## A New Synthesis of β,β-Diphenylalanine and Related Unnatural α-Amino Acids[1]

*Sir:*

We wish to report a new, excellent route to the unnatural amino acid, dl-β,β-diphenylalanine (I), a method which we believe is general for the preparation of many aryl analogs of this amino acid and to be much superior to previously described methods[2] for the synthesis of I.

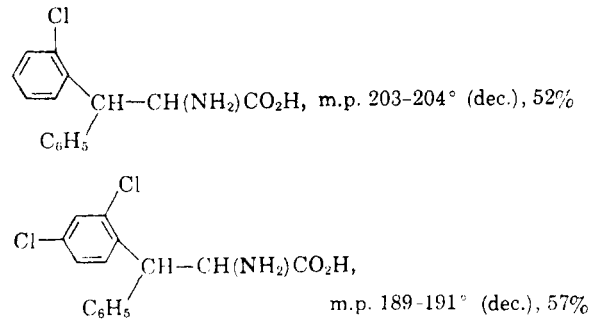
$$(C_6H_5)_2CH—CH(NH_2)COOH$$
I

Unsaturated azlactones are frequently converted to α-amino acids by hydrolytic and reductive methods. Compound I cannot be obtained by this conventional route because all attempts to prepare the required azlactone, derived from benzophenone and aceturic (or hippuric) acid, have been unsuccessful.

We have previously reported,[3] however, that 2-phenyl-4-benzylidene-5-(4H)-oxazolone (II) reacted readily with benzene in the presence of anhydrous aluminum chloride to give the 1,4 addition product, 2-phenyl-4-benzhydryl-5-oxazolone (III). When this reaction is conducted in a nitrogen atmosphere, yields of 70–75% of III are obtained. This saturated azlactone has been converted in nearly quantitative yield to the *N*-benzoyl derivative of I, m.p. 192–193°, by heating under reflux with ethanolic sodium hydroxide for twenty-four hours. Calcd. for $C_{22}H_{18}NO_3$: C, 76.52; H, 5.51%. Found: C, 76.47; H, 5.44%. This compound was identical with the derivative prepared from a sample of I which had been obtained *via* the hydantoin route.[2c]

The hydrobromide of I, m.p. 205°, was then obtained in 90% yield by heating the *N*-benzoyl compound under reflux for six hours with a 1:2 (by volume) mixture of 48% hydrobromic acid and glacial acetic acid. Calcd. for $C_{15}H_{16}NO_2Br$: C, 55.90; H, 4.96; N, 4.34. Found: C, 56.17; H, 5.16; N, 4.24. The hydrobromide was converted to the hydrochloride, from which β,β-diphenylalanine, m.p. 234° (dec.), was isolated by dissolving the salt in water and carefully adding 0.1*N* sodium hydroxide until precipitation occurred (*p*H 7). The over-all yield from II was 63%.

An indication of the scope of the method is illustrated by the preparation of the following new amino acids from the appropriately substituted azlactones:




and $(p\text{-}NO_2C_6H_4)(C_6H_5)CH—CH(NH_2)CO_2H\cdot HBr$, m.p. 215–217°, 80%.

Other preliminary results indicate that while electron-withdrawing substituents on the arylidene ring enhance the addition reaction, electron donating groups (*e.g.*, —$OCH_3$ and —$CH_3$) give much lower yields of the corresponding saturated azlactones. Full details of the method will be reported in a forthcoming paper.

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## Steroids and Related Natural Products. IV. Reduction of Lactones to Cyclic Ethers[1,2]

*Sir:*

A recent communication from this laboratory described the direct reduction of several esters to ether derivatives employing a reagent prepared from lithium aluminum hydride and boron trifluoride etherate.[3] We wish now to report the successful replacement of lithium aluminum hydride by lithium or sodium borohydride[4,5] and the course of this novel reduction reaction with several five-, six-, and seven-membered lactones and formic acid esters.

In general, reduction was accomplished by adding a boron trifluoride (15–30 moles) etherate solu-

(1) This research was supported by a grant (CY 4532) from the National Cancer Institute, National Institutes of Health, USPHS.

(2) (a) C. R. Harington and W. McCartney, *J. Chem. Soc.*, 892 (1929); (b) J. H. Burckhalter and V. C. Stephens, *J. Am. Chem. Soc.*, **73**, 56 (1951); (c) J. Anatol, *Compt. rend.*, **235**, 249 (1952).

(3) R. Filler and L. M. Hebron, *J. Org. Chem.*, **23**, 1815 (1958).

(1) Refer to G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 986 (1961), for Part III of this series.

(2) This investigation was supported by PHS Research Grant CY-4074 (C2S2) from the National Cancer Institute, Public Health Service; National Science Foundation Research Grant G-9585; and aided by Grant T-79A from the American Cancer Society.

(3) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **25**, 875 (1960).

(4) An interesting study of preparative procedures for the hydroboration of olefins by H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4233 (1960), indicates that several related reagents might also prove effective.

(5) These experiments suggested that a reagent derived from boron trifluoride and diborane might be responsible for the unusual course of the reduction reaction. Evidence favoring this proposal will be presented in a subsequent paper by G. R. Pettit and T. R. Kasturi.