9: MS (70 eV): $C_{11}H_{13}DO$ m/e 163 (24 %), 148 (28 %), 145 (81 %, *128.99), 135 (20 %), 130 (100 %, *116.55), 129 (36 %, *114.77), 128 (6 %), 120 (56 %), 118 (19 %), 117 (18 %), 116 (24 %), 115 (38 %), 106 (20 %), 105 (81 %), 104 (62 %), 92 (34 %), 91 (38 %).
^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.30 (s; 3H, -CD(OH)-$C\underline{H}_3$), 1.99 (s; austauschbar mit D_2O, 1H, -OH), 2.30 (s; 3H, Ø-CH_3), 6.04, 6.70 (AB; J = 16 Hz, 2H, -CH=CH-), 6.95–7.51 (m; 4H, Ø-H).

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Synthesis of Some Metabolites of Promethazine

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The synthesis of the *N*-methylnitrone **11**, *N*-monoalkylhydroxylamine **9**, *N,N*-dialkylhydroxylamine **10**, oxime **8** and other potential metabolites of promethazine (**1**) and of its *N*-dealkyl derivatives **2, 3** are described.

Synthese einiger Metabolite von Promethazin

Über die Synthese des N-Methylnitrons **11**, N-Monoalkylhydroxylamins **9**, N,N-Dialkylhydroxylamins **10**, Oxims **8** und anderer potentieller Metabolite von Promethazin (**1**) und seiner N-desalkylierten Derivate wird berichtet.

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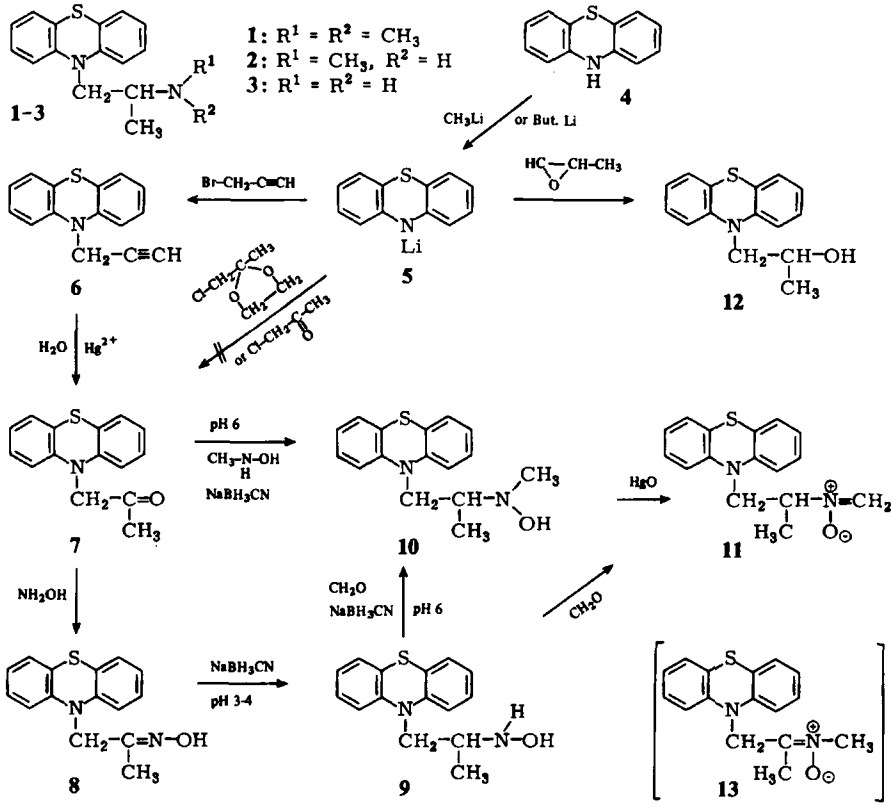
Promethazine (**1**) was first reported as a potent antihistamine in 1946[1] but adequate metabolic studies have not been carried out.

