[CONTRIBUTION FROM QUEEN MARY COLLEGE, UNIVERSITY OF LONDON, LONDON, ENG.]

New Heteroaromatic Compounds. XIV.[1] Boron-containing Analogs of Purine, Quinazoline and Perimidine

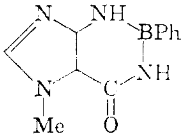
BY S. S. CHISSICK, M. J. S. DEWAR[2] AND P. M. MAITLIS

RECEIVED DECEMBER 3, 1960

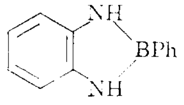
The preparations of a number of boron-containing analogs of purine, pyrimidine and perimidine derivatives are described and their properties discussed. These compounds were easily hydrolyzed and in general much less stable than heteroaromatic boron compounds containing only one other hetero atom (*e.g.*, 10,9-borazarophenanthrene or 2,1-borazaronaphthalene).

We recently reported[3] the synthesis of two new heterocyclic compounds containing boron, one an analog of a purine, the other an analog of a quinazoline. Here we describe this work in more detail and also the preparation of a number of related compounds.

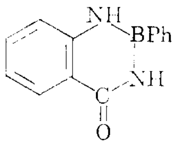
Considerable interest has recently been shown in the preparation of compounds containing boron which might act as anti-metabolites to neoplastic cells or which might be preferentially absorbed by these cells and so be used in cancer therapy by neutron capture irradiation.[4] An obvious class of such compounds are analogs of purines containing boron in the ring, such as I. The previously reported synthesis and properties of compounds such as II suggested that these boradihydropurines[5] and other related compounds might be relatively stable.[7]



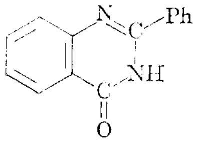
I



II



III

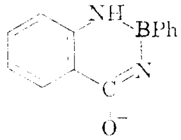


IV

As a model for the synthesis of 2-phenyl-6-hydroxy-7-methyl-2-boradihydropurine (I) we first prepared 2-phenyl-2-boradihydro-4-quinazolone (III). This compound was obtained from *o*-aminobenzamide by three different routes: by reaction with phenylboron dichloride in benzene (20–30% yield); by heating with dibutyl phenylboronate with continuous removal of butanol (63% yield); or (best) by removal of the solvent from a solution of *o*-aminobenzamide and phenylboronic acid (82% yield in ethanol, 91% yield in benzene).

2-Phenyl-2-boradihydro-4-quinazolone (III) was a colorless crystalline solid, m.p. 210–211°, stable to air and moisture. The structure follows from the methods of synthesis, from analysis, and from the lack of NH_2 and B–O bands in the infrared spectrum. The ultraviolet spectrum of a freshly prepared solution of III in 95% ethanol was quite different from that of an equimolecular mixture of *o*-aminobenzamide and phenylboronic acid (Fig. 1). The spectrum of III changed with time, however, and after 24 hours resembled that of the mixture. This suggests that III is slowly solvolyzed in 95% ethanol. Similar results were obtained in the presence of acid or alkali, though in the latter case the solvolysis seemed to be slower.

The ease of hydrolysis of III and the marked difference between its spectrum and that of the analogous quinazolone IV[8] indicate that III is less aromatic than the compounds described[7] by Dewar, Kubba and Pettit (*e.g.*, II). This conclusion was supported by the infrared spectrum of solid III which showed a carbonyl band; and by a large bathochromic shift of the main ultraviolet absorption of III (from 312 to 358 mμ) on addition of alkali. This spectral shift must be due to a deprotonation of III to the conjugate ion V. The quinazolone IV shows no such change in its ultraviolet spectrum on treatment with alkali.



V

Attempts to O-alkylate III with dimethyl sulfate and alkali or with diazomethane failed; similar results have been reported[9] for hydroxypyrimidines. With alkali and dimethyl sulfate III gave only *o*-dimethylaminobenzamide, while the only reaction with diazomethane was a slow catalyzed decomposition to polymer.[10] Attempts to chlorinate the compound with phosphorus oxychloride either alone or in the presence of dimethylaniline[11] failed. In the first case only *o*-aminobenzamide hydrochloride was obtained; in the second, tars. An attempt to prepare an enamine from III and pyrrolidine by azeotropic distillation in benzene also failed.[12]

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(1) Part XIII, M. J. S. Dewar and P. M. Maitlis, *Tetrahedron*, in press.

