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A Rearrangement in the Pyrrolidine-Piperidine Series during Thermal Decomposition of N-Alkyl-3-piperidyl Phenothiazine-10-carboxylates

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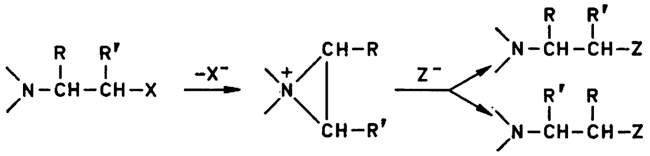
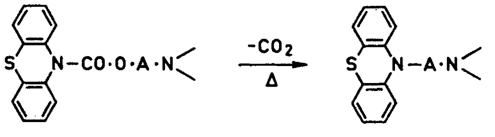
A series of N-alkyl-3-piperidyl phenothiazine-10-carboxylates have been submitted to thermal decarboxylation. The product obtained is invariably a 10-(N-alkyl-2-pyrrolidinylmethyl)-phenothiazine. A contraction of the piperidine ring to a pyrrolidine ring has consequently taken place during the reaction.

The preparation of 10-dialkylaminoalkylphenothiazines is usually carried out by treatment of a phenothiazine with a dialkylaminoalkyl halogenide in the presence of a strong base such as sodium amide. This procedure may, however, lead to reaction products of uncertain structure. For instance, aminoalkylations with halogeno compounds having a nitrogen atom in the β-position to the halogen are supposed to proceed *via* a cyclic immonium ion, and if the α- and β-carbon atoms carry different substituents, the immonium ion may react with a nucleophilic agent (Z^-) to give one of two possible isomeric products or a mixture of both, depending on which of the carbon atoms is attacked by the nucleophilic agent.[1,2]



Rearrangements of this type have been reported to occur also when the anion of phenothiazine serves as the nucleophile in this reaction.[3-6] If the nitrogen atom and part of the alkylene chain together form a heterocyclic ring, possibilities evidently exist for ring contraction or expansion, which also has been reported.[7-10]

Another useful method for obtaining 10-aminoalkylphenothiazines consists in the thermal decarboxylation of aminoalkyl esters of phenothiazine-10-carboxylic acids.[11,12]



A = alkylene

Very little is known about the mechanism of this decarboxylation reaction. Rearrangements in the aminoalkyl moiety analogous to those observed in the aminoalkylation reaction have been reported in some cases,[13,14] but the method seems generally to have been used uncritically, without sufficiently investigating the structures of the products.

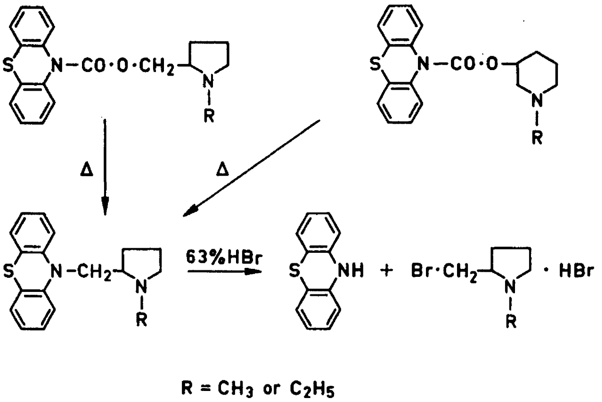
In a paper from these laboratories some years ago, the syntheses of twelve N-alkyl-3-piperidyl esters of phenothiazine-10-carboxylic acids were reported,[15] and we consequently deemed it of interest to study the structures of the compounds obtained upon decarboxylation of these esters.

When the esters were heated either alone or in *o*-dichlorobenzene at 200—210°, decarboxylation occurred and 10-aminoalkylphenothiazines were obtained. However, it soon became evident that the reaction was not quite so straight-forward. When the N-methyl- and N-ethyl-2-pyrrolidinylmethyl esters of phenothiazine-10-carboxylic acid were prepared and submitted to the decarboxylation reaction, they gave the same products as the N-methyl- and N-ethyl-3-piperidyl esters. Accordingly, rearrangement must have occurred during the decarboxylation of one of the ester types.

