B.—Compound **3a** (0.15 g, 0.394 mmol) was dissolved in 5 ml of THF and added dropwise to the suspension of $LiAlH_4$ (0.456 g) in 10 ml of THF. The mixture was refluxed for 8 hr and then worked up as in method A. The product (0.07 g, 59%) had a melting point of 141–142°. It showed no depression of its melting point when mixed with a sample obtained by method A. The infrared spectra were also in agreement.

Registry No.—**1**, 17182-23-9; **2a**, 17223-91-5; **2b**, 17223-92-6; **3a**, 17223-93-7; **3b**, 17223-94-8.

The Borane Reduction of Amido Esters

MILTON J. KORNET, POO AN THIO, AND SIP IE TAN

Department of Pharmaceutical Chemistry, University of Kentucky, Lexington, Kentucky 40506

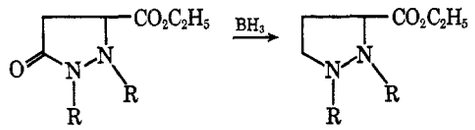
Received March 21, 1968

The requirement of various amino ester intermediates for other studies and the ready availability of amido ester precursors has led us to investigate the reduction of amido esters by borane. Our hope was the selective borane reduction of an amide functional group in the presence of an ester group.

The facile borane reduction of simple amides to amines in high yields has been described by Brown and Heim.[1] Borane reduction of fluoroacetamides to fluoroethylamines,[2] trifluoroacetamides to trifluoroethylamines,[3] and N-(2-haloethyl)benzamides to N-(2-haloethyl)benzylamines[4,5] illustrates the selectivity shown by this reagent when both amide and halogen groups are present in the same molecule. Selectivity was also shown in the borane reduction of the carbonyl of a trifluoroacetamido substituent without affecting the carbonyl of a carbamate moiety present in ethyl 4-trifluoroacetylpiperazine-1-carboxylate.[6]

Esters, on the other hand, are only slowly reduced by borane to the alcohol stage.[7,8]

Treatment of 1,2-diethyl-5-ethoxycarbonyl-3-pyrazolidinone (**1b**) with borane in tetrahydrofuran yielded ethyl 1,2-diethylpyrazolidine-3-carboxylate (**2b**, 60%). Similar treatment of 1,2-dimethyl-5-ethoxycarbonyl-3-pyrazolidinone (**1a**) with borane gave ethyl 1,2-dimethylpyrazolidine-3-carboxylate (**2a**, 59%). The structural assignments for these novel heterocycles are based on elemental analyses and infrared and nmr spectra.

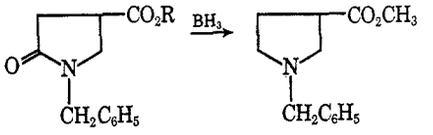


1a, R = Me
b, R = Et

2a, R = Me
b, R = Et

Several different methods of decomposing excess borane and boron complexes were tried including (1) cold 6 *N* hydrochloric acid, (2) boiling with the alcohol from which the ester is derived, and (3) refluxing with alcoholic hydrogen chloride. The latter method proved to be the best as evidenced by the absence of contamination of reaction products by amino complexed borane.

Borane reduction of 1-benzyl-3-methoxycarbonyl-5-pyrrolidinone (**3a**) gave methyl 1-benzyl-3-pyrrolidinecarboxylate (**4**, 54%). The utility of this synthesis may be realized by comparison with the previous three-step procedure[9] for the preparation of this compound from **3b** in an over-all yield of 28%.

