Synthesis of two in vivo metabolites of *N*-(*n*-propyl)phentermine

RONALD T. COUTTS, ABRAHAM BENDERLY, ALLAN L. C. MAK, AND WESLEY G. TAYLOR
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alta., Canada T6G 2N8

Received April 26, 1978

RONALD T. COUTTS, ABRAHAM BENDERLY, ALLAN L. C. MAK, and WESLEY G. TAYLOR. Can. J. Chem. **56**, 3054 (1978).

The phenolic metabolite, 1-(4-hydroxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**1***e*) was prepared by a Ritter reaction from either 3-(4-methoxyphenyl)-2-methyl-1-propene or 3-(4-methoxyphenyl)-2-methyl-2-propanol and propionitrile. Three other products of the Ritter reaction were isolated and identified by interpretation of their mass spectra. Another phenolic metabolite, 1-(4-hydroxy-3-methoxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**1***f*) could not be prepared by a Ritter reaction but was obtained from the product of the reaction between 3-(4-benzyloxy-3-methoxyphenyl)-2-methyl-1-propene and iodine isocyanate.

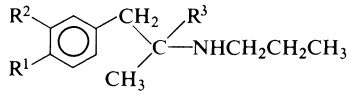
RONALD T. COUTTS, ABRAHAM BENDERLY, ALLAN L. C. MAK et WESLEY G. TAYLOR. Can. J. Chem. **56**, 3054 (1978).

On a préparé le métabolite phénolique (hydroxy-4 phényl)-1 méthyl-2 (*n*-propylamino)-2 propane (**1***e*) par réaction de Ritter à partir du propionitrile et du (méthoxy-4 phényl)-3 méthyl-2 propène-1 ou du (méthoxy-4 phényl)-3 méthyl-2 propanol-2. On a isolé trois autres produits de la réaction de Ritter et on les a identifiés par interprétation de leurs spectres de masse. Un autre métabolite phénolique, l'(hydroxy-4 méthoxy-3 phényl)-1 méthyl-2 (*n*-propylamino)-2 propane (**1***f*), qu'on n'a pas réussi à préparer par réaction de Ritter, a été obtenu à partir du produit de la réaction entre l'isocyanate d'iode et le (benzyloxy-4 méthoxy-3 phényl)-3 méthyl-2 propène-1.

[Traduit par le journal]

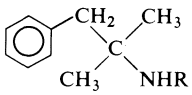
In a continuation of studies on the effect on in vitro and in vivo metabolism of increasing the length of the *N*-alkyl chain of clinically useful drugs (1, 2), *N*-(*n*-propyl)phentermine (**1***d*, NPP), a higher homolog of the anorectic sympathomimetic drug mephentermine (**2***b*) was metabolized in vivo in the rat and two major phenolic metabolites were isolated.[1] Interpretation of their mass spectra suggested that these new metabolites were 1-(4-hydroxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**1***e*) and 1-(4-hydroxy-3-methoxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**1***f*). Conclusive identification of the metabolites was not possible in the absence of authentic samples of **1***e* and **1***f*. Both metabolites were also required for quantitative analysis studies. This note describes our approaches to the synthesis of **1***e* and **1***f*.

Phentermines are not as readily obtained synthetically as amphetamines (1). Patented procedures for the synthesis of phentermine (**2***a*) and mephentermine (**2***b*) are complex (3) and are not easily applicable to phenolic derivatives of phentermine. The Ritter reaction (4), however, provides a direct synthetic route to these compounds. Treatment of the alkene (**3**) or the tertiary alcohol (**4**) with propionitrile under Ritter conditions was more complex than anticipated and gave four products which were readily separated by gc. The mass spectra of the two major products were readily interpretable in terms of



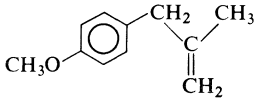
1

a $R^1 = R^2 = R^3 = H$
b $R^1 = OH, R^2 = R^3 = H$
c $R^1 = OH, R^2 = OCH_3, R^3 = H$
d $R^1 = R^2 = H, R^3 = CH_3$
e $R^1 = OH, R^2 = H, R^3 = CH_3$
f $R^1 = OH, R^2 = OCH_3, R^3 = CH_3$

