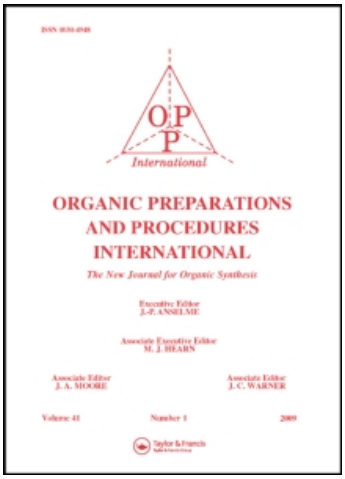


**Organic Preparations and Procedures International**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

# A FACILE SYNTHETIC ROUTE TO HYDROXY METABOLITES OF TRICYCLIC ANTIDEPRESSANTS

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**To cite this Article** Adamczyk, Maciek , Chen, Yon-Yih and Fishpaugh, Jeffrey R.(1991) 'A FACILE SYNTHETIC ROUTE TO HYDROXY METABOLITES OF TRICYCLIC ANTIDEPRESSANTS', Organic Preparations and Procedures International, 23: 3, 365 — 372
**To link to this Article: DOI:** 10.1080/00304949109458211
**URL:** http://dx.doi.org/10.1080/00304949109458211

ORGANIC PREPARATIONS AND PROCEDURES INT., 23 (3), 365-372 (1991)

# A FACILE SYNTHETIC ROUTE TO HYDROXY METABOLITES OF TRICYCLIC ANTIDEPRESSANTS

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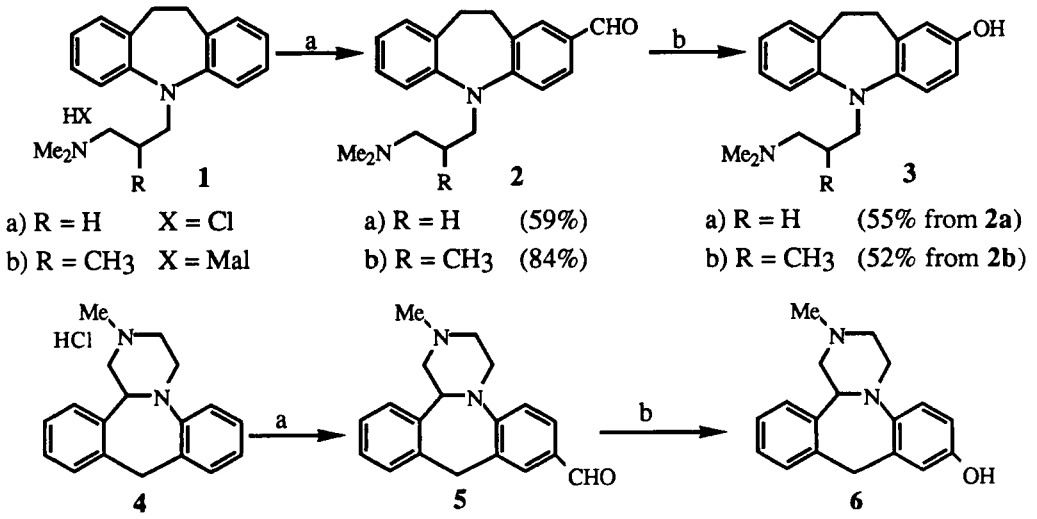
Our current efforts in developing immunoassays for tricyclic antidepressant drugs required the metabolites of imipramine (IMI, **1a**), trimipramine (TMI, **1b**) and desipramine (DMI, **7**). All three drugs are known to metabolize to the corresponding phenolic derivatives: 2-hydroxy-imipramine (**3a**),[1] 2-hydroxytrimipramine (**3b**)[2] and 2-hydroxydesipramine (**13**).[3] Although the synthesis of 2-hydroxyimipramine in five steps from iminodibenzyl has been described,[1] the other tricyclic hydroxy compounds had not been previously synthesized. The literature procedure for the synthesis of 2-hydroxyimipramine (**3a**) was repeated in our laboratories, and was found to be unsuitable to scale-up or for the facile synthesis of 2-hydroxydesipramine (**13**). Our newly developed route for the synthesis of hydroxy tricyclic



