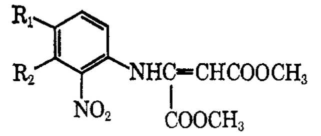
TABLE II

DIMETHYL ANILINOFUMARATES



R_1	R_2	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	H	95	130–131	$C_{12}H_{12}NO_6$	51.43	4.32	10.00	51.60	4.35	9.79
OCH_3	H	87	138–139	$C_{13}H_{14}N_2O_7$	50.32	4.55	9.03	50.39	4.68	9.09
Cl	H	67	120.5–122	$C_{12}H_{11}ClN_2O_6$	45.80	3.53	8.90	45.65	3.66	8.89
CH_3	H	68	109–110	$C_{13}H_{14}N_2O_6$	53.06	4.79	9.52	53.06	4.93	9.48
CH_3	CH_3	72	126–127.5	$C_{14}H_{16}N_2O_6$	54.54	5.23	9.09	54.46	5.45	9.16

Experimental Section[16]

Condensation of the Aromatic Amines (I) with Dimethyl Acetylenedicarboxylate. Formation of the Michael Adducts (III).—An equimolar amount (0.02 mole) of the aniline and dimethyl acetylenedicarboxylate (II) was mixed in 100 ml of anhydrous methanol and refluxed for 24 to 48 hr. The reaction mixture was cooled in ice and the precipitated product removed by filtration. Successive crystal crops could be obtained by concentration *in vacuo* of the mother liquors. Yields and analytical results are reported in Table II. The adducts could be obtained in analytical purity by two recrystallizations from methanol.

Three adduct analogs which were not precursors of 8-nitroquinolones were prepared for comparison purposes. The adduct of aniline and (II) and its cyclization have already been described.[4,9] The adduct of *m*-nitroaniline was prepared by the above procedure in 69% yield with only 4 hr of reflux, mp 94–95°.

Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.52; H, 4.59; N, 9.89.

Similarly, *p*-nitroaniline was condensed with II in 78% yield after 48-hr reflux. The buff-yellow crystals, from methanol, melted at 124.5–125°.

Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.52; H, 4.29; N, 9.91.

Cyclization of the Michael Adducts (III) to 8-Nitro-4(1H)-Quinolones (IV).—A paste, formed from intimately mixing 2 to 4 g of the adduct (III) with 20 to 30 g of polyphosphoric acid, was heated with stirring at 140–180° for 30 min. Considerable foaming resulted, and the mixture turned progressively darker. After cooling to 100°, the viscous solution was poured into a mixture of chopped ice and water and scratched with a glass rod to induce crystallization. If allowed to stand at ice bath temperatures for 5–10 hr prior to filtration, the filterability of the product was improved. The solid, removed by vacuum filtration, was air dried and recrystallized from methanol. All of the quinolones could be obtained in analytical purity by sublimation at 0.5 mm at a temperature 20° under their melting points. Analytical data and yields are reported in Table I.

The cyclization of the adducts of (II) with *m*-nitroaniline and *p*-nitroaniline, respectively, could be carried out in diphenyl ether.

Methyl 7-nitro-4(1H)-quinolone-2-carboxylate was prepared in 74% yield by refluxing 0.30 g of dimethyl (*m*-nitroanilino)-fumarate in 4.0 g of diphenyl ether for 1 min. The crystals of the product began to precipitate in the hot reaction medium, and dilution with 50 ml of light petroleum ether (bp 30–60°) completed the precipitation. The crystals were filtered, washed well with hexane, and recrystallized from methanol (sparingly soluble). Vacuum sublimation gave analytical material, mp 268–269.5°.

Anal. Calcd for $C_{11}H_8N_2O_5$: C, 53.22; H, 3.25; N, 11.29. Found: C, 53.35; H, 3.44; N, 10.98.

The presence of the 5-nitro isomer was ruled out on the basis of the nmr spectrum.[17]

Methyl 6-nitro-4(1H)-quinolone-2-carboxylate was prepared in 85% yield from dimethyl (*p*-nitroanilino)fumarate by the method described for the 7-nitro isomer. The pale yellow solid was recrystallized from methanol–benzene (sparingly soluble) and melted at 295–297°.