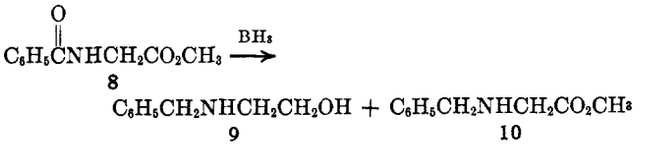


3a, R = Me
b, R = Et

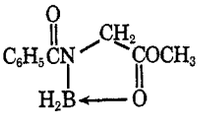
4

Ethyl N,N-diethylsuccinamate (**5**), upon treatment with borane for 2 hr at room temperature, afforded a mediocre (36%) yield of the selectively reduced product, ethyl 4-diethylaminobutanoate (**6**), which was obtained by distillation. In addition, considerable pot residue remained which was treated with 6 *N* hydrochloric acid and subsequently afforded the corresponding amino alcohol, 4-diethylamino-1-butanol (**7**, 7.3%). The infrared spectrum of **7** was identical with that of a sample of **7** synthesized by the lithium aluminum hydride reduction of **5**.[10] Refluxing **5** with borane for differing periods of time always gave lower yields of **6**.

As examples of compounds in which the amide nitrogen is monosubstituted, the borane reduction of methyl hippurate (**8**) and methyl *p*-acetamidobenzoate (**12**) was explored. Compound **8** gave a mixture of organic products consisting of 2-benzylaminoethanol (**9**, 85%), methyl 2-benzylaminoacetate (**10**, 11%), and an unidentified product (4%). The amino alcohol **9** and the amino ester **10** were identified by comparison with authentic samples. The large proportion of **9**



means that the reduction of the ester grouping is competitive with the reduction of the amide group. Presumably, a cyclic intermediate such as **11** is involved

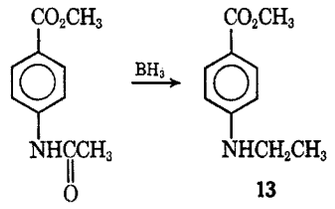


11

in which the ester carbonyl oxygen forms a coordinate covalent bond with boron and thereby results in an

(1) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).
(2) Z. B. Papanastassiou and R. J. Bruni, *J. Org. Chem.*, **29**, 2870 (1964).
(3) E. R. Bissell and M. Finger, *ibid.*, **24**, 1256 (1959).
(4) G. R. Pettit, S. K. Gupta, and P. A. Whitehouse, *J. Med. Chem.*, **10**, 692 (1967).
(5) When the halogen is chlorine or bromine, selectivity is observed; however, borane reduction of N-(2-iodoethyl)benzamides results in hydrogenolysis of the carbon–iodine bond in addition to reduction of the amide group.
(6) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **31**, 3867 (1966).
(7) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960).
(8) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, p 253.
(9) J. F. Cavalla, *J. Chem. Soc.*, 851 (1959).
(10) A. W. D. Avison, *J. Appl. Chem.* (London), **1**, 469 (195[illegible]).

increase in the electrophilic character of the ester carbonyl carbon. Reduction of **12** in which a phenylene group is interposed between the ester group and the N-monosubstituted amide group produced a 66% yield of methyl *p*-N-ethylaminobenzoate (**13**). The

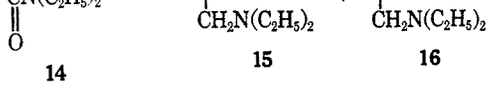


12 **13**

amino ester **13** was identical, by several criteria, with a genuine sample of **13** obtained from the ethylation of methyl *p*-aminobenzoate by ethyl sulfate.[11]

No attempt was made to determine whether any of the corresponding amino alcohol was also formed. The slightly higher yield obtained in the above reaction may be due to the fact that esters derived from aromatic carboxylic acids are reduced at a slower rate than those derived from aliphatic acids.[7]

Finally, the reduction of ethyl N,N-diethyloxamate (**14**), in which the ester and amide functional groups are as close together as possible, was examined. Somewhat surprisingly, the mixture of organic products was shown to be ethyl N,N-diethylaminoacetate (**15**, 94%), diethylaminoethanol (**16**, 5%), and an unidentified product (1%). Thus, a high degree of selectivity is



14 **15** **16**

obtained despite the proximity of the two functional groups.