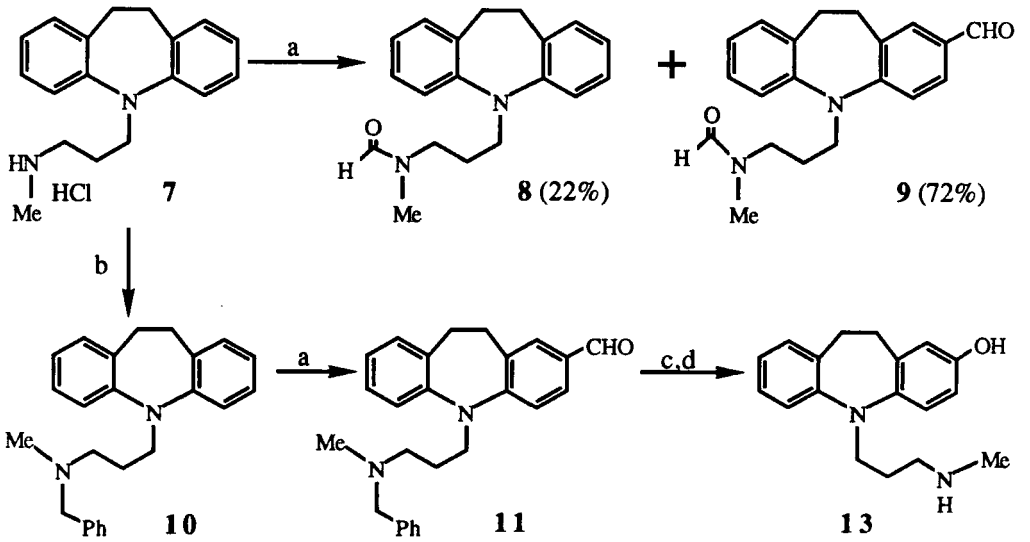

a) $POCl_3$, DMF, 95°; b) *m*-CPBA, TFA, $CH_2Cl_2$, then HCl, MeOH.

Scheme 1

metabolites in three steps from the respective parent drugs is described in Scheme 1.

The synthesis of 2-hydroxyimipramine, 2-hydroxytrimipramine and 8-hydroxymianserin, (**3a**, **3b** and **6** respectively), was accomplished as shown in Scheme 1. Imipramine hydrochloride (**1a**) was readily formylated with the Vilsmeier reagent to give 2-formyl-imipramine (**2a**) in 59% yield. Subsequent transformation of the formyl group to the desired phenol was accomplished in two steps: modified Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) and trifluoroacetic acid[4] followed by acidic hydrolysis of the resulting formate to afford the desired phenol (**3a**) Trimipramine maleate (**1b**) and the tetracylic antidepressant drug mianserin hydrochloride (**4**) were transformed in a similar manner to give respectively, 2-hydroxytrimipramine (**3b**) and 8-hydroxymianserin (**6**).[5]

Desipramine hydrochloride (**7**) could not be cleanly transformed into 2 formyl-desipramine; the product was a mixture of N-formyl DMI (**8**) and the N-formyl aldehyde (**9**). N-Benzyl-protected desipramine (**10**) available from **7** in one step, was readily formylated, oxidized and hydrolyzed as described above to yield *N*-benzyl-2-hydroxy-desimpramine (**12**) as shown in Scheme 2. Hydrogenation of **12** afforded the desired




a) $POCl_3$, DMF, 95°; b) $PhCHO$, $NaBH_3CN$, EtOH;

c) *m*-CPBA, TFA, $CH_2Cl_2$, then HCl, MeOH; d) $H_2$, Pd/C, EtOH.

Scheme 2

phenol (**13**)[6] in 22% overall yield from desipramine hydrochloride.