Anal. Calcd for $C_{11}H_8N_2O_5$: C, 53.22; H, 3.25; N, 11.29. Found: C, 53.43; H, 3.30; N, 11.48.

Saponification–Decarboxylation of the 8-Nitroquinolones (IV).—To 300 cc of 18% by weight aqueous sodium hydroxide was added 35 g of methyl 8-nitro-4-(1H)-quinolone-2-carboxylate in small portions with vigorous stirring. The majority of the solid dissolved in 10 min, and the solution was filtered and then heated at 60° for 30 min. The carboxylic acid was precipitated by addition of cold 6 *N* HCl, filtered off, washed with 3 *N* HCl, and dried overnight in a vacuum oven. Twenty-four grams of this dried acid were pulverized to a fine powder and added with stirring to 300 ml of Nujol at 245°. After all the acid had been added, the oil was heated for 0.5 hour, cooled to room temperature, and diluted with 300 ml of petroleum ether. The black solids were removed by filtration and charged to a Soxhlet thimble. Extraction of the methanol soluble organic material and evaporation of the extracts produced 62% of the 8-nitro-4(1*H*)-quinolone, mp 200–202° (lit.[8] mp 199–200°).

By the procedure described above, methyl 6-methoxy-8-nitro-4(1*H*)-quinolone-2-carboxylate was saponified and decarboxylated to 6-methoxy-8-nitro-4(1H)-quinolone in 38% yield. The product was purified by recrystallization from methanol and sublimation *in vacuo*, mp 225–227°.

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.54; H, 3.63; N, 12.72. Found: C, 54.54; H, 3.66; N, 12.70.

---

[16] Combustion analyses were performed in these laboratories by one of us (V. B. F.) or obtained from Robertson Microanalytical Laboratories, Florham Park, N. J.

[17] In trifluoroacetic acid solvent the unsplit methyl appeared at 3.82 ppm, the singlet proton on C-3 at 7.67 ppm, the singlet C-8 proton at 8.75 ppm, and an A-B quartet was centered at 8.27 ppm for the mutually coupled ($J = 9$ cps) C-5 and C-6 protons. The Gould–Jacobs cyclization of *m*-nitroaniline leads to the 7-nitroquinoline: C. C. Price, H. R. Snyder, O. H. Bullitt, Jr., and P. Kovacic, *J. Am. Chem. Soc.*, **69**, 374 (1947).

The Hydroboration and Subsequent Oxidation of Several Enamines[1]

IRVING J. BOROWITZ[2] AND GREGORY J. WILLIAMS

Department of Chemistry, Lehigh University,
Bethlehem, Pennsylvania,
and the Belfer Graduate School of Science,
Yeshiva University, New York, New York 10033

Received July 25, 1967

We wish to report that hydroboration of the morpholine or pyrrolidine enamine of cyclohexanone or the pyrrolidine enamine of 2-methylcyclohexanone, followed by basic hydrogen peroxide treatment, leads to the corresponding *trans*-*β*-aminocyclohexanols in good yield.[3]

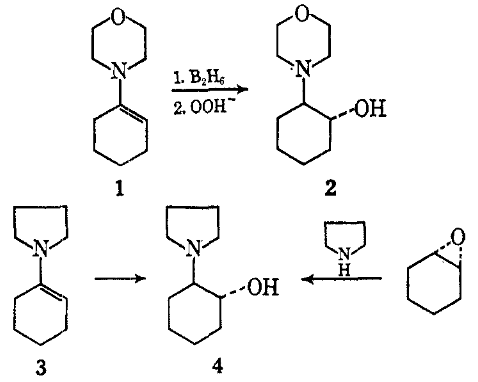
---

[1] This investigation was supported in part by the U. S. Public Health Service Research Grant AI 06303 (to I. J. B.) from the National Institute of Allergy and Infectious Diseases. The initial phase was done at Columbia University in Professor Gilbert Stork's laboratory and was supported by the National Science Foundation and the National Institute of Health.

[2] To whom correspondence should be addressed at the Belfer Graduate School of Science, Yeshiva University.

[3] Preliminary results quoted by J. Szmuszkovicz, "Advances in Organic Chemistry, Methods and Results," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 1.

