYLPHOSPHINE[a]

| Reaction conditions[b] | Yields, % II | Acetophenone[c] | Triphenylphosphine oxide |
|---|---|---|---|
| In anhydrous benzene, 1.5 hr. | 79 | 6 | 19 |
| In anhydrous benzene with excess methanol added | 6 | 64 | 92 |
| In anhydrous benzene with excess acetic acid | 12 | 73 | 29 |
| In anhydrous acetonitrile | 80 | .. | 20 |
| In anhydrous acetonitrile with 2.5 equiv. of dimedone | 40 | 35[d] | 43 |
| In anhydrous diethyl malonate | 35 | 61 | 62 |

[a] All products gave satisfactory infrared spectra or melting points and were compared to genuine samples by thin layer chromatography. [b] All reactions were run in refluxing solvents. [c] Yields were based on conversion to the 2,4-dinitrophenylhydrazone. [d] A 6% yield of 5,5-dimethyl-3-bromocyclohexenone was also obtained and was identical with a genuine sample.[4a]

stage of reaction.[8] It also has been found that the reaction of 2-bromocyclohexanone with triphenylphosphine in refluxing acetonitrile to form the enol triphenylphosphonium bromide (III)[4] can be intercepted by the initial presence of diethyl malonate. Under such conditions cyclohexanone (IV) is obtained in 73% yield after 6 hr. while it is obtained in only 15% yield if the malonate is added after the reaction is allowed to proceed for 7.5 hr. Thus, once an enol phosphonium salt is formed it no longer reacts with diethyl malonate, at least to any major extent, although it can still react with an alcohol.[4c] Therefore, an enol phosphonium salt is not in equilibrium with an enolate bromophosphonium ion pair.[9]

The reaction sequence for 2-bromocyclohexanone therefore would appear to be: bromoketone to enolate bromophosphonium ion pair (Va) to III, while for phenacyl bromide the sequence is: bromoketone to enolate bromophosphonium ion pair (Vb) to II.




In contrast to these results, the formation of phenacyltriphenylphosphonium chloride (VI),[10] which occurs in 65% yield from the reaction of phenacyl chloride with 1.02 equivalents of triphenylphosphine in refluxing anhydrous benzene for 24 hr., is not greatly affected by the initial presence of excess methanol since a 56% yield of VI is still obtained. Thus phenacyl chloride reacts with triphenylphosphine primarily *via* straightforward displacement of chloride ion.[11]

Work is now in progress on the related reactions of haloketones with phosphites.

**Acknowledgment.**—The authors are indebted to Mr. Joseph Pugach of Columbia University for some of the vapor phase chromatography.

(8) As a control a mixture of diethyl malonate and phenacyl bromide, after being refluxed for 22 hr., gave no other compounds as determined by thin layer chromatography. Phenacyl bromide was recovered in 87% yield.

(9) The enol phosphonium salt derived from 2-bromocyclohexanone is also not in equilibrium with starting compounds. Unpublished results by George Gonis, Department of Chemistry, Lehigh University, demonstrated the absence of triphenylphosphine after 1.5 hr. of reaction with 2-bromocyclohexanone in dry 1,2-dimethoxyethane. At this time no alkylation of phosphine with butyl iodide was detected, whereas initially alkylation occurred as the major process in competition with enol phosphonium salt formation.

(10) Identified by conversion, in 66% yield, to the known phosphorane, m.p. 183–185°; genuine phosphorane prepared from II. See ref. 2.

(11) However, the reaction of desyl chloride with triphenylphosphine gives an enolphosphonium salt which then is converted to diphenylacetylene; see ref. 4c. In this case nucleophilic attack on chlorine leading to enolate formation may be enhanced because of the adjacent phenyl ring.

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## A Stereospecific Synthesis of *dl*-Quinic Acid

*Sir:*

We found it necessary to devise a synthesis of quinic acid, I, utilizing non-symmetrical intermediates, in order that C-14 could be incorporated into specific positions of the molecule. The first total synthesis of quinic acid was reported by Grewe, Lorenzen and Vining[1] in 1954. This route was not applicable to our needs in that their procedure involved the symmetrical molecule hydroquinone in the formation of the ring system of quinic acid.

The synthesis was performed through an initial Diels–Alder reaction of *trans,trans*-1,4-dichlorobuta-1,3-diene,[2] II, with benzyl $\alpha$-acetoxyacrylate. The latter was prepared from benzyl pyruvate upon refluxing with acetic anhydride in the presence of *p*-toluenesulfonic acid; b.p. 99–101 (0.5 mm.); $n^{22}D$ 1.5075: yield, 32%; *Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.68; H, 5.59. Benzyl pyruvate was prepared in 92% yield by refluxing pyruvic acid and benzyl alcohol in anhydrous benzene and removing the water which was formed by azeotropic distillation. The literature values,[3] 103–105° (26 mm.), 103–104° (36 mm.), were inconsistent with our results, 103–105° (2 mm.), $n^{21.5}D$ 1.5100. *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.76; H, 5.74.