(2) Department of Chemistry, University of Chicago, Chicago 37, Ill.

(3) S. S. Chissick, M. J. S. Dewar and P. M. Maitlis, *J. Am. Chem. Soc.*, **81**, 6329 (1959).

(4) A. H. Soloway, *ibid.*, **81**, 3017 (1959), and references therein.

(5) The terminology of Dewar and Dietz[6] for heteroaromatic boron compounds is not directly applicable in this case. Since the compounds so far prepared show no marked stability, we have therefore used conventional terminology for them. We believe that the 6-boradihydropurines will show stability of a much higher order, but no such compounds have yet been described.

(6) M. J. S. Dewar and R. Dietz, *J. Chem. Soc.*, 2728 (1959).

(7) M. J. S. Dewar, Ved P. Kubba and R. Pettit, *ibid.*, 3076 (1958).

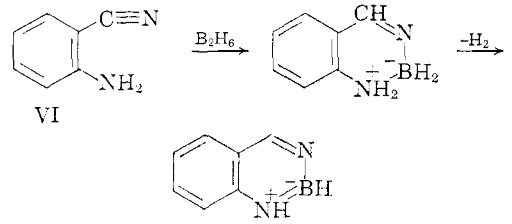
(8) M. Korner, *J. prakt. Chem.*, [2] **36**, 155 (1888).

(9) D. Davidson and O. Baudisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).

(10) *Cf.* M. J. S. Dewar and P. M. Maitlis, *ibid.*, **83**, 187 (1961).

(11) *Cf.* G. W. Kenner, B. Lythgoe, A. R. Todd and A. Topham, *J. Chem. Soc.*, 574 (1953); J. Baddiley and A. Topham, *ibid.*, 678 (1954).

Diborane is known to react with nitriles to give adducts of the type RCH = N—BH_2[13]; it will also react with amines to form complexes which on warming lose hydrogen to form aminoboranes.[14] We therefore hoped that *o*-aminobenzonitrile (VI) might react with diborane to form a quinazoline analog (VII) by the route



VI

VII

Only polymers were obtained, however, using diborane prepared *in situ*[15,16] or trimethylamineborine[17] in boiling xylene or high-boiling petroleum ether. The infrared spectrum of this polymer showed only a weak C≡N band and no BH band; hydrolysis gave only *o*-aminobenzonitrile (VI). Attempts to treat VI with phenylboron dichloride also gave polymers exclusively.

2 - Phenyl - 6 - hydroxy - 7 - methyl - 2 - boradihydropurine (I) was obtained in 62% yield by heating 4-amino-1-methyl-5-imidazolecarboxamide (VIII)[18] with dibutyl phenylboronate with continuous removal of butanol. A more convenient method of preparation was to mix hot concentrated ethanolic solutions of VIII and phenylboronic anhydride (IX) (the latter being presumably converted to diethyl phenylboronate); on cooling compound I crystallized in 97% yield. The boradihydropurine was a high melting compound, stable to air, which was insoluble in all solvents tried other than alcohols. The structure of I was indicated by the method of preparation, analysis, and the infrared spectrum. The ultraviolet spectrum of I in ethanolic solution was, however, identical with that of a mixture of VIII and IX; this suggests that I is immediately solvolyzed, a conclusion supported by the fact that compound I dissolved only on prolonged boiling with a large volume of alcohol but did not separate from solution until most of the solvent had been removed.

The solvolysis presumably gives ethyl phenylboronate and VIII reversibly; on removing the solvent, recombination to I takes place. Similar reactions occur in the case of III which slowly solvolyzes in ethanol to *o*-aminobenzamide and ethyl phenylboronate; the boradihydroquinazolone crystallized when strong alcoholic solutions of the two components were mixed.