Diborane was produced by the addition of boron trifluoride etherate to lithium aluminum hydride in anhydrous ether and slowly swept by a nitrogen stream into a solution of morpholinocyclohexene (**1**) in tetrahydrofuran.[4] Work-up with basic hydrogen peroxide[5a] (see Experimental Section) yielded *trans*-2-hydroxymorpholinocyclohexane (**2**, 82%). This amino alcohol was identical by several criteria with a genuine sample of **2** obtained from the *trans* opening of cyclohexene oxide with morpholine.[6] Furthermore the picrates of the aminocyclohexanols obtained from the two routes were identical. Similar treatment of pyrrolidinocyclohexene (**3**) with diborane gave *trans*-2-hydroxypyrrolidinocyclohexane (**4**, 78%). This was identical in its infrared spectrum with a genuine sample prepared from cyclohexene oxide and pyrrolidine.

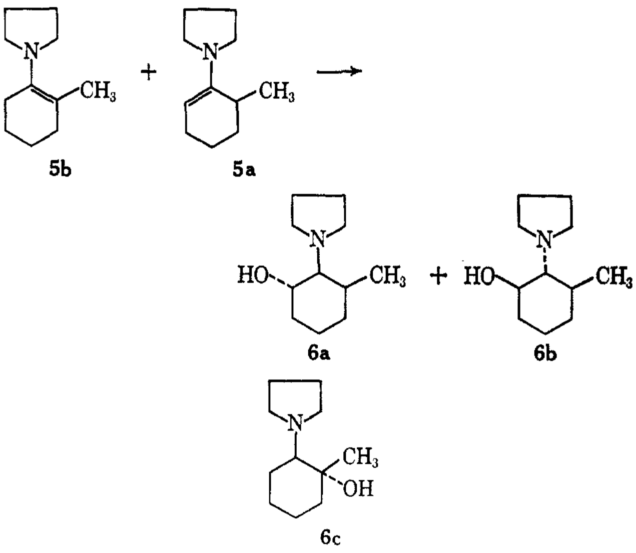


As a check on experimental conditions, treatment of **2** with a large excess of basic hydrogen peroxide gave an 80% recovery of **2** and no evidence for N-oxide formation. The above-mentioned yields were obtained with diborane generated from 2.3 moles of boron trifluoride etherate and 1.4 moles of lithium aluminum hydride per mole of enamine. If a small (*ca.* 20%) molar excess of the diborane-generating reagents was used, lesser yields of 68 and 60% of **2** and **4**, respectively, were obtained. While the enhancement in yield of aminocyclohexanol with excess diborane may simply reflect a smaller loss of diborane during the nitrogen sweep, another and possibly a significant factor is the ability of the enamine nitrogen to complex with 1 equiv of borine. Since such complex formation may effectively remove borine from being available for hydroboration, a large excess of diborane may be needed for optimum hydroboration of an enamine. It is recognized that even a 1:1 diborane/enamine ratio should represent a large stoichimetric excess of diborane.[5b]

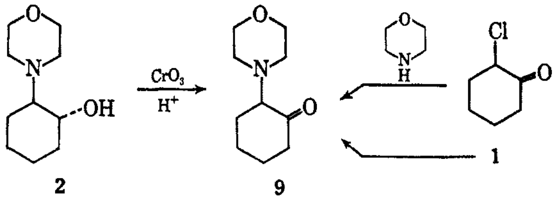
The above experimental conditions gave our best conversions. The *in situ* reaction of diborane with **1** in ether gave a poor yield of impure **2** while some variation of the *ex situ* conditions gave poorer yields of **2** as well.

β-Aminoboranes have been previously obtained from cyclohexanone enamines[7] and from *trans*-β-pyrrolidinostyrene.[8] They have been shown not to eliminate the elements of the amine and borine to form an olefin as do other β-substituted boranes.

