

## A New Synthetic Approach to 3-Amino-2-phenylthietanes as Potential Monoamine Oxidase Inhibitors

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**Abstract** □ 3-Amino-2-phenylthietane derivatives were considered as a useful tool to elucidate the mechanism of inhibition of MAO by tranylcypromine-type inhibitors. The synthesis of 3-benzoylamino-2-phenylthietane, 3-amino-2-phenylthietane, and 3-N, N-dimethylamino-2-p-nitrophenylthietane was attempted using the reaction between 1,3-dihalogeno alkanes with alkali sulfide. When 1-phenyl-1,3-dihalo-2-benzoylamino-2-phenyl-4-benzylidene-2-oxazoline was treated with sodium sulfide, 2-phenyl-4-benzylidene-2-oxazoline was isolated, indicating the ease of elimination reaction compared to ring formation. The reaction of 1-p-nitrophenyl-1,3-dichloro-2-N, N-dimethylamino-2-phenyl-4-benzylidene-2-oxazoline with sodium sulfide gave bis (1-p-nitrophenyl-2-N, N-dimethylamino-3-chloropropane) sulfide. The mechanism of reaction was discussed.

**Keyphrases** □ Attempted synthesis of 3-amino-2-phenylthietanes—1,3-dihalogeno alkanes—alkali sulfide. Synthesis of 2-phenyl-4-benzylidene-2-oxazoline. Synthesis of bis (1-p-nitrophenyl-2-N, N-dimethylamino-3-chloropropane) sulfide.

Tranylcypromine has been extensively studied as a model compound to elucidate the mechanism of inhibition of MAO because of its relatively rigid and simple structure and unique geometry. However, the relationship of tranylcypromine with active site of MAO has not been disclosed with the same detail as have recent studies of phenylhydrazine<sup>1)</sup>

and pargyline.<sup>2)</sup> It was postulated by Belleau and Moran<sup>3)</sup> that the chemical role of cyclopropane ring of tranylcypromine could consist in promoting charge-transfer complex formation through its sp<sup>2</sup>-like electrons with the flavin cofactor. The importance of the cyclopropane ring as an electron donor has been supported by the fact that relative to tranylcypromine, 2-phenylcyclobutylamine is only 1/1000 times as active by *in vitro* testing.<sup>4)</sup> The difference in activity is presumably due to the loss of electronic delocalization. Contribution of geometrical factors seems to be minimum since 3-amino-2-phenylazetidide showed MAO inhibitory activity.<sup>5)</sup> N-Substituted tranylcypromine derivatives such as N-carbethoxy and N-carbobenzoxy compounds also showed a fair degree of activity.<sup>6)</sup> The activity of the acyl derivatives is presumably due to their hydrolysis *in vivo* to the parent amines.

3-Amino-2-phenylthietanes appear a good model to provide evidence for the importance of electronic properties of the cyclopropane ring in tranylcypromine derivatives. This stems from the fact that sulfur is known to participate in conjugation and thus may enhance electron density of the ring so that

attachment to the active site of MAO could be strengthened, resulting in stronger inhibitory activity. Previous attempts to synthesize 3-amino-2-phenylthietanes by reducing 3-dimethylamino-2-phenylthietane 1,1-dioxides<sup>7)</sup> or by modifying the hydroxyl group of 2-phenylthietanol<sup>8)</sup> were not successful. In this report, we describe a new synthetic approach to obtain 3-benzoylamino-2-phenylthietane, 3-amino-2-phenylthietane, and 3-N,N-dimethylamino-2-*p*-nitrophenylthietane adopting the reaction of sodium sulfide with 1,3-dihalogeno compounds which has been successfully applied to prepare the intermediates for lipoic acid.<sup>9,10)</sup>

#### EXPERIMENTAL

Melting points were determined using a Thomas-Hoover Melting Point Apparatus. All melting points and boiling points were uncorrected. A Beckman IR-10 Infrared Spectrophotometer was used to record all infrared spectra. NMR (100 MHz) spectra were determined using a Varian HA-100 NMR Spectrometer and tetramethylsilane as the internal standard. Peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), b (broad), and m (multiplet). UV spectra were obtained using a Beckman Model 25 Spectrophotometer. Mass spectra and GC-MS data were obtained using a Varian MAT 111 Mass Spectrometer. The ionizing voltage was 80 eV unless specified. Microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany. *p*-Nitrophenylserinol was obtained from Chong Kun Dang Corporation, Seoul.