In view of the current interest in 8-azapurines as carcinostatic agents 2,8-diphenyl-6-hydroxy-(1H) 8-bora-8-azadihydropurine (X) was also synthesized. The only feasible route to this was by heating 3-amino-1-phenyl-1,2,5-triazole-4-carboxamide (XI) with one mole of dibutyl phenylboronate, X being obtained in 23% yield and purified by vacuum sublimation. Attempts to crystallize the compound from ethanol led to solvolysis.

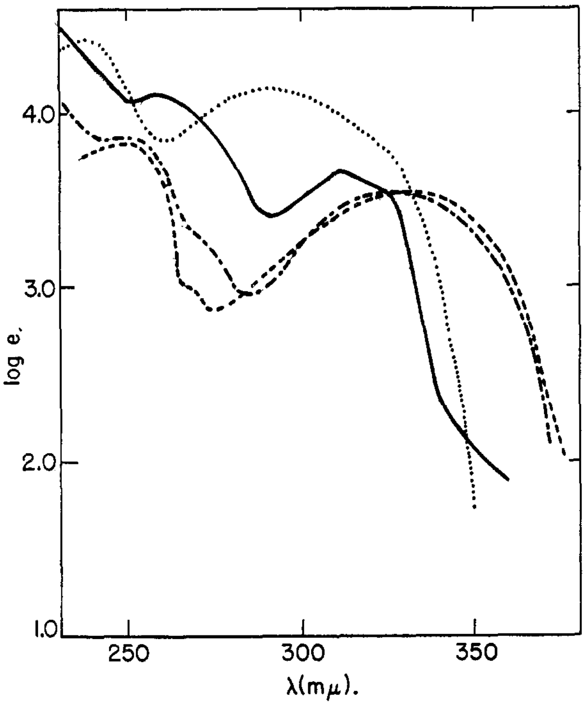
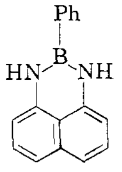
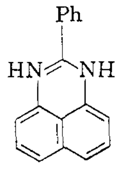


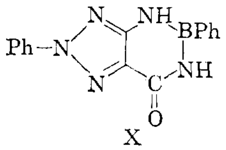
Fig. 1.—Ultraviolet spectra in 95% ethanol of III, freshly prepared (———) and after 24 hours (—·—·—·); of an equimolecular mixture of *o*-aminobenzamide and phenylboronic acid (---------) and of IV (......).



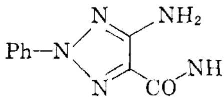
XII



XIII



X



XI

The infrared spectra of these compounds show the expected characteristics. There are no bands which correspond to normal OH, NH_2 or B–O vibrations. All show strong NH bands, at 3.14 μ in I, at 3.01 and 3.08 μ in III, and at 3.03 and 3.13 μ in X. Strong carbonyl bands appeared in the three compounds at 6.10, 6.10 and 6.00 μ, respectively, the region quoted for carbonyl absorption in secondary amides.[19] *o*-Aminobenzamide has NH_2 bands at 2.94, 3.01 and 3.13 μ and a carbonyl band at 6.04 μ; these bands appear at 3.00, 3.12, 3.20 and 5.93 μ in VIII and at 2.89, 2.93 and 5.95 μ in XI.

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[12] *Cf.* M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959).

[13] H. I. Schlesinger and A. B. Burg, *Chem. Revs.*, **31**, 1 (1942).

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[16] A. E. Finholt, A. C. Bond, K. E. Wilzbach and H. I. Schlesinger, *ibid.*, **69**, 2692 (1947).

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[18] J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, **7**, 713 (1924).

[19] L. J. Bellamy, "Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 181.

