15,16-Dihydro-15α-hydroxy-14α,16-oxidovirescenol B Diacetate (9b). A stirring solution of 200 mg (0.375 mmol) of ketone **9c** in 5 mL of tetrahydrofuran under nitrogen at −5 °C was treated with lithium tri-*sec*-butylborohydride (1 M, 2.5 mL), and the mixture was allowed to reach room temperature and stirred for 3 h. After the addition of sodium hydroxide (3 M, 2 mL) and hydrogen peroxide solutions (30%, 2 mL), the mixture was stirred at room temperature for 0.5 h and then poured into ice-water. It was extracted with chloroform and the extract dried (Na_2SO_4) and evaporated. Chromatography of the residue (120 mg) on silica gel and elution with 19:1 chloroform–methanol gave 75 mg (38%) of the alcohol isomer **9b** (spectra given above).

Registry No. **5**, 11051-39-1; **6**, 72478-92-3; **7a**, isomer 1, 72478-93-4; **7a**, isomer 2, 72478-94-5; **7b**, isomer 1, 72522-14-6; **7b**, isomer 2, 72522-15-7; **8**, 68671-08-9; **9a**, 72478-95-6; **9b**, 72478-96-7; **9c**, 72478-97-8; **9d**, 72478-98-9.

Synthetic Applications and Mechanism of the Pyrolysis of Phenothiazine Carbamates

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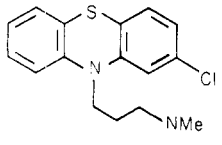
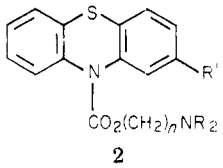
N-[(Dialkylamino)alkyl]phenothiazine derivatives such as chlorpromazine (**1**) have played an important role in the



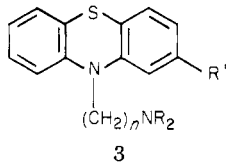
1

study and treatment of a variety of neurological disorders.[1] More recently, interest has developed in the phenothiazine psychotropic drugs as potential antitumor agents.[2] While a very large number of phenothiazines related to **1** have been prepared, nearly all have been synthesized by direct alkylation of the phenothiazine ring system with aminoalkyl halides.[3] We wish to report the results of our study of an alternative procedure starting with phenothiazine carbamates.

According to a German patent issued in 1956,[4] phenothiazine carbamates of type **2** (R = Et, R′ = H) decomposed upon distillation at 180–200 °C to afford the corresponding alkylated derivatives, **3**. The following year,