This phenothiazine compound was chosen as an example to study the importance of N or α C-oxidation when the α-C between basic group and ring system is branched. Potential metabolic reference compounds were required, the synthesis and properties are described herein and their importance in the metabolism of **1**, **2** and **3** will be reported elsewhere.

Scheme 1



A synthetic route including the ketone **7** and the oxime **8** (both potential metabolites) to obtain the hydroxylamines **9**, **10** and the nitrone **11** was attractive. The reaction route described in scheme **1** (**4**→**11**) represents this purpose using reductive methods of synthesis of hydroxylamines (**8**→**9**, **9**→**10**, **7**→**10**) which have been discussed recently[2] and applied to the synthesis of N-oxygenated products of 3,4-dimethoxyamphetamine[2].

This sequence involves three steps (**7**→**8**, **8**→**9**, **9**→**10**)which were also successfully used for the synthesis of N-hydroxy compounds of promazine[3]. Although compounds **6**, **7** and **12** have been reported previously the recorded physical and spectroscopic data,

important in identification of possible metabolites, were incomplete and therefore are included in the present report.

5: Methyllithium in ether [4] was chosen as the base and produced the required lithium salt **5** within 30 min at room temp. The use of CH_3Li is considered to be superior to the use of lithium-amide in liquid ammonia, which requires a longer reaction time and stronger conditions[3] which result in more impure compounds. N-butyllithium (But. Li) gave in our hands similar results to those obtained using CH_3Li.

6: The method of *Dumont* et al.[4] was used (**4** → **5** → **6**); as reported it gave the acetylene **6** and not the isomeric acetylene described by *Zaugg*[5]. However, the purification was simplified and a high yield of analytically pure sample was obtained.

7: The addition of water to the acetylene **6** in the presence of mercuric sulphate was carried out successfully. The conditions and the composition of the catalyst reported by *Dumont* et al.[4] had to be changed since no reaction occurred when applying his method to gram quantities of material. Compound **7** was obtained indirectly (**5** → **6** → **7**) involving the acetylene **6** because the alternative route (**5** → **7**) was unsuccessfull. No reaction took place between the lithium salt **5** and chloracetone or its ketal, 2-(chloromethyl)-2-methyl-1,3-dioxolane, the starting materials always being recovered unchanged.

8: The oxime was prepared by a standard method yielding a mixture of the *E* and *Z* isomer (2 : 1) as indicated by NMR analysis.

9, 10: Reduction of the oxime **8** with sodium cyanoborohydride[2)3)6)] at pH 3–4 produced the primary hydroxylamine **9** in reasonable yield (61 %) although a comparatively long reaction time (24 h) was needed. Reductive N-methylation of **9** at pH 6 yielded the secondary hydroxylamine **10** which could also be prepared in a very high yield (85 %) by reductive methyl-hydroxylamination of the ketone (**7** → **10**). No over-reduction of the hydroylamines was observed. The hydroxylamines were further characterised and converted to their more stable oxalic acid salts.

11: It is known that primary hydroxylamines react with aldehydes and ketones to give nitrones[7)8)]. Condensation of the primary hydroxylamine **9** with formaldehyde gave a semi solid mass which was shown by NMR to consist mainly of the nitrone **11.**

A purer compound was obtained by oxidation of the secondary hydroxylamine **10** with yellow mercuric oxide. The NMR confirmed that again **11** rather than the possible isomer **13** was formed; this compound was shown to be fairly pure by NMR and its TLC and MS characteristics. The viscous mass was hygroscopic and a satisfactory elemental analysis has not been obtained. There are few reports of this type of nitrone (α-unsubstituted or N-alkylated derivatives of formaldoxime) in the literature (see[2] for a review). Recently *Coutts* and *Kovach* prepared a similar nitrone from N-hydroxy-N-methylamphetamine[9].

