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

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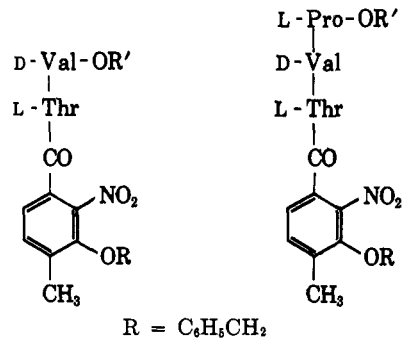
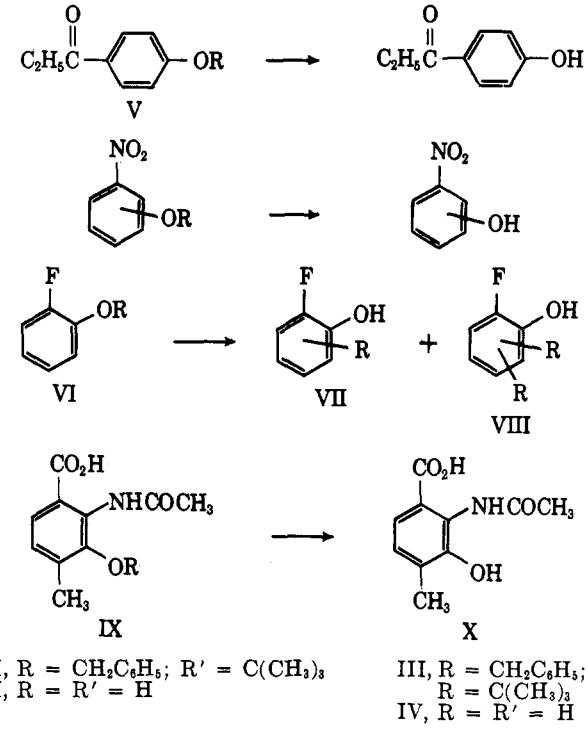
As part of a program in the synthesis of actinomycin analogs trifluoroacetic acid was used to cleave the *t*-butyl esters of the blocked peptides (I and III).[2] The products of these reactions were, surprisingly, the nitrophenols II and IV as shown by their indicator properties, n.m.r. spectra, and 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

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(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).

the respective benzyl ether in trifluoroacetic acid, the *ortho* isomer was completely debenzylated by the time the n.m.r. measurement could be made (<5 min.), the *meta* isomer was 65% debenzylated after 56 min., and the *para* isomer was 48% debenzylated after 56 min.

The *o*-fluoro ether VI pointed out a complication of this debenzylation technique. The products of the reaction were the monobenzylfluorophenols (VII) and dibenzylfluorophenols (VIII) as shown by n.m.r. studies and by gas chromatography. No significant amount of *o*-fluorophenol was noted in the reaction product, although small amounts of the compound would probably be missed in the work-up procedure used.

This method of ether cleavage, at least using the conditions employed with aromatic benzyl ethers, is apparently restricted to aromatic ethers since benzyl ethyl ether and benzyl *n*-butyl ether were unaffected by trifluoroacetic acid at room temperature.

Experimental

Boiling points and melting points, the latter obtained with the Thomas–Hoover apparatus, are uncorrected. The n.m.r. spectra were run in deuteriochloroform using tetramethylsilane (TMS) as an internal standard or in trifluoroacetic acid using TMS as an external standard and were obtained with the Varian A-60 spectrometer. The vapor phase chromatographs were obtained using a 10 ft. × $^3/_8$ in. polydiethylene glycol succinate column. Magnesium sulfate was used to dry organic solutions.

Reaction of Trifluoroacetic Acid with *p*-Benzyloxypropiophenone (V).—A solution of 2.0 g. of *p*-benzyloxypropiophenone in 25 ml. of trifluoroacetic acid was allowed to stand at room temperature for 18 hr., then was evaporated *in vacuo* (bath temperature <40°). The residue was freed of traces of trifluoroacetic acid by three treatments with 25 ml. of benzene, each solution being evaporated *in vacuo*. The residue was partitioned between 20-ml. portions of 1 *N* aqueous sodium hydroxide and ethyl acetate. The alkaline extract was adjusted to pH 1 with 6 *N* hydrochloric acid and extracted with 20 ml. of ethyl acetate. The extract was dried and evaporated *in vacuo*, and the residue was recrystallized twice from water yielding 0.76 g. (61%) of *p*-hydroxypropiophenone, m.p. 145–147° (lit.[6] m.p. 147–148°).