In conclusion, a short synthetic route has been developed for the synthesis of hydroxy tricyclic antidepressant metabolites in three steps from the parent drugs. While this route works very well for tertiary amines, secondary amines must be protected as their *N*-benzyl derivatives. We are in the process of testing these compounds to assess the selectivity of our antibodies to be used in immunoassays for the parent drugs and will report these results in a future communication.

## EXPERIMENTAL SECTION

Trimipramine maleate salt, imipramine, desipramine and mianserin hydrochlorides were purchased from Sigma. Phosphorus oxychloride, *m*-chloroperbenzoic acid (*m*-CPBA), trifluoroacetic acid, benzaldehyde, 10% palladium on carbon and sodium cyanoborohydride were purchased from Aldrich. Silica gel 60 was purchased from EM Science. *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride and stored over 4 \O(A,°) molecular sieves; methylene chloride was distilled from calcium hydride immediately prior to use. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were obtained on a GE-300 NMR spectrometer and mass spectra were run on a Nermag 3010 instrument.



2-Formylimipramine (**2a**).- Phosphorus oxychloride (0.70 mL, 7.5 mmol) was carefully added to dimethylformamide (DMF) (1.2 mL, 15.4 mmol) at 0° and warmed to room temperature over 10 min to afford a dark viscous solution. Imipramine hydrochloride (**1a**) (951 mg, 3.00 mmol) was added, heated to 100° for 4 hrs then quenched by pouring onto 10 mL ice water. Work-up consisted of adjustment of the pH to 12 with 2N NaOH, extraction of the aqueous layer with $CHCl_3$ (4 x 50 mL) and finally evaporation of the combined organic layers *in vacuo* to yield a dark brown oil. Purification by column chromatography [100g $SiO_2$; 95% THF/5% hexane/ 0.5% $Et_3N$; v/v] gave 552 mg (59%) of the light yellow oil **2a** . $^1$H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.61 (dd, J = 8.46 Hz, J = 2.20 Hz, 1H), 7.55 (d, J = 2.20 Hz, 1H), 7.19-7.07 (m, 4H), 7.02 (dt, J = 7.17 Hz, J = 1.48 Hz, 1H), 3.86 (t, J = 6.99 Hz, 2H), 3.16 (br s, 4H), 2.32 (t, J = 7.35 Hz, 2H), 2.16 (s, 6H), 1.74 (p, J = 7.08 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 190.9, 152.7, 147.3, 136.8, 132.7, 131.0, 129.3, 128.6, 128.4, 126.6, 124.2, 121.9, 118.9, 57.1, 49.6, 45.1(2C), 33.9, 30.8, 25.7. LRMS [DCI, $NH_3$] $(M+H)^+$ 309.

2-Hydroxyimipramine (**3a**).- Trifluoroacetic acid (TFA) (0.19 mL, 2.5 mmol) was slowly

added to a solution of **2a** (220 mg, 0.71 mmol) in 5 mL $CH_2Cl_2$ at 0°. This was followed by the addition of a solution of *m*-chloroperbenzoic acid (*m*-CPBA) (195 mg, 0.90 mmol) in 3 mL $CH_2Cl_2$ over 5 min. The reaction was stirred 1 hr at 5°, 1 hr at room temp and quenched with 5 mL 1M $NaHSO_3$. Work-up consisted of pouring the reaction mixture into 30 mL $H_2O$, adjustment of the pH to 8 with 2N NaOH, extraction with $CHCl_3$ (3 x 30 mL) and evaporation of the combined organic layers *in vacuo* to afford the crude formate as a yellow oil which was hydrolyzed as described below. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.15-6.95 (m, 4H), 6.85-6.72 (m, 3H), 3.63 (t, J = 7.0 Hz, 2H), 3.03 (s, 4 H), 2.19 (t, J = 7.1 Hz, 2H), 2.04 (s, 6H), 1.60 (p, J = 7.0 Hz, 2H).

