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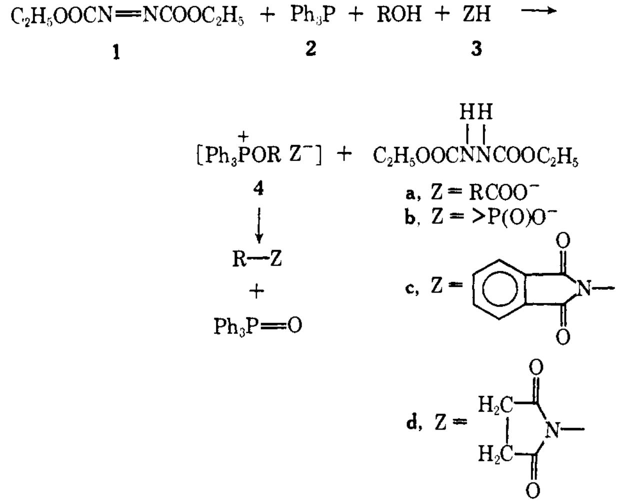
Stereospecific and Stereoselective Reactions. I. Preparation of Amines from Alcohols

Sir:

Syntheses of amines under mild conditions have received much attention and many methods have been devised.[1] Generally, the hydroxyl group of an alcohol must first be converted to another functional group such as the halogens before an amine can be synthesized from an alcohol. While many kinds of two-step routes are widely used, they may involve stereochemical uncertainties because of the displacement nature of the steps.[2] Recently, White, *et al.*,[3] and Burgess, *et al.*,[4] have reported a one-step route for the preparation of amines and urethanes from alcohols.

In this communication, we wish to report a stereospecific one-stage formation of *N*-alkylphthalimides and *N*-alkylsuccinimides from alcohols.

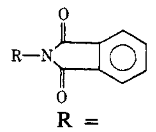
The preceding papers describe how the reaction of alcohols or nucleosides with either carboxylic acids or hydrogen phosphate esters in the presence of equimolar amounts of diethyl azodicarboxylate (**1**) and triphenylphosphine (**2**) afforded carboxylic esters or phosphoric esters.[5] High stereospecificity was observed in the formation of carboxylic esters.[5c] An alkoxyphosphonium salt (**4**) was assumed to be the intermediate of the reaction, from which the alkyl group was presumably transferred to carboxylate or phosphate anions.



These results and those obtained in other laboratories[6] show that alkoxyphosphonium salts are powerful alkyl group donors and anions such as carboxylate, phosphate, or halide act as alkyl group acceptors. These considerations suggested the possibility that various nucleophiles might be alkylated by the alkoxyphosphonium salt under proper conditions. Thus, alkylation of phthalimide by means of an alcohol, **1**, and **2** was tried.

When various alcohols (1–1.5 mmol) were allowed to react with 1 mmol each of phthalimide (**3c**), **1**, and **2** in tetrahydrofuran (THF) at room temperature, the corresponding *N*-alkylphthalimides[7] were obtained in good yields as expected (Table I). Similarly, the reaction of (±)-ethyl lactate (1 mmol) with equimolar amounts of **1**, **2**, and **3c** resulted in the formation of (±)-phthalylalanine ethyl ester[8] in a 58% yield (mp 59–61°).[9]

Table I. Preparation of *N*-Alkylphthalimides

Alcohol ROH R =	Product  R =	Yield, %
C_2H_5	C_2H_5	91
n-C_3H_7	n-C_3H_7	93
n-C_4H_9	n-C_4H_9	81
(±)-$CH_3CHC_2H_5$	(±)-$CH_3CHC_2H_5$	75
(±)-$CH_3CHC_6H_{13}$	(±)-$CH_3CHC_6H_{13}$	82
(±)-$CH_3CHCO_2C_2H_5$	(±)-$CH_3CHCO_2C_2H_5$	58

The reaction of *n*-butyl alcohol (1 ml) with 10 mmol each of succinimide (**3d**), **1**, and **2** in THF at room temperature gave *N*-*n*-butylsuccinimide in a 76% yield (bp 140° (23 mm)).

When *n*-butyl *N*,*N*′-tetraethylphosphorodiamidite and **3d** were treated with **1** in THF at room temperature, *N*-butylsuccinimide was isolated in a 95% yield by distillation (bp 72–75° (3 mm)).

Although only a few investigations have been reported on the stereochemistry of the decomposition of alkoxyphosphonium salts, they show that there is a

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(1) (a) Houben-Weyl, "Methoden der Organischen Chemie," Vol. XI, Part 1, Georg Thieme Verlag, Stuttgart, 1957; (b) S. R. Sandler and W. Kars, "Organic Functional Group Preparation," Academic Press, New York, N. Y., 1968; (c) C. A. Buehler and D. E. Pearson, "Survey of Organic Syntheses," Wiley-Interscience, New York, N. Y., 1970.

(2) Streitwieser and Schaeffer have demonstrated that the direct displacement reaction of sulfonate esters with azide ion proceeds with nearly complete inversion: A. Streitwieser, Jr., and W. D. Schaeffer, *J. Amer. Chem. Soc.*, **78**, 5597 (1956).