The results obtained in this study indicate that the selective borane reduction of N-monosubstituted and N,N-disubstituted amide functional groups in the presence of an ester group is possible in a variety of compounds. However, with certain amido esters, because of their inherent structure, a practically useful selective reduction may be impossible as is the case with methyl hippurate. Nevertheless, the synthetic procedure described herein should find wide application in organic synthesis.

Experimental Section

Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Nmr spectra were recorded on a Varian A-60A spectrometer with tetramethylsilane as the internal reference. Melting points were taken on a Fisher-Johns apparatus and are corrected, and boiling points are uncorrected. The vpc analyses were obtained with an Aerograph A-700 Autoprep gas chromatograph using a 20 ft × $^3/_8$ in. aluminum column packed with 30% silicone gum rubber SE 30 on Chromosorb W (45–60 mesh); helium was used as the carrier gas and percentage compositions refer to the relative areas observed for the different components. The 1.0 *M* borane in tetrahydrofuran solution used in this work was supplied by the Ventron Corp.

Methyl Hippurate (8).—Sufficient ethereal diazomethane was added to 10.0 g (0.0518 mol) of hippuric acid in 100 ml of ether to give a yellow color which persisted. The clear solution was evaporated to dryness *in vacuo* and gave a quantitative yield of ester, mp 79–81°. Recrystallization from benzene gave the pure acid, mp 81–82° (lit.[12] mp 81–82°).

General Procedure for Diborane Reductions.—A 500-ml round-bottomed flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a gas-inlet tube, and a condenser (the outlet end was attached to a tube leading to a mercury bubbler) was thoroughly purged with nitrogen. A solution of the amido ester (0.1 mol) in 100 ml of anhydrous tetrahydrofuran (THF) was added dropwise with stirring in a nitrogen atmosphere to 150–180 ml of 1.0 *M* borane in THF (0.15–0.18 mol of BH_3) cooled in an ice bath. After completion of the addition the mixture was refluxed for 1 hr on an oil bath and cooled to room temperature. Decomposition of excess borane and boron complexes was effected by the dropwise addition of 75 ml of ethanolic hydrogen chloride in the case of ethyl esters (MeOH–HCl for methyl esters) followed by refluxing for 1 hr. After removal of the solvents under reduced pressure another 75 ml of ethanolic hydrogen chloride was added, and the mixture was refluxed an additional 1 hr. The solvents were again removed *in vacuo* and the residue was treated with 15 ml of water and extracted with 25 ml of ether or chloroform. The aqueous layer was basified with 40% aqueous sodium hydroxide with ice-bath cooling and extracted twice more with 50-ml portions of solvent. The combined solvent extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was distilled or recrystallized from a suitable solvent.

Ethyl 1,2-Diethylpyrazolidine-3-carboxylate (2b).—Treatment of **1b**[13] (21.4 g, 0.10 mol) in THF (100 ml) with 1.0 *M* borane in THF (150 ml) gave 11.9 g (60%) of **2b**: bp 91–92° (9 mm); $n^{20}D$ 1.4482; ir (film), 5.76 (ester C=O), no absorption at 5.92 μ (amide C=O); nmr ($CDCl_3$), δ 4.20 (q, 2, OCH_2), 2.05–3.60 (m, 9, NCH_2 and ring protons), 0.92–1.45 (m, 9, CH_3).

Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.83; H, 10.10; N, 14.21.

Ethyl 1,2-Dimethylpyrazolidine-3-carboxylate (2a).—Reduction of **1a**[14] (10.98 g, 0.059 mol) in THF (60 ml) with 1.0 *M* borane in THF (89 ml) led to 6.0 g (59%) of **2a**: bp 99–101° (21 mm); $n^{20}D$ 1.4502; ir (film), 5.77 (ester C=O), no absorption at 5.92 μ (amide C=O); nmr ($CDCl_3$), δ 4.24 (q, 2, OCH_2), 2.0–3.43 (m, 11, including two NCH_3 singlets at 2.52 and 2.58), 1.30 (t, 3, C—CH_3). Vpc analysis indicated a purity of 95%. Preparative vpc of the major peak followed by microdistillation afforded the analytical sample.

Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.71; H, 9.40; N, 16.43.

Methyl 1-Benzylpyrrolidine-3-carboxylate (4).—Reduction of **3a**[15] (5.8 g, 0.025 mol) in THF (25 ml) with 1.0 *M* borane in THF (37.5 ml) afforded 2.95 g (54%) of **4**: bp 98–98.5° (0.18 mm); $n^{20}D$ 1.5228 [lit.[9] bp 122° (0.8 mm), $n^{20}D$ 1.5207]; ir (film), 5.78 μ (ester C=O); nmr ($CDCl_3$), δ 7.33 (s, 5, C_6H_5), 3.70 (s, 3, OCH_3), 3.63 (s, 2, NCH_2), 1.87–3.37 (m, 7, aliphatic ring protons). Vpc analysis indicated the presence of a single component.

The ester **4** (1 g) was hydrolyzed by stirring overnight with 5 ml of 1 *N* sodium hydroxide in methanol–water (11 ml, 6:5) at room temperature. The mixture was neutralized with 5 ml of 1 *N* hydrochloric acid and evaporated to dryness *in vacuo*. The residue was extracted three times with 15-ml portions of THF, and the combined extracts were dried ($MgSO_4$). The solvent was stripped off under reduced pressure and the oily liquid residue was crystallized upon standing. Recrystallization from dry acetone gave 0.5 g (54%) of 1-benzyl-3-pyrrolidinecarboxylic acid: mp 108–109.5° (lit.[9] mp 106–108°); ir (film), 6.32 μ (carboxyl C=O).

Reduction of Ethyl N,N-Diethylsuccinamate (5) by Diborane.—Treatment of **5**[10] (10.0 g, 0.05 mol) in THF (50 ml) with 1.0 *M* borane in THF (83.5 ml) for 2 hr at room temperature led to 3.37 g (36%) of **6**: bp 94.5–98° (13 mm); $n^{20}D$ 1.4320 [lit.[16] bp 103–105° (16–17 mm); $n^{20}D$ 1.4342]; ir (film), 5.78 μ (ester C=O); nmr ($CDCl_3$), δ 4.16 (q, 2, OCH_2), 2.48 (m, 8), 1.80 (m,

(11) A. R. Surrey and H. F. Hammer, *J. Amer. Chem. Soc.*, **66**, 2127 (1944).

(12) H. Rinderknecht and C. Niemann, *ibid.*, **70**, 2605 (1948).

(13) M. J. Kornet, *J. Med. Chem.*, **9**, 493 (1966).

(14) M. J. Kornet and P. A. Thio, to be published.

(15) Y. H. Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).

(16) O. Magidson and I. Th. Strukov, *Arch. Pharm.* (Weinheim), **271**, 573 (1933).

2), 1.13 (m, 9). Vpc analysis indicated the sample to be 98% pure.

A crystalline hydrochloride derivative of **6** was prepared and recrystallized from absolute ethanol–ether: mp 110–112° (lit.[17,18] mp 113°, 111–112°); ir (KBr), 5.76 μ (ester C=O).

The residue which remained from the distillation of the amino ester **6** was treated with 6 *N* hydrochloric acid and resulted in gas evolution. After cessation of gas evolution the mixture was made alkaline with 40% (w/w) aqueous potassium hydroxide, extracted with ether, and dried ($MgSO_4$). After removal of the ether, the residue was distilled giving 0.53 g (7.3%) of **7**: bp 117–120° (24 mm); ir (film), 2.92 μ (associated OH). The infrared spectrum was identical with that of an authentic sample prepared by the lithium aluminum hydride reduction of ethyl N,N-diethylsuccinamate according to the procedure of Avison.[10]

Reduction of Methyl Hippurate (8) by Diborane.—Reaction of **8** (4.83 g, 0.025 mol) in THF (50 ml) with 1.0 *M* borane in THF (45 ml) gave 3.0 g of a colorless liquid, bp 91–95° (0.30 mm). Vpc analysis indicated the sample to be a mixture of three components (4, 85, and 11%) in order of increasing retention times. The infrared spectrum showed strong absorption at 3.02 (OH) and a weak band at 5.74 μ (ester C=O). Preparative vpc was employed in the separation of the major component.