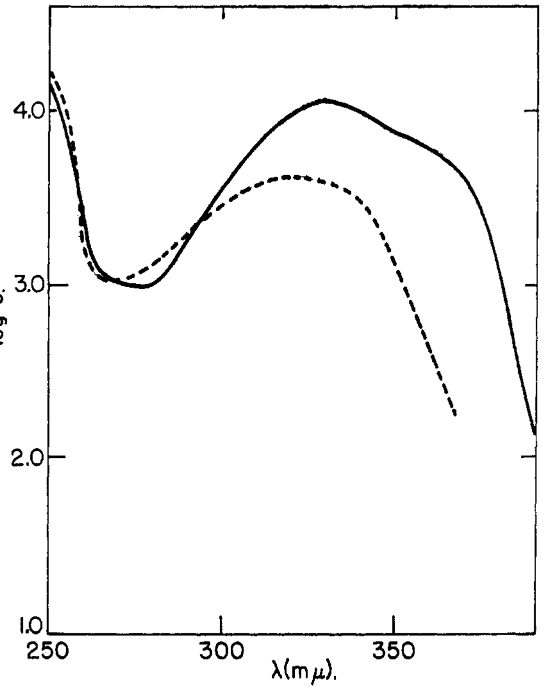

Fig. 2.—Ultraviolet spectra in alcoholic hydrochloric acid (0.5 *N*) of XII (———) and of an equimolecular mixture of 1,8-diaminonaphthalene and phenylboronic acid (---------).

One other cyclic boron compound, 2-phenyl-2-boradihydroperimidine (XII), has also been prepared. It was obtained in low yield from 1,8-diaminonaphthalene and phenylboron dichloride in boiling benzene, or better by fusing the diamine with phenylboronic anhydride at 100° under reduced pressure. The compound could be sublimed in a vacuum or crystallized from petroleum ether, forming pale yellow crystals which slowly turned red on standing in air. The infrared spectrum showed no B–O or NH_2 bands, and had a single NH band at 2.91 μ. The ultraviolet spectrum resembled closely that of a mixture of phenylboronic anhydride and 1,8-diaminonaphthalene; since, however, the spectrum of XII was quite reproducible and significantly different from that of the mixture, and since it did not change with time, it seems clear that the spectrum is that of XII rather than its solvolysis products. The difference was moreover accentuated by addition of acid, the main band of XII increasing in intensity whereas that of the mixture is reduced (Fig. 2). It seems clear that XII is much more stable to solvolysis than the other new boron compounds described here; however, the ultraviolet spectrum of XII was very different from that of 2-phenylperimidine (XIII).

All these compounds are clearly much less stable than the 10,9-borazarophenanthrenes,[20] 2,1-borazaronaphthalenes,[6] 10,9-boroxarophenanthrenes[21] or 9,10-borazaroanthracenes.[22] It seems clear that real stability is observed only in compounds where at least one of the ring atoms adjacent to boron is carbon. The stability is still further decreased by introduction of hydroxyl groups; thus the perimidine analog XII was the most stable of the new compounds described here. This is what might have been expected. Compounds in which both the ring atoms adjacent to boron are heteroatoms are easily hydrolyzed since the high polarity of the bonds between boron and nitrogen, oxygen or sulfur, increases the susceptibility of the boron atoms in such compounds to nucleophilic attack; while introduction of hydroxyl groups into nitrogen heterocycles is well known to reduce their aromaticity by cross-conjugation.

This suggests that purine analogs are only likely to be of interest as chemotherapeutic agents if they contain boron in positions adjacent to carbon in the ring. We are currently trying to prepare compounds of this type.

Experimental

Ultraviolet spectra were determined in 95% ethanol on a Unicam SP 500 spectrophotometer. Boron analyses were carried out by decomposing the compound in a mixture of hot acetone and water and titrating the phenylboronic acid formed in the presence of mannitol.

***o*-Aminobenzamide.** *o*-Nitrobenzamide was prepared in 68% yield from *o*-nitrobenzoic acid by conversion to the acid chloride with thionyl chloride followed by treatment with ammonia and crystallization from benzene; m.p. 174–175° (lit.[23] 174°).

Hydrazine hydrate (25 ml.) was added during 45 minutes to a mixture of *o*-nitrobenzamide (20 g.), palladized charcoal (10% Pd, 0.6 g.) and ethanol (250 ml.) heated under reflux on a steam-bath. After a further 30 minutes the solution was filtered and evaporated and the residue dried in a vacuum and crystallized from benzene, giving *o*-aminobenzamide (15.6 g., 95%), m.p. 111–112° (lit.[24] 109–111°).