12: The alcohol **12** was prepared in excellent yield (92 %) by reaction of **5** with propylene oxide. After a short reaction time (without reflux) and removal of the solvent crystals were obtained which did not require further purification. In comparison with the methods reported in the literature[10)11)] using $NaNH_2$, the use of CH_3Li had advantages. *Dahlbom*[11)] described a colourless almost glassy mass after distillation. The use of the above potential metabolites facilitated the metabolic studies involving promethazine.

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Experimental

IR spectra: Perkin Elmer model 157 G, *NMR spectra*: 90 MHZ Perkin Elmer R-32. Spin decoupling were applied to the NMR analyses of the heterosteric ABC spin system[12] which is present in the compounds ($C_{12}H_8SNCH_2CHCH_3$-). *Mass spectra*: VG Micromass 16F mass spectrometer linked to a VG Digispec 2035 data system. *GLC*: Perkin Elmer F-11 instrument equipped with a flame ionisation detector; system: 1 m glass column, 3 mm i.d. packed with 3 % OV 17 on acid washed DMCS treated Gas Chrom Q 80–100 mesh; carrier gas N_2 at a flow rate 1.7 cm^3 sec^{-1}; column temp. 220°; injection port temp. 270°. The progress of the reactions was monitored either by GLC (for compounds stable on GLC) or by TLC using micro-TLC plates (aluminium, 6.5 + 2 cm, 0.2 mm, silica gel F_{254}, Merck). Solvent system (i) chloroform-methanol (9 : 1); (ii) Toluene-methanol-diethylamine (8 : 1 : 1). Spots were visalised under UV light (254 nm). Hyxdroxylamine **9, 10** were sprayed with triphenyltetrazolium chloride (TTC) (0.1 % in 10 % methanolic KOH).

Materials

Methyllithium – lithium bromide complex, 2M solution in diethylether, n-butyllithium 1.6M solution in hexane, propargyl bromide 80 % solution in toluene (Aldrich). Al_2O_3 neutral for column chromatography, activity grade 1 (Woelm Pharma).

Procedures

Phenothiazines are sensitive to light, therefore all procedures were carried out in subdued light.

10-Lithium phenothiazine **(5)**

To a stirred solution of 20 g (0.1 mol) phenothiazine (Aldrich) in 250 ml ether was added dropwise 50 ml (0.1 mol) of the solution of CH_3Li in ether (or 63 ml of n-But.Li in n-hexane) and stirring was continued until the gas production ceased (30 min.).

10-(2-Propynyl)phenothiazine **(6)**

To the lithium salt **5** was added dropwise 17.8 g (0.12 mol) of the solution of propargyl bromide (80 %) in toluene over a period of 10 min. Stirring was continued for 1 h at room temp. The mixture was poured into 100 ml of water, the organic layer was separated dried over $CaCl_2$ and the solvent removed by rotary evaporation. The brown residue was dissolved gradually in n-hexane and the solution was sucked through a sinter glass funnel covered with an extra layer of neutral Al_2O_3. After removal of the hexane by rotary evaporation 17.5 g (74 %) of analytically pure white powder remained. m.p. 91° (lit.[4] m.p. 92°). – GLC: R_{t4} = 1.6 min.; R_{t6} = 2.8 min. – IR (KBr): 3290 (≡ C–H), 2120 cm^{-1} (C ≡ C). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.20–6.75 (m, 8 ArH); 4.50 (d, J = 3 Hz, CH_2); 2.37 (t, J = 3 Hz, CH). – MS (70 eV): m/e = 237 (23 % M^+), 199 (15 %), 198 (100 %), 154 (7 %). $C_{15}H_{11}NS$ (237.3) Calc. C 75.9 H 4.67 N 5.9 S 13.5 Found C 75.8 H 4.70 N 6.1 S 13.3.