Determination of the structures of the products was therefore necessary. It has been shown recently that N-alkyl-2-pyrrolidinylmethyl esters of carboxylic acids may undergo rearrangement to the corresponding N-alkyl-3-piperidyl esters on distillation,[10,16] and it was therefore reasonable to suppose that a similar rearrangement had occurred also with the esters of phenothiazine-10-carboxylic acid. However, degradation of the products with 63 % hydrobromic acid yielded phenothiazine and a compound which upon reduction yielded not the expected N-alkylpiperidine but N-methyl- and N-ethyl-2-methylpyrrolidine, respectively. The degradation products were found to be identical with an authentic sample of the appropriate N-alkyl-2-bromomethylpyrrolidine hydrobromide. It could be shown that the N-methyl- and N-ethyl-3-bromopiperidine hydrobromides are quite stable under the conditions of the degradation, hence the pyrrolidine ring clearly is present in the material subjected to the degradation procedure.

The decarboxylated products from all the N-alkyl-3-piperidyl esters were degraded in the same way, and all the products were found to be N-alkylated 2-bromomethylpyrrolidine hydrobromides.

It may be noted that the hydrobromides of the N-alkyl-3-bromopiperidines and the N-alkyl-2-bromomethylpyrrolidines are distinguishable on the basis



of their infrared spectra, the former showing C-Br stretching absorption at 710—715 and the latter at 670—675 cm^{-1}.

The fact that 10-(N-alkyl-2-pyrrolidinylmethyl)-phenothiazines are formed upon decarboxylation of N-alkyl-3-piperidyl esters of phenothiazine 10-carboxylic acids emphasises the need to determine the structure of the 10-aminoalkylphenothiazines obtained by the decarboxylation of the aminoalkyl esters of phenothiazine-10-carboxylic acids in general.

The 10-(N-alkyl-2-pyrrolidinylmethyl)-phenothiazines were tested for antihistaminic and anticholinergic effects, using diphenhydramine as standard. The antihistaminic effect ranged from 0.04—0.4 relative to that of the standard, compounds I and II being the most active. The anticholinergic activity ranged from 0.7—1.4 times that of diphenhydramine, compounds I and II being the most active also in this test. Some compounds, including the chloro derivatives IX and X, were compared with chloropromazine with respect to their ability to block conditioned reflex in rats. However, they had little or no effect in this test.

EXPERIMENTAL

Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Infrared spectra were run on a Perkin-Elmer 237 spectrophotometer with grating monochromator using KBr discs. Ultraviolet spectra were recorded by means of Bausch & Lomb Spectronic 505 spectrophotometer. Microanalyses were carried out in the laboratories of Dr. A. Bernhardt, Mülheim, Germany.

The amino alcohols used were all racemic mixtures. *N-Methyl- and N-ethyl-2-hydroxymethylpyrrolidine* were obtained from Beecham Research Laboratories, Betchworth, England. The latter compound was also prepared from DL-proline (Fluka) through acetylation and reduction with lithium aluminium hydride essentially by a method later described in the literature.[17] *N-Methyl- and N-ethyl-3-hydroxypiperidine* were obtained from Lakeside Laboratories, Milwaukee, U.S.A. The *N-methyl- and N-ethyl-3-piperidyl phenothiazine-10-carboxylates* were prepared as described by Dahlbom and Björkqvist.[15]

N-Methyl-2-pyrrolidinylmethyl phenothiazine-10-carboxylate. A mixture of phenothiazine-10-carbonyl chloride (5.24 g, 0.02 mole), N-methyl-2-pyrrolidinylmethanol (2.32 g, 0.02 mole), triethylamine (4.2 ml, *d* 0.72), and toluene (40 ml) was refluxed under stirring for 5 h. After cooling, the triethylamine hydrochloride was removed by filtration, the toluene solution washed with water and then extracted with 1 N hydrochloric acid.

The extract was made alkaline with 1 N sodium hydroxide, whereupon the reaction product separated in crystalline form. Recrystallisation from light petroleum (b.p. 40—60°) yielded crystals (4.0 g, 59 %) of m.p. 81.5—82.5°. (Found: C 66.8; H 6.03; N 8.01. Calc. for $C_{19}H_{20}N_2O_2S$: C 67.0; H 5.92; N 8.23).

