which cleared in a few minutes with deposition of crystals; this process was repeated until no further turbidity was produced by addition of ligroin. The yield of anilide was 1.2 g (87%). Recrystallization from ethanol gave an analytical sample, mp 158–160°, $[\alpha]^{23}D$ −83° (*c* 1.0, absolute EtOH).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: neut equiv, 262. Found: neut equiv, 259.5.

The anilide was soluble in dioxane and THF, sparingly soluble in water and diethyl ether, and insoluble in ligroin. For positive identification it was also prepared by the alternate route described below.

B. From Oxanilyl Chloride and L-Proline.—Oxanilyl chloride[8] was prepared by addition of aniline hydrochloride in small portions to three parts of oxalyl chloride in ten parts of THF, with stirring and protection from moisture. After 30 min of continued stirring, a small amount of undissolved solid material was removed by filtration, and the solvent and excess oxalyl chloride were removed in a rotary evaporator. Without further purification, the oxanilyl chloride was redissolved in a little THF and added to an equivalent quantity of L-proline suspended in THF. An excess of trimethylamine was added slowly, the solid material removed by filtration, and the filtrate concentrated to dryness in a rotary evaporator. The residue was recrystallized from ethanol to yield crystalline II, mp 158–160°, identical with that obtained *via* route A by mixture melting point and comparison of infrared spectra.

N,N'-Oxalylbis(L-proline methyl ester) (IV). A. By Methylation of the Product (III) from L-Proline-N-oxalic Anhydride and L-Proline.—To 1.2 g (0.0071 mole) of I suspended in dioxane was added 0.82 g (0.0071 mole) of proline under anhydrous conditions. After the reaction mixture had been stirred for 2 hr at 60°, the solution was decanted from a small amount of undissolved material and the solvent was evaporated to give 1.0 g (53%) of N,N'-oxalylbis(L-proline) (III) melting at 135–145° after one recrystallization from dioxane. Without further purification, 0.7 g of III was suspended in ether and treated with an excess of ethereal diazomethane. As soon as the rapid evolution of gas had ceased, the ether was decanted from a small amount of undissolved material and evaporated to give 0.42 g (53%) of slightly yellow crystals. Decolorization with charcoal and two recrystallizations from water gave an analytical sample, mp, 147.5–148.5°.

Anal. Calcd for $C_{14}H_{21}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 54.10; H, 6.40; N, 8.91.

B. From Oxalyl Chloride and L-Proline Methyl Ester. For comparison IV was also synthesized by a general method[9] for N,N'-oxalylbis(amino acid esters). L-Proline (10.0 g, 0.087 mole) was dissolved in 100 ml of methanol. Anhydrous HCl was passed into the solution until evolution of heat had ceased and the mixture was then refluxed gently for 8 hr with exclusion of moisture. After removal of excess methanol and HCl in a rotary evaporator, L-proline methyl ester hydrochloride was obtained as a thick syrup which did not crystallize readily. To the syrup was added with constant stirring 70 ml of sodium-dried benzene, followed over a period of 1 hr by small portions of 5.5 g (0.043 mole) of oxalyl chloride dissolved in 30 ml of benzene. The reaction mixture was refluxed for 4 hr and the benzene solution then decanted from a considerable amount of undissolved material. Evaporation of the solvent gave a thick syrup which crystallized upon standing for 24 hr. The yield of crystalline IV was 1.5 g (12.5%). Decolorization with charcoal and two recrystallizations from water gave an analytical sample, mp 147.5–148.5°.

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 54.36; H, 6.55; N, 9.02.

This product was found to be identical with IV obtained *via* A by mixture melting point and comparison of infrared spectra.

Registry No.—I, 13673-68-2; II, 13673-69-3; IV, 13673-70-6.

Acknowledgment.—Support of this work in part by Research Grant RG-5781(A) of the Division of General Medical Sciences of the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., is gratefully acknowledged.

(8) I. G. Farbenindustrie A.-G., German Patent 463,140 (July 1928); *Chem. Abstr.*, **22**, 4130 (1928).

(9) J. Bornwater, *Rec. Trav. Chim.*, **31**, 105 (1912).