10-(2-Propanone)phenothiazine **(7)**

8 g (0.034 mol) **6** were dissolved in 150 ml methanol and then mixed with a solution of 1 g $HgSO_4$ in 3 ml H_2O and 1.5 g H_2SO_4 conc. The mixture was refluxed for 30 min and then poured into 200 ml of ice cold water and the brown precipitate formed was dried and recrystallised from methanol to obtain 5.8 g (67 %) of faint yellow needles. m.p. 144° (lit.[4] m.p. 144°). – GLC: R_{t7} = 3.2 min. – IR (KBr): 1710 cm^{-1} (C=O). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.24–6.33 (m, 8 ArH); 4.42 (s, CH_2); 2.17 (s, CH_3). –

MS (70 eV): m/e = 255 (29 % M^+), 213 (16 %), 212 (100 %), 195 (5 %), 180 (50 %), 179 (11 %). $C_{15}H_{13}NOS$ (255.3) Calc. C 70.6 H 5.13 N 5.5 S 12.6 Found C 70.6 H 5.20 N 5.3 S 12.4.

10-(2-Propanoneoxime)phenothiazine **(8)**

A mixture of 6 g hydroxylammonium chloride (Fisons), 40 ml H_2O, 60 ml 1N-NaOH, 3 g (0.012 mol) **7** and 150 ml ethanol was refluxed for 10 min until a clear solution was obtained. The solution was cooled with ice and after the addition of 100 ml water extracted with ether. The solvent was dried ($CaCl_2$) and then removed by rotary evaporation. The oily residue was dissolved in chloroform and extracted with water. After drying and evaporation of the chloroform 2.8 g (88 %) of a yellow powder remained (no crystallisation could be achieved). Decomp. during distillation. m.p. 56°. – TLC: Rf_7 = 0.84, Rf_8 = 0.62, system (i). – IR (KBr): 3600–3200 (b, OH); 1690 cm^{-1} (C=N). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.03 (s, OH); 7.30–6.67 (m, 8 ArH); 4.77 and 4.55 (2s, CH_2); 1.92 and 1.83 (2s, CH_3). – MS (70 eV): m/e = 270 (19 % M^+), 254 (5 %), 212 (8 %), 200 (14 %), 199 (82 %), 198 (100 %), 180 (10 %), 167 (17 %), 166 (14 %), 41 (18 %). $C_{15}H_{14}N_2OS$ (270.4) Calc. C 66.6 H 5.22 N 10.3 S 11.8 Found C 66.0 H 5.72 N 9.9 S 10.5.

10-(N-Hydroxy-2-aminopropyl)phenothiazine (N-hydroxy-didesmethylpromethazine) **(9)**

To a stirred solution of 1.72 g (6.4 mmol) **8** and 0.44 g (7 mmol) $NaBH_3CN$ (Aldrich) in 30 ml methanol at room temp. was added dropwise 10 % methanolic HCl at a rate sufficient to maintain a pH of 3–3.5. The reation consumed acid very fast for the first min, as indicated by the rise in pH. The reaction was monitored by TLC showing that even after stirring for 24 h some oxime remained unchanged (TLC: Rf_8 = 0.62, Rf_9 = 0.38, red with TTC, solvent system (i). The reaction was stopped by destroying the excess of reducing agent by adding sufficient acid to lower and maintain the pH at 1. The solvent was removed by rotary evaporation. The residue was taken up in 100 ml water, the pH adjusted to 8 with 20 % K_2CO_3 and extracted with 3 · 50 ml of ether. The ethereal extracts were combined and dried over $CaCl_2$ and concentrated to afford a pale yellow solid which was shown by NMR to consist of a mixture of the starting oxime **8** (25 %) and the hydroxylamine **9.** In order to separate the hydroxylamine an oxalate was prepared by adding an ethereal saturated solution of oxalic acid to a solution of the mixture in dry ether to give 1.4 g (61 %) of the hemi oxalate. m.p. 140–142° (decomp.). – IR (KBr): 3100–2700 cm^{-1} (b, OH). – ^{1}H-NMR ($CDCl_3$, base extracted from the acid oxalate salt with D_2O/KOH): δ (ppm) = 7.30–6.81 (m, 8 ArH); 4.30–3.60 (m, CH_2); 3.58–3.32 (m, CH); 1.17 (d, CH_3). – MS (70 eV): m/e = 273 (6 %), 272 (13 % M^+), 270 (18 %), 256 (11 %), 254 (16 %), 214 (24 %), 213 (88 %), 212 (71 %), 200 (18 %), 199 (68 %), 198 (100 %), 180 (40 %), 167 (24 %), 166 (12 %), 154 (9 %), 71 (15 %), 60 (11 %), 59 (11 %), 57 (24 %), 55 (13 %), 44 (15 %), 43 (22 %), 41 (16 %). $C_{17}H_{18}N_2O_5S$ (362.4) Calc. C 56.3 H 5.01 N 7.7 S 8.8 Found C 56.7 H 5.16 N 7.7 S 8.6.