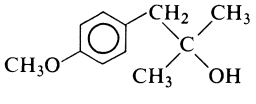


2

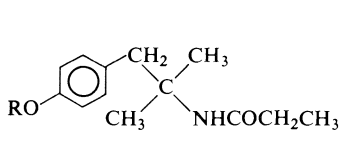
a R = H
b R = CH_3



3

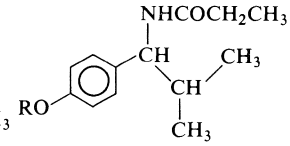


4

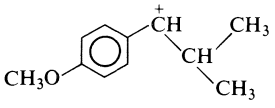


5

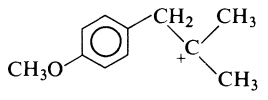
a R = H *b* R = CH_3



6

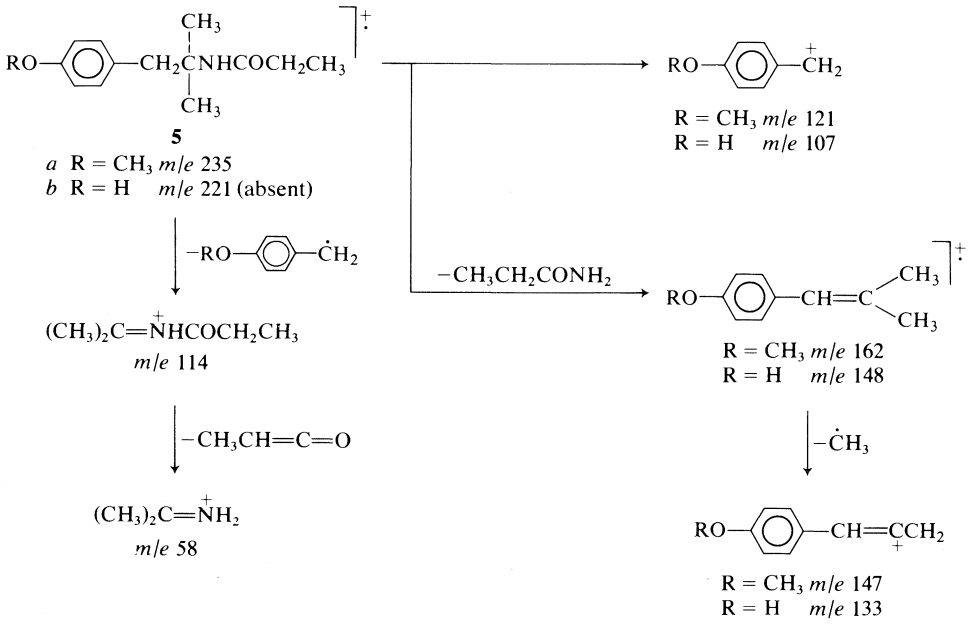


7



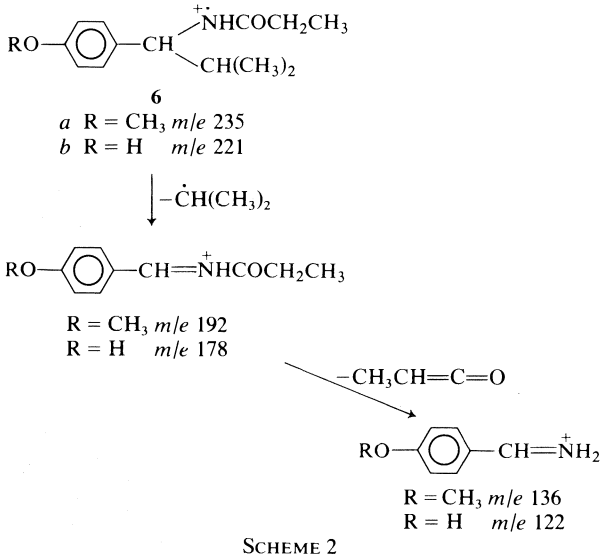
8

[1]R. T. Coutts and W. G. Taylor. Unpublished results.



