least partially, the hydrochloride of Ia and was recrystallized from water containing a small amount of triethylamine. The yellow crystals (69% yield) were identified as 7-amino[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine (Ia) by their melting point (250–252°) and infrared and ultraviolet spectra.[14]

Hydrolysis of IIc.—A mixture of 100 mg. of IIc and 10 ml. of 1 *N* sodium hydroxide was stirred at room temperature for 24 hr., heated under reflux for 4.5 hr., cooled, and acidified to pH 1. Concentration of the solution yielded 40 mg. (65%) of 4-amino-1,2,5-thiadiazole-3-carboxylic acid,[13] which was identified by its melting point (220–222°) and infrared spectrum.

Cyclization of 5-Amino-*v*-triazole-4-carboxamidine (VIa) to Va.—A mixture of 500 mg. of VIa hydrochloride and 20 ml. of triethyl orthoformate heated under anhydrous conditions at the reflux temperature for 7 hr. and then chilled yielded 477 mg. of a white precipitate. A suspension of the precipitate in water was adjusted to pH 7 with sodium bicarbonate, stirred for 0.5 hr., and filtered. The white solid, which amounted to 385 mg. (92% yield) after it had been washed with water and dried, was identified as Va by its ultraviolet and infrared spectra.

Acknowledgment.—The authors express their appreciation to Drs. W. J. Barrett, W. C. Coburn, Jr., P. D. Sternglanz, and associates of the Analytical Section of this Institute for microanalyses and spectral determinations and to Dr. J. A. Montgomery for encouragement in this work.

Derivatives of 6-Hydroxyhomoveratramide

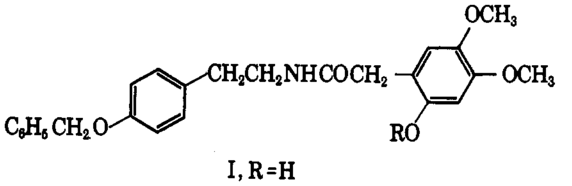
WILLIAM C. AGOSTA[1]

Department of Chemistry, University of California, Berkeley, California

Received February 11, 1965

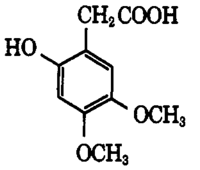
In connection with an investigation since discontinued, we prepared amide I and its benzyl ether II. The amine component of these amides, β-(*p*-benzyloxyphenyl)ethylamine, was prepared from the known[2] *p*-benzyloxybenzaldehyde. Base-catalyzed condensation of the aldehyde and nitromethane led to *p*-benzyloxy-β-nitrostyrene. Reduction of this latter material with lithium aluminum hydride in refluxing ether yielded the desired amine, which was conveniently purified as the hydrochloride.

For acylation of this amine the most convenient derivative of 6-hydroxyhomoveratric acid (III) appeared to be the corresponding lactone IV.[3,4] A suitable route to this compound entailed the following steps. Methyl 6-nitrohomoveratrate (V), available through Fischer esterification of the easily accessible[5] acid, was hydrogenated in benzene solution over 5% palladium on carbon to give the corresponding amino ester. This was diazotized and the diazonium salt was hydrolyzed in boiling aqueous sulfuric acid to hydroxy acid III. Acid-catalyzed dehydration to lactone IV proceeded smoothly in hot benzene solution with continuous removal of the water formed. This procedure from V led to IV in an over-all yield of 47% without purification of intermediates; the assigned structure of this lactone is supported by infrared carbonyl absorption at 5.57 μ.

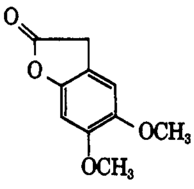


I, R = H

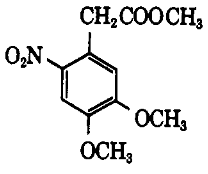
II, R = $C_6H_5CH_2$



III



IV



V

When β-(*p*-benzyloxyphenyl)ethylamine and III were heated together in benzene solution, the desired amide I formed in 85% yield. It gave a positive ferric chloride test and showed infrared absorption at 6.11 and 6.30 μ. It reacted with benzyl chloride in methanol containing 1 equiv. of lithium methoxide to yield the benzyloxy derivative II.

Experimental[6]

***p*-Benzyloxy-β-nitrostyrene.**—A solution of 12.0 g. of *p*-benzyloxybenzaldehyde[2] in 400 ml. of ethanol was cooled to 5° and 6.85 g. of nitromethane was added. This solution was stirred while a solution of 5.7 g. of sodium hydroxide in 100 ml. of ethanol, precooled to 5°, was added dropwise. The mixture was stirred 30 min. at 5–10° and then poured into a stirred solution of 68 ml. of concentrated hydrochloric acid in 104 ml. of water at room temperature. After 2 hr. the crude product was filtered. Recrystallization from ethanol gave 10.9 g. (75%). Two further recrystallizations from ethanol gave an analytical sample, m.p. 120–121°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.84; H, 5.09; N, 5.61.