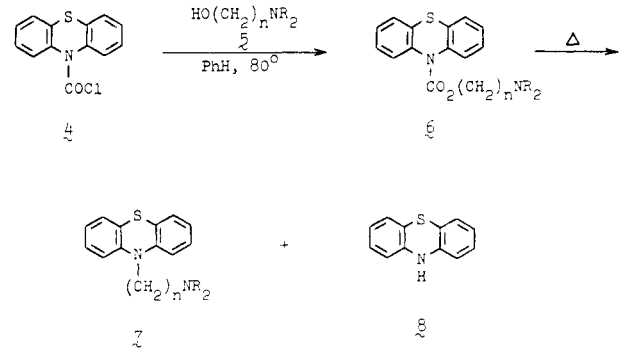
2



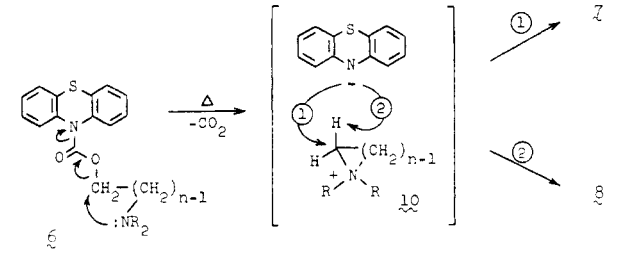
3

n = 2, 3

Scheme I

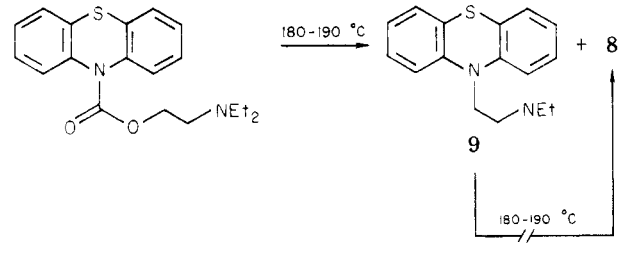


Scheme II



Schmitt and co-workers[5] reported that 3-substituted phenothiazine carbamates (**2**: R = Me, Et; R′ = COMe, COEt, OMe, etc.) could be pyrolyzed to their N-alkylated counterparts **3** in yields ranging from 45 to 80%.

To define the scope and synthetic utility of this reaction, we studied the carbamates **6a–i** listed in Table I. They were prepared from phenothiazine-10-carbonyl chloride (**4**) and either the appropriate amino alcohol or its sodium derivative (Scheme I). It was necessary to use the sodium aminoalkoxide in the preparation of **6h** and **6i**; the free amino alcohols were used in all other instances following literature procedures.[5] Pyrolysis experiments were carried out by heating the carbamates neat at about 10 °C above their decomposition temperatures for 30 min after cessation of gas evolution. Isolation of the products corresponding to **7** was readily accomplished by acid–base extractions. Invariably, the neutral layer from the workup contained phenothiazine (**8**) (Table I). We believe that the phenothiazine is not the result of thermal cracking of the N-alkylated products since, in the case of the pyrolysis of **6b**, no phenothiazine was formed when the product **9** was subjected to the same pyrolysis conditions.[6]



It was found that the ratio of the N-alkylated products to phenothiazine could be increased by employing carbamates purified via their hydrochloride salts. Thus, pyrolysis of "crude" (but devoid of phenothiazine) carbamate **6f** at 230 °C for 90 min afforded an oil whose NMR spectrum indicated a mixture of 84% N-alkylated product

(1) See, for example, A. Burger, Ed., "Medicinal Chemistry", 3rd ed., Wiley-Interscience, New York, 1970, pp 1428–37.

(2) J. S. Driscoll, N. R. Melnick, F. R. Quinn, N. Lomax, J. P. Davignon, R. Ing, B. J. Abbott, G. Congleton, and L. Dudeck, *Cancer Treat. Rep.*, **62**, 45 (1978), and references cited therein.

(3) For reviews on the chemistry of phenothiazine and its derivatives, see: (a) C. Bodea and I. Silberg, *Adv. Heterocycl. Chem.*, **9**, 321–460 (1968). (b) S. P. Massie, *Chem. Rev.*, **54**, 797 (1954). Recently the technique of phase-transfer catalysis has been reported to give improved yields for the direct alkylation of 2-chlorophenothiazines [J. Masse, *Synthesis*, 341 (1977)].

(4) H. H. Frederich, O. A. Grosskinsky, and A. Amann, German Offen. 939630 (1956); *Chem. Abstr.*, **53**, 8172e (1959).

(5) J. Schmitt, J. Biotard, P. Comoy, A. Hallot, and M. Suquet, *Bull. Soc. Chim. Fr.*, 938 (1957); J. Schmitt, A. Hallot, P. Comoy, M. Suquet, R. Fallard, and J. Boitard, *ibid.*, 1474 (1957).

(6) At higher temperatures, however, compound **9** does decompose to produce phenothiazine: heating at 260 °C for 2 h resulted in a 33% yield of **8** (58% of the starting material was recovered).