Reaction of Nitro Anions with N,N-Dimethyl-*p*-hydroxybenzylamine. A New Synthesis of α-Methyltyrosine

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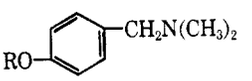
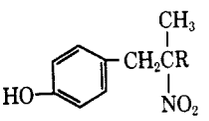
The reactions of nitroparaffin anions with benzyl halides may proceed to give products resulting from either carbon or oxygen alkylation.[1] The O-alkylation product, a nitronic ester, is not usually stable under the conditions of the reaction and it is assumed that it decomposes to give the observed products, an oxime and a carbonyl compound.[1a,2] In a study of the reaction of a series of *para*-substituted benzyl halides with the sodium salt of 2-nitropropane, only the *para*-nitro derivative was observed to give carbon alkylation.[1a,3] All other *para*-substituted benzyl halides investigated led to products resulting from reaction at oxygen.

The hydroxy derivative, N,N-dimethyl-*p*-hydroxybenzylamine (**1**), has now been found to give predominately carbon alkylation in reactions with the sodium salts of 2-nitropropane and ethyl α-nitropropionate. One of these products, ethyl 2-(*p*-hydroxybenzyl)-2-nitropropionate (**3**), has been converted to α-methyltyrosine, a potent inhibitor of tyrosine hydroxylase, an enzyme involved in the biosynthesis of norepinephrine.[4]

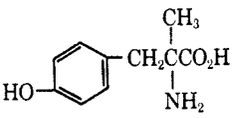
Reaction of **1** (prepared by the reductive alkylation of dimethylamine with *p*-hydroxybenzaldehyde) with ethyl α-nitropropionate and a catalytic amount of sodium hydride in refluxing toluene gave **3** in 57% yield, based on isolated material.[5] Thin layer chromatography of the crude reaction product indicated that only a small amount of the O-alkylation product, *p*-hydroxybenzaldehyde, was formed in the reaction.



1, R = H
2, R = CH_3



3, R = $CO_2C_2H_5$
4, R = CH_3



5

The infrared spectrum ($CHCl_3$) of **3** contains absorption bands at 1745, 1550, and 1345 cm^{-1} indicating the presence of aliphatic ester[6a] and nitro[6b] functions.

(1) (a) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 1767 (1949); (b) H. B. Hass, E. J. Berry, and M. L. Bender, *ibid.*, **71**, 2290 (1949); (c) R. C. Kerber, G. W. Urry, and N. Kornblum, *ibid.*, **87**, 4520 (1965); (d) N. Kornblum and P. Pink, *Tetrahedron, Suppl. 1*, **19**, 17 (1963).

(2) N. Kornblum and R. A. Brown, *J. Am. Chem. Soc.*, **86**, 2681 (1964).

(3) The nature of the leaving group is also important since some *p*-nitrobenzyl derivatives give predominately oxygen alkylation.[1c,d]

(4) S. Udenfriend, *Pharmacol. Rev.*, **18**, 43 (1966).

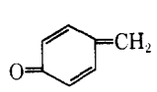
(5) Formation of carbon–carbon bonds by displacement of tertiary amines has been reviewed: J. H. Brewster and E. L. Eliel, *Org. Reactions*, **7**, 99 (1953).

(6) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 179; (b) pp 298–301.

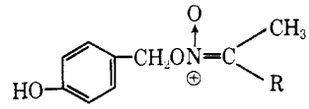
The nmr spectrum consists of two unsymmetrical doublets (J = 14.5 cps) centered at δ 3.32 and 3.62 ppm for the two benzyl protons and a multiplet centered at 6.87 for the four aromatic hydrogens. The α-methyl group appears as a singlet at δ 1.67 ppm and the ethyl ester group appears as the expected triplet–quartet combination centered at 1.28 and 4.27. The structure of **3** was further confirmed by catalytic hydrogenation and hydrolysis to the known α-methyltyrosine (**5**).[7]

A similar reaction between **1** and 2-nitropropane produced **4** in 25% yield. Again, only a small amount of *p*-hydroxybenzaldehyde resulting from O-alkylation appeared to be formed in the reaction.

These reactions of **1** may proceed through a quinone methide intermediate (**6**), or through a bimolecular transition state having some of the character of **6**. Similar intermediates have been proposed for the reactions of nucleophiles with some phenol Mannich base methiodides and oxides,[8a] hydroxybenzyl alcohols and ethers,[8b] and 1-ethylthiomethyl-2-naphthol.[8c] Attack of nucleophilic reagents at the terminal methylene of *para*-quinone methides has been well documented.[9] The fact that the methoxy analog **2** did not react with ethyl α-nitropropionate under conditions which lead to essentially complete reaction of the phenol **1** is consistent with the formation of **6** as an intermediate. Under even more vigorous conditions, most of the *p*-methoxybenzylamine was still recovered unchanged.