Concentrated HCl (7 mL, 84 mmol) was added to a solution of crude formate in 5 mL MeOH, stirred 2 hrs and poured into 25 mL water. The pH was adjusted to 8 with 2 N NaOH, extracted with $CHCl_3$ (4 x 35 mL) and the combined organic extracts were evaporated *in vacuo* to give a brown solid. Purification by column chromatography [30 g $SiO_2$; 15% MeOH/85% $CH_2Cl_2$/ 0.5% $Et_3N$; v/v] afforded 116 mg (55%) of the yellow solid **3a:** mp 149-150° (lit.[1] 134-135°). $^1H$ NMR (300 MHz, $CDCl_3$ + 2 drops $CD_3OD$): δ 8.45 (br s, 1H), 7.11-6.98 (m, 3H), 6.85 (dd, J = 7.17 Hz, J = 1.23 Hz, 1H), 6.79 (d, J = 8.63 Hz, 1H), 6.56 (d, J = 2.95 Hz, 1H), 6.37 (dd, J = 8.63 Hz, J = 2.95 Hz, 1H), 3.68 (t, J = 6.80 Hz, 2H), 3.25-3.04 (m, 4H), 2.46 (t, J = 7.53 Hz, 2H), 2.23 (s, 6H), 1.78 (p, J = 7.35 Hz, 2H). $^{13}C$ NMR (75 MHz, $CDCl_3$ + 2 drops $CD_3OD$): δ 152.8, 148.3, 140.0, 137.1, 132.3, 130.4, 126.3, 121.7, 121.3, 118.7, 115.9, 113.1, 56.9, 48.0, 45.8, 44.1(2C), 32.8, 31.4, 24.3. HRMS: Calcd for $C_{19}H_{24}N_2O$ *m/z* 296.1889. Found *m/z* 296.1890.[8]

2-Formyltrimipramine (**2b**).- The synthesis of **2b** was performed as described for **2a** with the exception that 820 mg (2 mmol) of **1b** was reacted with the Vilsmeier reagent generated from 0.47 mL (5 mmol) of $POCl_3$ in 0.77 mL (10 mmol) of DMF. Purification by column chromatography (100 g $SiO_2$; 40% THF/60% hexane/0.5% $Et_3N$; v/v) afforded 542 mg (84%) of the desired aldehyde **2b** as a light yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.66 (dd, J = 8.09 Hz, J = 1.84 Hz, 1H), 7.59 (d, J = 1.84 Hz, 1H), 7.30-7.10 (m, 4H), 7.08-6.99 (m, 1H), 3.99 (dd, J = 13.14 Hz, J = 5.15 Hz, 1H), 3.37 (dd, J = 13.14 Hz, J = 8.09 Hz,

1H), 3.15 (s, 4H), 2.18 (dd, J = 12.13 Hz, J = 6.99 Hz, 1H), 2.05 (s, 6H), 1.99 (dd, J = 12.13 Hz, J = 6.99 Hz, 1H), 1.90-1.75 (m, 1H), 0.84 (d, J = 6.25 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 191.1, 152.5, 147.5, 136.2, 132.5, 130.6, 129.0, 128.6, 128.1, 126.6, 124.0, 121.9, 119.0, 64.2, 56.2, 45.7, 33.4, 30.3, 29.2. LRMS [DCI, $NH_3$]: m/z $(M+H)^+$ 323.