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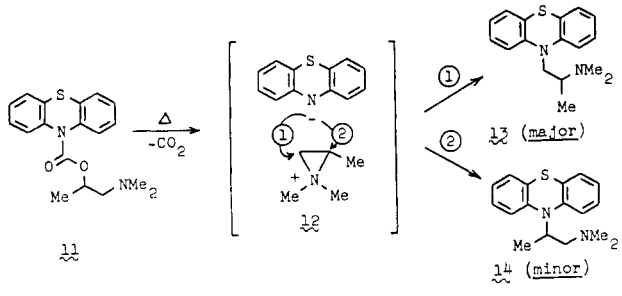
Table I. Pyrolysis of Phenothiazine Carbamates (6)

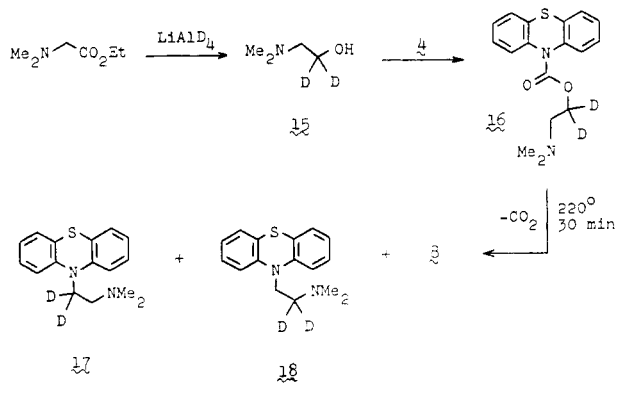
compd	n	R	mp,[k,l] °C	pyrolysis temp, °C	composn,[a] mol % 7	composn,[a] mol % 8	matl bal,[b] %
6a	2	Me	213-214 dec[f]	220	94	6	87
6b	2	Et	165-166 dec[g]	180-190	91	9	96
6c	2	Pr	207-208 dec	180-190	74	26	90
6d	2		218 dec[h]	190-205	71	19	100[c]
6e	3	Me	192-193 dec[i]	200-205	71	29	88
6f	3	Et	195-197 dec	190-200	97	3	69
6g	3		164.5-167 dec[j]	215-225	96	4	65
6h	4	Et	172 dec	200	0	89[d]	e
6i	5	Et	158 dec	170-210	0	83[d]	e

[a] Pyrolysate composition based on the ratio of the weight of one of the isolated components (7 or 8) to the total amount of material isolated (7 + 8). [b] Material balance of isolated components. Comparison of the isolated weight of 7 + 8 to the theoretical weight of the crude pyrolysate (based on the pyrolysate composition). [c] Recovered 10% starting material; data obtained by integration of the NMR spectrum of the crude pyrolysate. [d] Yield of isolated 8. [e] See text. [f] Lit.[14] mp 212-213. [g] Lit.[14] mp 165-166 dec. [h] Lit.[14] mp 213-214 dec. [i] Lit.[15] mp 192-193 dec. [j] Free base, mp 95.5-97 °C. [k] Satisfactory analytical data (±0.4% for C, H, and N) were reported for new hydrochlorides. [l] Melting point of the carbamate hydrochloride.

Scheme III



Scheme IV



(7, n = 3, R = Et) and 16% phenothiazine. However, when the carbamate was purified by conversion to its hydrochloride salt, recrystallization of the salt from ethanol, and reconversion to the free base, pyrolysis under the same conditions produced a mixture consisting of 97% 7 (n = 3, R = Et) and 3% phenothiazine.

A priori, one can postulate several mechanisms for the formation of N-alkylated products 7 and phenothiazine (8) from the pyrolysis of carbamates 6. Perhaps the most likely one involves the achimerically assisted loss of carbon dioxide to produce a cyclic ammonium ion 10[7] and the phenothiazine anion, as outlined in Scheme II. The anion could react with 10 either as a nucleophile (path 1) to afford the N-alkylated phenothiazine 7 or as a base (path 2) to produce phenothiazine (8). Strong evidence for this mechanism was provided by the experiments outlined in Schemes III and IV. According to the first, pyrolysis of compound 11 at 180–220 °C produced a mixture of isomers 13 and 14 in the approximate ratio of 2 to 1 (based on the NMR spectrum of the crude pyrolysate after removal of phenothiazine). This result suggests the intermediacy of the unsymmetrical aziridinium ion 12, which suffers preferential S_N2 displacement[8] by the phenothiazine anion at its less hindered annular carbon atom (path 1, Scheme III). Charpentier[9] obtained a similar result upon alkylating phenothiazine with 2-chloro-1-(dimethylamino)propane in the presence of sodium hydride. In this report, the major product isolated and identified was the phenothiazine 13 (having the rearranged side chain), apparently derived from the same aziridinium species 12.