2-Phenyl-2-boradihydro-4-quinazolone (III). (a) **From *o*-Aminobenzamide and Phenylboron Dichloride.**—Phenylboron dichloride (2.2 g.) in benzene (10 ml.) was added to a hot benzene solution of *o*-aminobenzamide (1.8 g., 60 ml.). A yellow precipitate formed which on refluxing turned paler; refluxing was continued for 24 hours after which the solution was filtered hot and the precipitate washed several times with boiling benzene. The insoluble precipitate remaining was polymeric (1.6 g.) and was not further investigated. On cooling the benzene filtrate the boradihydroquinazolone (III) crystallized; recrystallization from benzene gave 0.6 g. (20%) of the cyclic compound, m.p. 210–211°.

Anal. Calcd. for $C_{13}H_{11}ON_2B$: C, 70.27; H, 4.95; N, 12.61; B, 5.0; mol. wt., 213. Found: C, 70.22; H, 4.86; N, 12.68; B, 5.1; mol. wt. (Rast), 213.

(b) **From *o*-Aminobenzamide and Dibutyl Phenylboranate.**—*o*-Aminobenzamide (3 g.) and dibutyl phenylboronate (10 ml.) were heated together in an oil-bath at 150° for 12 hours. The mixture of butanol and dibutyl phenylboronate was then removed under vacuum and the solid residue was crystallized from benzene to give III (3.2 g., 63%) m.p. 206–209°, mixed m.p. with authentic material 209–210°.

(c) **From *o*-Aminobenzamide and Phenylboronic Anhydride.**—*o*-Aminobenzamide (0.6 g.) in ethanol (10 ml.) was added to a solution of phenylboronic anhydride (0.55 g.) in ethanol (10 ml.). The solution was boiled vigorously until the volume had been reduced to *ca.* 5 ml. On cooling, crystals of III (0.8 g., 82%), m.p. and mixed m.p. with authentic material 210–211°, were obtained.

When benzene was used as solvent, a slightly higher yield (91%) of rather more impure material, m.p. 206–209° was obtained.

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(20) M. J. S. Dewar, Ved P. Kubba and R. Pettit, *J. Chem. Soc.*, 3073 (1958).

(21) M. J. S. Dewar and R. Dietz, *ibid.*, 1344 (1960).

(22) P. M. Maitlis, *ibid.*, 425 (1961).

(23) C. P. Baertlein, *Ber.*, **10**, 1713 (1877).

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2-Phenyl-6-hydroxy-7-methyl-(1H)2-boradihydropurine (I); (a) From 4-Amino-1-methyl-5-imidazolecarboxamide (VIII) and Dibutyl Phenylboronate.—Using method b for preparing III, the boraropurine I was obtained from the imidazolecarboxamide VIII[17] in 63% yield. It dissolved in a large volume of ethanol on prolonged boiling, but no solid separated on cooling. Crystals of I began to form only when the solution had been concentrated to a very small volume; Compound I had no m.p., subliming slowly above 300° (copper block).

Anal. Calcd. for $C_{11}H_{11}ON_4B$: C, 58.41; H, 4.87; N, 24.78; B, 4.9. Found: C, 58.40; H, 4.78; N, 24.66; B, 4.9.

(b) **From VIII and Phenylboronic Anhydride.**—Using method c for III, Compound I was obtained in 97% yield.

2,8-Diphenyl-6-hydroxy-(1H)2-bora-8-azidihydropurine (X).—A mixture of 3-amino-2-phenyl-1,2,5-triazole-4-carboxamide (XI)[25] (3.0 g.) and dibutyl phenylboronate (3.4 g.) was heated to 160° until the initial vigorous reaction had subsided. The temperature was then raised to 190°. After 3 hours the mixture was cooled and the solid which had separated filtered and washed with hot dry benzene to give the borazadihydropurine X as pale brown crystals (1.0 g., 23%). Crystallization from ethanol gave only XI; X was insoluble in all other solvents. Sublimation at 240° (2 mm.) gave colorless needles, m.p. 300°, which gave a poor carbon analysis.

Anal. Calcd. for $C_{15}H_{12}ON_5B$: C, 62.28; H, 4.15; N, 24.22; Found: C, 60.75; H, 4.24; N, 24.36.