Treatment of the pyrrolidine enamine of 2-methylcyclohexanone, found to be *ca.* 93% **5a** and 7% **5b** (by nmr),[9] with excess diborane gave a 64% yield of the isomeric aminocyclohexanols **6a** and **b**. Examination of the mixture by nmr (see Experimental Section) gave a 63:37 ratio of isomers. We tentatively assign the stereochemistry of **6a** to the major isomer. This is based on the assumption that the addition of diborane to **5a** occurs on the side opposite to the methyl group which is believed to be in a quasi-axial position.[10] No nmr evidence was found for the presence of the tertiary alcohol **6c**. The stereochemistry of **6c** is based on the assumption of *cis* addition of borine to **5b**. No further elucidation of the actual stereochemistry of the isomeric mixture obtained was performed at the time.



The amino alcohol **2** was oxidized to 2-morpholinocyclohexanone **9** in 52% yield with chromic acid and excess sulfuric acid. The infrared spectrum of **9** obtained in this manner was nearly identical with that of a sample of **9** synthesized from 2-chlorocyclohexanone and morpholine.[6] Amino ketone **9** was also characterized *via* its picrate. Among other attempted oxidations, the reaction of **2** with chromium trioxide in acetone or in acetic acid gave incomplete conversion to **9**. Chromic acid oxidations of **2** with small amounts of sulfuric acid present also gave poor yields of **9**. In the early phase of this work the direct conversion of **1** to **9** was attempted *via* hydroboration and chromic



---

(4) The apparatus used and the technique employed were essentially those suggested by H. C. Brown, *Org. Reactions*, **13**, 21 (1963).

(5) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962: (a) pp 69-72; (b) pp 3-11.

(6) M. Mousseron, J. Jullien, and Y. Jolchin, *Bull. Soc. Chim. France*, **19**, 757 (1952).

(7) J. W. Lewis and A. A. Pearce, *Tetrahedron Letters*, 2039 (1964).

(8) D. J. Pasto and R. Snyder, *J. Org. Chem.*, **31**, 2777 (1966).

(9) (a) I. J. Borowitz and G. J. Williams, unpublished data; (b) W. D. Gurowitz and M. A. Joseph, *Tetrahedron Letters*, 4433 (1965); (c) G. Stork, Abstracts of Sixteenth National Organic Symposium, June 15-17, 1959, Seattle, Wash., p 45.

(10) F. Johnson and A. Whitehead, *Tetrahedron Letters*, 3825 (1964).

acid oxidation.[11] The best yield achieved was 57% of **9**.

Thus the addition of diborane to several enamines of cyclohexanones occurs in the usual *cis* manner[5] and leads predominantly to the β-aminoborane. This directive influence of a dialkylamino group in hydroboration can be explained by the known polarization of the enamine double bond wherein the β carbon has considerable carbanion character.[12] In addition steric factors direct hydroboration to the less substituted position in an aminocyclohexene just as they do in methylcyclohexene.[13] One or both of these factors is presumably involved in the hydroboration of ethoxycyclohexene to *trans*-2-ethoxycyclohexanol as the principal product.[14]

Experimental Section

Microanalyses were performed by Professor V. B. Fish of the Department of Chemistry, Lehigh University, and Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Nmr spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane (τ 10) as an internal standard. Melting points were taken on a Mel-Temp apparatus and are corrected while boiling points are uncorrected.

Reaction of Morpholinocyclohexene with Diborane and Subsequent Oxidation to *trans*-2-Hydroxy-1-morpholinocyclohexane (2).—Boron trifluoride etherate (50%, 20 g, 0.14 mole) was added dropwise to a solution of lithium aluminum hydride (3.2 g, 0.084 mole) in dry diethyl ether (200 ml) which was stirred and cooled in an ice bath. A slow stream of dry prepurified nitrogen swept the diborane, which formed exothermally, into a flask, at room temperature, which contained morpholinocyclohexene (**1**) (10.0 g, 0.060 mole) in dry tetrahydrofuran (70 ml). The gas was bubbled in *via* a sintered-glass stick below the surface of the tetrahydrofuran solution which was stirred. The addition of the boron trifluoride etherate took 80 min, nitrogen sweeping was continued for 2 hr, and the tetrahydrofuran solution was kept at room temperature for 12 hr and then evaporated *in vacuo* to leave a syrup. The syrup was dissolved in 95% ethanol (160 ml) with strong effervescence, sodium hydroxide (8 g, 0.2 mole) and then 30% hydrogen peroxide (24 ml, 0.2 mole) were added dropwise to give a very exothermic reaction. Further ethanol (40 ml) was added and the mixture was heated at reflux for 2.5 hr on a steam bath. It was then continuously extracted with ether for 18 hr; the organic liquid phase was dried over magnesium sulfate[15] and gave, upon distillation, **2** as a colorless liquid, 9.0 g, bp 98–98.5° (0.6 mm), in 85% yield. The same procedure using one-half the amount of boron trifluoride etherate, lithium aluminum hydride, sodium hydroxide, and hydrogen peroxide gave **2**, 7.5 g, 68%, bp 95–95.5° (0.5 mm). A sample was redistilled for analysis. *Anal.* Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.70; H, 10.52; N, 7.48. The amino alcohol was a solid below room temperature.