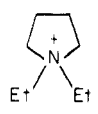
A second experiment which provided evidence for the mechanism proposed in Scheme II consisted of pyrolyzing the deuterated carbamate 16, prepared as shown in Scheme IV and purified via its hydrochloride salt (vide supra). In addition to the presence of phenothiazine (8, 22%), the NMR spectrum of the crude pyrolysate indicated an equimolar ratio[10] of the labeled amines 17 and 18. This isomer distribution strongly suggests indiscriminate[10] attack by the phenothiazine anion at both annular carbon atoms of an aziridinium ion intermediate. The number of methylene units in the carbamate side chain is important for the extrusion–alkylation pathway since the two carbamates having more than three methylene groups, namely, compounds 6h (n = 4) and 6i (n = 5), produced no detectable quantities of the corresponding N-alkylated phenothiazines upon pyrolysis. Instead, the major product in each case was phenothiazine itself, accompanied by small amounts of N-ethylpyrrolidine and N-ethylpiperidine, respectively. It is likely that the proposed intermediates 19 and 20 (i.e., intermediate 10 for which n = 4 or 5 and R = Et) are more stable toward nucleophilic attack than their three- and four-membered counterparts. Since N-ethylphenothiazine was not de-

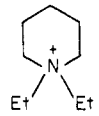
(7) Indeed, this kind of intermediate has been invoked for related rearrangements of amidones. See ref 3b.

(8) O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines", Academic Press, New York, 1969, p 207.

(9) P. Charpentier, French Patent 986718 (1951); *Chem. Abstr.*, 50, 7880g (1956).

(10) The value determined by integration of the methylene singlets is actually 1.00:1.07 17/18. Although an isotope effect is anticipated as a consequence of this mechanism, the sensitivity of the NMR experiment is such that the apparent deviation from an (exactly) equal isomer distribution cannot be interpreted as a measure of this effect.


19


20

tected in the pyrolysates of **6h** and **6i**, it is probable that the proposed intermediates **19** and **20** decompose by loss of ethylene.

It would seem, then, that the synthesis of phenothiazine derivatives of type **7** by pyrolysis of the carbamates **6** is efficient for compounds with unsubstituted (or symmetrically substituted) aminoalkyl side chains for which n = 2 or 3.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on a 60-MHz Varian Associates A-60A spectrometer at a sweep width of 500 Hz. Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane standard. Thin-layer chromatography was accomplished with Eastman silica gel Chromagram sheets with fluorescent indicator. Results were visualized by exposure to ultraviolet light or iodine vapor. The amino alcohols **5** were either used as purchased or prepared by literature methods. Anhdyrous solvents were generally prepared by drying over 4A molecular sieves.

General Procedure for the Preparation and Purification of (Dialkylamino)alkyl Phenothiazine-10-carboxylates (6). Carbamates **6a–g** in Table I were obtained by adaptation of a published procedure.[5] Typically, the reaction between phenothiazine-10-carbonyl chloride (**4**) and 2 molar equiv of the appropriate amino alcohol was carried out and worked up in the manner described for the deuterated carbamate **16**. The hydrochlorides of the carbamates **6a**, **6b**, and **6d–f** are known, and the melting points of our hydrochlorides corresponded well with the literature values. The NMR spectra of the carbamate bases were also satisfactory.

Carbamates **6h** and **6i** could not be obtained in pure form by the above procedure. Instead they were prepared from the reaction between the sodium derivative of the amino alcohol (prepared by refluxing a mixture of the amino alcohol and 1.1 equiv of sodium hydride in toluene for 3 h) and **4**. After the cooled toluene solution was washed with water, it was concentrated to dryness. The residue was dissolved in methylene chloride, and the solution was shaken once with a 5% hydrochloric acid solution. When the methylene chloride solution was evaporated to dryness and the residue triturated in ether, the carbamate hydrochloride became crystalline. The hydrochlorides were recrystallized from acetone–ether.