SCHEME 1

structures **5***a* and **5***b* (Scheme 1). Comparable fragmentation patterns are observed in the spectra of structurally related methoxylated and phenolic amines (5). The two minor products had very simple mass spectra, each containing only three ions. These spectra were also readily interpreted (Scheme 2) and indicated that the structures of the minor reaction products were **6***a* and **6***b*. The formation of the latter two products is consistent with the formation of significant quantities of the benzylic carbonium ion (**7**) in addition to the expected tertiary ion (**8**) during the course of the Ritter reaction.



SCHEME 2

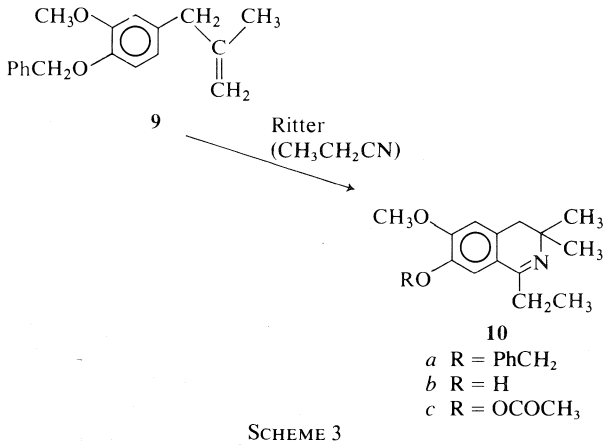
An effort was made to improve the yield of the desired compound (**5***a*) by altering the conditions of the Ritter reaction. The ratio of sulfuric acid to glacial acetic acid used proved to be critical; by suitably altering this ratio, either the phenol (**5***a*) or the methyl ether (**5***b*) was the major product of the reaction with **3** or **4** (Table 1). The phenolic compounds **5***a* and **6***a* were separated from **5***b* and **6***b* by alkaline extraction and from each other by column chromatography or fractional crystallization. Reduction of **5***a* with diborane (6) gave the desired 1-(4-hydroxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**1***e*).

The Ritter reaction was not applicable to the synthesis of 1-(4-hydroxy-3-methoxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**1***f*). The presence of the electron-donating group at the C-3 position of **9** promoted ring closure (3) to a mixture of the 3,4-dihydroisoquinoline derivative (**10***a*), the corresponding phenol (**10***b*) and the phenol acetate (**10***c*) (Scheme 3). An alternative method of synthesizing **1***f* was sought. It is well documented that iodine isocyanate (INCO) adds regioselectively to unsymmetrical alkenes, whereby the isocyanate function appears at the more substituted double-bond carbon atom (7). When this reagent and the unsymmetrical alkene (**9**) were allowed to react, the desired addition occurred and 4-benzyloxy-3-methoxyphentermine (**12**, R = H) was subsequently obtained as illustrated in Scheme 4. The *N*-propionyl derivative (**12**, R = $COCH_2CH_3$) was prepared and reduced with diborane to 1-(4-benzyloxy-3-methoxyphenyl)-2-

TABLE 1. Preparation of isomeric amides **5***a* and **6***a*, **5***b* and **6***b* by the Ritter reaction

Starting material	H_2SO_4 to CH_3COOH ratio (vol)	Products (%)*				Total gc yield (%)
		5*a*	**5***b*	**6***a*	**6***b*	
4	1:1.2	87.1	4.0	3.7	5.3	75
4	1:1.5	39.0	30.0	12.6	16.4	46
4	1:4.4	15.5	66.5	8.5	10.1	85
3	1:1.2	62.0	11.6	17.0	9.4	74
3	1:4.0	1.7	84.3	3.3	8.3	56