β-(*p*-Benzyloxyphenyl)ethylamine.—In a Soxhlet apparatus 10.66 g. of *p*-benzyloxy-β-nitrostyrene was extracted over a 9–10-hr. period into 500 ml. of ether containing 6.5 g. of lithium aluminum hydride. The solution was heated at reflux an additional 8 hr. and then worked up with 5.65 ml. of water, 4.5 ml. of 20% aqueous sodium hydroxide, and finally 17 ml. of water. The resulting ether solution was filtered free of salts and dried over potassium carbonate. There was recovered 9.18 g. of colorless crystals (97%). The amine proved difficult to purify and was accordingly converted to the hydrochloride with 0.5 *M* hydrochloric acid for analysis. Three recrystallizations from isopropyl alcohol gave material of analytical purity, m.p. 196–206° dec.

Anal. Calcd. for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.12; H, 6.76; N, 5.17.

Methyl 6-Nitrohomoveratrate (V).—A solution of 66.4 g. of 6-nitrohomoveratric acid[5] in 800 ml. of methanol containing 20 ml. of concentrated sulfuric acid was heated under reflux for 18 hr. and then cooled to 0°. There were added 500 ml. of cold 6% aqueous sodium hydroxide and some ice. The resulting precipitate was filtered, dried, and recrystallized from methanol, yield 64.4 g. (91%). A sample was recrystallized further from ethyl acetate and then sublimed for analysis, m.p. 112.5–113°.

Anal. Calcd. for $C_{11}H_{13}NO_6$: C, 51.76; H, 5.13; N, 5.49. Found: C, 51.71; H, 5.11; N, 5.34.

5,6-Dimethoxycoumaran-2-one (IV).—The preparation of this compound was carried out from the above nitro ester without purification of intermediate compounds.

A solution of 5.00 g. of nitro ester in 100 ml. of benzene containing 500 mg. of 5% palladium on carbon was stirred under hydrogen at normal temperature and pressure. The theoretical

---

[1] The Rockefeller Institute, New York, N. Y. 10021.

[2] E. Wörner, *Ber.*, **29**, 139 (1896).

[3] Compound III itself has been described. *Cf.* L. E. Smith, and F. B. LaForge, *J. Am. Chem. Soc.*, **56**, 2431 (1934); O. Dann, J. Lang, and H. Vohl, *Ann.*, **631**, 116 (1960).

[4] *Cf.* G. Cramer, *Ber.*, **31**, 2813 (1898).

[5] R. K. Callow, J. M. Gulland, and R. D. Haworth, *J. Chem. Soc.*, 658 (1929).

[6] Chemical analyses were performed in the microanalytical laboratory of the University of California. All melting points are corrected.

amount of hydrogen was absorbed in 7 hr. Catalyst was removed by filtration through Celite and the solution was evaporated to dryness at room temperature *in vacuo*. The resulting crude amino ester was diazotized directly. It was dissolved at 0° in 65 ml. of water containing 2.62 ml. of concentrated sulfuric acid, to which was added dropwise 1.35 g. (1.0 equiv.) of sodium nitrite in 8.5 ml. of water. After 15-min. stirring at 0°, this solution was added to 350 ml. of 43% aqueous sulfuric acid at reflux. The mixture was heated at reflux 30 min., cooled, saturated with ammonium sulfate, and extracted several times with ether. The ether solution was washed with water and dried over magnesium sulfate; it yielded 2.12 g. of crude 6-hydroxyhomoveratric acid (III). This was dehydrated to the desired lactone by heating overnight in a water separator a benzene solution containing a trace of *p*-toluenesulfonic acid. After charcoal treatment the solution yielded 1.80 g. of yellow crystals (47% based on starting nitro ester). Recrystallization from benzene–cyclohexane and then sublimation yielded an analytical sample, m.p 148.5–150°, infrared absorption at 5.57 μ ($CHCl_3$).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.08; H, 5.31.

N-β-(4′-Benzyloxyphenyl)ethyl-6-hydroxyhomoveratramide (I).—A solution of 44 mg. of lactone IV and 52 mg. of amine (freshly prepared from the purified hydrochloride) in 5.0 ml. of benzene was heated at reflux for 5 hr. and then allowed to stand at room temperature overnight. The colorless crystals were filtered and washed with 1:1 benzene–cyclohexane, yield 82 mg. (85%). Two recrystallizations from benzene gave an analytical sample, m.p. 163–164°, positive ferric chloride test, infrared absorption at 6.11 and 6.30 μ ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.3. Found: C, 71.13; H, 6.68; N, 3.5.