The major product was identified as **9**: $n^{25}D$ 1.5411 (lit.[19] $n^{25}D$ 1.5395); ir (film), 3.02 μ (OH); nmr ($CDCl_3$), δ 7.33 (s, 5, C_6H_5), 3.79 (s, 2, NCH_2), 3.63 (t, 2, OCH_2), 2.76 (t, 2, NCH_2), 2.53 (s, 2, NH, OH). The infrared and nmr spectra were identical in all respects with the spectra of an authentic sample prepared by the reaction of ethanolamine and benzyl chloride according to the published procedure.[20]

The second major component could not be obtained in a pure state by preparative vpc, but was shown to be methyl 2-benzylaminoacetate (**10**) by a mixed vapor phase chromatograph with an authentic sample.[21] The minor component was not identified.

Reduction of Methyl *p*-Acetamidobenzoate (12) by Diborane.—Treatment of **12**[22] (5.79 g, 0.030 mol) in THF (50 ml) with 1.0 *M* borane in THF (54 ml) gave white crystals. Recrystallization from absolute methanol afforded 2.84 g of **13**, mp 135.5–138.5° (lit.[11] mp 138–139°). Concentration of the mother liquor yielded a second crop (0.56 g, mp 132–137.5°) and a third crop which was recrystallized and amounted to an additional 0.14 g, mp 137–140°, giving a total yield of 65.9%. A portion of the first crop was recrystallized again to give the pure compound: mp 138–140°; mmp 139–141° with an authentic sample;[11] ir (KBr), 2.96 (NH), 5.95 μ (ester C=O); nmr ($CDCl_3$), δ 7.90 (d, 2), 6.57 (d, 2), 3.86 (s, 4, NH, OCH_3), 3.21 (q, 2, NCH_2), 1.25 (t, 3, $C-CH_3$). The infrared spectrum of the product was identical with that of an authentic sample obtained from the ethylation of methyl *p*-aminobenzoate with ethyl sulfate according to the published procedure.[11]

Reduction of Ethyl N,N-Diethyloxamate (14) by Diborane.—Treatment of **14**[23] (6.93 g, 0.040 mol) in THF (50 ml) with 1.0 *M* borane in THF (60 ml) gave 3.97 g of an oil, bp 76–80° (27 mm). The infrared spectrum revealed strong absorption at 5.8 (ester C=O), a weak broad band at 2.9 (associated OH), and the absence of absorption at 6.06 μ (amide C=O). Vpc analysis indicated three components (5, 1, and 94%) in order of increasing retention times. Separation of the major component was achieved by preparative vpc.

The major component was identified as ethyl N,N-diethylaminoacetate (**15**): $n^{24}D$ 1.4211 (lit.[24] $n^{21.5}D$ 1.4230); ir (film), 5.80 μ (ester C=O); nmr ($CDCl_3$), δ 4.20 (q, 2, OCH_2), 3.32 (s, 2, $NCH_2C=O$), 2.68 (q, 4, NCH_2C), 1.18 (m, 9).

The component corresponding to 5% of the reaction mixture was shown to be N,N-diethylaminoethanol (**16**) by a mixed vapor phase chromatograph with an authentic sample. The third component was not identified.

(17) F. F. Blicke, W. B. Wright, Jr., and M. F. Zienty, *J. Amer. Chem. Soc.*, **63**, 2488 (1941).

(18) L. Canonica, A. Fiecchi, and M. Adobbati, *Rend. Ist. Lombardo Sci. Lettere, B*, **87**, 257 (1954); *Chem. Abstr.*, **50**, 6377 (1956).

(19) L. P. Kyrides, F. C. Meyer, F. B. Zienty, J. Harvey, and L. W. Bannister, *J. Amer. Chem. Soc.*, **72**, 745 (1950).