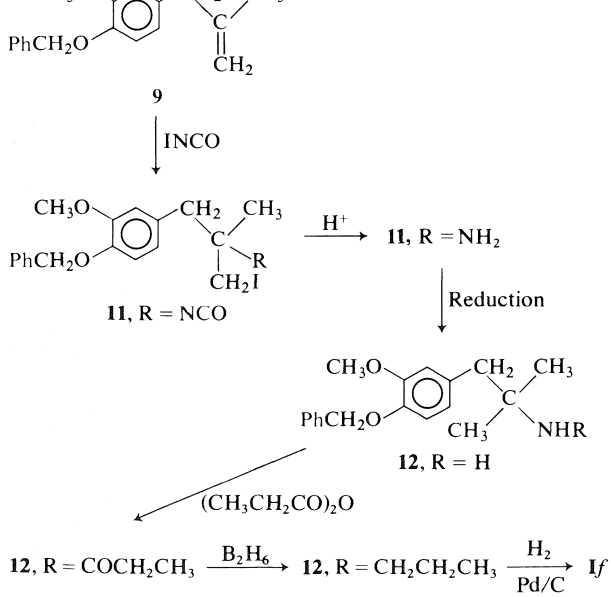
*Based on peak areas.



SCHEME 3

methyl-2-*n*-propylamino)propane (**12**, R = $CH_2CH_2CH_3$), which was catalytically hydrogenated to the required **1***f* (Scheme 4).

The synthetic compounds **1***e* and **1***f* were identical in gc and gc–ms behavior to the two phenolic in-vivo metabolites of NPP.



SCHEME 4

Experimental

Melting points are uncorrected. The ^{1}Hmr spectra were determined for solutions in deuteriochloroform with a Varian Associates EM 360A (60 MHz) spectrometer, with TMS as internal standard. Combined gc–ms was performed on a Hewlett Packard 5710A gas chromatograph – Hewlett Packard 5980A mass spectrometer using a glass column, 0.85 m long, 4 mm id, packed with 5% OV-101 on Chromosorb 750 at 160°C, helium flow rate 60 ml/min. Accurate mass measurements were made on an A.E.I., MS-9 or MS-12 mass spectrometer at an ionizing potential of 70 eV. The starting materials, 1-(4-benzyloxy-3-methoxy)phenyl-2-propanone and 1-(4-methoxy)-phenyl-2-propanone were prepared by a reported procedure (8).

1-(4-Methoxyphenyl)-2-methyl-2-propanol (4)

A benzene solution (40 ml) of 1-(4-methoxy)phenyl-2-propanone (19.2 g, 0.1 mol) was added dropwise (40 min) to an ether solutions of methyllithium (Alfa Inorganic, Inc., 250 ml of 0.6 *M*) at −65°C under N_2. After stirring for 2 h and warming up to room temperature (1 h), the reaction mixture was quenched with 5% aqueous NH_4Cl (100 ml) and extracted with ether (3 × 50 ml). The organic phase was then dried (Na_2SO_4) and concentrated. Bulb-to-bulb distillation of the residue (70°C/0.02 Torr) provided 17 g (95%) of **4** as a colorless solid, mp 37.5–38.5°C; ^{1}Hmr δ: 1.22 (6H, s, $C(CH_3)_2$), 1.6 (1H, s, br, OH), 3.8 (3H, s, CH_3), 7.0 (4H, q, *J* = 8–9 Hz, C_6H_4); ms *m/e* (% relative abundance): 181 (1), 180 (9), 165 (9), 123 (10), 122 (100), 121 (38), 107 (18), 92 (4), 91 (11), 79 (5), 78 (11), 65 (5), 59 (66). *Exact mass* calcd. for $C_{11}H_{16}O_2$: 180.1146; found: 180.1152. *Anal.* calcd. for $C_{11}H_{16}O_2$: C 73.30, H 8.95; found: C 73.04, H 8.81.