N-β-(4′-Benzyloxyphenyl)ethyl-6-benzyloxyhomoveratramide (II).—A suspension of 500 mg. of the above phenolic amide in 8.0 ml. of methanol was flushed with dry nitrogen and then treated with 1.0 equiv. of lithium in methanol (2.5 ml. of a solution of 165 mg. of lithium in 50 ml. of methanol) followed by 303 mg. (2.0 equiv.) of benzyl chloride. This mixture was heated at reflux under nitrogen for 10.5 hr. The initial purple color faded rapidly to pale brown. After cooling, the mixture was diluted with water and extracted with ether. Extraction of the ether with dilute sodium hydroxide yielded 110 mg. of unreacted starting material. The ether solution was further washed with dilute hydrochloric acid, water, and brine. From it were recovered the desired neutral product and a trace of unconsumed benzyl chloride. The latter was removed *in vacuo*, and the product was recrystallized from ethyl acetate–benzene to give 350 mg. (74% based on unrecovered starting material). Two additional recrystallizations from the same solvent pair gave an analytical sample, m.p. 113–115°.

Anal. Calcd. for $C_{32}H_{33}NO_5$: C, 75.12; H, 6.50; N, 2.74. Found: C, 74.76; H, 6.53; N, 2.94.

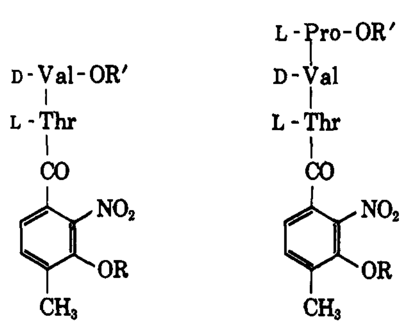
Removal of O-Benzyl Blocking Groups with Trifluoroacetic Acid[1]

JOHN P. MARSH, JR., AND LEON GOODMAN

Life Sciences Research, Stanford Research Institute,
Menlo Park, California

Received February 3, 1965

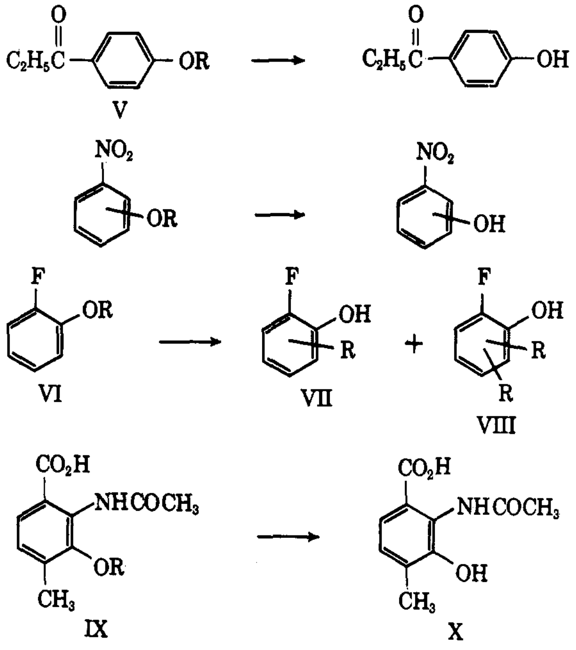
As part of a program in the synthesis of actinomycin analogs trifluoroacetic acid was used to cleave the *t*-butyl esters of the blocked peptides (I and III).[2] The products of these reactions were, surprisingly, the nitrophenols II and IV as shown by their indicator properties, n.m.r. spectra, and elemental analyses. Thus concomitant debenzylation accompanied the peptide ester cleavage. Although a number of methods of removing O-benzyl blocking groups are available such as catalytic hydrogenolysis,[3] sodium and ammonia treatment,[4] and reaction with hot hydrochloric acid,[5] the use of trifluoroacetic acid at room temperature seemed to offer a novel and mild method of debenzylation; some observations on the reaction are noted in this manuscript.



R = $C_6H_5CH_2$

Trifluoroacetic acid, at room temperature, served to cleave a number of aromatic benzyl ethers when the aromatic ring contained either *meta*-directing or *ortho-para*-directing groups. The reactions investigated are summarized in Chart I. There was a significant difference in the rate of debenzylation of the *o*-, *m*-, and *p*-benzyloxynitrobenzenes to give the corresponding nitrophenols. These reactions could be followed by monitoring the n.m.r. signal of the methylene protons of the ether benzyl group. In an 0.11 *M* solution of

CHART I



I, R = $CH_2C_6H_5$; R′ = $C(CH_3)_3$
II, R = R′ = H

III, R = $CH_2C_6H_5$;
R = $C(CH_3)_3$
IV, R = R′ = H

---

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U.S. Public Health Service, Contract No. PH 43-64-500. The opinions expressed are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center.

(2) The synthesis and further reactions of I and III will be reported in a separate manuscript.

(3) W. H. Hartung and R. Siminoff, *Org. Reactions*, **7**, 263 (1953).

(4) E. J. Reist, V. J. Bartuska, and L. Goodman, *J. Org. Chem.*, **29**, 3725 (1964).

(5) (a) W. Baker and N. C. Brown, *J. Chem. Soc.*, 2303 (1948). (b) A referee pointed out that the *o*-benzyl group of a tyrosine residue has been removed with 4 *N* hydrogen bromide in acetic acid: M. Bodanszky and V. du Vigneaud, *Nature*, **183**, 1324 (1959).