(3) E. H. White and C. A. Elliger, *ibid.*, **87**, 5261 (1965), and references therein.

(4) E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *ibid.*, **92**, 5224 (1970).

(5) (a) O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Jap.*, **40**, 2380 (1967); (b) O. Mitsunobu, K. Kato, and J. Kimura, *J. Amer. Chem. Soc.*, **91**, 6510 (1969); (c) O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Jap.*, **44**, 3427 (1971); (d) O. Mitsunobu, J. Kimura, and Y. Fujisawa, *ibid.*, in press.

(6) (a) R. G. Harvey and E. R. De Sombre, *Top. Phosphorus Chem.*, **1**, 57 (1964); (b) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965; (c) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967.

(7) The *N*-alkylphthalimides were separated by means of preparative thin-layer chromatography on silica gel (Wakogel B-5) utilizing benzene or chloroform as eluent. Satisfactory infrared and nmr data were obtained for these products.

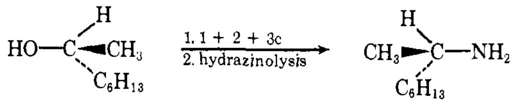
(8) Satisfactory analytical, infrared, and nmr data were obtained for this product.

(9) As it is well known that, on hydrolysis or hydrazinolysis, *N*-alkylphthalimides and phthalylamino acids afford corresponding primary amines and amino acids, we made no attempts to cleave these products.

remarkable tendency for inversion of the alkyl group.[3c,10,11] We therefore investigated the steric course of the present reaction using an optically active alcohol.

When (S)-(+)-2-octanol,[12] $[\alpha]_D$ +14.3° (101% optical purity,[13] 6.99 mg/1 ml of n-heptane), was allowed to react with **1**, **2**, and **3c** in THF at room temperature, followed by column chromatography (Wakogel B-5, eluate, benzene), N-2-octylphthalimide was obtained in a 79% yield. The product was then treated with hydrazine hydrate (80%) in ethanol and (R)-(−)-2-octylamine was obtained in a 48% yield (based on (S)-(+)-2-octanol) by distillation (bp 70–72° (31 mm)).[14] The 2-octylamine showed $[\alpha]_D$ −7.13° (in benzene, 0.01206 g/1 ml), and this value corresponded to 108% optical purity.[15]

The results described above and in the preceding paper[3c] indicated that, at least in the cases studied, the alkylation by means of alkoxyphosphonium salts proceeded stereospecifically with (nearly) complete inversion of the configuration of the alkyl group.



(S)-(+) (R)-(−)

This reaction may possibly be used to infer the absolute configuration of either an alcohol or its homologous amine when that of only one of them is known. Analogous studies of the reactions of alkoxyphosphonium salts with various nucleophiles are now under investigation.

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[10] W. Gerrard and W. J. Green, *J. Chem. Soc.*, 2550 (1951).

[11] R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **35**, 1627 (1970); and references therein.

[12] A. W. Ingersoll, "Organic Reactions," Vol. 2, R. Adams, Ed., Wiley, New York, N. Y., 1960, p 376. Optical rotations were measured with a JASCO ORD/UV-5.

[13] M. K. Hargreaves has reported that (+)-2-octanol showed optical activities (in n-heptane) of $[\alpha]_D$ +13.1° (l = 2, 10.817 g/100 cm^3) and +14.1° (l = 2, 4.973 g/100 cm^3). The specific rotatory power increases with dilution until a concentration of about 3% is reached, where it becomes constant. Thus, our (S)-(+)-2-octanol was about 100% optical purity (*J. Chem. Soc.*, 2953 (1953)).

[14] It has been demonstrated that (+)-2-octanol was converted to (−)-2-octylamine with >97% inversion of configuration,[2] the absolute configuration of the (−)-2-octylamine being the R configuration.

[15] The recorded molecular rotation of (+)-2-octylamine is $[M]_D$ 8.50° (in 5.953% benzene solution) which corresponds to $[\alpha]_D$ + 6.59°: F. G. Mann and J. W. G. Porter, *J. Chem. Soc.*, 456 (1944).

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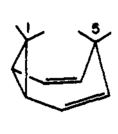
Three Homobullvalenones. Synthesis and Cope Rearrangements[1,2]

Sir:

Theoretical speculation has been stimulated anew by the fluxional properties of bridged homotropilidenes (**1**).[3–5] We report here the first extension of this series



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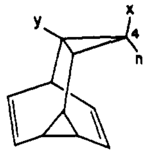

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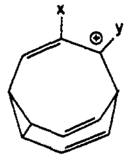
beyond its third member (bullvalene) and indicate some theoretical problems and opportunities which then ensue.