(20) P. Rumpf and R. Kwass, *Bull. Soc. Chim. Fr.*, **10**, 347 (1943).

(21) J. A. King and F. H. McMillan, *J. Amer. Chem. Soc.*, **72**, 1236 (1950).

(22) G. W. K. Cavill and J. M. Vincent, *J. Soc. Chem. Ind.* (London), **67**, 25 (1948).

(23) R. Barre and L. Favreau, *Compt. Rend.*, **230**, 848 (1950).

(24) D. Edwards, D. Hamer, and W. H. Stewart, *J. Pharm. Pharmacol.*, **16**, 618 (1964).

Registry No.—**2a**, 17012-19-0; **2b**, 17012-20-3; **4**, 17012-21-4; **5**, 7497-63-4; **8**, 1205-08-9; **12**, 17012-22-5; **14**, 5411-58-5; borane, 13283-31-3.

The Beckmann Rearrangement of Norcamphor Oxime[1]

B. LAWRENCE FOX AND JAMES E. REBOULET

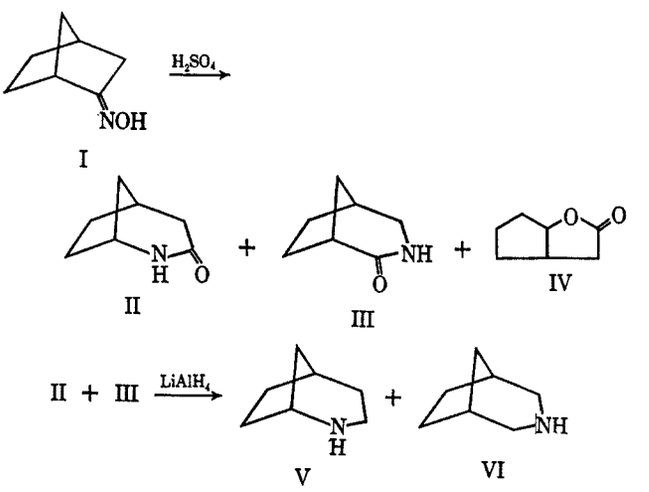
Wohlleben Laboratory of Chemistry, University of Dayton, Dayton, Ohio 45409

Received March 27, 1968

The Beckmann rearrangement of norcamphor oxime (I) in 85% sulfuric acid has been reported to yield 2-azabicyclo[3.2.1]octan-3-one (II).[2,3] Other workers[4,5] have had difficulty duplicating these results, but have failed to report the structures of the other products obtained in the reaction. Our interest in bicyclic amines prompted us to repeat this work, and we wish to report our results.

A solution of I in 85% sulfuric acid was slowly added to a flask heated to 110°.[6] Subsequent work-up produced a crude product having a wide boiling point range.

The lower boiling fractions were clear colorless liquids, composed chiefly of the lactone of *cis*-2-hydroxycyclopentane acetic acid (IV),[7] along with small amounts of II and 3-azabicyclo[3.2.1]octan-2-one (III). The structure of the lactone was established by comparison of this material with an authentic sample of IV prepared from cyclopentadiene following a known procedure.[8]



(1) Taken in part from the senior research problem of J. E. Reboulet.

(2) Swiss Patent 287,863 (1953) (to Inventa AG, Lucerne).

(3) R. Griot, *Helv. Chim. Acta*, **42**, 67 (1959).

(4) H. K. Hall, *J. Amer. Chem. Soc.*, **82**, 1209 (1960).

(5) R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, **26**, 1703 (1961). These authors report an alternate rearrangement procedure. We find that the alternate procedure, followed by hydride reduction, also yields a mixture of the same two amines (V and VI) obtained above.

(6) For an explanation of this modification of the published procedure, see the Experimental Section.

(7) This lactone is also produced when norcamphor oxime is heated in polyphosphoric acid. We wish to thank Professor R. T. Conley of Wright State University for informing us of this result prior to publication, since this simplified our identification of IV.

(8) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).