3-(4-Benzyloxy-3-methoxyphenyl)-2-methyl-1-propene (9)

To a magnetically-stirred suspension of triphenylphosphonium bromide (10.49 g, 0.029 mol) in THF (50 ml) at −78°C was added dropwise, *n*-butyllithium solution (18.5 ml, 1.55 *M* in hexane) under N_2. The reaction mixture was allowed to warm up to room temperature and it was maintained at this temperature for 2 h. The solution was cooled again to −78°C and the ketone, 1-(4-benzyloxy-3-methoxyphenyl)-2-propanone (7.2 g, 0.029 mol) in THF (70 ml) was then added dropwise (1 h). The reaction mixture was warmed up to room temperature (1 h), stirred at this temperature for 2 h then at reflux temperature for 20 h. After cooling, the mixture was concentrated and 40 ml of ether–pentane (5:1) solution was added. The resulting precipitate of triphenylphosphine oxide was filtered off. Elution chromatography of the concentrated filtrate on silica gel (cyclohexane–ether, 4:1) afforded 7.2 g (94%) of **9**. Molecular distillation (70°C/0.02 Torr) resulted in a colorless oil which solidified on standing, mp 29–30°C; ^{1}Hmr δ: 1.63 (3H, s, CH_3), 3.3 (2H, s, $ArCH_2$), 3.9 (3H, s, OCH_3), 4.85 (2H, s, br, $C{=}CH_2$), 5.25 (2H, s, OCH_2), 6.8 (3H, m, C_6H_3), 7.6 (5H, m, C_6H_5); ms *m/e* (% relative abun-

dance): 268 (33), 177 (27), 117 (7), 107 (5), 91 (100), 55 (5). *Exact mass* calcd. for $C_{18}H_{20}O_2$: 268.1458; found: 268.1463. *Anal.* calcd. for $C_{18}H_{20}O_2$: C 80.56, H 7.51; found: C 80.40, H 7.50.

*3-(4-Methoxyphenyl)-2-methyl-1-propene (**3**)*

Using a procedure similar to that employed in the preparation of **9**, 1-(4-methoxy)phenyl-2-propanone (3.3 g) was reacted to give 3.05 g (94%) of the alkene **3**, bp 44–45°C 0.12 Torr; ^{1}Hmr δ: 1.63 (3H, s, CH_3), 3.25 (2H, s, $ArCH_2$), 3.8 (3H, s, OCH_3), 4.75 (2H, s, br, $C{=}CH_2$), 7.0 (4H, q, J = 8–9 Hz, C_6H_4); ms *m/e* (% relative abundance): 163 (22), 162 (100), 161 (10), 149 (7), 147 (88), 137 (16), 135 (5), 121 (56), 117 (9), 115 (10), 103 (8), 91 (26), 78 (14), 77 (13). *Exact mass* calcd. for $C_{11}H_{14}O$: 162.1040; found: 162.1048. *Anal.* calcd. for $C_{11}H_{14}O$: C 81.44, H 8.70; found: C 81.78, H 8.66.

N-*[1-(4-Hydroxyphenyl)-2-methyl-2-propyl]propionamide (5a)*

Concentrated H_2SO_4 (3 ml, Baker, 96%) was added to a stirred solution of propionitrile (0.66 g, 0.012 mol) in glacial acetic acid (2.5 ml) at ice bath temperature. The alcohol (**4**) (1.8 g, 0.01 mol) dissolved in acetic acid (1 ml) was added dropwise and the mixture was stirred at room temperature for 18 h, neutralized with 10% Na_2CO_3 and extracted (3 × 20 ml) with ether – methylene chloride (14:11). Gas chromatographic analysis showed four peaks, the retention times of which were **5***b*, 10.51 min; **6***b*, 12.66 min; **5***a*, 13.94 min; **6***a*, 14.88 min; gc–ms *m/e* (% relative abundance) **5***b*: 235 (5), 162 (65), 147 (12), 121 (30), 114 (42), 58 (100); **6***b*, m/e 235 (5), 192 (74), 136 (100); **5***a*, m/e 148 (41), 133 (21), 114 (50), 77 (14), 58 (100); **6***a*: 221 (12), 178 (81), 122 (100).