6



7, R = CH_3, $CO_2C_2H_5$

Isolation of predominately C-alkylation products in these reactions may be due in part to a dissociation of the less stable O-alkylation product, the nitronic ester **7**, to the original nitro anion and **6** and eventual realkylation at carbon to give the more stable C-alkylated product.[10a,b]

In connection with these studies, the reactions of ethyl α-nitropropionate anion with *p*-nitrobenzyl halides and benzyl chloride were also examined. As expected, *p*-nitrobenzyl chloride and the sodium salt of ethyl α-nitropropionate in dimethylformamide at 80° gave the C-alkylation product **8** in 52% yield. When *p*-nitrobenzyl bromide was substituted for the chloride, the yield of **8** was reduced to 30%.[11] Reaction of benzyl chloride with ethyl α-nitropropionate under these same conditions afforded a 31% yield of benzaldehyde, presumably the result of O-alkylation. No other pure products were isolated from this reaction.

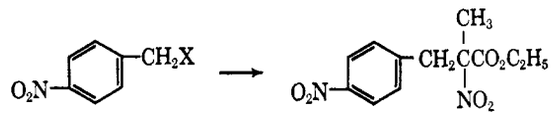
(7) G. A. Stein, H. A. Bronner, and K. Pfister, III, *J. Am. Chem. Soc.*, **77**, 700 (1955).

(8) (a) P. D. Gardner, H. S. Rafsanjani, and L. Rand, *ibid.*, **81**, 3364 (1959); (b) A. Merijan and P. D. Gardner, *J. Org. Chem.*, **30**, 3965 (1965); (c) F. Poppelsdorf and S. J. Holt, *J. Chem. Soc.*, 4094 (1954).

(9) A. B. Turner, *Quart. Rev.* (London), **18**, 347 (1964).

(10) (a) A similar argument has been advanced to explain the C-alkylation of 2-nitropropane by cycloheptatrienylium bromide: M. Bersohn, *J. Am. Chem. Soc.*, **83**, 2136 (1961). (b) Michael additions employing nitro anions also result in C-alkylation of the nitroparaffin: E. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(11) Decreased yields of C-alkylation product in going from *p*-nitrobenzyl chloride to the bromide have also been observed in the alkylation of 2-nitropropane.[10c,d]



X = Br, Cl **8**

Experimental Section

Nmr spectra were recorded in $CDCl_3$ solution with a Varian A-60A spectrometer with tetramethylsilane serving as an internal standard. Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. All boiling and melting points are uncorrected.

N,N-Dimethyl-*p*-hydroxybenzylamine (1).—A mixture of 6.1 g (0.050 mole) of *p*-hydroxybenzaldehyde, 30 g of a 25% aqueous solution of dimethylamine, and 1.0 g of a 5% palladium-on-carbon catalyst was hydrogenated in a Paar apparatus for 1 hr until one equivalent of hydrogen had been taken up. The catalyst was removed by filtration and excess dimethylamine removed under vacuum. After acidification with 6 *N* hydrochloric acid and ether extraction to remove a small amount of oil, the pH of the aqueous solution was adjusted to 8–9 with 10% sodium hydroxide and the solution saturated with sodium chloride and extracted with ethyl ether. The ether extract was washed with water saturated with sodium chloride and dried over anhydrous sodium sulfate. After filtering and concentrating, the residue was recrystallized from a benzene–hexane mixture to give 4.05 g (53.5%) of product, mp 103–107° (lit.[12] mp 106–108°). A sample was sublimed at 75–80° (0.05 mm) for analysis.

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.26; H, 8.59; N, 9.25.

Ethyl 2-(*p*-Hydroxybenzyl)-2-nitropropionate (3).—A mixture of 2.0 g (0.0132 mole) of N,N-dimethyl-*p*-hydroxybenzylamine (**1**), 2.0 g (0.0136 mole) of ethyl α-nitropropionate,[13] 20 mg of a 53% sodium hydride dispersion in mineral oil, and 30 ml of toluene was heated at reflux. Nitrogen was bubbled through the reaction mixture to remove dimethylamine as it formed. The reaction was followed by testing for dimethylamine in the effluent nitrogen stream or by thin layer chromatography on a silica plate developed with 5% methanol–chloroform. After heating at reflux for 12 hr, the reaction mixture was cooled, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was distilled through a semimicro Vigreux column to give 1.9 g (56.9%) of the nitro ester **3**, bp 159–162° (0.2 mm). An analytical sample was obtained by redistillation through a short-path column.

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.02; H, 6.02; N, 5.23.

