Easily Cleaved, Optically Active Protective Groups of the Urethane Type

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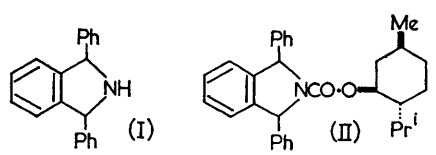
RACEMIC primary and secondary amines are rarely resolved by conversion into a set of diastereomeric amides since hydrolysis of the separated amides often involves conditions so drastic as to render the method impractical.[1] In order to confirm a recent stereochemical assignment[2] of the isomeric *cis*- and *trans*-1,3-dihydro-1,3-diphenylisoindoles (I) partial resolution of the *trans*-isomer was investigated. Resolution through use of a number of salts of optically active acids [*e.g.*, (+)-tartaric, (+)-camphor-10-sulphonic and (−)-malic] was unsuccessful. Similarly although the diastereoisomeric amides derived from hydratropic acid were easily separable we were unable to hydrolyse the amides even under drastic conditions.[3] We subsequently overcame this difficulty by a simple technique which promises to be of general applicability.

Substitution of a carbamate for an amide in this process allows one to choose among a host of systems many of which allow conversion of the separated diastereomeric urethanes into the resolved amine under conditions little different from those involved in the common technique using amine salts. The Table summarizes data on the ease of cleavage of model carbamates derived from several of the most commonly available optically active alcohols of potential interest in this connection. As expected the α-phenylethyloxycarbonyl and isobornyloxycarbonyl groups are cleaved about as easily as the classical t-butyloxycarbonyl group. Although the (−)-menthyloxycarbonyl group is not cleaved under the conditions described in the Table, it

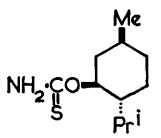
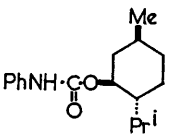
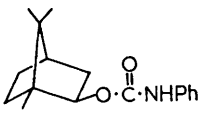
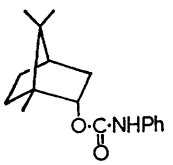
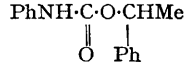


R·CO·O·CHPh·CH_3 (III)

was chosen for further study in the present work since (−)-menthol is commercially available in large quantity in optically pure form. A convenient procedure for cleavage of the (−)-menthyloxycarbonyl group involved brief treatment with anhydrous hydrogen bromide in hot acetic acid. Treatment of (−)-menthol with phosgene and pyridine in methylene dichloride solution gave (−)-menthyl chloroformate[4] which with racemic *trans*-(I) in pyridine solution gave 27% of the

TABLE

Approximate times required for cleavage of carbamates by hydrogen halides in nitromethane[a]

Carbamate		HCl	HBr
(IV)[e]		13	1
V)[d]		N.C.	N.C.
(VI)[e]		4	Inst.
(VII)[f]		N.C.	N.C.
(VIII)[g]		1	Inst.

[a] Times were recorded in minutes when a definite precipitate of amine hydrohalide appeared at room temperature; inst. = instantaneous; N.C. = not cleaved in 24 hr. at the concentrations used. The general method was similar to that previously described.[b]

[b] L. A. Carpino, P. H. Terry, and P. J. Crowley, *J. Org. Chem.*, 1961, **26**, 4336.

[c] B. Holmberg and W. Rosen, *Ber.*, 1925, **58**, 1834. The effect of thion substitution agrees with that observed previously (ref. b).

[d] R. H. Picard and W. O. Littlebury, *J. Chem. Soc.*, 1912, **101**, 109.

[e] J. Bertram and H. Wahlbaum, *J. prakt. Chem.*, 1894, [2], **49**, 5. The model carbamate was obtained from racemic isoborneol.

[f] R. Leuckart, *Ber.*, 1887, **20**, 114. The model carbamate was obtained from (−)-borneol obtained by hydrolysis of (−)-bornyl acetate.

[g] A. Klages and P. Allendorf, *Ber.*, 1898, **31**, 998.

carbamate (II), m.p. 228—230°, after fractional crystallization from ethanol–nitromethane. Cleavage of (II) by passage of hydrogen bromide through its solution in boiling acetic acid for 15 min., or by refluxing for 8—10 hr. with 48% hydrobromic acid–acetic acid (1 : 1) gave after basification, extraction into ether, precipitation with anhydrous hydrogen bromide, filtration, and re-basification 55% of dextrorotatory (I), m.p. 117—119·5°, $[\alpha]_D^{27}$ = +206·2° (*c*, 1·03, chloroform).

The other protective groups listed in the Table could probably also be introduced by means of the corresponding chloroformates[5,6] although α-phenylethyl chloroformate, because of its instability,[7] may not be generally useful. In its place we have made use of the stable azidoformate[8] (III; R = N_3). Treatment of racemic α-phenylethanol with methyl thiolchloroformate and pyridine in methylene dichloride gave in 71% yield α-phenylethyl *S*-methyl thiolcarbonate (III; R = SMe), b.p. 112—117° (5 mm.), which by reaction with hydrazine hydrate in methanol at room temperature for a period of 24 hr. gave in 84% yield the carbazate (III; R = NH·NH_2) as a thick colourless oil, b.p. 152—154° (5 mm.). Diazotization of (III; R = NH·NH_2) gave in about 80% yield the azidoformate (III; R = N_3) which showed acylating ability somewhat similar to that of the t-butyl derivative.[9]

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[1] W. Theilacker, "Methoden der Organischen Chemie," ed. E. Müller, Vol. 4/2, Georg Thieme Verlag, Stuttgart, 1955, p. 509.

[2] L. A. Carpino, *Chem. Comm.*, 1966, 494.

[3] The two diastereoisomers (A; m.p. 275—276·5° and B; m.p. 197—199°) were separated by recrystallization from chloroform, in which only the latter is readily soluble. Refluxing form (A) or (B) for 24 hr. with either 48% hydrobromic acid–acetic acid (1 : 1) or potassium hydroxide in ethylene glycol was without effect.

[4] *Cf.*, A. Einhorn and L. Rothlauf, *Annalen*, 1911, **382**, 237. It was neither necessary nor desirable to distil the crude acid chloride.

[5] Bornyl chloroformate has been reported previously. See R. H. Pickard and W. O. Littlebury, *J. Chem. Soc.*, 1907, **91**, 1973.

[6] Attempts to obtain (−)-menthyl thionochloroformate by treatment of (−)-menthol with thiophosgene in the presence of pyridine or antipyrine were unsuccessful.

[7] K. B. Wiberg and T. M. Shryne, *J. Amer. Chem. Soc.*, 1955, **77**, 2774.

[8] Obtained by a procedure analogous to that used for the t-butyl derivative. See L. A. Carpino, *J. Org. Chem.*, 1963, **28**, 1909.

[9] L. A. Carpino, *J. Amer. Chem. Soc.*, 1957, **79**, 4427.