To separate the phenolic compounds, the organic layer was washed with 10% NaOH. After acidification, the aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent produced 0.98 g (42%) of **5***a*, mp 138–139°C (from ether–hexane); ^{1}Hmr δ: 1.0–1.5 (9H, m, $C(CH_3)_2$, CH_2CH_3), 2.0 (2H, q, J = 7 Hz, CH_2), 3.0 (2H, s, $ArCH_2$), 5.2 (H, s, br, OH), 6.4 (4H, q, J = 8–9 Hz, C_6H_4). *Exact mass* calcd. for $C_{13}H_{19}NO_2$: 221.1411; found: 221.1413. *Anal.* calcd. for $C_{13}H_{19}NO_2$: C 70.56, H 8.65, N 6.33; found: C 70.59, H 8.72, N 6.02.

*1-(4-Hydroxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**1e**)*

To a solution of borane in THF (8 ml, 0.10 *M*) in a 50 ml flask equipped with a reflux condenser, dropping funnel, and a magnetic stirring bar and maintained under N_2, was added 0.5 g (2.3 mmol) of the amide (**5***a*) in THF (8 ml) over 15 min. The temperature was maintained at 0°C during the addition. The colorless solution was then refluxed for 10 h, cooled to room temperature, and treated with 6 *N* HCl (5 ml). After stirring for 0.5 h, the aqueous layer was separated, washed with ether, basified with 20% Na_2CO_3 (pH 9–9.5), and extracted (2 × 15 ml) with ether–CH_2Cl_2 (14:11). The combined extract was washed with brine and dried (Na_2SO_4). Removal of the solvent gave 0.4 g (86%) of **1***e*, mp 89.5–90.5°C (from hexane–CCl_4); ^{1}Hmr δ: 0.7–1.9 (11H, m, $C(CH_3)_2$, $CH_2CH_2CH_3$), 2.4–3.0 (4H, m, $ArCH_2$, $CH_2CH_2CH_3$), 5.3 (2H, s, br, NH, OH), 6.9 (4H, q, J = 8–9 Hz, C_6H_4); ms *m/e* (% relative abundance): 192 (2), 101 (7), 100 (100), 58 (60). *Exact mass* calcd. for $C_{12}H_{18}NO$ $(M - CH_3)^+$: 192.1384; found: 192.1386. *Anal.* calcd. for $C_{13}H_{21}NO$: C 75.32, H 10.21, N 6.76; found: C 75.11, H 10.03, N 6.67.

*1-Ethyl-7-hydroxy-6-methoxy-3,3-dimethyl-3,4-dihydroisoquinoline (**10**b)*

Concentrated H_2SO_4 (14 ml) was added to a stirred mixture of glacial acetic acid (40 ml) and propionitrile (1.3 ml, 0.018 mol) at 0°C. The alkene (**9**) (4 g, 0.015 mol) in glacial acetic acid (10 ml) was added dropwise at ice-bath temperature. The resulting mixture was stirred at room temperature for 15 h. The mixture was neutralized with 20% Na_2CO_3, then extracted with methylene chloride (2 × 30 ml) and the combined extracts were dried and evaporated *in vacuo*. The residue (4.05 g) was shown by ^{1}Hmr to be a mixture of **10***b* (60%), **10***a* (24%), and **10***c* (16%). The phenolic compound **10***b* was separated from the remainder (3 g) of the mixture (**10***a–c*) as described for **5***a* and 1.5 g of **10***b* was obtained, mp 146–148°C (from chloroform); ^{1}Hmr δ: 1.0–1.5 (9H, m, $C(CH_3)_2$, CH_2CH_3), 2.4–2.9 (4H, m, $ArCH_2$, CH_2CH_3), 3.9 (3H, s, OCH_3), 6.7 (1H, s, C_6H), 7.2 (1H, s, C_6H), 8.9 (1H, s, br, OH); ms *m/e* (% relative abundance): 234 (13), 233 (79), 232 (41), 219 (16), 218 (100), 216 (10), 204 (8), 203 (16), 191 (36), 190 (23), 177 (6), 164 (9), 163 (10), 161 (11), 145 (8), 117 (10), 91 (12). *Exact mass* calcd. for $C_{14}H_{19}NO_2$: 233.1411; found: 233.1412.

