(24, M - 3 $COOCH_3$), 288 (28, M - $COOCH_3$ - $HCOOCH_3$ - 2 OCH_3), 232 (28, M - 3 $COOCH_3$ - $HCOOCH_3$).

Anal. Calcd for $C_{25}H_{27}NO_8$ (mol wt 469.50): C, 63.96; H, 5.80; N, 2.99. Found: C, 64.21; H, 5.88; N, 2.93.

The compound was also obtained, in 69% yield, from reaction of the 1:1 adduct **13**[4] with 1 equiv of DMAD in refluxing benzene for 8 h, as shown by melting point, mixture melting point, and NMR comparison with the sample prepared from **11**.

Acknowledgment. It is a pleasure to acknowledge support of V.K. through teaching assistantships from the University of Minnesota (Sept–June of 1967–68, 1968–69, and 1970–71) and for fellowships from the Shell Oil Co. (first summer session 1968), E. I. du Pont de Nemours and Co. (first summer session 1969), Union Carbide Corp. (Sept 1969–Aug 1970), and the Eastman Kodak Co. (first summer session 1971), and for a research assistantship granted by W.E.N. under U.S. Public Health Service Grant No. CA-04073-11 (July 15–Sept 15, 1969). We are indebted to Rodney D. DeKruif for determining, on a Cary 17D spectrophotometer, all[13,14] UV spectra on **15**, except that in 95% ethanol. We gratefully acknowledge purchase of the Cary 17D UV spectrophotometer on NSF Equipment Grant CHE-78-23857.

Registry No. **1a**, 31554-37-7; **4**, 76756-25-7; **11**, 39157-79-4; **13**, 76756-26-8; **15**, 76756-27-9; 2,3-dihydro-1*H*-inden-1-one, 83-33-0; pyrrolidine, 123-75-1; dimethyl acetylenedicarboxylate, 762-42-5; 2,3-dihydro-1*H*-inden-2-one, 615-13-4.

(14) The $CHCl_3$ UV solution faded perceptibly visually and the UV spectrum changed with time, even when the solution was kept in the refrigerator most of the time: after 2 days, 266 (4.11), 319 (3.97), 391 (4.05); after 3 days, 277 (4.26), 390 (3.71). In contrast, a concentrated (0.173 M) $CDCl_3$ NMR solution appeared to be more stable. The solution was kept for 8 days and then diluted to 1.23×10^{-4} M with $CHCl_3$ and then run promptly, giving UV ($CHCl_3$) 265 (~4.3) 320 (~4.2), 391 (~4.3).

A Convenient Method for O-Alkylation of N-Substituted Tyrosines Using a Crown Ether[1]

Aleksander M. Kolodziejczyk and Maurice Manning*

Department of Biochemistry, Medical College of Ohio, Toledo, Ohio 43699

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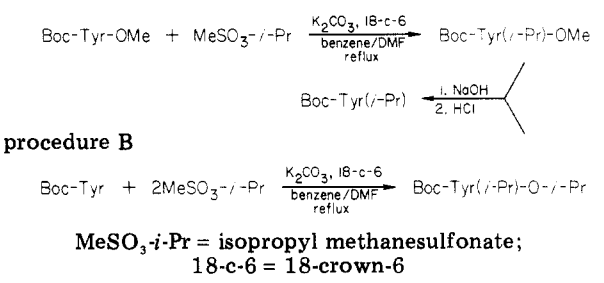
O-Methyltyrosine [Tyr(Me)] and *O*-ethyltyrosine [Tyr(Et)] substitutions at position two in selected analogues of oxytocin and arginine vasopressin (AVP) have proved to be extremely valuable for the design of antagonists of the characteristic biological responses of these peptide hormones.[2] For antidiuretic antagonists the *O*-ethyl-substituted analogues are almost twice as potent as *O*-methyl-containing analogues.[2d] We wished to explore the effects on antidiuretic antagonism of further increasing the size of the *O*-alkyltyrosine substituents, i.e., by the incorporation of *O*-isopropyltyrosine [Tyr(iPr)] and *O*-*n*-propyltyrosine [Tyr(*n*Pr)] in some of our most potent antagonists. The present study was prompted by the unavailability of Tyr(*i*Pr) or Tyr(*n*Pr). Both Tyr(Me) and Tyr(Et) are commercially available as their *tert*-butyloxycarbonyl (Boc) derivatives. Also, higher alkyl ethers of tyrosine, starting from the butyl derivative, can be readily prepared by alkylation of unprotected tyrosine with alkyl halides in the presence of NaOH in H_2O/Me_2SO solution.[3] However, the only reported synthesis of Tyr(*i*Pr) afforded this material in only a 4% yield following an 11-day reaction.[4]