In an initial synthetic approach, the dibromocyclopropane (**2**, y = H, n = x = Br, 42%, mp 116°),[6] appropriately obtained from bullvalene,[7,8] was transformed by n-Bu$_3$SnH[9] into its epimeric monobromides (**2**, y = H, x = Br, n = H, 35%, mp 59°, nmr $\tau_{H\text{-}4}$ (CCl_4) 6.82 (t, J = 3.2 Hz) and **2**, x = y = H, n = Br, 30%, mp 79°, nmr $\tau_{H\text{-}4}$ (CCl_4) 7.19 (t, J = 7.9 Hz).[10] Subsequent and varied attempts at solvolytic cleavage,[13] however, proved to be fruitless.

To the degree that such difficulties might indirectly reflect the structural proximity of **3** (y = H) to the



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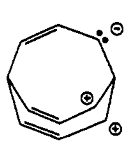

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electronically uncomfortable **4**,[14] relief should be accessible *via* an appropriately electron-donating y. However accurate this diagnosis, analogous transfor-

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[1] Presented in part at the International Symposium on the Chemistry of Nonbenzenoid Aromatic Compounds, Sendai, Japan, Aug 1970.

[2] *Chemical Abstract* names: **5a**, tricyclo[4.3.2.0^{2,9}]undeca-4,7,10-trien-3-one; **5b**, tricyclo[4.3.2.0^{2,9}]undeca-3,7,10-trien-5-one; **5c**, tricyclo[4.3.2.0^{3,9}]undeca-4,7,10-trien-2-one; **2**, 4-bromo-, 4,4-dibromo-, 5-methoxy-4-bromo-, and 5-methoxy-4,4-dibromotetracyclo[4.3.2.0^{2,9}.0^{3,5}]undeca-7,10-diene.

[3] W. v. E. Doering and W. R. Roth, *Angew. Chem.*, **75**, 27 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963); G. Schröder, J. F. M. Oth, and R. Merényi, *Angew. Chem.*, **77**, 774 (1965); *Angew. Chem., Int. Ed. Engl.*, **4**, 752 (1965); G. Schröder and J. F. M. Oth, *Angew. Chem.*, **79**, 458 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 414 (1967).

[4] (a) R. Hoffmann, *Tetrahedron Lett.*, 2907 (1970); H. Günther, *ibid.*, 5173 (1970); (b) R. Hoffmann and W.-D. Stohrer, *J. Amer. Chem. Soc.*, **93**, 6941 (1971); (c) A. Brown, M. J. S. Dewar, and W. Schoeller, *ibid.*, **92**, 5516 (1970); M. J. S. Dewar and W. W. Schoeller, *ibid.*, **93**, 1481 (1971); M. J. S. Dewar and D. H. Lo, *ibid.*, **93**, 7201 (1971); M. J. S. Dewar, *Pure Appl. Chem.*, in press.

[5] (a) M. J. Goldstein, *J. Amer. Chem. Soc.*, **89**, 6357 (1967); (b) M. J. Goldstein and R. Hoffmann, *ibid.*, **93**, 6193 (1971).

[6] C, H, and Br analyses of all isolated compounds agreed with expectation to within ±0.3%.

[7] D. Seyferth, *et al.*, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

[8] W. v. E. Doering and A. K. Hoffmann, *ibid.*, **76**, 6162 (1954); L. Skattebøl, *Org. Syn.*, **49**, 35 (1969).

[9] H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968); D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963).

[10] The temperature-dependent pmr spectra resemble those of the dichloride (y = H, x = n = Cl)[11a] and parent hydrocarbon (y = x = n = H).[12]

[11] (a) R. Merényi, J. F. M. Oth, and G. Schröder, *Chem. Ber.*, **97**, 3150 (1964); (b) J. F. M. Oth, R. Merényi, J. Nielsen, and G. Schröder, *Chem. Ber.*, **98**, 3358 (1965); (c) J. F. M. Oth, R. Merényi, H. Röttele, and G. Schröder, *Tetrahedron Lett.*, 3941 (1968); (d) J. F. M. Oth, E. Machens, H. Röttele, and G. Schröder, *Justus Liebigs Ann. Chem.*, **745**, 112 (1971).

[12] A. de Meijere and C. Weitemeyer, *Angew. Chem.*, **82**, 359 (1970); *Angew. Chem., Int. Ed. Engl.*, **9**, 376 (1970).

[13] (a) U. Schöllkopf, *Angew. Chem.*, **80**, 603 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 588 (1968); W. E. Parham, *et al.*, *J. Amer. Chem. Soc.*, **87**, 321 (1965); G. Stork, M. Nussim, and B. August, *Tetrahedron, Suppl.*, **No. 8**, 105 (1966); (b) A. J. Birch, J. M. Brown, and F. Stansfield, *J. Chem. Soc.*, 5343 (1964); C. D. Gutsche and D. Redman, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

[14] Like the cyclopentadienyl cation, **4** requires a half-filled (if stabilized) doubly degenerate MO.[5b] The D_{3h} barbaralyl cation provides an informative contrast. *Cf.* R. Hoffmann, W.-D. Stohrer, and M. J. Goldstein, *Bull. Chem. Soc. Jap.*, submitted for publication; S. Yoneda, S. Winstein, and Z. Yoshida, *ibid.*, submitted for publication.