α-Methyltyrosine (5).—A solution of 1.5 g (5.94 mmoles) of ethyl 2-(*p*-hydroxybenzyl)-2-nitropropionate (**3**) in 50 ml of absolute ethanol was heated under reflux with a small amount of Raney nickel catalyst for 1 hr.[14,15] The Raney nickel was removed by filtration and a platinum oxide catalyst (0.1 g) was added to the filtrate which was then hydrogenated in a Paar apparatus. After 20 hr, the theoretical amount of hydrogen had been taken up. The catalyst was removed by filtration, 30 ml of 6 *N* hydrochloric acid was added, and the solution was concentrated under vacuum to remove most of the ethanol. Hydrolysis was completed by heating the aqueous acid solution at 100° for 2 hr. The reaction mixture was concentrated under vacuum, about 10 ml of isopropyl alcohol was added to the residue, and the mixture was evaporated to dryness. Twenty milliliters of water was added and the pH of the solution was adjusted to 5–6 with diethylamine. After cooling, filtration gave 0.58 g (50.2%) of α-methyltyrosine, mp 312–318° dec. One recrystallization from hot water gave an analytical sample, mp 318–320° dec (lit.[7] mp 320° dec), which was identical with an authentic sample of α-methyltyrosine as determined by mixture melting point, thin layer chromatography (silica plate

(12) K. Friedrich and H. Kreuschner, *Angew. Chem.*, **72**, 780 (1960).

(13) N. Kornblum and R. K. Blackwood, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 454.

(14) The Raney nickel treatment is necessary for a smooth reduction. A similar situation has also been encountered in the catalytic hydrogenation of some nitroalkylpyrroles.[15]

(15) W. Herz and U. Toggweiler, *J. Org. Chem.*, **29**, 213 (1964).

developed with a 3:1:1 *n*-butyl alcohol–water–acetic acid mixture), and a comparison of the infrared spectra (KBr).

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.55; H, 6.71. Found: C, 61.53; H, 7.07.

2-(*p*-Hydroxybenzyl)-2-nitropropane (4).—A mixture of 2.0 g (0.0132 mole) of N,N-dimethyl-*p*-hydroxybenzylamine (**1**), 1.21 g (0.0136 mole) of 2-nitropropane, and 20 mg of a 53% sodium hydride dispersion in mineral oil in 30 ml of toluene was heated at reflux under nitrogen for 18 hr. The cooled toluene solution was separated from an insoluble gum, washed with water, and dried over anhydrous sodium sulfate. After filtering, the solvent was removed under reduced pressure to give 1.03 g (40.2%) of **4**, mp 105–111°. Since recrystallizations from several solvents did not improve the melting point, the crude product was chromatographed on a silicic acid column and eluted with methylene chloride to give 0.65 g (25.3%) of product, mp 111.3–112.8°. The melting point was unchanged after recrystallization from an ethyl acetate–hexane mixture. The infrared spectrum ($CHCl_3$) contained strong absorption bands at 3580 (sharp) and 3320 (broad) (OH), 1530 and 1345 cm^{-1} (NO_2).[6b] Singlets were observed in the nmr spectrum at δ 1.58 ppm ($2CH_3$), 3.14 (CH_2), and 5.63, broad (OH); the four aromatic protons were observed as a multiplet centered at δ 6.85 ppm.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.82; H, 6.52; N, 7.51.

Reaction of N,N-Dimethyl-*p*-methoxybenzylamine (2) with Ethyl α-Nitropropionate.—A mixture of 2.0 g (0.0121 mole) of N,N-dimethyl-*p*-methoxybenzylamine,[16] 1.84 g (0.0125 mole) of ethyl α-nitropropionate,[13] and 20 mg of a 53% sodium hydride dispersion in mineral oil in 30 ml of toluene was heated at reflux under nitrogen for 20 hr. The absence of dimethylamine in the effluent nitrogen stream and thin layer chromatography (silica plate developed with a 5% methanol–chloroform mixture) indicated that no reaction had occurred. The toluene was replaced with 30 ml of xylene and the reaction was heated again at reflux for 36 hr. After washing with a dilute sodium hydroxide solution and water, the xylene extract was dried over anhydrous sodium sulfate, filtered, and concentrated to give 1.45 g (72.6%) of recovered N,N-dimethyl-*p*-methoxybenzylamine, identified by thin layer chromatography and infrared spectra.

Ethyl α-Nitropropionate Sodium Salt.—To a stirred solution of 1.0 g (6.8 mmoles) of ethyl α-nitropropionate[13] in 25 ml of dry benzene was added 0.38 g (8.08 mmoles) of a 51% sodium hydride–mineral oil dispersion. After stirring for 0.5 hr, excess sodium hydride was decomposed with a few drops of ethanol. The product was collected and dried to give a quantitative yield of the sodium salt, mp 196.0–197.5° dec, softening at 193°. A sample was recrystallized from absolute ethanol to give an analytical sample, mp 198.0–199.5° dec.