Scheme I



$MeSO_3$-*i*-Pr = isopropyl methanesulfonate; 18-c-6 = 18-crown-6

We now report a new convenient and rapid method for the preparation in good yield of both Boc-Tyr(*i*Pr) and Boc-Tyr(*n*Pr) suitable for direct use in peptide synthesis. The general usefulness of this method is further demonstrated by the synthesis in excellent yields of Boc-L- and -D-Tyr(Me), Boc-L- and -D-Tyr(Et), *N*-(benzyloxy)-carbonyl-Tyr(Et), and *N*-formyl-Tyr(Me) (Table I). This method is an adaptation of a recently described synthesis of ethers of alcohols or phenols from alkyl halides in the presence of catalytic amounts of tetraalkylammonium salts or crown ethers and K_2CO_3 as base.[5] Boc-tyrosine methyl ester (procedure A) or Boc-tyrosine (procedure B), commercially available or readily prepared, can be used as starting materials. Both procedures are illustrated in the following schematic syntheses of Boc-Tyr(*i*Pr) (Scheme I).

The experimental conditions used for the preparation of all the aforementioned *O*-alkyl derivatives are given in Table I. The use of Boc-tyrosine methyl ester as starting material has a number of advantages: (a) it enconomizes on the use of the more expensive higher alkylating reagents; (b) the methyl ester group is more readily removed by hydrolysis; (c) the methyl esters can be used directly in couplings by the azide method. Because short-chain alkyl halides are too volatile for alkylations performed in boiling benzene we used commercial methyl and ethyl sulfates to obtain the methyl and ethyl ethers. The methanesulfonic acid esters of isopropyl and *n*-propyl alcohol were used in the syntheses of the higher homologues because methanesulfonates are better alkylation reagents than sulfates.[6] They are also more readily prepared in the laboratory. The alkylations of N-protected tyrosine with methyl and ethyl sulfates in boiling benzene proceed rapidly (Table I) whereas the reactions with both the propyl and isopropyl methanesulfonates under these conditions are sluggish. The addition of 10% DMF facilitates completion of these alkylations[7] over an extended reaction time.

Both the alkylation reactions and the basic hydrolysis of the tyrosine ester groups proceed with nearly quantitative yields as evidenced by TLC. Losses in varying degrees were incurred during the ensuing crystallizations (Table I). However, the crude products in all cases were

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Table I. Conditions and Products of N-Protected Tyrosine Alkylation Reactions[h]