*Synthesis of 1-phenyl-1,3-dichloro-2-benzoylaminopropane (Ia)*—*threo*-N-Benzoyl phenylserinol<sup>11)</sup> (2.71 g, 0.01 mole) with freshly distilled SOCl<sub>2</sub> (59.5 g, 0.5 mole) was heated on the water bath for 1.5 hours. After evaporating SOCl<sub>2</sub> under reduced pressure, the resulting residue was treated with dry ether to obtain a solid (2.89 g). Purified product was obtained on recrystallization from benzene (1.75 g, 56.8%). mp 148–150; IR<sub>max</sub><sup>KBr</sup> cm<sup>-1</sup>δ; 3330 (NH), 1640, 1530 (amide), no hydroxyl; NMR (CDCl<sub>3</sub>)δ; 7.50–7.73 (2H, m, protons ortho to carbonyl group), 7.60–7.37 (8H, m, phenyl protons), 6.40 (1H, b, -NH-CO-), 5.32 (1H, d, C<sub>6</sub>H<sub>5</sub>-CHCl-), 4.43–5.00 (1H, m, C<sub>6</sub>H<sub>5</sub>-CH-CH-), 3.50 (2H, m, -CH<sub>2</sub> Cl); MS (m/e); 105 (100), 130 (90), 146 (32), 182 (30), 235 (31); Anal. Calcd. for C<sub>16</sub>H<sub>15</sub>NCl<sub>2</sub>O: C, 62.33; H, 4.91; Cl, 23.02; mol. wt., 308.05. Found: C, 62.21; H, 4.89; Cl, 23.20.

*Synthesis of 1-phenyl-1,3-dibromo-2-benzoylaminopropane (Ib)*—A general procedure for this synthesis was taken from the literature.<sup>12,13)</sup> mp 132–134° (lit.<sup>13)</sup> 132–134°; IR<sub>max</sub><sup>KBr</sup> cm<sup>-1</sup>; 1650, 1530 (amide), 3320 (NH); NMR (CDCl<sub>3</sub>)δ; 7.60–7.86 (2H, m, protons ortho to carbonyl group), 7.13–7.57 (8H, m, phenyl protons), 6.50 (1H, b, -NH-CO-), 5.38 (1H, d, C<sub>6</sub>H<sub>5</sub>-CH-Br-), 4.63–5.0 (1H, m, C<sub>6</sub>H<sub>5</sub>-CH-CH-), 3.5 (2H, m, -CH<sub>2</sub> Br); MS (m/e); 105 (76), 77 (29), 146 (20), 103 (20), 235 (15), 82 (14).

*Reaction of 1-phenyl-1,3-dihalo-2-benzoylaminopropane with Na<sub>2</sub>S (Synthesis of 2-phenyl-4-benzylidene-2-oxazoline, V)*—To dibromo compound (*Ib*) (397 mg, 0.001 mole) in EtOH (10 ml), Na<sub>2</sub>S·9H<sub>2</sub>O (360 mg, 0.0015