2-Hydroxytrimipramine (**3b**).- Baeyer-Villiger oxidation of **2b** and subsequent acid hydrolysis of the crude formate were run as described above with the exception that 542 mg (1.68 mmol) of aldehyde **2b** was rearranged to the intermediate formate which was hydrolyzed in 10 mL MeOH/15 mL conc. HCl. Purification by column chromatography (50 g $SiO_2$; 15% MeOH/85% $CH_2Cl_2$/0.5% $Et_3N$; v/v) afforded 271 mg (52%) of the desired phenol (**3b**) as a waxy oil. $^1$H NMR (300 MHz, $CD_3OD$): δ 7.06-6.91 (m, 4H), 6.84-6.78 (m, 1H), 6.58-6.50 (m, 2H), 3.59 (dd, J = 12.87 Hz, J = 6.62 Hz, 1H), 3.36-3.29 (m, 1H), 3.08 (s, 4H), 2.36 (dd, J = 12.14 Hz, J = 5.14 Hz, 1H), 2.15-2.08 (m, 1H), 2.11 (s, 6H), 2.00-1.80 (m, 1H), 0.93 (d, J = 6.25 Hz, 3H). $^{13}$C NMR (75 MHz, $CD_3OD$): δ 154.0, 150.0, 142.6, 138.2, 133.6, 131.4, 127.3, 124.6, 122.7, 122.4, 119.8, 116.5, 113.9, 66.2, 56.8, 46.1(2C), 33.9, 32.7, 30.4, 17.8. HRMS: Calcd for $C_{20}H_{26}N_2O$ *m/z* 310.2046. Found *m/z* 310.2047.[8]

8-Formylmianserin (**5**).- The synthesis of **5** was performed as described for **2a** with the exception that 500 mg (1.66 mmol) of **4** was reacted with the Vilsmeier reagent generated from 0.39 mL (4.16 mmol) of $POCl_3$ in 0.64 mL (8.30 mmol) of DMF. Purification by column chromatography (100 g $SiO_2$; 70% THF/30% hexane/0.5% $Et_3N$; v/v) afforded 262 mg (54%) of the desired aldehyde **5** as a light yellow oil. $^1$H NMR (300 MHz,$CDCl_3$): δ 9.81 (s, 1H), 7.66 (dd, J = 8.28 Hz, J = 1.84 Hz, 1H), 7.62 (d, J = 1.84 Hz, 1H), 7.26-7.00 (m, 5H), 4.71 (d, J = 12.87 Hz, 1H), 4.23 (dd, J = 10.30 Hz, J = 2.20 Hz, 1H), 3.47-3.33 (m, 3H), 3.01 (dq, J = 11.03 Hz, J = 1.84 Hz, 1H), 2.89 (dt, J = 11.39 Hz, J = 2.20 Hz, 1H), 2.53-2.34 (m, 2H), 2.38 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 191.1, 154.6, 139.1, 138.2, 136.2, 130.5, 130.2, 129.5, 128.0, 127.5, 127.3, 126.9, 119.1, 66.3, 64.2, 55.1, 51.2, 45.5, 38.7. LRMS [DCI, $NH_3$] $(M+H)^+$ 293.

8-Hydroxymianserin (**6**).- Baeyer-Villiger oxidation of **5** and subsequent acid hydrolysis of the crude formate were run as described above with the exception that 522 mg (1.79 mmol) of

aldehyde **5** was rearranged to the intermediate formate which was hydrolyzed in 10 mL MeOH/15 mL conc. HCl. Purification by column chromatography (100 g $SiO_2$; 5% MeOH/95% $CH_2Cl_2$/0.2% $Et_3N$; v/v) afforded 258 mg (52%) of the desired phenol (**6**) as a yellow solid: mp 138-140° (dec). $^1H$ NMR (300 MHz, $CD_3OD$): δ 7.13-6.95 (m, 4H), 6.87-6.85 (m, 1H), 6.60-6.50 (m, 1H), 6.58 (s, 1H), 4.77 (d, J = 12.5 Hz, 1H), 3.91 (dd, J = 10.66 Hz, J = 2.21 Hz, 1H), 3.30-3.10 (m, 3H), 3.00-2.93 (m, 1H), 2.90-2.85 (m, 1H), 2.42-2.32 (m, 2H), 2.35 (s, 3H). $^{13}C$ NMR (75 MHz, $CD_3OD$): δ 153.3, 142.4, 141.7, 140.6, 138.3, 130.2, 129.2, 127.8, 127.4, 120.5, 114.5, 113.9, 67.6, 65.4, 56.3, 52.8, 45.8, 39.4. HRMS: Calcd for $C_{18}H_{20}N_2O$ *m/z* 280.1576. Found *m/z* 280.1575.[8]