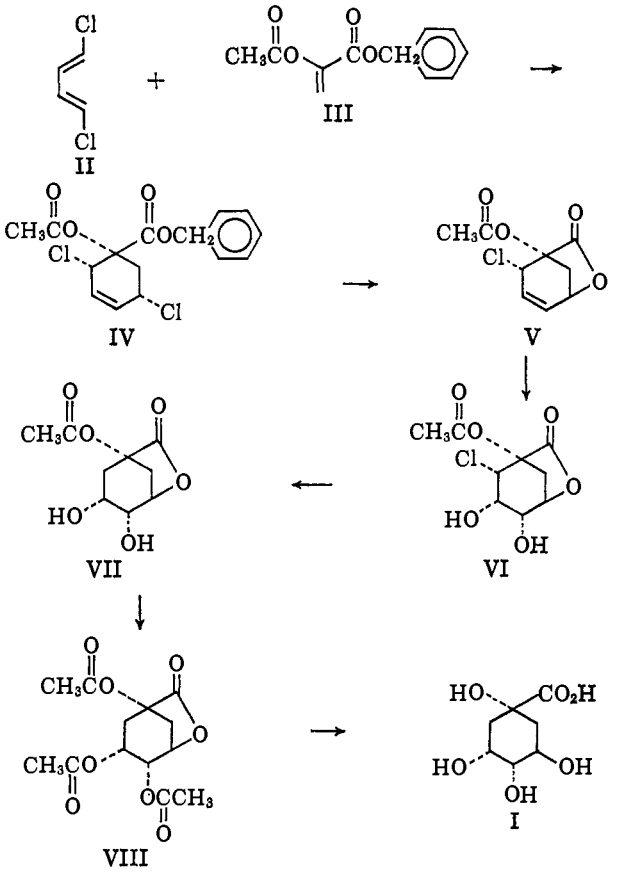
Benzyl 1$\alpha$-acetoxy-2$\alpha$,5$\alpha$-dichlorocyclohex-3-ene-1$\beta$-carboxylate, IV, was converted to the chlorolactone, V, by heating at 150° for 22 hr. The chlorolactone, V, (b.p. 150–152° (0.5 mm.)) was *cis*-hydroxylated using osmium tetroxide to give 1-acetyl-6-chloroquinide, VI, in 46% yield; m.p. 183–185°. *Anal.* Calcd. for $C_9H_{11}ClO_6$: C, 43.13; H, 4.42; Cl, 14.14. Found: C, 43.82; H, 4.20; Cl, 13.80. Hydrogenolysis of the chlorine atom was effected utilizing a freshly prepared W-6 Raney nickel catalyst to yield *dl*-1-acetylquinide, VII, in 87% yield, m.p. 215–216° dec. *Anal.* Calcd. for $C_9H_{12}O_6$: C, 50.00; H, 5.60. Found: C, 49.42; H, 5.45. *dl*-1-Acetylquinide was converted to the triacetyl derivative, VIII, by refluxing in acetic anhydride. The same derivative was prepared from the natural (−)-quinic acid according to the method of Erwig and Koenigs[4] in order to compare the infrared and nuclear magnetic resonance spectra in solution.

(1) R. Grewe, W. Lorenzen and L. Vining, *Chem. Ber.*, **87**, 793 (1954).

(2) W. Reppe, O. Schlichting, K. Klager and T. Toepl, *Ann.*, **560**, 1 (1948).

(3) L. Simon, *Bull. soc. chim. France*, [3] **13**, 483 (1895); *Ann. Chem. Phys.*, [7] **9**, 502 (1896).

(4) E. Erwig and W. Koenigs, *Chem. Ber.*, **22**, 1457 (1899).



The infrared and nuclear magnetic resonance spectra of the triacetyl derivatives were essentially identical. Triacetylquinide, VIII, is readily converted to quinic acid by heating in aqueous potassium hydroxide solution followed by ion-exchange chromatography to yield the free acid.[5]

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(5) R. Grewe, W. Lorenzen and L. Vining, *Chem. Ber.*, **87**, 793 (1954).

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## Chemical Shifts of Axial and Equatorial α-Protons in the N.m.r. of Steroidal α-Haloketones

*Sir:*

The discovery[1] that axial hydrogens are more highly shielded than corresponding equatorial ones increased the use of n.m.r. chemical shift data in structural studies of cyclohexane systems. Interpretations of this differential shielding have been proposed[2,3a,c,d] and scattered examples of exceptions to the rule have been reported.[1b,4] We have found that a carbonyl group adjacent to a monohalogenated carbon in steroidal α-haloketones has the net effect of deshielding the remaining α-hydrogen when it is axial and of shielding it when it is equatorial. The effects are pronounced enough to reverse the usual axial–equatorial relationship and therefore are of practical importance for stereochemical studies as well as of theoretical interest.