mole) in EtOH (10 ml) was added at room temperature over 30 minutes. The mixture was refluxed for 1.5 hours on a water bath. Precipitated NaBr was filtered and the solvent distilled at reduced pressure to give a residue. After adding H<sub>2</sub>O (10 ml), the mixture was extracted with CHCl<sub>3</sub> (3×100 ml). Drying over anhydrous Na<sub>2</sub>SO<sub>4</sub> and distillation of CHCl<sub>3</sub> gave a yellow viscous material. Tlc (silica gel, iodine chamber, CHCl<sub>3</sub>: cyclohexane 1:1) showed three spots at Rf 0.2 (A), 0.5 (B), and 0.7 (C). The residue was fractionated on a column using silica gel and CHCl<sub>3</sub> for elution. Fractions showing Rf 0.7 were isolated. Partition on the column was monitored by its yellow bands. Distillation of CHCl<sub>3</sub> gave yellow crystals of the oxazoline (120 mg, 50.6%). Recrystallization from hexane on dry ice-acetone gave needle-like yellow crystals. mp 92–94°; UV  $\lambda_{max}^{EtOH}$  nm ( $\epsilon$ ); 201 (24,000), 241 (19,000), 344 (16,000); NMR (CDCl<sub>3</sub>) $\delta$ ; 7.67–8.10 (4H, m, 4 phenyl protons), 7.10–7.40 (6H, m, 6 phenyl protons), 5.73 (1H, t, C<sub>6</sub>H<sub>5</sub>CH=), 5.05 (2H, d, -CH<sub>2</sub>-O); MS (m/e); 235 (M<sup>+</sup>, 25), 105 (100), 77 (37), 103 (31), 91 (23).; Anal. Calcd. for C<sub>16</sub>H<sub>13</sub>NO: C, 81.67; H, 5.57; N, 5.80; mol. wt., 235.11. Found: C, 81.56; H, 5.65; N, 5.81. A and B were obtained as viscous liquids having amide bands at 1540 and 1650 cm<sup>-1</sup> in the ir spectrum. Oxazoline was similarly obtained from 1-phenyl-1,3-dichloro-2-benzoylamino-propane. mp. 90–93°. The IR of the product was superimposable with that from the 1,3-dibromo compound reaction.

*Synthesis of N,N-dimethyl-p-nitrophenylserinol(VII).* —D(-)-thero-p-nitrophenylseri-

inol (6.36 g, 0.03 mole) with 37% formaldehyde (12.5 g, 0.154 mole) and 85% formic acid (7.5 g, 0.139 mole) was stirred at 80–100° for 13 hours. After making alkaline to litmus using 50% NaOH, the mixture was extracted with ether (3×150 ml). Drying on anhydrous Na<sub>2</sub>SO<sub>4</sub> and distillation of the solvent gave a brown solid. Recrystallization from ether-hexane gave white crystals (5.24 g, 72.2%). mp 90–92°; IR  $\nu_{max}^{KBr}$  cm<sup>-1</sup>; 1530, 1360 (-NO<sub>2</sub>), disappearance of NH<sub>2</sub> (1580); NMR (CDCl<sub>3</sub>) $\delta$ ; 8.07 (2H, d, ortho to nitro group), 7.47 (2H, d, meta to nitro group), 4.50 (1H, d, NO<sub>2</sub>C<sub>6</sub>H<sub>5</sub>CHOH-), 3.52 (2H, d, -CH<sub>2</sub>OH), 3.10 (2H, b, hydroxyl OH, disappeared on addition of D<sub>2</sub>O), 2.33–2.66 (7H, m, -CHN(CH<sub>3</sub>)<sub>2</sub>); MS (m/e); 88 (100), 58 (64), 209 (6), 163 (6). Anal. Calcd. for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 54.94; H, 6.72; N, 11.67; mol. wt., 240.15. Found: C, 55.09; H, 6.71; N, 11.54.