To **2** (0.40 g, 0.0022 mole) in 95% ethanol (2 ml) was added picric acid (11 ml of a solution containing 0.0024 mole) to give a yellow picrate (0.866 g, 0.0022 mole, 99%), mp 144–146.5°; mixture melting point with genuine picrate of **2** (see below) of mp 144–145° was 144–148°. The analytical sample, recrystallized from ethanol, had mp 145.5–146.5°, lit.[6] mp 137–138°. *Anal.* Calcd for $C_{16}H_{22}N_4O_9$: C, 46.37; H, 5.35; N, 13.52. Found: C, 46.29; H, 5.51; N, 13.32.

The infrared spectrum (neat) of **2** is identical with that of genuine **2** (see below). It includes absorption at 3420 (OH), 2920 (s), 2840 (s), 1455 (s), 1300 (m), 1265 (m), 1120 (s), 1080 (m), 943 (m), and 868 cm^{-1} (m). Comparison of **2** from hydroboration with a genuine sample (see below) by tlc on Brinkman silica HF_{254} plates using 25% methanol–benzene as developing solvent gave a single spot for each with iodine vapor at R_f 0.45. The nmr spectrum ($CHCl_3$) exhibits a triplet centered at τ 6.47 (4 H of CH_2O, J = 4.5 cps), a singlet at τ 6.72 (1 H of OH), one peak at τ 6.65 (part of 1 H multiplet for C_2 hydrogen), a multiplet at τ 7.25–7.8 (5 H of CH_2N), and diffuse multiplets at τ 8.2–8.4 and 8.6–8.9 (8 methylene H).

***trans*-2-Hydroxy-1-morpholinocyclohexane (2).**—Reaction of cyclohexene oxide (10 g, 0.102 mole) with morpholine (18 g, 0.27 mole) at reflux for 24 hr gave **2**, 15.3 g, 0.083 mole, 81%, bp 110–112° (0.1 mm). This sample was used for comparison with **2** formed by hydroboration of **1**.

***trans*-2-Hydroxy-1-pyrrolidinocyclohexane (4).**—Similar reaction of cyclohexene oxide with pyrrolidine gave **4** (72%), bp 99–101° (2 mm). The infrared spectrum of **4** ($CHCl_3$) exhibited an OH peak at 3315 cm^{-1}.

Reaction of Pyrrolidinocyclohexene with Diborane and Subsequent Oxidation to 4.—Treatment of **3** (9.0 g, 0.06 mole) with diborane from boron trifluoride etherate (0.14 mole) and lithium aluminum hydride (0.084 mole) *via* the above-described procedure led to **4**, 7.9 g (78%), bp 72–72.5° (0.35 mm). The use of one-half of the amount of diborane-producing reagents gave **4** in 60% yield. *Anal.* Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.88; H, 11.33; N, 8.20, 8.23. The infrared spectrum of **4** thus synthesized was identical with that of **4** obtained from cyclohexene oxide. The nmr spectrum (CCl_4) of **4** exhibited a singlet at τ 6.38 (1 H of OH), a sextet centered at τ 6.72 (1 H of C_2), two nearly superimposed triplets centered at τ 7.42 (4 H of CH_2N), and multiplets at τ 7.62–7.7 (1 H of CHN), 8.2–8.33, and 8.68–8.8 (12 methylene H).

