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.

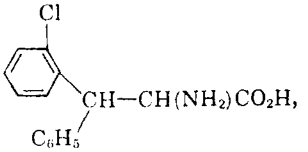
$$(C_6H_5)_2CH{-}CH(NH_2)COOH$$
I

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.

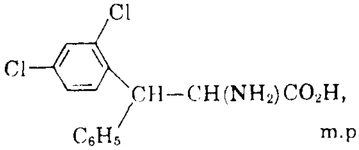
We have previously reported,[3] however, that 2-phenyl-4-benzylidene-5-(4H)-oxazolone (II) reacted readily with benzene in the presence of anhydrous aluminum chloride to give the 1,4 addition product, 2-phenyl-4-benzhydryl-5-oxazolone (III). When this reaction is conducted in a nitrogen atmosphere, yields 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:



m.p. 203-204° (dec.), 52%



m.p. 189-191° (dec.), 57%

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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Received November 28, 1960

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[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).

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-

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[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.

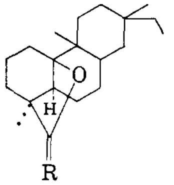
[5] These experiments suggested that a reagent derived from boron trifluoride and diborane might be responsible for the unusual course of the reduction reaction. Evidence favoring this proposal will be presented in a subsequent paper by G. R. Pettit and T. R. Kasturi.

tion of the ester (1 mole) to a cooled (ice bath) solution of the hydride (2 moles) in ethyl ether, tetrahydrofuran or tetrahydrofuran-diglyme (convenient with sodium borohydride). Before isolating the product, cooling was continued for 45 min. followed by heating at reflux for 2 hr.

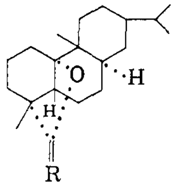
Rosenonolactone,[6] a metabolite of the mold *Trichothecium roseum* Link, was converted to lactone Ia.[7] Boron trifluoride etherate–lithium aluminum hydride reduction of the γ-lactone (Ia, 0.80 g.) yielded a unique diterpenoid ether (Ib, 0.45 g.); b.p. 110° (0.03 mm.), $[\alpha]_D^{22}$ +81.9° (chloroform). *Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.67; H, 11.70; O, 6.00; active H, 0.0. Analogous reduction of dihydroabietic γ-lactone (IIa, 3.00 g.)[8] afforded 12α,15-epoxy-12-nor-13β-methyl-11β,14α-abietane (IIb); b.p. 120–122° (0.2–0.3 mm.), $[\alpha]_D^{22}$ −35.3° (chloroform), 55–81% yields (*Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.72; H, 11.58; O, 5.69). Replacing lithium aluminum hydride by lithium or sodium borohydride led to comparable yields (64 and 80%, respectively) of this product (IIb).

Conversion of δ-lactone IIIa[9] (3.30 g.) to 3-methoxy-17a-oxa-D-homoestra-1,3,5(10)-triene (IIIb) was readily accomplished employing boron trifluoride–sodium borohydride; 71% yield. The product (IIIb) recrystallized from methanol as colorless leaflets; m.p. 150–151°, $[\alpha]_D^{22}$ +83.6° (chloroform). *Anal.* Calcd. for $C_{19}H_{26}O_2$(286); C, 79.68; H, 9.15; O, 11.17; OCH_3, 10.83. Found: C, 79.81; H, 9.13; O, 11.14; OCH_3, 10.96; Rast mol. wt., 272. Reduction of the 17a-oxa steroid (IIIb, 0.20 g.) with lithium and *t*-butyl alcohol in liquid ammonia led to 3-oxo-17a-oxa-D-homoestra-4-ene (IV, 0.145 g.); colorless needles, m.p. 163–164.5°, $[\alpha]_D^{20}$ +41.5° (chloroform). *Anal.* Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55; O, 11.66. Found: C, 78.61, H, 9.44; O, 11.81.

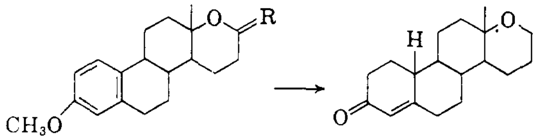
A convenient synthesis of 3β-acetoxy-7a-oxa-5α-B-homocholestane (V, 0.38 g.), colorless blades, m.p. 103–104°, $[\alpha]_D^{20}$ −20.4° (chloroform), was achieved by reducing 3β-hydroxy-7-oxo-7a-oxa-5α-B-homocholestane[10] (0.73 g.) with a boron trifluoride–lithium aluminum hydride reagent and treating the crude product with acetic anhydride–pyridine. Elemental analyses (*Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28; O, 10.75. Found: C, 77.77; H, 11.12; O, 11.26) were consistent with the structural assignment.



Ia. R = O
b. R = H₂

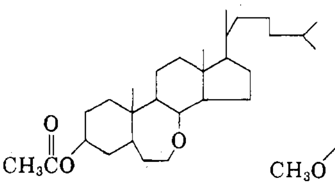


IIa. R = O
b. R = H₂

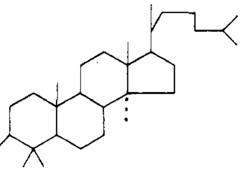


IIIa. R = O
b. R = H₂

IV



V



VI

Reduction of 5α-lanostane 3β-formate (1.34 g.), m.p. 136–138°, $[\alpha]_D^{22}$ +36.8° (chloroform), to 3β-methoxy-5α-lanostane (VI, 0.36 g.), m.p. 137–138° (*Anal.* Calcd. for $C_{31}H_{56}O$: C, 83.71; H, 12.69. Found: C, 83.44; H, 12.63), $[\alpha]_D^{20}$ +49.9° (chloroform), was carried out using the boron trifluoride-sodium borohydride procedure. Synthesis of 3β-methoxy-cholestane was accomplished in a similar manner. This reaction sequence illustrates a new route to methyl ether derivatives of secondary alcohols.

Preliminary examination of this new reaction employing several esters and lactones derived from primary alcohols has indicated that, in these cases, essentially complete conversion to the respective alcohols or glycols may be expected.

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[7] *Cf.*, A. Harris, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1799 (1958).

[8] L. J. Gough, T. F. Sanderson, V. I. Stenberg, and E. Wenkert, *J. Org. Chem.*, **25**, 1269 (1960). We wish to thank Dr. T. F. Sanderson for providing this substance.

[9] R. P. Jacobsen, *J. Biol. Chem.*, **171**, 91 (1947).

[10] K. Bloch, *Helv. Chim. Acta*, **36**, 1611 (1953).