*N*-Benzyldesipramine (**10**).- A modification of the Borch procedure[7] for reductive amination using an amine hydrochloride is as follows. Potassium hydroxide (225 mg, 4 mmol) was added to a solution of desipramine hydrochloride (**7**) (4.36 g, 14.4 mmol) in 25 mL MeOH, stirred until the KOH had dissolved whereupon benzaldehyde (1.5 mL, 14.7 mmol) was added. The reaction mixture was stirred for 15 min and $NaBH_3CN$ (310 mg, 4.9 mmol) was added, stirred for another 15 min then potassium hydroxide (900 mg, 16 mmol) was added and stirred 45 min. The mixture was evaporated *in vacuo*, dissolved in 1 N NaOH (50 mL) and $CHCl_3$ (75 mL), separated, the aqueous layer was extracted with $CHCl_3$ (2 x 50 mL) and the combined organic layers were stripped *in vacuo* to give an oil. Purification by column chromatography (200 g $SiO_2$; 30% THF/70% hexane/0.5% $Et_3N$; v/v) afforded 2.55 g (48%) **10** as a colorless oil. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.26–7.17 (m, 5H), 7.15-7.04 (m, 6H), 6.89 (dt, J = 7.17 Hz, J = 1.84 Hz, 2H), 3.77 (t, J = 6.62 Hz, 2H), 3.40 (s, 2H), 3.06 (s, 4H), 2.39 (t, J = 7.17 Hz, 2H), 2.11 (s, 3H), 1.75 (p, J = 6.96 Hz, 2H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 148.3(2C), 139.1, 134.2(2C), 129.7(2C), 128.9(2C), 128.1(2C), 126.8, 126.3(2C), 122.2(2C), 119.9(2C), 54.9, 48.5, 42.3, 32.2(2C), 25.7. LRMS [DCI, $NH_3$] $(M+H)^+$ 357.

*N*-Benzyl-2-formyldesipramine (**11**).- The synthesis of **11** was performed as described for **2a** with the exception that 580 mg (1.63 mmol) **10** was reacted with the Vilsmeier reagent generated from 0.40 mL (4.2 mmol) $POCl_3$ in 0.80 mL (10 mmol) DMF. Purification by column chromatography (50 g $SiO_2$; 40% THF/60% hexane/0.5 % $Et_3N$; v/v) afforded 426

mg (68%) of the desired aldehyde (**11**) as a light yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.62 (dd, J = 8.27 Hz, J = 1.84 Hz, 1H), 7.55 (d, J = 1.84 Hz, 1H), 7.24-7.08 (m, 9 H), 7.02 (dt, J = 7.17 Hz, J = 1.47 Hz, 1H), 3.87 (t, J = 6.62 Hz, 2H), 3.41 (s, 2H), 3.14-2.97 (m, 4H), 2.36 (t, J = 6.80 Hz, 2H), 2.13 (s, 3H), 1.75 (p, J = 6.80 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 191.0, 152.9, 147.3, 138.9, 137.0, 132.8, 131.1, 129.3, 128.8(2C), 128.7, 128.5, 128.2(2C), 126.9, 126.7, 124.2, 122.0, 118.9, 62.5, 54.4, 49.4, 42.3, 34.0, 30.8, 25.6. LRMS [DCI, $NH_3$] $(M+H)^+$ 385.

