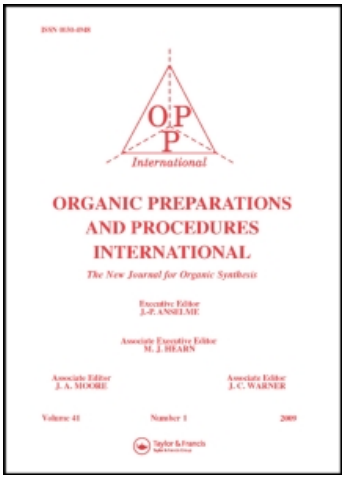

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EFFICIENT SYNTHESIS OF TRICYCLIC ANTIDEPRESSANT NORMETABOLITES

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EFFICIENT SYNTHESIS OF TRICYCLIC ANTIDEPRESSANT NORMETABOLITES

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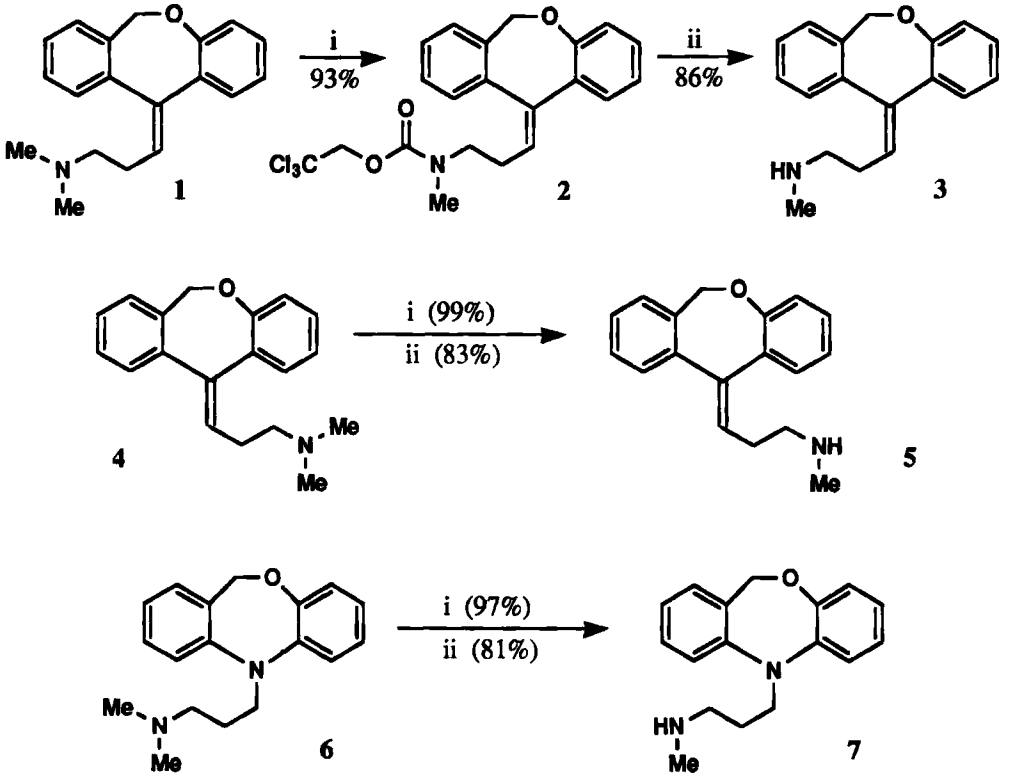
Our current efforts in developing immunoassays for tricyclic antidepressant drugs required normetabolites of *E*-doxepin (**1**), *Z*-doxepin (**4**), and 5,11-dihydro-5-[3,3-(dimethylamino)propyl]-dibenz-[b,e] [1,4]-oxazepine (**6**). All three compounds are known to metabolize *in vivo* to the corresponding secondary amines **3**[1a], **5**[1a], and **7**[1b] by an N-demethylation sequence. The only known synthesis of desmethyldoxepin required six steps and gave a mixture of *E*- and *Z*-desmethyldoxepins.[2a] Our improved synthesis of desmethyldoxepin is based upon a synthetic N-demethylation of pure *E*- or *Z*-doxepin[2a,2b] to give pure *E*- or *Z*-desmethyldoxepin (**3** and **5** respectively). Initial synthetic results for the N-demethylation of **1** gave only moderate amounts (67%) of the intermediate carbamate **2** using triethylamine, while the hindered base *N,N*-diisopropylethylamine (Hunig's base)