N	substrates: tyrosine deriv	substrates: alkylating agent	conditions of alkylation: time, h	conditions of alkylation: solvent	product	crystn solvent system	% yield	mp, °C	$[\alpha]^{26}_D$ (c 1, EtOH)
1	Boc-Tyr-OMe	$SO_2(OMe)_2$	1.5	benzene	Boc-Tyr(Me)[g]	AcOEt/ *n*-hexane	97	92-94	+42.9[a]
2	Boc-Tyr	$SO_2(OMe)_2$	1.5	benzene	Boc-Tyr(Me)	AcOEt/ *n*-hexane	94	92-94	+42.0[a]
3	Boc-D-Tyr-OMe	$SO_2(OMe)_2$	1.5	benzene	Boc-D-Tyr(Me)	AcOEt/ *n*-hexane	95	92-94	-42.1
4	Boc-Tyr-OMe	$SO_2(OEt)_2$	1.5	benzene	Boc-Tyr(Et)[g]	toluene/ *n*-hexane	87	90-92	+39.8[b]
5	Boc-D-Tyr-OMe	$SO_2(OEt)_2$	1.5	benzene	Boc-D-Tyr(Et)	toluene/ *n*-hexane	85	90-92	-39.7
6	Boc-Tyr-OMe	$MeSO_3$-*n*-Pr	3.0	benzene/ DMF	Boc-Tyr(*n*-Pr)[g]	*n*-heptane	64	84-86	+31.5[c]
7	Boc-Tyr-OMe	$MeSO_3$-*i*-Pr	5.0	10:1 benzene/ DMF	Boc-Tyr(*i*-Pr)[g]	*n*-hexane	61	87-91	+24.6[d]
8	Boc-Tyr	$MeSO_3$-*i*-Pr	6.0	10:1 benzene/ DMF	Boc-Tyr(*i*-Pr)	*n*-hexane	55	86-90	+23.7
9	Z-Tyr	$SO_2(OEt)_2$	1.5	benzene	Z-Tyr(Et)	toluene/ *n*-hexane	84	79-81	-35.1[e] (c 1, DMF)
10	CHO-Tyr	$SO_2(OMe)_2$	1.5	benzene	CHO-Tyr(Me)	water	95	155-156	+94.6[f]

[a] A Bachem sample: mp 91-94 °C; $[\alpha]^{26}_D$ +40.8° (c 1, EtOH). [b] A Bachem sample: mp 78-84 °C; $[\alpha]^{26}_D$ +33.8° (c 1, EtOH). [c] NMR ($CDCl_3$): δ 1.1 (3 H, CH_3), 1.4 (9 H, Boc), 1.8 (2 H, CH_2-*n*-Pr), 3.2 (2 H, CH_2-β), 3.9 (2 H, CH_2-O), 4.5 (1 H, CH-α), 7.0 (4 H, aromatic). [d] NMR ($CDCl_3$): δ 1.3 (6 H, *i*-Pr), 1.4 (9 H, Boc), 3.2 (2 H, CH-β), 4.5 (2 H, CH-α + O-CH, *i*-Pr), 7.0 (4 H, aromatic). [e] Lit.[12] yield 49%; mp 76-78 °C; $[\alpha]^{20}_D$ -34.2° (c 1, DMF). [f] Lit.[13] yield 91%; mp 152-154 °C; $[\alpha]_D$ +94.7 (c 2, EtOH). [g] Satisfactory analytical data (±0.4%) for C, H, N were reported for all new compounds listed in the table. Elemental analyses were performed by Integral Microanalytical Laboratories Inc., Raleigh, NC. [h] Abbreviations: Boc, (*tert*-butyloxy)carbonyl; Z, (benzyloxy)carbonyl; CHO, formyl; Me, methyl; Et, ethyl; Pr, propyl; $MeSO_3$-AKL, alkyl methanesulfonate; Tyr-OR, tyrosine alkyl ester; Tyr(R), tyrosine alkyl ether.

chromatographically pure and could be used directly in peptide synthesis. Thus this method affords a rapid and efficient means of obtaining primary and secondary *O*-alkyl ethers of a variety of N-substituted tyrosine derivatives which can be utilized directly in peptide synthesis. The Boc-Tyr(*i*Pr), Boc-Tyr(*n*Pr), Boc-Tyr(Me), Boc-Tyr(Et), and Boc-D-Tyr(Me) derivatives described here have been incorporated successfully into synthetic analogues of AVP.

Experimental Section

Boc-Tyr, Z-Tyr, TyrOMe·HCl, and D-Tyr were obtained from Chemalog; 18-crown-6 and di-*tert*-butyl dicarbonate [$(Boc)_2O$] were obtained from Fluka AG.