Addition of ethereal hydrogen chloride to a solution of the base in ether afforded the *hydrochloride*, m.p. 192—193° (from ethanol—ether). The infrared spectrum showed an ester absorption band at 1720 cm^{-1}. The ultraviolet spectrum in ethanol exhibited the characteristic features [18] of an aminoalkyl ester of phenothiazine-10-carboxylic acid with maxima at 226 mμ (log ε 4.32) and at 254 mμ (log ε 3.86), and a shoulder at 268 mμ (log ε 3.65). It was not possible to obtain a satisfactory elemental analysis for this salt.

N-Ethyl-2-pyrrolidinylmethyl phenothiazine-10-carboxylate was obtained similarly in 66 % yield, m.p. 59—60° (from light petroleum). (Found: C 67.6; H 6.33; N 8.04. Calc. for $C_{20}H_{22}N_2O_2S$: C 67.8; H 6.26; N 7.90).

The *hydrochloride* had m.p. 195—196° (from ethanol—ether), ν_{max} (KBr) 1730 cm^{-1}, λ_{max} (EtOH) 226 mμ (log ε 4.31), 254 mμ (log ε 3.89) and 270 mμ sh. (log ε 3.69). (Found: N 7.13. Calc. for $C_{20}H_{22}N_2O_2S \cdot HCl$: N 7.17). It was not possible to obtain a satisfactory carbon analysis for this salt.

N-Methyl-3-bromopiperidine hydrobromide. N-Methyl-3-hydroxypiperidine (3.2 g, 0.028 mole) was heated with 63 % hydrobromic acid (20 ml, *d* 1.78) at 150° for 10 h in a sealed glass-tube. The solution was evaporated under vacuum and the last traces of water were removed by repeated evaporations with toluene and ethanol. The resulting reddish-brown crystalline mass was dissolved in ethanol, decolourised with carbon and filtered through a Celite pad. On addition of dry ether a white product was obtained, which was recrystallised from ethanol—ether affording crystals (2.7 g, 38 %) of m.p. 132—133°, ν_{max} (KBr) 715 cm^{-1} (C—Br). (Found: C 28.0; H 5.01; Br 61.7; N 5.35. Calc. for $C_6H_{12}BrN \cdot HBr$: C 27.8; H 5.06; Br 61.7; N 5.41).

N-Ethyl-3-bromopiperidine hydrobromide was prepared similarly in 54 % yield, m.p. 185—186.5° (from ethanol—ether), ν_{max} (KBr) 710 cm^{-1} (C—Br). (Found: C 30.8; H 5.95; Br 58.3; N 5.30. Calc. for $C_7H_{14}BrN \cdot HBr$: C 30.8; H 5.54; Br 58.5; N 5.13).

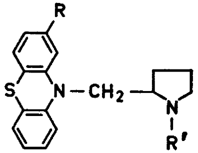
N-Methyl-2-bromomethylpyrrolidine hydrobromide. Treatment of N-methyl-2-hydroxymethylpyrrolidine with 63 % hydrobromic acid afforded this compound in 61 % yield, m.p. 151—152° (from ethanol—ether), ν_{max} (KBr) 675 cm^{-1} (C—Br). (Found: C 27.8; H 5.53; Br 61.4; N 5.34. Calc. for $C_6H_{12}BrN \cdot HBr$: C 27.8; H 5.06; Br 61.7; N 5.41). This compound was also prepared by an alternative method: N-Methyl-2-hydroxymethylpyrrolidine hydrobromide (9.8 g) was refluxed under stirring with thionyl bromide (4.5 ml, *d* 2.7) in toluene (50 ml) for 3 h. The toluene was decanted from the crystalline mass formed during the reaction, and the product was crystallised from ethanol—dioxane, yielding crystals (5.5 g, 42 %) of m.p. 150.5—152°, identical (mixed m.p., infrared spectrum) with the product obtained by the previous method.

N-Ethyl-2-bromomethylpyrrolidine hydrobromide was obtained in 91 % yield from N-ethyl-2-hydroxymethylpyrrolidine and 63 % hydrobromic acid, m.p. 174—175.5° (from ethanol—ether), ν_{max} (KBr) 670 cm^{-1} (C—Br). (Found: C 30.8; H 5.50; Br 58.75; N 5.06. Calc. for $C_7H_{14}BrN \cdot HBr$: C 30.8; H 5.54; Br 58.5; N 5.13). After completion of this work, this compound was reported,[17] m.p. 165—166°.