i. 2,2,2-Trichloroethylchloroformate, Hunig's base. ii. Zn, THF / pH 5 phosphate buffer.

gave a very high yield (93%) of the desired carbamate **2**. Subsequent zinc promoted deprotection afforded the secondary amine **3** in 80% overall yield as shown above. Similar results were obtained

for the the transformations of **4** to **5** (60% to intermediate carbamate with Et_3N, 99% with Hunig's base) and **6** to **7** (62%, Et_3N; 97%, Hunig's base).

In conclusion, a simple, efficient route to *E*-desmethyldoxepin (**3**), *Z*-desmethyldoxepin (**5**), and 5,11-dihydro-5-[3-(methylamino)propyl]-dibenz-[b,e][1,4]-oxazepine (**7**) was realized while the choice of Hunig's base greatly increased the overall yield of the N-demethylation sequence.

EXPERIMENTAL SECTION

Doxepin hydrochloride was purchased from Sigma as an 85:15 (*E*:*Z*) mixture and separated into pure *E*-doxepin and *Z*-doxepin as described in references 2a and 2b. *N,N*-Diisopropylethylamine, 2,2,2-trichloroethylchloroformate, chloroform, and tetrahydrofuran were purchased from Aldrich. Silica gel 60 was purchased from EM Science. ^1H and ^{13}C NMR spectra were obtained on a GE-300 NMR spectrometer and mass spectra were determined on a Nermag 3010 instrument under either EI $(M)^+$ or FAB $(M+H)^+$ conditions.

E-Desmethyldoxepin (3).- 2,2,2-Trichloroethylchloroformate (0.19 mL, 1.38 mmol) was added to a 0° solution of **1**[2a,2b] (174 mg, 0.623 mmol), *N,N*-diisopropylethylamine (0.25 mL, 1.4 mmol) and 3 mL chloroform; warmed to room temperature and stirred for 3 hours. The reaction mixture was poured into 20 mL water, pH adjusted to 13 with 2.0N NaOH and extracted with 3 x 25 mL chloroform. The solvents were removed *in vacuo* to give an orange oil which was purified by flash chromatography[3] [20 mm diameter column, 25% EtOAc/75% hexane/ 0.1% Et_3N; v/v] to afford 256 mg (93%) of the desired carbamate **2** as an oil. The carbamate **2** exists as two rotamers; the following are spectral data of the major amide rotamer: ^1H NMR ($CDCl_3$): δ 7.40-7.16 (m, 5H), 7.12 (t, J = 7.80 Hz, 1H), 6.86 (t, J = 7.56 Hz, 1H), 6.75 (d, J = 8.09 Hz, 1H), 5.98 (t, 7.72 Hz, 1H), 5.51 (v br s, 1H), 4.71 (s, 2H), 4.63 (v br s, 1H), 3.60-3.32 (m, 2H), 2.80 (s, 3H), 2.56-2.40 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 155.0, 154.2, 141.8, 140.7, 134.4, 129.9, 129.1, 128.5, 128.3, 127.9, 127.8 (2C), 126.9, 121.0, 119.2, 95.4, 75.1, 70.0, 48.6, 34.9, 28.0; MS: m/z $(M+H)^+$ Calcd. (for $C_{21}H_{21}{}^{35}Cl_3N_1O_3$) 440.0587, obsd 440.0585.