Treatment of 2 with Excess Basic Hydrogen Peroxide.—A mixture of **2** (1.01 g, 0.0054 mole), 30% hydrogen peroxide (5 ml, 0.043 mole), and sodium hydroxide (1.4 g, 0.035 mole) in 95% ethanol (30 ml) was refluxed for 5 hr. After being cooled, the mixture was diluted with ether and washed with ferrous sulfate, then sodium hydroxide, and dried over magnesium sulfate and molecular sieve to give 0.8 g of recovered **2** (80% recovery) with infrared spectrum ($CHCl_3$) identical with that of **2**.

Reaction of the Pyrrolidine Enamine of 2-Methylcyclohexanone 5a and b with Diborane and Subsequent Oxidation to 6a and b.—Treatment of **5a** and **b** (9.9 g, 0.06 mole) with diborane as described for the preparation of **2** gave the amino alcohols assigned as **6a** and **b**, 7.05 g, bp 72–73° (0.25 mm) in 64% yield. *Anal.* Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.84; H, 11.80; N, 7.49. The nmr spectrum (neat) of **6a** and **b** exhibited a singlet at τ 6.16 (1 H of OH, exchangeable with D_2O), two overlapping triplets centered at τ 7.22 (4 H of CH_2N), several multiplets between τ 7.55 and 8.75 (13 methylene and methine H), and two partially overlapping doublets centered at τ 8.95 and 9.10 (J = 6.5 cps, 3 H methyl protons of **6b** and **a** in 37:63 ratio). No signal attributable to the methyl of **6c** (singlet) was found. The integrated areas for the overlapping methyl doublets of **6a** and **b** added up to the expected three protons.

Chromic Acid Oxidation of *trans*-2-Hydroxy-1-morpholinocyclohexane to 2-Morpholinocyclohexanone (9).—To amino alcohol **2** (6.00 g, 0.0324 mole) was added sodium dichromate (9.6 g, 0.0324 mole) in water (36 ml) at ice-bath temperature under a nitrogen atmosphere. To this mixture concentrated sulfuric acid (24 ml) was added dropwise over 1.5 hr with stirring. The mixture was left at *ca.* 0° for 1 hr and then a slurry of sodium bisulfite (6.8 g) in water (24 ml) was slowly added. The resultant acidic aqueous solution was extracted with ether and the organic layer was discarded (to remove neutral impurities). The aqueous layer was then adjusted to pH 8–9 with sodium hydroxide solution and continuously extracted with ether for 30 hr. The ether extract was dried over magnesium sulfate and gave **9** as a liquid, 3.08 g (0.0167 mole, 52%), bp 107–108° (0.4 mm). The infrared spectrum (neat) of **9** exhibited carbonyl absorption at 1715 cm^{-1}. It was nearly identical with the infrared spectrum of **9** obtained from 2-chlorocyclohexanone (see below). The nmr spectrum (carbon tetrachloride) of **9** exhibited a triplet centered at τ 6.58 (J = 5 cps, 4 H of CH_2O), a triplet centered at τ 7.45 (J = 5 cps, 1 H of C_2), a triplet centered at τ 7.62 (J = 5 cps, 4 H of CH_2N), an unsymmetrical triplet centered at τ 7.90, and a diffuse doublet centered at τ 8.21 (8 methylene H). The picrate of **9**, formed in 92% yield, had mp 147.3–149.3° (recrystallization from ethanol) and mixture melting point with picrate of amino alcohol

---

[11] H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961).

[12] (a) A related argument for the hydroboration of styrene is given in ref 5, p 122. (b) Whether or not the directive effect of a free enamine is important depends upon the extent to which it is complexed with borine, as already discussed.

[13] Reference 5, pp 124–126.

[14] D. J. Pasto and C. C. Cumbo, *J. Am. Chem. Soc.*, **86**, 4343 (1964).

[15] Initially the ether solution was washed with ferrous sulfate to remove peroxides. This step may have lowered the yield of **2** which is quite water soluble. The washing was left out with no resultant danger during work-up.

2 (mp 145.5–146.5°) 139–149°. *Anal.* Calcd for $C_{16}H_{20}N_4O_9$: C, 46.61; H, 4.89; N, 13.59. Found: C, 46.90; H, 5.00; N, 13.44.