The free carbamates **6** used in the pyrolysis studies were obtained from the respective carbamate hydrochlorides essentially by the procedure used in the preparation of **16**.

1-[2-(Dimethylamino)ethyl-*1,1-d*$_2$] Phenothiazine-10-carboxylate (16). A solution of phenothiazine-10-carbonyl chloride (**4**; 1.04 g, 4.0 mmol) and 2-(dimethylamino)ethan-*1,1-d*$_2$-ol[11] (**15**, 0.71 g, 8.0 mmol) in dry benzene (10 mL) was heated at reflux for 12 h. The solution was allowed to cool to room temperature and washed with water. The separated aqueous layer was washed with benzene, and the combined benzene layers were washed with brine (4 × 25 mL), treated with anhydrous $MgSO_4$ and charcoal, and filtered. The filtrate was concentrated in vacuo to produce crude **16** (1.09 g, 87%) as a viscous amber oil.

Compound **16** (0.89 g, 2.8 mmol) was purified by dissolving it in anhydrous ether (10 mL) in a test tube equipped with a magnetic stirrer, chilling the solution in ice, and bubbling gaseous HCl into the solution. The resulting pale green precipitate was filtered and washed with ether to produce the crude hydrochloride salt of **16** as a pale green solid (mp 213–214 °C). The solid was dissolved in hot, absolute ethanol (8 mL) to which charcoal had been added, and the mixture was filtered hot. When the solution cooled, the purified HCl salt crystallized. It was collected by filtration, washed with cold EtOH–ether (1:1) and then ether, and dried. The white salt (0.73 g) decomposed sharply at 215.5 °C. Recovery of the free base **16** was effected by dissolving the salt in water (5 mL) and treating the resulting solution with 5% NaOH solution (5 mL) at 0 °C. The basified mixture was extracted into ether, and the combined extracts were washed with brine (5 × 25 mL), treated with anhydrous $MgSO_4$ and charcoal, and filtered through Celite. The filtrate was concentrated in vacuo to produce 1-[2-(dimethylamino)ethyl-*1,1-d*$_2$] phenothiazine-10-carboxylate (**16**) as a clear, colorless oil (0.52 g, 58% recovery on purification): NMR (CCl_4) δ 2.10 (s, 6 H, CH_3), 2.41 (s, 2 H, CH_2), 6.8–7.7 (m, ca. 8 H, aromatic H); MS (15 eV) m/e 316 (M^+), 243, 199, 167, 75, 74 (base peak), 73, 58. Anal. Calcd for $C_{17}H_{17}D_2N_2O_2SCl$: C, 57.86; H, 5.99; N, 7.94. Found: C, 57.88; H, 5.95; N, 8.09.

General Procedure for the Pyrolysis of Carbamates 6. The purified carbamates **6** were placed in a tared round-bottomed flask affixed with a drying tube, and the flask was inserted into an oil bath at such a depth that the level of the oil was ca. 1 cm above the level of the sample. The bath was heated slowly until the sample started bubbling and was maintained at 10–15 °C above this temperature for 30 min after CO_2 evolution ceased. The flask was then withdrawn from the bath and allowed to cool to room temperature, and the weight of its contents was determined. The pyrolysate was assayed by TLC and NMR spectral analysis (vide infra). The N-alkylated products (**7**) of this reaction could be separated from any phenothiazine (**8**) by acid–base extraction.

Pyrolysis of 2-[2-(Dimethylamino)propyl] Phenothiazine-10-carboxylate (11). The carbamate **11**[12] (2.36 g, 7.20 mmol) was pyrolyzed at 180–220 °C for 2.5 h and allowed to cool to room temperature. Phenothiazine (**8**, 0.84 g) was separated by acid–base workup. The acidic layer was shown (by NMR spectral analysis) to contain the regioisomeric phenothiazines **13** and **14** in a ratio of ca. 2:1 (total 1.30 g). The mixture could be separated by column chromatography [silica gel; benzene–ether (9:1) for **14** (148 mg) and then ether–EtOAc (1:1) for **13** (454 mg)].