2-Phenyl-2-boradihydroperimidine (VII).—Recrystallized "pure" grade 1,8-diaminonaphthalene (1.9 g.) and phenylboronic anhydride (1.3 g.) were mixed intimately and fused under high vacuum for 1 hour at 100°; the liquid bubbled and turned brown. The temperature was raised briefly to 140° and then the liquid was allowed to cool to a glass. This was crystallized from ether–petroleum ether (b.p. 40–60°) to give 2-phenyl-2-boradihydroperimidine (2.1 g., 71%), m.p. 92–95°. Sublimation at 180° (1 mm.) gave the material pure in very pale yellow needles (which turned deep red on standing in air for 4 days), m.p. 95–96°.

Anal. Calcd. for $C_{16}H_{13}N_2B$: C, 78.69; H, 5.33; N, 11.47; mol. wt., 244. Found: C, 78.55; H, 5.15; N, 11.22; mol. wt. (Rast), 225.

Acknowledgments.—The authors wish to thank British Petroleum Ltd. for the award of a Fellowship to P M. M., the Department of Scientific and Industrial Research for the award of a studentship to S. S. C., and Mr. P. Cook for determining the infrared spectra.

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[25] E. Richter and E. C. Taylor, *J. Am. Chem. Soc.*, **78**, 5850 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, CALIF., AND THE DEPARTMENT OF CHEMISTRY, HARRISON LABORATORY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PENNA.]

The Dipole Moment and Structure of Some α-Halocamphors, α-Haloindanones and 2-Bromo-4-phenylcyclohexanone

BY W. D. KUMLER, N. PEARSON AND F. V. BRUTCHER, JR.

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The dipole moments of α-chlorocamphor, α′-chlorocamphor, α-bromocamphor, α,α′-dibromocamphor, 1-chloro-2-indanone, 1-bromo-2-indanone and 2-bromo-4-phenylcyclohexanone have been measured in different solvents. α-Chlorocamphor and α′-chlorocamphor have identical moments indicating that the chlorine atoms occupy an intermediate bisectional position between axial and equational in these compounds. The α-haloindanones have smaller moments than the α-halocamphors by an amount expected to result from the presence of the phenyl ring. The moments are in keeping with the geometry, about the halogen and carbonyl groups, being essentially the same in the two cases. The lack of variation of the dipole moment with change of solvent in the case of the halocamphors, indicates a rigid five-member ring structure, and the variation of the moment in case of the indanones suggests some flexibility in this five-membered ring structure. The moment of 2-bromo-4-phenylcyclohexanone indicates the bromine is in the axial position.

Introduction

Dipole moments have been of use in the elucidation of the structure of α-halocyclohexanones and α-halocyclopentanones.[1-4] Infrared spectra[4] have been used to study the conformation of substituted cyclopentanes including the important α-halocamphors and α-haloindanones. It is of interest to measure the dipole moments to see if the two methods are in agreement with regard to the conformation of these compounds.

Experimental

The dipole moments were measured using an apparatus described previously,[5] and the solvents were purified as before.[5] The dipole moments were calculated using the equation and method of Halverstadt and Kumler.[6]

$$P_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\,\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$\mu = 0.01281\,\sqrt{(P_{2_0} - P_{\mathrm{E}_2})T}$$

The plots of ϵ_{12} *versus* ω_2 and v_{12} *versus* ω_2 were straight lines within the limits of experimental error. The values of ϵ_1 and v_1 were obtained by the method of least squares. The standard error in the dipole moments were calculated from the equation $\delta\,\mu = 0.0046\,M\delta\alpha/\mu^7$ and the standard error in α from the equation[7,8]

$$\delta\alpha = \pm \left\{\frac{n}{n-2}\left[\frac{\Sigma(\epsilon' - \epsilon_{12})^2}{n\Sigma(\omega_2)^2 - (\Sigma\omega_2)^2}\right]\right\}^{1/2}$$

The errors from scatter of the points for specific volume do not need to be considered since even large errors in β produce only very small errors in the dipole moment.[9] The α-halocamphors and α-haloindanones were from the same samples or were prepared in the same way and had the same melting point as the compounds used in the infrared paper.[4] The 2-bromo-4-phenylcyclohexanone was a carefully purified sample supplied by Professor E. J. Corey to whom we express our thanks. We also wish to than Howard Schultz for making some of the preliminary measurements.

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