Conversion of 2-Chlorocyclohexanone to 2-Morpholinocyclohexanone.[6]—2-Chlorocyclohexanone (5 g, 0.038 mole) was reacted with morpholine (7 g, 0.081 mole) by the procedure of Mousseron[6] to give 9 as a light yellow oil; 1.45 g, 0.0079 mole, 21%, bp 85–86° (0.25 mm). The infrared spectrum of 9 thus obtained was nearly identical with that of 9 as formed above. This procedure is not recommended and should be improved by the use of a solvent.

Direct Conversion of Morpholinocyclohexene to 2-Morpholinocyclohexanone.—A solution of 1 (15 g, 0.090 mole) in tetrahydrofuran (150 ml) was treated with diborane from boron trifluoride etherate (0.136 mole) and lithium aluminum hydride (0.136 mole) as already described. A one-third aliquot was evaporated *in vacuo*, water (50 ml) was added, and then chromium trioxide (3.3 g, 0.033 mole) in water (25 ml)–sulfuric acid (5 ml) was added dropwise over 45 min with stirring and ice-bath cooling. The resultant mixture was stirred for 3 hr and a mixture of chromium trioxide (6.6 g, 0.066 mole) in water (12 ml)–sulfuric acid (10 ml) was added dropwise over 30 min at 0°. The resultant mixture was stirred for 2 hr, sodium bisulfite was added to reduce any chromium trioxide left, and the mixture was continuously extracted with ether for 12 hr. Distillation gave 9, 3.14 g, 57%, bp 96–97° (0.3 mm), with nearly identical infrared spectrum with that of 9 obtained from 2-chlorocyclohexanone.

Registry No.—**2**, 14909-79-6; picrate of **2**, 14909-80-9; **4**, 14909-81-0; **6a**, 14909-82-1; **6b**, 14909-83-2; **9**, 14909-84-3; picrate of **9**, 14909-85-4.

Acknowledgment.—The authors wish to thank Professor Gilbert Stork of Columbia University for his original suggestion of this problem and for his guidance of this work in its initial phase at Columbia University. His continued interest is also appreciated.

A Useful Method for the Conversion of Alcohols into Iodides

E. J. Corey and Jerome E. Anderson[1]

Department of Chemistry, Harvard University,
Cambridge, Massachusetts 02138

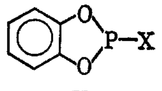
Received July 10, 1967

The standard methods for the preparation of iodides from alcohols and alcohol derivatives[2a] cannot be used effectively in certain cases because substitution is accompanied by complicating side reactions such as elimination and acid or base-catalyzed decomposition of sensitive functional groups. This Note reports a simple and convenient method for the formation of iodides under mild conditions which is especially valuable in systems which are prone to elimination.

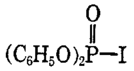
Forsman and Lipkin[2b] have reported that cyclohexyl iodide is formed upon treatment of cyclohexyl diphenyl phosphite (Ib) with iodine. In our experience the utility of this reaction for the conversion of alcohols into iodides is limited by the tendency of the required reagent, diphenyl phosphorochloridite (Ia), to disproportionate, by the necessity of purifying the intermediate phosphite (Ib) in order to obtain the iodide in good yield, and by the necessity of removing the difficultly hydrolyzable by-product, diphenyl iodophosphate (II), by ammonolysis. We have found that all of these problems can be avoided by employing the cyclic analog of Ia, *o*-phenylene phosphorochloridite (IIIa), a stable reagent which is easily prepared from catechol and phosphorus trichloride.[3] Reaction of IIIa in ether solution with an alcohol in the presence of pyridine affords, after removal of pyridine hydrochloride by filtration, a nearly quantitative yield of the corresponding phosphite IIIb sufficiently pure for use in the subsequent reaction. Treatment of a methylene chloride solution of the phosphite IIIb with iodine at 25° for 6 hr produces the desired iodide whose isolation is facilitated by the rapid base-catalyzed hydrolysis of the by-product, *o*-phenylene iodophosphate IV. The results for representative cases are summarized in Table I.