The compounds examined were seventeen steroidal α-haloketones, which include the complete set of stereoisomeric 6-monohalo-5α-cholestan-7-ones (halogen = F, Cl, Br, I). Because of the relative rigidity of ring B, this set is of value for correlation of stereochemistry with chemical shifts, with vicinal coupling constants and their dependence on the nature of attached substituents, with long range shielding and deshielding effects, etc. Table I lists the chemical shifts in deuteriochloroform (in p.p.m. downfield from tetramethylsilane) for the hydrogen on the halogen-bearing carbon. The values for five epimeric pairs

TABLE I

| Number | Compound[a] | H conformation[b] | Chemical shift, δ, p.p.m.[c] |
|---|---|---|---|
| 1 | 6α-Fluoro-5α-cholestan-7-one | a | 4.51 |
| 2 | 6β-Fluoro-5α-cholestan-7-one | e | 4.40 |
| 3 | 6α-Chloro-5α-cholestan-7-one | a | 4.43 |
| 4 | 6β-Chloro-5α-cholestan-7-one | e | 4.01 |
| 5 | 6α-Bromo-5α-cholestan-7-one | a | 4.63 |
| 6 | 6β-Bromo-5α-cholestan-7-one | e | 4.13 |
| 7 | 6α-Iodo-5α-cholestan-7-one | a | 4.91 |
| 8 | 6β-Iodo-5α-cholestan-7-one | e | 4.37 |
| 9 | 3β-Bromo-5α-cholestan-2-one | a | 4.61 |
| 10 | 3α-Bromo-5α-cholestan-2-one | e | 4.28 |
| 11 | 3α-Iodo-5α-cholestan-2-one | e | 4.60 |
| 12 | 7α-Bromo-5α-cholestan-6-one | e | 4.17 |
| 13 | 4α-Bromo-2α-methylcholestan-5α-3-one | a | 4.64 |
| 14 | 4β-Bromo-5β-cholestan-3-one | a | 5.03 |
| 15 | 2α-Chloro-5α-cholestan-3-one | a | 4.65 |
| 16 | 2α-Bromo-5α-cholestan-3-one | a | 4.80 |
| 17 | 2α-Iodo-5α-cholestan-3-one | a | 4.97 |
| 18 | 6α-Bromo-5α-cholestane | a | 3.99 |
| 19 | 6β-Bromo-5α-cholestan-3β-ol acetate | e | 4.27 |
| 20 | 6α-Chloro-5α-cholestane | a | 3.74 |
| 21 | 3β-Bromo-5α-cholestane | a | 3.90 |
| 22 | 3α-Bromo-5α-cholestane | e | 4.63 |
| 23 | Cyclohexyl fluoride | a | 4.28 |
| 24 | Cyclohexyl fluoride | e | 4.72 |
| 25 | Cyclohexyl chloride | a | 3.73 |
| 26 | Cyclohexyl chloride | e | 4.43 |
| 27 | Cyclohexyl bromide | a | 3.92 |
| 28 | Cyclohexyl bromide | e | 4.64 |
| 29 | Cyclohexyl iodide | a | 4.08 |
| 30 | Cyclohexyl iodide | e | 4.83 |

[a] **1**, m.p. 160–161°, α −18°; **2**, m.p. 100.5–101°, α −80°; **3**, m.p. 143–143.5°, α −8°; **4**, m.p. 108.5–109°, α +33°; **5**, m.p. 153.5–154°, α −7°; **6**, m.p. 106–106.5°, α +68°; **7**, m.p. 148.5–149°, α +1°; **8**, m.p. 99–99.5°, α +114°. All new haloketones gave satisfactory analytical data and were characterized by infrared and ultraviolet absorption, by optical rotations measured in chloroform and at the sodium D line by optical rotatory dispersion, by chemical transformations, and by the n.m.r. coupling constants cited in this paper. Their syntheses will be described in a forthcoming publication. Compounds **9**, **10** and **11** were kindly supplied by Professor C. Djerassi [C. Djerassi, H. Wolf and E. Bunnenberg, *J. Am. Chem. Soc.*, **85**, 324 (1963)]. Compounds **12–22** were prepared according to reported procedures. Data for the cyclohexyl halides (**23–30**) are those recorded by A. J. Berlin and F. R. Jensen [*Chem. Ind.* (London), 998 (1960)] in their study of conformational equilibria at low temperatures in carbon disulfide solution. [b] Conformations (a = axial; e = equatorial) refer to the hydrogen attached to the halogenated carbon. [c] The n.m.r. spectra of compounds **1–22** were recorded in deuteriochloroform at 60 Mc./sec. (Varian A-60 spectrometer). Chemical shifts (δ) are recorded in p.p.m. as displacements downfield from tetramethylsilane, used as internal reference. All entries in Tables I and II represent averages of several scans.

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(2) A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, **70**, 833 (1958).

(3) (a) L. M. Jackman, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, Chapter 7; (b) p. 52; (c) J. I. Musher, *J. Chem. Phys.*, **35**, 1159 (1961); **37**, 34, 192 (1962); (d) R. F. Zurcher, *Helv. Chim. Acta*, **44**, 1755 (1961).

(4) (a) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); (b) A. S. Matlack, J. C. W. Chien and D. S. Breslow, *J. Org. Chem.*, **26**, 1455 (1961); (c) E. Campaigne, N. F. Chamberlin and B. E. Edwards, *ibid.*, **27**, 135, 4718 (1962); (d) J. Tadanier and W. Cole, *ibid.*, **27**, 4610, 4624 (1962).