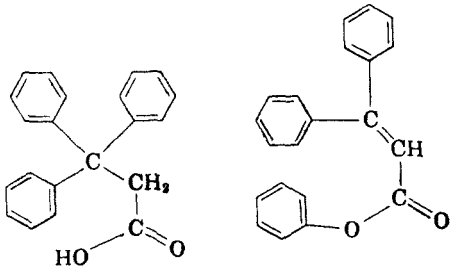
Communications TO THE EDITOR

An Anomalous Hunsdiecker Reaction Involving Rearrangement

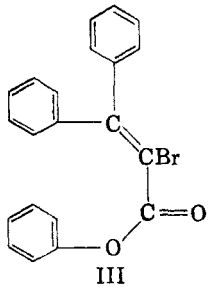
Sir:

We have recently observed the conversion of β,β,β-triphenylpropionic acid (I) to phenyl β,β-diphenylacrylate (II) and phenyl α-bromo-β,β-diphenylacrylate (III) during an attempted Hunsdiecker[1] degradation. This appears to be the first reported instance in silver salt-bromine reactions of *internal ester formation accompanied by rearrangement.*[2] Bromodecarboxylation, the expected reaction, only amounted to *ca.* 3–5%.



I

II



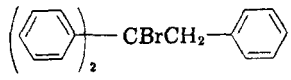
III

β,β,β-Triphenylpropionic acid[3] (m.p. 179–180°, Calc'd for $C_{21}H_{18}O_2$: C, 83.40; H, 6.00. Found:[4] C, 83.24; H, 6.11; Neut. equiv., 302.8) was converted to its silver salt (0.078 mole) and treated while being stirred in dry carbon tetrachloride (30 ml.) under a slow nitrogen gas sweep with bromine (0.078 mole) at 25° over a period of ¾ hour, followed by reflux (76°) for 1 hour. Only *ca.* 3% of the theoretical carbon dioxide was evolved. The standard workup followed by chromatography (alumina, petroleum ether-benzene eluant) and vacuum sublimation gave II [8.6%, m.p. 123.5–124.5°, λ_{EtOH}^{max} 285 mμ (log ε 4.23), λ_{EtOH}^{min} 245 mμ (log ε 3.96), I. R. (KBr pellet) 1736s cm.$^{-1}$ (ester C=O), 1618s—1594s—1579s cm.$^{-1}$ (aromatic with conj. double bond). Decolorized ½% $KMnO_4$. Calc'd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 84.15; H, 5.38] and III [20.5%, m.p. 90.5–91.5°, λ_{EtOH}^{max} (shoulder) 285 mμ (log ε 4.22), λ_{EtOH}^{min} 267 mμ (log ε 4.18), I.R. (KBr pellet) 1740s cm.$^{-1}$ (ester C=O), 1594w—1494m cm.$^{-1}$ (aromatic), stable to ½% $KMnO_4$ and to hot, ethanolic $AgNO_3$. Calc'd for $C_{21}H_{15}BrO_2$: C, 66.60; H, 3.99; Br, 21.05. Found: C, 66.42; H, 4.07; Br, 20.80]. I (67%, m.p. 179–180°) was recovered from the reaction.

The structure of II was confirmed by mixture melting points and identity of spectra with authentic material prepared from ββ-diphenylacrylic acid[5] and phenol *via* the acid chloride.

The structure of III was similarly confirmed by mixture melting points and identity of spectra with authentic material prepared from α-bromo-β,β-diphenylacrylic acid[6] and phenol *via* the acid chloride.

The identity of the bromodecarboxylated product is uncertain, but preliminary results indicate it to be an easily dehydrobrominated substance, possibly the expected compound IV.



IV

Work on this reaction and its mechanism is continuing.

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(1) Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 291 (1942).

(2) Roberts and Simmons, *J. Am. Chem. Soc.*, **73**, 5487 (1951) showed the presence of cyclopropylcarbinyl cyclobutanecarboxylate in the Hunsdiecker reaction of cyclobutanecarboxylic acid. This is, however, not internal ester formation and is distinctly different from the situation described herein.

(3) Hellerman, *J. Am. Chem. Soc.*, **49**, 1738 (1927).

(4) Analyses by Galbraith Laboratories, Knoxville, Tenn.

(5) Kharasch, Kane, and Brown, *J. Am. Chem. Soc.*, **64**, 333 (1942).

(6) Newman and Owen, *J. Chem. Soc.*, 4726 (1952).

Synthesis of Histidyl Peptides

Sir:

Since histidine occurs widely in proteins and polypeptides, the development of methods for the synthesis of histidyl peptides is desirable. Holley and Sondheimer[1] employed the azide procedure for preparation of a number of histidyl peptides but alternate methods are needed.

(1) R. Holley and E. Sondheimer, *J. Am. Chem. Soc.*, **76**, 1326 (1954).

Temporary protection of the imidazole ring of histidine by the benzyl group could enable the use of anhydrides for coupling. Thus, du Vigneaud and Behrens[2] have prepared *im*-benzyl-L-histidine as an intermediate in the synthesis of L-amino-methyl-histidine. The benzyl group was removed by sodium in liquid ammonia.