Activated zinc[4] (456 mg, 6.98 mmol, 15 eq.) was added to a solution of the carbamate **2** (205 mg, 0.465 mmol) in 8 mL tetrahydrofuran/1.5 mL 0.5 M phosphate buffer (pH = 5.0) and stirred for 3.5 hours at room temperature. The mixture was filtered through a scintered glass funnel, washed 2 x 10 mL 0.3N HCl and 2 x 20 mL chloroform; the filtrate was transferred to a separatory funnel and the aqueous layer was adjusted to pH 12 with 2N NaOH. The lower chloroform layer was separated and the remaining aqueous layer was extracted with 2 x 20 mL chloroform. The combined organic extracts were evaporated *in vacuo* to give a dark yellow oil which was purified by flash chromatography [20 mm diam. column, 20% methanol-80% methylene chloride-0.5% Et_3N; v/v] to afford 106 mg (86%) of the desired secondary amine **3**[6] as a pale yellow oil. ^1H NMR ($CDCl_3$): δ 7.39-7.20 (m, 5H), 7.11 (dt, J = 7.72, 1.84 Hz, 1H), 6.87 (dt, J = 7.57, 1.10 Hz, 1H), 6.75 (dd, J = 8.09, 1.10 Hz, 1H), 6.01 (t, J = 7.54 Hz, 1H), 5.52 (v br s, 1H), 4.83 (v br s, 1H), 2.71 (t, J = 7.17 Hz, 2H), 2.66 (s, 1H), 2.45-2.34 (m, 2H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.0, 141.0, 140.8, 134.2, 130.0, 129.3,

129.0, 128.5, 128.1, 127.9, 127.8, 127.2, 120.9, 119.1, 70.1, 51.4, 35.9, 29.3; MS: m/z $(M+H)^+$ calcd 266.1545, obsd 266.1544.

Z-Desmethyldoxepin (5).- The intermediate carbamate was generated as described above using **4**[2a,2b] (115 mg, 0.412 mmol) which, after purification by flash chromatography, afforded an oil (181 mg, 99%). Spectral data for the major rotamer: ^{1}H NMR ($CDCl_3$): δ 7.37-7.22 (m, 4H), 7.20-7.08 (m, 2H), 6.93-6.84 (m, 2H), 5.65 (t, J = 6.25 Hz, 1H), 5.40 (v br s, 2H), 4.71 (s, 2H), 3.58-3.46 (m, 2H), 2.93 (s, 3H), 2.80-2.65 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 155.6, 154.2, 145.3, 141.9, 133.6, 131.1, 129.4, 129.1, 128.1, 127.7, 127.5, 126.1, 123.8, 120.5, 119.8, 95.5, 75.1, 70.4, 48.8, 34.9, 28.3; MS: m/z $(M+H)^+$ Calcd. (for $C_{21}H_{21}{}^{35}Cl_3N_1O_3$) 440.0587, obsd 440.0585.

The secondary amine **5** was produced as described above by treating 128.7 mg (0.292 mmol) of the carbamate with activated zinc (288 mg, 4.41 mmol) to afford, after purification, 64 mg (83%) of the desired amine **5**[6] as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.34-7.21 (m, 4H), 7.18-7.12 (m, 2H), 6.90 (dt, J = 7.36, 1.10 Hz, 1H), 6.85 (dd, J = 7.35, 1.10 Hz, 1H), 5.67 (t, J = 7.17 Hz, 1H), 5.19 (br s, 2H), 2.77 (t, J = 6.98 Hz, 2H), 2.66 (t, J = 6.75 Hz, 2H), 2.53 (s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.4, 145.1, 141.1, 133.6, 131.1, 129.3(2C), 128.9, 127.5, 127.3, 126.2, 124.2, 120.6, 119.6, 70.5, 51.2, 35.4, 29.3; MS: m/z $(M+H)^+$ calcd 266.1545, obsd 266.1543.