*1-(4-Benzyloxy-3-methoxyphenyl)-2-iodomethyl-2-propylisocyanate (**11**, R = NCO)*

A slurry of iodine (9 g, 0.035 mol) and freshly prepared silver isocyanate (6.88 g, 0.046 mol) in dry ether (10 ml) was stirred for 1 h at 25°C under dry N_2. The mixture was then cooled to −20°C and the alkene (**9**) (6.7 g, 0.025 mol) in ether (25 ml) was added dropwise. After stirring at room temperature for 36 h, the reaction mixture was filtered through Celite and washed with a saturated Na_2SO_3 solution to remove excess iodine. The ether layer was then washed with brine, dried (Na_2SO_4), and evaporated, to yield 9.18 g of a pale yellow oil (mixture by ^{1}Hmr of 73% **11**, R = NCO and 20% **9**); ir (neat) ν_{max} 2250 (NCO) cm^{-1}; ^{1}Hmr of **11**, R = NCO δ: 1.45 (3H, s, CH_3), 2.85 (2H, s, CH_2I), 3.3 (2H, s, $ArCH_2$), 3.85 (3H, s, OCH_3), 5.2 (2H, s, OCH_2), 6.8 (3H, m, C_6H_3), 7.5 (5H, m, C_6H_5).

*1-(4-Benzyloxy-3-methoxyphenyl)-2-methyl-2-aminopropane (**12**, R = H)*

To the crude iodoisocyanate (**11**, R = NCO) (9.18 g, containing 20% of **9**) in ether (100 ml) was added dropwise concentrated HCl (35 ml). The mixture was stirred for 6 h, and the precipitate of the iodoamine (**11**, R = NH_2) hydrochloride salt which formed was filtered and washed with ether (5.6 g, 68%).

To a suspension of LAH (2 g) in dry DME (125 ml) under N_2 the dried hydrochloride salt of **11**, R = NH_2 (5.6 g) was added portionwise. After refluxing for 36 h, the mixture was cooled to 0°C and was treated with 40 ml of 4 *N* HCl. The mixture was stirred (3 h), filtered through Celite, and washed with water. The resulting solution was basified with solid NaOH, and extracted with ether (3 × 50 ml). Evaporation of the combined ether extracts gave 2.1 g (57%) of **12**, R = H, as a colorless solid; ^{1}Hmr δ: 1.2 (6H, s, $C(CH_3)_2$), 1.6 (2H, s, br, NH_2), 2.65 (2H, s, $ArCH_2$), 3.9 (3H, s, OCH_3), 5.25 (2H, s, OCH_2), 6.8 (3H, m, C_6H_3), 7.5 (5H, m, C_6H_5); ms *m/e* (% relative abundance): 286 (1), 285 (3), 270 (4), 229 (4), 228 (24), 137 (6), 107 (8), 91 (61), 65 (20), 59 (23), 58 (100), 51 (5). *Exact mass* calcd. for $C_{18}H_{23}NO_2$: 285,1727; found: 285.1728. The hydrochloride of the title compound had mp 178–179°C. *Anal.* calcd. for $C_{18}H_{24}ClNO_2$: C 67.17, H 7.52, N 4.35, Cl 11.02; found: C 67.13, H 7.30, N 4.14, Cl 11.15.

*1-(4-Benzyloxy-3-methoxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**12**, R = $CH_2CH_2CH_3$)*

To a solution of **12**, R = H (2.10 g, 7.37 mmol) in dry THF (40 ml) and triethylamine (3.1 ml, 22.1 mmol) was added dropwise and with stirring, a solution of propionic anhydride (1.5 ml, 11 mmol) in THF (10 ml). Stirring was continued for

15 h then a solution of 2 *N* NaOH (10 ml) was added and the mixture was stirred for a further 2 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 25 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to provide the amide (**12**, R = $COCH_2CH_3$) as a colorless oil 2.4 g (97%) which solidified on standing, mp 80–82°C (diethyl ether).