Reaction of *o*-Benzyloxynitrobenzene with Trifluoroacetic Acid.—A solution of 2.34 g. of *o*-benzyloxynitrobenzene in 25 ml. of trifluoroacetic acid was allowed to stand at room temperature for 30 min., then was evaporated *in vacuo*. The reaction work-up was the same as that described above for the deblocking of *p*-benzyloxypropiophenone except that ethyl ether was used as the extraction solvent. The product, 0.98 g. (68%) after crystallization from ethanol–water, had m.p. 42–43° (lit.[7] m.p. 44.9°).

Reaction of *o*-Benzyloxyfluorobenzene (VI) with Trifluoroacetic Acid.—A solution of 3.5 g. of VI in 25 ml. of trifluoroacetic acid was allowed to stand at room temperature for 18 hr. at the end of which period the reaction mixture had separated into two layers. The upper layer, A, was removed with a pipet and dissolved in 10 ml. of benzene, and the solution was evaporated *in vacuo* leaving 0.80 g. of a very viscous oil.

The lower layer, B, was poured into 100 ml. of water and the resulting mixture was extracted with 25 ml. of dichloromethane. The extract was dried and evaporated *in vacuo* giving as a residue 2.42 g. of a mobile yellow liquid. The residue was distilled yielding, at 90–92° (0.15 mm.), a colorless distillate C. Vapor phase chromatography of C at 150° showed it to be a mixture of approximately equal amounts of two components. The n.m.r. of C showed (τ/integrated intensity) 2.7–3.5 (multiplet)/8, 4.7 (broad)/1, and 6.1 and 6.3 (singlets)/2. The proton at τ 4.7 was found to be exchangeable with deuterium oxide and must be the hydroxyl proton of VII. These data indicate that C is a mixture of two monobenzyl fluorophenols.

Anal. Calcd. for $C_{13}H_{11}FO$: C, 77.2; H, 5.48; F, 9.40. Found: C, 76.5; H, 5.40; F, 9.25.

The residue from layer A, 0.80 g., was added to the distillation residue from layer B. No volatile material could be obtained up to a bath temperature of 240° at 0.15 mm., and gas chromatography at 240° showed no volatile product. The n.m.r. of the mixture showed (τ/integrated intensity) 2.7–3.7 (multiplet)/12, 5.0 (singlet)/1, and 6.0–6.4 (multiplet)/4. The singlet at τ 5.0 was exchangeable with deuterium oxide. These data are compatible with the formulation of this material as VIII.

Reaction of 2-Acetamido-3-benzyloxy-*p*-toluic Acid (IX) with Trifluoroacetic Acid.—A solution of 1.57 g. of IX[8] in 25 ml. of trifluoroacetic acid was allowed to stand at room temperature for 2.5 hr., then was evaporated *in vacuo*. Traces of acid were removed by the addition and evaporation of 25 ml. of benzene. The infrared spectrum of the crude residue was essentially identical with that of 2-acetamido-3-hydroxy-*p*-toluic acid (X) (prepared by the catalytic hydrogenolysis of IX). Recrystallization of the solid from ethanol–water resulted in partial N→O migration of the acetyl group according to the infrared spectrum of the crystallized product.

(6) W. H. Hartung, J. C. Munch, E. Miller, and F. Crossley, *J. Am. Chem. Soc.*, **53**, 4149 (1931).

(7) N. V. Sidgwick, W. J. Spurrell, and T. E. Davies, *J. Chem. Soc.*, **107**, 1208 (1915).

(8) Prepared from 3-benzyloxy-2-nitro-*p*-toluic acid[9] by reduction with sodium borohydride in the presence of palladium on charcoal[10] followed by acetylation of the product. It is interesting that this method did not result in debenzylation; a number of other methods attempted were either not selective for the nitro group or gave back starting material.

(9) B. Weinstein, O. P. Crews, M. Leaffer, B. R. Baker, and L. Goodman, *J. Org. Chem.*, **27**, 1389 (1962).

(10) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).