Pyrolysis of 1-[2-(Dimethylamino)ethyl-*1,1-d*$_2$] Phenothiazine-10-carboxylate (16). The purified carbamate **16** (0.42 g, 13 mmol) was dispensed into a 25-mL round-bottomed flask, and the flask was immersed in an oil bath as described above. Heating at 220 °C for 30 min produced a clear, amber oil (0.34 g). Careful integration of the NMR spectrum of the oil indicated it to be a mixture of deuterated amines **17** and **18** and phenothiazine (**8**) in a molar ratio of 1.0:1.1:0.6, respectively.[13]

Registry No. **4**, 18956-87-1; **5a**, 108-01-0; **5b**, 100-37-8; **5c**, 3238-75-3; **5d**, 622-40-2; **5e**, 3179-63-3; **5f**, 622-93-5; **5g**, 4441-30-9; **5h**, 2683-56-9; **5i**, 2683-57-0; **6a**, 31066-28-1; **6a**·HCl, 72331-90-9; **6b**, 82-00-8; **6b**·HCl, 298-51-1; **6c**, 72331-91-0; **6c**·HCl, 72331-92-1; **6d**, 72331-93-2; **6d**·HCl, 72331-94-3; **6e**, 72331-95-4; **6e**·HCl, 72331-96-5; **6f**, 72331-97-6; **6f**·HCl, 72331-98-7; **6g**, 72331-99-8; **6g**·HCl, 72332-00-4; **6h**, 72332-01-5; **6h**·HCl, 72332-02-6; **6i**, 72332-03-7; **6i**·HCl, 72332-04-8; **7a**, 522-24-7; **7b**, 60-91-3; **7c**, 72332-05-9; **7d**, 4734-59-2; **7e**, 58-40-2; **7f**, 47205-14-1; **7g**, 4935-70-0; **8**, 92-84-2; **11**, 72332-06-0; **13**, 60-87-7; **14**, 303-14-0; **15**, 72332-07-1; **16**, 72346-79-3; **16**·HCl, 72332-08-2; **17**, 72332-09-3; **18**, 72332-10-6.

(11) The deuterated alcohol **15** was prepared by reduction of ethyl (dimethylamino)acetate [M. Viscontini and J. Meier, *Helv. Chim. Acta*, **33**, 1773 (1950); *Chem. Abstr.*, **45**, 3802*f* (1951)] with lithium aluminum deuteride in anhydrous ether. Quenching with butylcarbitol followed by distillation produced **15** as a clear, colorless liquid in 31% yield [NMR (CCl_4) δ 2.20 (s, 6 H, CH_3), 2.38 (s, 2 H, CH_2), 4.60 (s, ca. 1 H, OH)].

(12) Prepared according to the general procedure from phenothiazine-10-carbonyl chloride (**4**) and 1-(dimethylamino)-2-propanol.

(13) The ratio of **17** to **18** in the pyrolysate was determined from the integrated areas under the methylene singlets at δ 2.60 (for **17**) and 3.88 (for **18**). Assignments were made on the basis of corresponding resonances in the NMR spectrum of the nondeuterated analogue (**7**, n = 2, R = Me). All other aspects of the NMR spectra were identical. The presence of phenothiazine in the crude pyrolysate was ascertained by TLC analysis. The amount of phenothiazine was calculated by integrating over the entire aromatic region of the NMR spectrum and allowing for compounds **17** and **18**.

(14) A. W. Weston, R. W. DeNet, and R. J. Michaels, Jr., *J. Am. Chem. Soc.*, **75**, 4006 (1953).

(15) H. Friederich and J. Bindig, British Patent 848737 (1960); *Chem. Abstr.*, **55**, 7445*g* (1961).