We describe here the synthesis of the remaining starting materials: *n*-propyl methanesulfonate, isopropyl methanesulfonate, D-tyrosine methyl ester hydrochloride, Boc-L-Tyr-OMe and Boc-D-Tyr-OMe, together with the synthesis of Boc-Tyr(*i*Pr) from Boc-Tyr-OMe (procedure A) and from Boc-Tyr (procedure B). The alkylation conditions utilized for the synthesis of Boc-Tyr(Me), Boc-Tyr(Et), Boc-D-Tyr(Et), Boc-Tyr(*n*Pr), Z-Tyr(Et), and CHO-Tyr(Me) by procedure A or procedure B together with their physical properties are presented in Table I. It will be noted that the melting points and optical rotations of the known derivatives are in excellent agreement with the literature values and with those available commercially.

***n*-Propyl Methanesulfonate.** A stirred solution of pyridine (139 mL, 129 g, 1 mol) in *n*-propanol (118 ml, 90 g, 1.5 mol) was cooled in a dry ice bath to -20 °C and methane-sulfonyl chloride (81 mL, 114.5 g, 1 mol) was added during a few minutes. The dry ice bath was replaced with an ice–water bath and stirring was continued. The temperature of the reaction solution rose slowly to 30 °C and then decreased. The ice–water bath was removed and stirring was continued at room temperature for 2 h. Ether (250 mL) and an ice–water mixture (150 mL) were added. The aqueous layer was removed and the organic layer was washed twice with cold water and dried with $MgSO_4$. After filtration and removal of ether the product was distilled under reduced pressure. The fraction with bp 96–98 °C (10 mmHg) [lit.[8] bp 103 °C (12 mm)] was collected to yield 89.7 g (65%).

Isopropyl Methanesulfonate. This was obtained by the same procedure from pyridine (139 mL, 129 g, 1 mol), 2-propanol (115 mL, 90 g, 1.5 mol), and methanesulfonyl chloride (81 mL, 114.5 g, 1 mol) to give the desired product: bp 86–88 °C (12 mmHg) [lit.[8] bp 86–88 °C (12 mm)]; yield 88.6 g (63%).

D-Tyrosine Methyl Ester Hydrochloride. Thionyl chloride (24.6 mL, 39.3 g, 0.33 mol) was dropped into methanol (300 mL) cooled in a dry ice bath, followed by addition of D-tyrosine (50 g, 0.28 mol). The reaction solution was stored at room temperature for 2 days and the solvent was removed by evaporation. The crystalline residue was triturated with methanol, reevaporated (twice), dissolved in hot methanol, diluted with ether, and left to crystallize: yield 56.1 g (88%); mp 189–191 °C $[\alpha]_D^{23}$ -68.0° (c 1.0, pyridine) [lit.[9] 60%; mp 189–190 °C; $[\alpha]_D^{23}$ -68° (c 1.04, pyridine)].

***tert*-(Butyloxycarbonyl)-L-tyrosine Methyl Ester.** A solution of D-TyrOMe·HCl (50 g, 0.216 mol) in water (100 mL) was mixed with a solution of K_2CO_3 (29.9 g, 0.216 mol) in water (100 mL) and after 10 min. the precipitated tyrosine methyl ester was collected by filtration, washed with water, and placed in a 1 L two-necked flask equipped with a condenser and a dropping funnel. A solution of *tert*-butyl alcohol (100 mL) in ether (150 mL) was added, followed by the dropwise addition with stirring of di-*tert*-butyl dicarbonate[10] (45.8 g, 0.210 mol) in 15 min. Complete solution was achieved during the first 10 min of the addition and the reaction was complete after a further 15 min. The reaction solution was diluted with ether (150 mL), washed 3 times with water, and dried with $MgSO_4$. After removal of ether and *tert*-butyl alcohol the crystalline residue was redissolved in toluene, reevaporated, and crystallized from toluene/*n*-hexane (1 day at room temperature and the second day in refigerator): yield 51.3 g (81g); mp 101–103 °C; $[\alpha]^{25}_D$ +10.6° (c 2, EtOH) [lit.[11]

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mp 102–104 °C; $[\alpha]_D$ +5.4 (MeOH)]; TLC (benzene/acetone 3:1) R_f 0.40. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 61.0; H, 7.2; N, 4.7. Found: C, 61.1; H, 7.3; N, 4.9.