Anal. Calcd for $C_5H_8NaNO_4$: N, 8.28. Found: N, 8.19.

Ethyl 2-Nitro-2-(4-nitrobenzyl)propionate (8).—A solution of 1.0 g (5.84 mmoles) of *p*-nitrobenzyl chloride in 10 ml of dry dimethylformamide was added over 20 min to a stirred solution of 1.0 g (5.92 mmoles) of the sodium salt of ethyl α-nitropropionate in 20 ml of dimethylformamide at 50°. The reaction mixture was stirred at 80° for 5 hr, cooled, and diluted with water. The product was extracted into ethyl ether which was then washed with water and dried over anhydrous sodium sulfate. After filtering and removing the solvent under vacuum, the crude product was recrystallized twice from isopropyl alcohol to give 0.86 g (52.2%) of **8**, mp 78–80°. Further recrystallization gave an analytical sample, mp 79.5–80.8°. The infrared spectrum (KBr) contained strong absorption bands at 1755 (ester),[6a] 1545 (aliphatic NO_2), 1510 (aromatic NO_2), and 1350–1340 cm^{-1} (NO_2).[6b]

Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.03; H, 5.11; N, 9.97.

When *p*-nitrobenzyl bromide was substituted for *p*-nitrobenzyl chloride, **8**, mp 77–79°, was isolated in 30.6% yield.

Reaction of Ethyl α-Nitropropionate with Benzyl Chloride.—The reaction of 25.4 g (0.20 mole) of benzyl chloride with 29.4 g (0.20 mole) of ethyl α-nitropropionate[13] and 9.06 g (0.20 mole) of a 53% suspension of sodium hydride in mineral oil in 150 ml of dimethylformamide was carried out as described for *p*-nitrobenzyl chloride. The crude product was distilled through an 18-in. Vigreux column to give a series of fractions which were analyzed by gas chromatography on a fluorosilicone column. The infrared spectrum of the product distilling at 77–80° (27 mm), 7.07 g, was identical with that of an authentic sample of benzaldehyde. However, since gas chromatography indicated that it contained only 92.6% benzaldehyde, the adjusted yield is 30.9%.

(16) E. Stedman, *J. Chem. Soc.*, 1904 (1927).

Acknowledgments.—The author wishes to thank K. B. Streeter, Y. Lee, and their associates for elemental analyses, W. R. McGaughran for the infrared spectral analyses, A. Augenblick for the gas chromatography work, and K. Shepard and P. Anderson for the nmr spectral analyses.

Determination of the Anomeric Configuration of 9-α-D-Mannofuranosyladenine and Preparation of 9-α-D-Lyxofuranosyladenine[1a]

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Recently the preparation of a 9-D-mannofuranosyladenine was reported.[2] The nucleoside was prepared by the condensation of 2,3:5,6-di-O-isopropylidene-D-mannofuranosyl chloride with 6-benzamidochloromercuripurine, which resulted in a product presumed to have an α configuration. The only evidence for this aspect of the structure was the molecular rotation (+22, 280°), which suggested an α configuration on the basis of comparison with a number of glycofuranosides of known anomeric configuration. The *trans* rule could not be relied on for further suggestive evidence inasmuch as the blocking isopropylidene group does not participate in the condensation reaction and therefore has no directive effect. Because of the lack of evidence pertaining to this structural feature of the nucleoside, it was decided to reinvestigate the compound in order to obtain more direct evidence as to its nature. For this purpose the reactions shown in Scheme I were carried out.

9-(2′,3′-O-Isopropylidene-D-mannofuranosyl)adenine (**1**),[2] an intermediate in the previously described preparation of 9-D-mannofuranosyladenine, was treated with sodium periodate and the resultant aldehyde product (**2**) was passed over an anion-exchange resin to remove iodate and excess periodate. The effluent from the column was collected in a flask containing sodium borohydride, bringing about an immediate reduction to 9-(2′,3′,-O-isopropylidene-α-D-lyxofuranosyl)adenine (**3**). The isopropylidene group was removed by hydrolysis with acetic acid to yield 9-α-D-lyxofuranosyladenine (**4**).

(1) (a) Supported in part by U. S. Public Health Service Grant No. CA-07960. (b) To whom requests for reprints should be addressed.

(2) L. M. Lerner and P. Kohn, *J. Org. Chem.*, **31**, 339 (1966).