Thermal decomposition of N-alkyl-3-piperidyl- and N-alkyl-2-pyrrolidinylmethyl phenothiazine-10-carboxylates. A. The appropriate N-alkyl-3-piperidyl ester (usually 0.02 mole of the free base) was heated in an oil bath at 200—210° at a pressure of 10 mm Hg until evolution of carbon dioxide had ceased (4—6 h). The residual brown oil was dissolved in ether and the solution filtered through a short column of aluminium oxide. The reaction product was precipitated as a salt by the addition of the appropriate acid dissolved in ether. This method was used for the preparation of compounds I—VI and IX (Table 1).

B. Alternatively, a high-boiling solvent was used in the decarboxylation reaction. The amino ester (0.02 mole) was dissolved in *o*-dichlorobenzene (50 ml) and heated at 200° (reflux) until evolution of carbon dioxide had ceased (6—20 h). After cooling, the solution was diluted with ether (100 ml) and extracted thoroughly with 0.5 N hydrochloric acid. The acid extract was made alkaline with dilute sodium hydroxide and the liberated base was extracted with ether. The ether extract was filtered through aluminium oxide, and the reaction product isolated as a salt as described above. This procedure was used for compounds VII, VIII and X—XII and in the decarboxylation of N-methyl- and N-ethyl-2-pyrrolidinylmethyl phenothiazine-10-carboxylate.

Table 1. 10-(N-Alkyl-2-pyrrolidinylmethyl)-phenothiazines.



No.	R	R′	Yield %[a]	Salt	Recryst. solvent[b]	M.p. °C	Formula	Calc. %			Found %		
								C	H	N	C	H	N
I	H	CH_3	94	Hydrochloride	E—Et	234—236(dec.)	$C_{18}H_{20}N_2S·HCl$	64.9	6.36	8.42	64.9	6.35	8.25
II	H	C_2H_5	78	Hydrochloride	E—Et	215—217	$C_{19}H_{22}N_2S·HCl$	65.8	6.68	8.08	65.9	6.65	7.86
III	CH_3	CH_3	53	Maleate	E—Et	163—165	$C_{19}H_{22}N_2S·C_4H_4O_4$	64.8	6.15	6.57	64.4	5.76	6.67
				Oxalate	Me	208—210(dec.)	$C_{19}H_{22}N_2S·C_2H_2O_4$	63.0	6.04	7.00	62.8	6.07	6.75
IV	CH_3	C_2H_5	70	Maleate	E—Et	171—173	$C_{20}H_{24}N_2S·C_4H_4O_4$	65.4	6.41	6.36	65.1	6.45	6.61
				Oxalate	Me—Et	178—180(dec.)	$C_{20}H_{24}N_2S·C_2H_2O_4$	63.7	6.32	6.76	63.9	6.12	6.73
V	C_2H_5	CH_3	35	Oxalate	Me—Et	181—183(dec.)	$C_{20}H_{24}N_2S·C_2H_2O_4$	63.7	6.32	6.76	64.1	6.42	6.59
VI	C_2H_5	C_2H_5	66	Hydrochloride	E—Et	173—174	$C_{21}H_{26}N_2S·HCl$	67.3	7.26	7.47	67.0	7.26	7.36
VII	CH_3O	CH_3	64	Hydrochloride	Ac—Et	196—198	$C_{19}H_{22}N_2OS·HCl$	62.9	6.39	7.72	62.5	6.20	7.82
VIII	CH_3O	C_2H_5	44	Hydrochloride	Ac	192—194	$C_{20}H_{24}N_2OS·HCl$	63.7	6.69	7.43	63.8	6.42	7.61
				Oxalate	Me—Et	195—196(dec.)	$C_{20}H_{24}N_2OS·C_2H_2O_4$	61.4	6.09	6.51	61.2	6.09	6.24
IX	Cl	CH_3	59	Hydrochloride	E—Et	208—209	$C_{18}H_{19}ClN_2S·HCl$	58.9	5.49	7.63	58.8	5.41	7.33
				Oxalate	Me—Et	227—228(dec.)	$C_{18}H_{19}ClN_2S·C_2H_2O_4$	57.1	5.03	6.66	57.0	4.88	6.36
X	Cl	C_2H_5	79	Hydrochloride	E—Et	187—189	$C_{19}H_{21}ClN_2S·HCl$	59.8	5.81	7.34	59.7	5.95	7.47
				Oxalate	Me—Et	194—196(dec.)	$C_{19}H_{21}ClN_2S·C_2H_2O_4$	58.0	5.33	6.44	57.9	5.05	6.17
XI	CH_3CO	CH_3	22	Hydrochloride	E—Et	225—227(dec.)	$C_{20}H_{22}N_2OS·HCl$	64.1	6.18	7.47	64.5	6.40	7.09
XII	CH_3CO	C_2H_5	32	Hydrochloride	E—Et	232—233(dec.)	$C_{21}H_{24}N_2OS·HCl$	64.8	6.48	7.20	64.7	6.34	7.14