*N*-Benzyl-2-hydroxydesipramine (**12**).- Baeyer-Villiger oxidation of **11** and subsequent acid hydrolysis of the crude formate were run as described above with the exception that 410 mg (1.06 mmol) of aldehyde **11** was rearranged to the intermediate formate which was hydrolyzed in 6 mL MeOH/1.1 mL conc. HCl. Purification by column chromatography (50 g $SiO_2$; 14% MeOH/86% $CH_2Cl_2$/0.5 % $Et_3N$; v/v) afforded 251 mg (63%) of the desired phenol **12** as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$ + 3 drops $CD_3OD$): δ 7.27-7.18 (m, 5H), 7.14-6.99 (m, 3H), 6.88 (d, J = 8.82 Hz, 1H), 6.87 (dt, J = 7.36 Hz, J = 1.29 Hz, 1H), 6.55 (d, J = 2.94 Hz, 1H), 6.48 (dd, J = 8.82 Hz, J = 2.94 Hz, 1H), 3.69 (t, J = 6.62 Hz, 2H), 3.47 (s, 2H), 3.09-2.94 (m, 4 H), 2.43 (t, J = 7.35 Hz, 2H), 2.15 (s, 3H), 1.77 (p, J = 7.17 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$ + 3 drops $CD_3OD$): δ 151.6, 148.6, 141.1, 137.7, 137.2, 132.5, 130.3, 129.4(2C), 128.2(2C), 127.2, 126.3, 121.6, 121.5, 118.9, 115.8, 112.9, 62.1, 54.8, 48.6, 41.9, 32.7, 31.5, 25.3. LRMS [DCI, $NH_3$] $(M+H)^+$ 373.

2-Hydroxydesipramine (**13**).- Palladium on carbon (10%, 41 mg) was added to a solution of **12** (48 mg, 0.13 mmol) in 2.5 mL EtOH and stirred for 5 hrs under 1 atm hydrogen. The mixture was filtered through Celite, evaporated *in vacuo* and the resulting oil was purified by column chromatography (20g $SiO_2$; 20% MeOH/80% $CH_2Cl_2$/0.5% $NH_4OH$; v/v) to afford 38 mg (99%) **13** as a light yellow waxy oil. .$^1$H NMR (300 MHz, $CD_3OD$ + $CDCl_3$): δ 7.13-7.01 (m, 3H), 6.92-6.83 (m, 2H), 6.62-6.57 (m, 2H), 3.69 (t, J = 6.62 Hz, 2H), 3.14-3.03 (m, 4H), 2.59 (t, J = 7.35 Hz, 2H), 2.32 (s, 3H), 1.76 (p, J = 7.62 Hz, 2H). $^{13}$C NMR (75 MHz, $CD_3OD$ + $CDCl_3$): δ 152.2, 148.1, 140.6, 136.9, 132.2, 130.2, 126.0, 121.5, 121.1, 118.5, 115.4, 112.7, 48.9, 47.8, 35.2, 32.5, 31.2, 26.8. HRMS: Calcd for $C_{18}H_{22}N_2O$ *m/z* 282.1732. Found

*m/z* 282.1731.[8]

## REFERENCES

1. W. Schindler, *Helv. Chim. Acta*, 43, 35 (1960).

2. a) A. D. Fraser, A. F. Isner and R. F. Perry, *J. Anal. Toxicol.*, 11, 168 (1987) b) R. F. Suckow and T. B. Cooper, *J. Pharm. Sci.*, 73, 1745 (1984) and references therein.

3. B. Herrmann and R. Pulver, *Archs. Int. Pharmacodyn.*, 126, 454 (1960).

4. S. S. C. Koch and A. Chamberlin, *Syn. Comm.*, 19, 829 (1989).

5. a) G. D. De Jongh, H. M. van den Wildenberg, H. Nieuwenhuyse and F. van der Veen, *Drug Metab. Dispos.*, 9, 48 (1981);. b) C. A. A. van Boeckel, L. P. C. Delbressine and F. M. Kaspersen, *Recl. Trav. Chim. Pays-Bas.*, 104, 259 (1985).

6. Differential NOE and 2D-COSY NMR experiments support the assigned structures for the phenolic metabolites **3a**, **3b**, **6** and **13**.

7. R. F. Borch, *Org. Syn.*, 52, 124 (1972).

8. The phenolic metabolites, **3a**, **3b**, **6** and **13**, are not stable to heat and slowly decomposed during drying to afford compounds which did not give satisfactory elemental analyses.

***(Received November 16, 1990; in revised form February 27, 1991)***