*Synthesis of 1-p-nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane HCl (VIII).* —N,N-dimethyl-p-nitrophenylserinol HCl (5.43 g, 0.02 mole) with freshly distilled thionyl chloride (50 ml) was heated at 70–80° for 1.5 hours. Distillation of the thionyl chloride under reduced pressure gave a viscous residue. After dissolving the residue by adding EtOH (20 ml), ether (150 ml) was added to obtain a precipitate. Recrystallization from EtOH-ether gave a dichloro compound (4.73 g, 75.4%). mp 161–163°; IR  $\nu_{max}^{KBr}$  cm<sup>-1</sup>; 3420 (tertiary amine), 1530, 1350 (-NO<sub>2</sub>), no strong absorption at 1,000–1,200; MS (m/e); 106 (100), 108 (32), 71 (19), 70 (6), 58 (5); Anal. Calcd. for C<sub>11</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>3</sub>: C, 42.10; H, 4.82; Cl, 33.93; mol. wt. 313.52. Found: C, 42.10;

H, 4.84; Cl, 33.81.

Reaction of 1-*p*-nitrophenyl-1,3-dichloro-2-*N,N*-dimethylaminopropane with  $\text{Na}_2\text{S}$ . (Synthesis of bis (1-*p*-nitrophenyl-2-*N,N*-dimethylamino-3-chloropropane) sulfide HCl, XII)— $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$  (1.414g, 0.006 mole) dissolved in EtOH (30 ml) was added to the solution of 1-*p*-nitrophenyl-1, 3-dichloro-2-*N,N*-dimethylaminopropane HCl (1.881 g, 0.006 mole) in EtOH (50 ml). The mixture was stirred for 3 hours at room temperature. The precipitated yellow crystals were filtered and triturated with  $\text{H}_2\text{O}$ . Yield 660 mg, mp. 115–120°; alkali fusion test sulfur, positive; NMR ( $\text{CDCl}_3$ )  $\delta$ ; 8.10 (4H, d, phenyl protons ortho to nitro group), 7.33 (4H, d, phenyl protons meta to nitro group), 2.37 (12H, s, dimethyl protons), 3.00–3.63 (8H, m,  $(\text{NO}_2\text{C}_6\text{H}_5\text{CHCHN}(\text{CH}_3)_2\text{CH}_2\text{Cl})_2\text{S}$ ) GC-MS (3 % OV-17 column, injector temperature 170°, column temperature 80–275°, programming 20°/min.) retention time 9.3 minutes, *m/e* 70 (61), 58 (44), 115 (19), 84 (14), 206 (12).

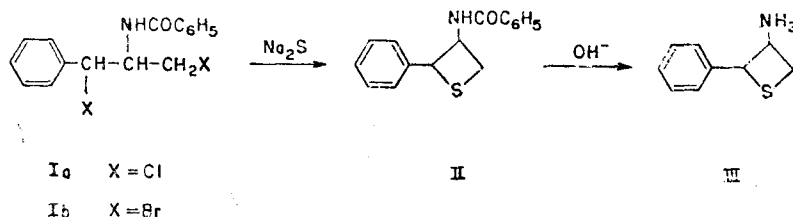
The free base (600 mg) was dissolved in ether (200 mg). A white crystal was obtained by passing HCl gas through the ether solution. Yield 560 mg (overall yield 15.4 %); mp 148° (dec.) (recrystallization from ether-EtOH and drying at 50°/0.1 mmHg for 5 hours); GC-MS

(3 % OV-17 column, injector temperature 170°, column temperature 80–275°, programming 20°/min.) retention time 9.3 minutes, *m/e* 70, 58, 84, 206, 115. Anal. Calcd. for  $\text{C}_{22}\text{H}_{32}\text{N}_4\text{O}_5\text{SCl}_4$ : C, 43.55; H, 5.32; N, 9.24; S, 5.29; mol. wt. 606.20. Found: C, 43.89; H, 5.24; N, 9.06; S, 4.98.

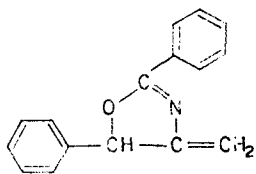
## RESULTS AND DISCUSSION

Synthetic approach to 3-benzoylamino-2-phenylthietane (II) and 3-amino-2-phenylthietane (III).