$(C_6H_5O)_2PX$

Ia, X = Cl
b, X = OR

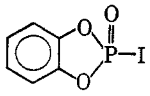


IIIa, X = Cl
b, X = OR



$$(C_6H_5O)_2\overset{\overset{\displaystyle O}{\|}}{P}{-}I$$

II



IV

Experimental Section

All of the iodides in Table I were prepared by essentially the same procedure, illustrated by the following.

Preparation of Cyclohexyl *o*-Phenylene Phosphite.—A mixture of 10.12 g (58.0 mmole) of *o*-phenylene phosphorochloridite[3] and 4.6 g (58.0 mmole) of pyridine in 100 ml of diethyl ether was placed in a 250-ml flask and cooled to 0°. Cyclohexanol (5.85 g, 57.5 mmole) in 100 ml of ether was then added with stirring. The flask was stoppered, and the mixture was allowed to warm to 25°. After 12 hr the pyridine hydrochloride was filtered off and rinsed well with ether. Solvent was removed from the combined filtrate under reduced pressure to give 13.0 g (95.4%) of the phosphite as a colorless, mobile oil.

Distillation of a portion of the material gave phosphite: bp 103–105° (1.0 mm); infrared λ_{max}^{neat} 3.55 (w), 3.39 (s), 3.50 (m), 6.8 (s), 8.1 (s), 9.9 (s), 10.1–10.3 (s), 11.9–12.2 (s), 13.3–13.6 (s), 14.4 (m) μ; nmr (δ, $DCCl_3$) 1.0–1.8 (10 H) multiplet, 3.85 (1 H) multiplet, 6.96 (4 H) multiplet; n^{25}D 1.5280.

Anal. Calcd for $C_{12}H_{15}O_3P$: C, 60.50; H, 6.35; P, 13.00. Found: C, 60.61; H, 6.43; P, 13.02.

Preparation of Cyclohexyl Iodide.—To a solution of 13.0 g (54.8 mmole) of crude cyclohexyl *o*-phenylene phosphite in 200 ml of methylene chloride was added 13.9 g (54.8 mmole) of iodine. After stirring for 6 hr at 25° the solution was extracted with 200 ml of 5% sodium hydroxide solution, then with 100 ml of 5% sodium hydrogen sulfite solution, and finally with 100 ml of a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed at reduced pressure. Vacuum distillation of the residue afforded 10.0 g (87.4%; 83.2%, based on cyclohexanol) of cyclohexyl iodide: bp 78° (20 mm); n^{20}D 1.5490 (lit.[4] n^{20}D 1.54765).

Identification and Physical Properties. A. Phosphites IIIb.—The intermediate phosphites (IIIb) were examined spectroscopically to confirm their structures: (1) from *n*-heptanol, infrared maxima at 3.25 (w), 3.39 (s), 3.49 (m), 6.23 (w), 6.32 (w), 6.8 (s), 8.1 (s), 9.9 (s), 10.25 (m), 11.9–12.2 (s), 13.3–13.6 (s), and 14.4 (m) μ; nmr peaks (parts per million downfield from tetramethylsilane) at 0.83 (3 H), triplet, $J = 5$, 1.0–1.7 (10 H), 3.52 (2 H), quartet, $J = 7$, 6.97 (4 H), multiplet; (2) from 3-chloro-*n*-propanol, infrared maxima at 3.25 (w), 3.35 (m), 3.47 (w), 6.22 (w), 6.32 (w), 6.78 (s), 8.1 (s), 9.85 (s), 10.35 (s), 11.9–12.2 (s), 13.3–13.6 (s), and 14.3 (s) μ; nmr peaks

---

(1) National Institutes of Health Predoctoral Fellow, 1965–1967.

(2) (a) For a review of the synthetic routes to alkyl iodides, see A. Roedig in "Methoden der Organischen Chemie" (Houben–Weyl), Vol. V/4, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1960, pp 517–678; (b) J. P. Forsman and D. Lipkin, *J. Am. Chem. Soc.*, **75**, 3145 (1953).

(3) P. C. Crofts, J. H. H. Markes, and H. N. Rydon, *J. Chem. Soc.*, 4250 (1958).

(4) A. I. Vogel, *J. Chem. Soc.*, 1813 (1948).