***tert*-(Butyloxycarbonyl)-D-tyrosine Methyl Ester.** This was obtained by the same procedure from D-TyrOMe·HCl (50 g, 0.216 mol), K_2CO_3 (29.9 g, 0.216 mol), *t*-BuOH (100 mL), and di-*tert*-butyl dicarbonate (45.8 g, 0.210 mol): yield 50.3 g (79%); mp 102–109 °C; $[\alpha]^{25}_D$ −10.50° (*c* 2, MeOH). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 61.0; H, 7.2; H, 4.7. Found: C, 61.2; H, 7.3; N, 4.8.

Boc-*O*-isopropyltyrosine (Procedure A, from Boc-L-TyrOMe). A mixture of Boc-L-TyrOMe (5.9 g, 20 mmol), K_2CO_3 (3.0 g, 22 mmol), 18-crown-6 (0.6 g, 2.2 mmol), and isopropyl methanesulfonate (3.0 g, 22 mmol) in benzene (90 mL) and DMF (10 mL) was stirred and heated to boiling in an 0.5-L flask equipped with an azeotropic distilling receiver and a condenser. After 5 h the reaction mixture was cooled and cold water (50 mL) added. The organic layer was separated, washed with water (twice), dried with $MgSO_4$ and evaporated. The residual colorless oil was dissolved in methanol (20 mL), cooled in an ice bath, and mixed with a solution of NaOH (0.9 g, 22.5 mmol) in water (10 mL) and left to stand for 0.5 h. After removal of methanol at room temperature, the residue was diluted with an ice–water mixture (100 mL) and acidified with 2 M HCl to pH 2. The precipitate was extracted with AcOEt (100 and 50 mL). The combined organic solutions were washed with NaCl solution (twice) and dried with $MgSO_4$. After removal of ethyl acetate, the crystalline residue was crystallized from *n*-hexane: yield 3.9 (61%); mp 87–91 °C; $[\alpha]^{25}_D$ +24.6° (*c* 1, EtOH).

Boc-*O*-isopropyl-L-tyrosine (Procedure B, from Boc-L-Tyr). A mixture of Boc-L-Tyr (5.6 g, 20 mmol), K_2CO_3 (6.0 g, 44 mmol), 18-crown-6 (0.6 g, 2.2 mmol), and isopropyl methanesulfonate (6.0 g, 44 mmol) in benzene (90 mL) and DMF (10 mL) was stirred and heated to boiling for 6 h as in procedure A. Further workup was similar to procedure A, except that the basic hydrolysis was prolonged to 1 h: yield 3.5 g (55%); mp 86–90 °C; $[\alpha]^{26}_D$ +23.7° (*c* 1, EtOH).

Registry No. Boc-Tyr-OMe, 4326-36-7; Boc-Tyr, 3978-80-1; Boc-D-Tyr-OMe, 76757-90-9; z-Tyr, 1164-16-5; CHO-Tyr, 13200-86-7; Boc-Tyr(Me), 53267-93-9; Boc-D-Tyr(Me), 68856-96-2; Boc-Tyr(Et), 76757-91-0; Boc-D-Tyr(Et), 76757-92-1; Boc-Tyr(*n*-Pr), 76757-93-2; Boc-Tyr(*i*-Pr), 76757-94-3; z-Tyr(Et), 66147-90-8; CHO-Tyr(Me), 76757-95-4; L-TyrOMe·HCl, 3417-91-2; *n*-propyl methanesulfonate, 1912-31-8; isopropyl methanesulfonate, 926-06-7; D-tyrosine methyl ester HCl, 3728-20-9; D-tyrosine, 556-02-5.