5,11-Dihydro-5-[3-(methylamino)propyl]-dibenz-[b,e][1,4]-oxazepine (7).- The intermediate carbamate was generated as described above using **6**[5] (150 mg, 0.524 mmol) which, after purification by flash chromatography, afforded an oil (228 mg, 97%). Spectral data for the major rotamer: ^{1}H NMR ($CDCl_3$): δ 7.36-7.27 (m, 2H), 7.12-6.95 (m, 3H), 6.88-6.77 (m, 3H), 5.33 (s, 2H), 4.63 (s, 2H), 3.78 (t, J = 6.62 Hz, 2H), 3.40 (t, J = 6.62 Hz, 2H), 2.86 (s, 3H), 2.00-1.86 (m, 2H); ^{13}C NMR($CDCl_3$): δ 154.3, 150.2, 149.3, 135.7, 131.6, 129.3, 128.7, 123.1, 122.7, 121.0, 120.1, 119.5, 119.4, 95.7, 74.9, 69.6, 47.3, 46.9, 35.0, 25.9; MS: m/z $(M)^+$ Calcd. (for $C_{20}H_{21}{}^{35}Cl_3N_2O_3$) 442.0618; obsd, 442.0633.

The secondary amine **7** was produced as described above by treating 164 mg (0.37 mmol) of the carbamate with activated zinc (360 mg, 15.5 mmol) to afford, after purification, 80 mg (81%) of the desired amine **7**[7] as a pale yellow oil. ^{1}H NMR($CDCl_3$): δ 7.34-7.26 (m, 2H), 7.11-6.98 (m, 3H), 6.86-6.77 (m, 3H), 5.29 (s, 2H), 3.78 (t, J = 6.80 Hz, 2H), 2.72 (s, 1H), 2.63 (t, J = 7.17 Hz, 2H), 2.35 (s, 3H), 1.85 (p, J = 6.99 Hz, 2H); ^{13}C NMR($CDCl_3$): δ 150.3, 149.2, 135.9, 131.6, 129.2, 128.6, 123.0, 122.6, 121.0, 120.2, 119.6, 119.3, 69.6, 49.2, 47.9, 35.7, 26.9; MS: m/z $(M)^+$ calcd 269.1654, obsd 269.1662.

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6. Reference 1a contains ^{1}H NMR and mass spectral data for both *E*-desmethyldoxepin (**3**) and *Z*-desmethyldoxepin (**5**).

7. The following reference contains ^{1}H NMR for 5,11-dihydro-5-[3,3-(dimethylamino)ethyl]-dibenz-[b,e][1,4]-oxazepine with a chemical shift of 5.24 for the O-CH_2 protons: H. L. Yale and F. A. Sowinski, *J. Med. Chem.*, **10**, 1022 (1967).

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SYNTHESIS OF PYRAZOLO[3,4-d]PYRIDAZINE, PYRAZOLO[3,4-d]PYRIMIDINE AND IMIDAZO[1,2-a]PYRIDINE DERIVATIVES USING HYDRAZONYL BROMIDES

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Although hydrazonyl bromides are interesting intermediates for heterocyclic synthesis,[1] very little attention was paid to the utility of hydrazonyl halides in the synthesis of the title compounds.[2] This paper describes the utility of hydrazonyl bromides in the synthesis of pyrazolo[3,4-d]pyridazine, pyrazolo[3,4-d]pyrimidine and imidazo[1,2-a]pyridine. For this purpose, we studied the reaction of hydrazonyl bromides (**1a-c**) with the sodium salt of dibenzoylmethane and of acetylacetone to give the previously unreported pyrazoles (**2**), which were converted to the pyrazolo[3,4-d]pyridazine (**3**) by condensation with hydrazine (Eq. 1).

Treatment of (**1a-c**) with malononitrile in the presence of sodium ethoxide at room temperature afforded the 4-cyano-5-aminopyrazole derivatives (Eq. 2). The structure of the latter products were based on their elemental analysis, spectral data and their reactions described below. Refluxing of 4-cyano-5-aminopyrazoles (**4**) in formamide for 4 hrs gave 4-amino-1-aryl-3-(2-naphthoyl)-pyrazolo[3,4-d]pyrimidines (**5**); heating of **4** in formic acid afforded 1-aryl-3-(2-naphthoyl)pyra-