The approach proposed for the synthesis of II and III is outlined in Scheme 1. Synthesized 1-phenyl-1,3-dichloro-2-benzoylamino-propane (Ia) showed different mp (148–150°) from the reported one (131–132°).<sup>14</sup> The structure of synthesized Ia was confirmed by IR, NMR, MS, and elemental analysis data. A ring closure reaction to thietane was performed using either Ia or Ib synthesized from cinnamyl alcohol.<sup>12,13</sup> Ib was preferable in the reaction to Ia since besides the fact that rearrangement of Ia to the ester resulted in low yield,<sup>15</sup> preparation of Ia starting from glycine and benzaldehyde was a time consuming process. The IR and NMR spectra of Ib showed identical patterns to those of Ia.

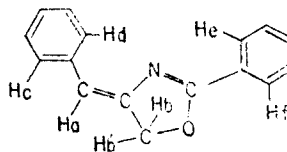


Scheme 1



IV

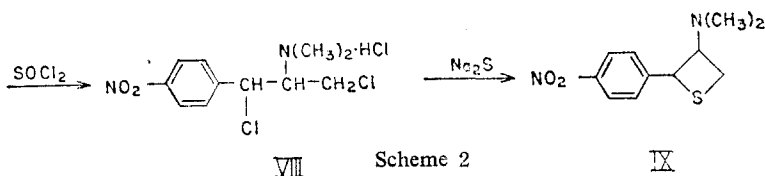
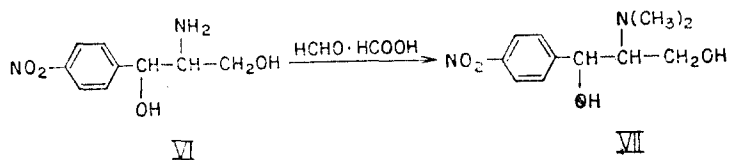
The reaction of *Ia* or *Ib* with  $\text{Na}_2\text{S}$  gave 3 spots by TLC. The major component at  $R_f$  0.7 showed absence of amide bands in the IR, which did not support the formation of a thietane. The yellow coloration denotes high conjugation of this compound. The elemental analysis data was consistent with either structure *IV* or *V*. The UV absorption of the major component showed three absorption maxima at 201 nm, 241 and 344. Absorption at 344 nm indicated the presence of extensive conjugated double bonds. According to the absorption data for oxazole derivatives,<sup>16)</sup> highly conjugated 2,4,5-triphenyloxazole showed absorption at 306 nm, whereas 2,4-diphenyloxazole and 2,5-diphenyloxazole showed absorption at 280 and 275 nm, respectively. Considering these oxazole examples and the fact that compound *V* is more extensively conjugated



V

than isomer *IV*, the UV data was considered to favor structure *V*. NMR data complied with structure *V*. Protons b of the ring are equivalent to the proton a. The peaks observed were a doublet at  $5.05 \delta$  (Hb) and triplet at  $5.73 \delta$  (Ha) with the long range coupling constant being 3 Hz. The lower field band at  $7.80 \delta$  was assigned to the c, d, e, and f protons, the deshielding of these ortho aromatic protons occurring because of the paramagnetic influence of nitrogen and oxygen atoms in the ring.

It appears therefore that the reaction of *Ia* or *Ib* with mild alkaline sodium sulfide favors formation of the oxazoline, *V* via an elimination reaction. The preferential formation of *V* might indicate that the elimination of 1-halo group occurs prior to ring formation. A similar reaction was reported by the



Scheme 2

conversion of  $\alpha$ -benzoylamino- $\beta$ -chloropropionic acid to 2-phenyl-4-carboxy oxazoline in sodium carbonate solution.<sup>17)</sup>