3′-*O*-Methylevomonoside: A New Cytotoxic Cardiac Glycoside from *Thevetia ahouia* A. DC (Apocynaceae)

Shivanand D. Jolad, Joseph J. Hoffmann, and Jack R. Cole*

College of Pharmacy, University of Arizona, Tucson, Arizona 85721

Michael S. Tempesta and Robert B. Bates

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

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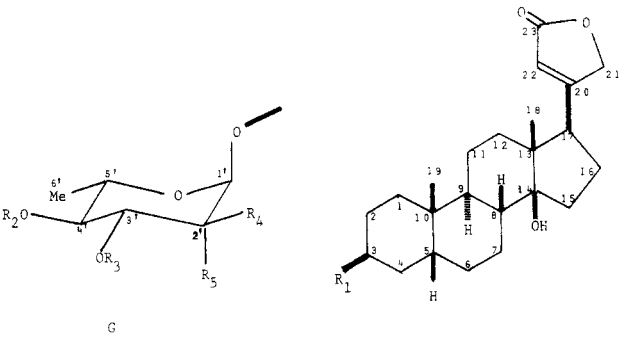
During the course of our search for plants having tumor inhibitory constituents, an ether extract of the title plant yielded a crystalline compound which exhibited strong cytotoxic activity against the human epidermoid carcinoma of the nasopharynx (KB) test system.[1] We present evidence that it is the previously unknown 3-*O*-methyl ether (3) of evomonoside (2)[2] and is thus the C-2′ epimer of neriifolin (4).[3]

Table I. ^{1}H NMR Chemical Shifts (δ) and Coupling Constants (Hertz, in Parentheses) for 3′-*O*-Methylevomonoside (3) and Neriifolin (4)

	3	4
3	3.97 m	3.97 m
16 α,β	2.0–2.25 m	2.0–2.25 m
17	2.28 dd (9.0, 5.3)	2.78 dd (8.8, 5.0)
18	0.88 s	0.88 s
19	0.94 s	0.97 s
21 α,β	4.82 dd (18.0, 1.5)	4.82 dd (18.0, 1.5)
	4.99 dd (18.0, 1.5)	4.98 dd (18.0, 1.5)
22	5.88 t (1.5)	5.88 t (1.5)
1′	4.92 d (1.7)	4.86 d (4.4)
2′	4.02 dd (3.1, 1.7)	3.58 dd (8.9, 4.4)
3′	3.42 dd (9.2, 3.1)	3.25 t (8.9)
4′	3.50 t (9.1)	3.15 t (9.0)
5′	3.73 dq (9.0, 6.3)	3.74 dq (9.0, 6.3)
6′	1.29 d (6.3)	1.26 d (6.3)
MeO	3.50 s	3.69 s



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	R_1	R_2	R_3	R_4	R_5
1	OH	-	-	-	-
2	G	H	H	H	OH
3	G	H	Me	H	OH
3a	G	Ac	Me	H	OAc
4	G	H	Me	OH	H

3′-*O*-Methylevomonoside (3), mp 203–204 °C, $[\alpha]^{25}_D$ −20.6°, and neriifolin (4) appeared on TLC with nearly identical R_f values. 3 displayed a hardly discernible molecular ion peak at *m/e* 534 (EI mass spectrum shifted to *m/e* 750 ($M^{+\cdot}$) in its Me_3Si derivative), which, combined with its elemental analysis, led to molecular formula $C_{30}H_{46}O_8$. The IR (KBr) spectrum of 3, which displayed characteristic dienone (1785, 1740 cm^{-1}) and broad hydroxyl (3490, 3420 cm^{-1}) bands, was very similar to that of neriifolin (4). The mass spectrum of 3 exhibited readily interpretable fragmentation peaks, *m/e* 357 [M − (sugar − H)], 339 (357 − H_2O), 246 (357 − $C_6H_7O_2$), 203 [246 − (CH_3 + CO)], 161 [M − (aglycon − H)], and 74 (base, $[CH_3OCH{=}CHOH]^{+\cdot}$), all suggesting 3 to have digitoxigenin linked to a deoxy-*O*-methyl hexose moiety.

The ^{1}H (Table I) and ^{13}C (Table II) NMR spectra of 3 and neriifolin (4) were very similar except for the sugar absorptions, strongly indicating that 3, like 4, is a glycoside of digitoxigenin (1). The ^{13}C NMR shifts of neriifolin (4)

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