In the present work *im*-benzyl-L-histidine was esterified by the Fischer procedure to give the corresponding methyl ester dihydrochloride (I) (m.p. 111–115°).[3] *Anal.* Calc'd for $C_{14}H_{19}Cl_2N_3O_2$: N, 12.64; Cl, 21.35. Found: N, 12.30; Cl, 20.95. Carbobenzoxy-L-phenylalanine was coupled with the ester (I) by the anhydride procedure.[4] Yield, 65–70%.

The oily carbobenzoxy-L-phenylalanyl-*im*-benzyl-L-histidine methyl ester (II) was saponified with *N* NaOH, diluted with water, and acidified with acetic acid. The precipitated acid was recrystallized from ethanol, m.p. 140–141°. *Anal.* Calc'd for $C_{30}H_{30}N_4O_5$: C, 68.42; H, 5.74. Found: C, 68.09; H, 5.85.

The ester II was treated with hydrazine monohydrate (100% excess) to give the carbobenzoxy-L-phenylalanyl-*im*-benzyl-L-histidylhydrazide (III). After recrystallization from 80% ethanol the hydrazide melted at 183–186°. Yield 75%. *Anal.* Calc'd for $C_{30}H_{32}N_6O_4$: C, 66.64; H, 5.96. Found: C, 66.65; H, 5.61. The hydrazide (III) was coupled with L-leucine benzyl ester hydrochloride[5] by the azide procedure. The azide was extracted from the acidic medium (acetic acid) with ethyl acetate. The product of coupling was saponified and treated as was the ester (II). The precipitated carbobenzoxy-L-phenylalanyl-*im*-benzyl-L-histidyl-L-leucine (IV) was recrystallized from ethanol, m.p. 163–165°. Yield 60%. *Anal.* Calc'd for $C_{26}H_{41}N_5O_6$: N, 10.94. Found: N, 10.65. The substituted tripeptide (IV) was hydrogenated in ethanol-water in the presence of palladium black to give the free tripeptide which crystallized from 40% ethanol. Paper chromatography in the 2-butanol–formic acid system[6] revealed one spot. The R*f* value was 0.33. The peptide gave a positive Pauli reaction. $[\alpha]_D^{24°} = +30.5°$ (c = 1.08 in acetic acid). *Anal.* Calc'd for $C_{21}H_{29}N_5O_4$: C, 60.70; H, 7.03; N, 16.85. Found: C, 60.97 H, 7.00; N, 16.58.

During the course of this work the following compounds also have been synthesized in a similar manner: Carbobenzoxy-*im*-benzyl-L-histidine, m.p. 210–213°. *Anal.* Calc'd for $C_{21}H_{21}N_3O_4$: C, 66.47; H, 5.55. Found: C, 66.31; H, 5.76. Carbobenzoxy-L-leucyl-*im*-benzyl-L-histidine, m.p. 177–178°. *Anal.* Calc'd for $C_{27}H_{32}N_4O_5$: C, 65.83; H, 6.54. Found: C, 65.58; H, 6.81. Carbobenzoxy-L-phenylalanyl-*im*-benzyl-L-histidyl-L-aspartic acid,[7] m.p. 193–196° (decomp.). *Anal.* Calc'd for $C_{34}H_{35}N_4O_8$: C, 63.63; H, 5.48. Found: C, 63.63; H, 5.67. Tritylglycyl-*im*-benzyl-L-histidine[8] (V), m.p. 198–201°. *Anal.* Calc'd for $C_{34}H_{32}N_4O_3$: N, 10.29. Found: N, 9.99. Glycyl-*im*-benzyl-L-histidyl-L-leucine (VI). This compound (VI) was prepared by coupling (V) with leucine benzyl ester hydrochloride in the anhydride procedure.[4] The product of coupling was saponified as was (II) and the precipitate was detritylated with acetic acid.[8] Paper chromatography in the 2-butanol–formic acid system[6] revealed one spot. The R*f* value was 0.17. *Anal.* Calc'd for $C_{21}H_{29}N_5O_4$: N, 16.85. Found: N, 16.60.

A detailed description will be presented at a later date. Thanks are due Mr. D. Rigakos for the analytical data reported here.

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(2) V. du Vigneaud and O. Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

(3) All melting points are uncorrected.

(4) R. Boissonas, *Helv. Chim. Acta*, **34**, 874 (1951); J. Vaughan and R. Osato, *J. Am. Chem. Soc.*, **73**, 553 (1951).

(5) H. Miller and H. Waelsch, *J. Am. Chem. Soc.*, **74**, 1092 (1952).

(6) W. Hausmann, *J. Am. Chem. Soc.*, **74**, 3181 (1952).

(7) The sequence Phe-His-Asp has been identified in Bacitracin A, W. Hausmann, J. Weisiger, and L. C. Craig, *J. Am. Chem. Soc.*, **77**, 723 (1955).

(8) Tritylglycine [L. Zervas and D. Theodoropoulos, *J. Am. Chem. Soc.*, **78**, 1359 (1956)] was coupled with the ester (I) by the anhydride procedure.[4] The product was treated as (II).