[a] Calc. on recrystallised products.

[b] E, ethanol; Et, ether; Me, methanol; Ac, acetone.

The products obtained from these two last-mentioned esters were in every respect identical (mixed m.p., infrared spectra) with those obtained from the corresponding N-methyl- and N-ethyl-3-piperidyl esters, respectively.

Physical constants and analytical data for the products are collected in Table 1.

Degradation of compounds I—XII. The following procedure is illustrative. Compound I, (10.0 g), obtained by decarboxylation of N-methyl-3-piperidyl phenothiazine-10-carboxylate, was dissolved in water (20 ml) and refluxed under stirring with 63 % hydrobromic acid (150 ml) for 1.5 h. After cooling, water (250 ml) was added, the precipitated phenothiazine was filtered off and the solution extracted with chloroform (4 × 50 ml) to remove the residual phenothiazine. The aqueous solution was evaporated under vacuum, and the last traces of water were removed by repeated evaporations with toluene and ethanol. The brown residue was dissolved in ethanol, decolourised with carbon and filtered through a Celite pad. Evaporation of the ethanol yielded a light yellow crystalline mass which after recrystallisation from ethanol—ether afforded a product (2.8 g, 38 %) of m.p. 150—151°, $\nu_{\max}$ (KBr) 675 cm^{-1}. It was identical in every respect (mixed m.p., infrared spectrum) with *N-methyl-2-bromomethylpyrrolidine hydrobromide*, prepared as described above from N-methyl-2-hydroxymethylpyrrolidine.

Treatment of II in the same way afforded a product in 74 % yield of m.p. 172—173°, $\nu_{\max}$ (KBr) 670 cm^{-1}, which was identical with *N-ethyl-2-bromomethylpyrrolidine hydrobromide* prepared from N-ethyl-2-hydroxymethylpyrrolidine.

Analogous degradation experiments with compounds III—XII afforded in every case N-methyl- or N-ethyl-2-bromomethylpyrrolidine hydrobromide in 50—75 % yield. The phenothiazine moiety of the molecule was recovered in almost quantitative yield. On degradation of VII and VIII the 2-methoxy group in the phenothiazine nucleus was also split off, yielding 2-hydroxyphenothiazine.

Reduction of N-methyl- and N-ethyl-2-bromomethylpyrrolidine hydrobromide with lithium aluminium hydride. N-Methyl-2-bromomethylpyrrolidine hydrobromide (2.0 g), obtained by degradation of compound I with 63 % HBr, was shaken with lithium aluminium hydride (0.4 g) in ether (50 ml) for 3 h. After filtration, a saturated solution of picric acid in ether was added, affording N-methyl-2-methylpyrrolidinium picrate, m.p. 235—237° (from ethanol), lit.[19] 233.5°.

Treatment of the N-ethyl analogue, obtained by degradation of compound II, in the same way yielded N-ethyl-2-methylpyrrolidinium picrate, m.p. 192.5—193.5° (from ethanol), lit.[20] 192—193.5°.

Stability of N-ethyl-3-bromopiperidine hydrobromide under the degradation conditions. N-Ethyl-3-bromopiperidine hydrobromide (2.0 g) was refluxed with 63 % hydrobromic acid (40 ml) for 2 h. Working up in the usual way afforded the unchanged starting material in 75 % yield.

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