A solution of the amide **12**, R = $COCH_2CH_3$ (2 g, 5.87 mmol) in THF (15 ml) was reduced with diborane (23.5 ml, 1 *M* in THF) according to the procedure described in the preparation of **1***e*, and **12**, R = $CH_2CH_2CH_3$ (1.51 g, 79%) was obtained as the hydrochloride salt, mp 190°C; ^{1}Hmr of base δ: 0.8–1.2 (9H, m, $C(CH_3)_2$, $CH_2CH_2CH_3$), 1.4 (2H, m, $CH_2CH_2CH_3$), 2.4–2.8 (5H, m, $ArCH_2$, NH, $RNHCH_2R$), 3.95 (3H, s, OCH_3), 5.2 (2H, s, OCH_2), 6.7 (3H, m, C_6H_3), 7.5 (5H, m, C_6H_5); ms *m/e* (% relative abundance): 327 (2), 268 (6), 223 (5), 177 (6), 150 (5), 149 (31), 114 (16), 101 (43), 100 (100), 92 (4), 91 (64), 70 (8), 58 (69). *Exact mass* calcd. for $C_{21}H_{29}NO_2$: 327.2190; found: 327.2193.

*1-(4-Hydroxy-3-methoxyphenyl)-2-methyl-2-(*n*-propylamino)propane (**1***f*)*

A solution of the amine (**12**, R = $CH_2CH_2CH_3$) (1.5 g, 4.59 mmol) in ethanol (100 ml) was hydrogenated over palladium–charcoal (2.7 g) at 40 psi for 17 h. The mixture was filtered through Celite and concentrated to give 0.7 g (82%) of **1***f*; ^{1}Hmr δ: 0.8–1.2 (9H, m, $C(CH_3)_2$, $CH_2CH_2CH_3$), 1.8 (2H, m, $CH_2CH_2CH_3$), 2.6–2.8 (4H, m, $ArCH_2$, $CH_2CH_2CH_3$), 3.85 (3H, s, OCH_3), 5.5 (2H, s, br, NH, OH), 6.8 (3H, m, C_6H_3); ms *m/e* (% relative abundance): 222 (1), 137 (5), 122 (2), 116 (1), 100 (100), 98 (2), 94 (2), 91 (2), 77 (2), 71 (1), 58 (27). *Exact mass* calcd. for $C_{13}H_{20}NO_2(M - CH_3)^+$: 222.1489; found: 222.1492. A sample for analysis was purified by gc (Varian aerograph 90-P instrument) and the product with retention time 9.1 min on a 180 cm × 4 mm id stainless steel column containing 3% OV-101 on Chromosorb W (column temperature 160°C; He flow rate 60 ml/min) was collected as colorless needles, mp 114–115°C. *Anal.* calcd. for $C_{14}H_{23}NO_2$: C 70.85, H 9.77, N 5.90; found: C 70.38, H 9.68, N 5.86.

Acknowledgements

Financial assistance from the Medical Research Council of Canada (grant No. MT-2993 to R.T.C.) is acknowledged with thanks. Useful discussions with Dr. G. R. Jones are also acknowledged.

1. R. T. Coutts, G. W. Dawson, C. W. Kazakoff, and J. Y. Wong. Drug Metab. Dispos. **4**, 256 (1976).
2. R. T. Coutts, G. W. Dawson, and A. H. Beckett. J. Pharm. Pharmacol. **28**, 815 (1976).
3. L. L. Abell, W. F. Bruce, and J. Seifter (to Wyeth Inc.). U.S. Patent No. 2,590,079 (March 25, 1952); Chem. Abstr. **46**, 10200e (1952).
4. J. J. Ritter and F. X. Murphy. J. Am. Chem. Soc. **74**, 763 (1952).
5. K. K. Midha, J. K. Cooper, I. J. McGilveray, R. T. Coutts, and R. Dawe. Drug Metab. Dispos. **4**, 568 (1976).
6. H. C. Brown and P. Heim. J. Org. Chem. **38**, 912 (1973).
7. A. Hassner, R. P. Hoblitt, C. Heathcock, J. E. Kropp, and M. Lorber. J. Am. Chem. Soc. **92**, 1326 (1970).
8. I. A. Pearl and D. L. Beyer. J. Org. Chem. **16**, 221 (1951).