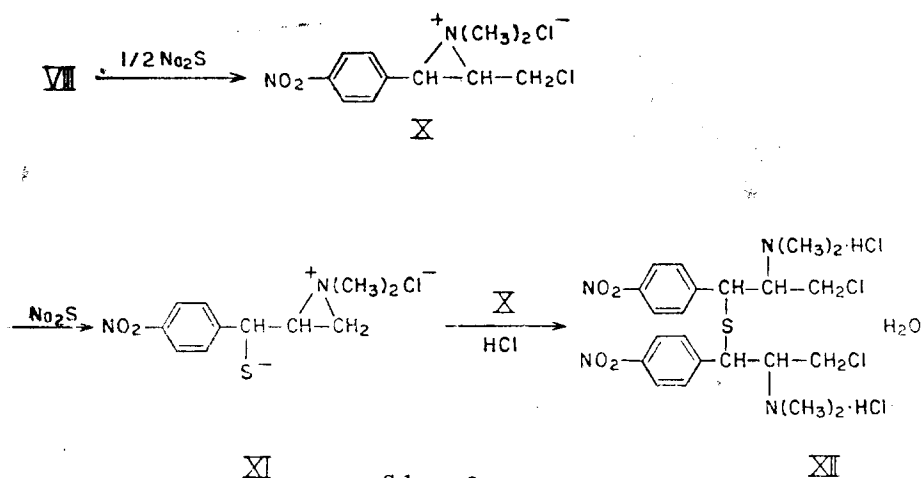
*Synthetic approach to 3-N, N-dimethylamino-2-p-nitrophenylthietane (IX)*

A further consideration of scheme 1 suggested that thietane synthesis might be possible if cyclization reaction of benzoylamido group could be avoided by using a tertiary amine compound as shown in Scheme 2. Dimethylamino compound, VII was prepared by the Clarke-Eschweiler method.<sup>18)</sup> In the NMR spectrum of VII a doublet for the benzylic proton at 4.5  $\delta$  indicated the threo form.

p-Nitro-N, N-dimethylphenylserinol (VII) was treated with an excess amount of DMF-SOCl<sub>2</sub> reagent to reduce racemization. The NMR of the compound isolated from the reaction of 1,3-dichloro compound, VIII (1 mole) with 2.25 mole (50 % excess) of sodium sulfide showed that the ratio of dimethylamino protons to phenyl protons was around 4:4. Possible elimination of the dimethylamino group during the reaction was further sup-

ported by the presence of olefinic protons at 6.40  $\delta$ . The major fractions of GC-MS were observed at retention times, 9.3 (A) and 11.3 minutes (B). The compound A contained dimethylamino group as indicated by a strong m/e 58 fragment. Fragment m/e 58 was not present in the mass spectrum of compound B. An assumption was made that the side products resulted from the elimination of the dimethylamino group and may be due to the alkaline condition of the reaction mixture and probably from the excess amount of sodium sulfide present. To determine the effects of the concentration of Na<sub>2</sub>S, a reaction was performed using 1 mole of Na<sub>2</sub>S to 1 mole of dichloro compound. The elemental analysis data and NMR spectrum of the isolated yellow material strongly suggested the formation of XII. A rational explanation for the formation of XII was attempted (Scheme 3).

The mass spectrum of the hydrochloride salt obtained by direct probe showed fragmentations at m/e 106 and 108 with the intensity ratio 3:1 (Cl isotope ratio), which implied the



Scheme 3

presence of  $N(CH_3)_2=CH-CH_2Cl$  resulting from the structure, *XII*. As shown in a report,<sup>19)</sup> exclusive formation of 3-hydroxy-2-phenylthietane is due to the favorable attack of sulfhydryl ion at C-1 carbon of 3-chloro-1-phenylpropylene oxide-1,2. By analogy, sulfhydryl ion would favor attack at the C-1 carbon of *X* to give *XI*. Besides this, the p-nitrophenyl group could also contribute to the exclusive formation of *XI* by favoring nucleophilic attack at the benzylic carbon atom. The formation of *XII* also indicated that nucleophilic attack of the sulfhydryl anion of *XI* on a second molecule of *X* is favorable compared to the intramolecular cyclization to form the thietane.

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