10-(N-Hydroxy-N-methyl-2-aminopropyl)phenothiazine(N-hydroxydesmethylpromethazine) **(10)**

a) By reductive N-methylhydroxylamination of **7:** To a solution of 1.84 g (0.022 mol) N-methylhydroxylamine hydrochloride (Aldrich) in 2 ml of water was added 2.55 g (0,01 mol) of **7** in 10 ml methanol, the pH of the mixture adjusted to 6 with 10 % KOH aq. After the addition of 0.79 g (0.0125 mol) of $NaBH_3CN$ the resulting mixture was stirred at room temp. until the starting ketone was no longer detected by TLC analysis (4 h; TLC: Rf_7 = 0.84, Rf_{10} = 0.54, system (i); Rf_7 = 0.75, Rf_{10} = 0.56, system (ii)). The pH of the reaction was maintained between 5 and 6 by the dropwise addition of 5 % HCl. Working up procedure as described unter **9.** After removal of the ether a solid remained which was shown to be nearly pure by NMR analysis. The compound was dissolved in dry ether and a saturated solution of oxalic acid was added. The precipitate, which had been formed after standing overnight, was washed with ether to afford 3.2 g (85 %) of the hemi oxalate. m.p.. 152–154°

(decomp.). – IR (KBr): 3100–2700 cm^{-1} (b, OH). – ^{1}H-NMR ($CDCl_3$, base): δ (ppm) = 9.05 (bs, OH); 7.30–6.71 (m, 8 ArH); 4.55–3.65 (m, CH_2); 3.52–3.05 (m, CH), 2.85 (s, N-CH_3); 1.22 (d, CH_3). – MS (70 eV): m/e = 286 (3 % M^+), 270 (3 %), 269 (2 %), 268 (11 %), 214 (12 %), 213 (79 %), 212 (49 %), 200 (8 %), 199 (49 %), 198 (34 %), 180 (34 %), 167 (19 %), 74 (23 %), 58 (100 %), 56 (22 %), MS (18 eV): m/e = 286 (9 % M^+). $C_{18}H_{20}N_2O_5S$ (376.4) Calc. C 57.4 H 5.36 N 7.4 S 8.5 Found C 57.2 H 5.42 N 7.6 S 8.5.

b) By reductive N-alkylation of **9** with formaldehyde: A solution containing 0.429 g (1.2 mmol) of **9**-oxalate and 0.14 ml of a 40 % solution of formaldehyd (0.039 g, 1.3 mmol) in 30 ml methanol was adjusted to pH 6 with 10 % KOH in methanol. 0.11 g (1.84 mmol) of $NaBH_3CN$ in 3 ml methanol was added and the mixture was stirred at room temp. while maintaining the pH at 6 by the addition of 5 % methanolic HCl. After 3 h TLC examination showed complete disappearance of the starting hydroxylamine **9** in favour of the product **10.** Working up and preparation of a hemi oxalate as described under a) to afford 0.28 g (63 %) of product, identical to the oxalate prepared in a) above.

N-((1-Methyl)-2-phenothiazine-10-yl)ethyl)methanimine N-oxide **(11)**

a) By oxidation of **10** with HgO: 0.5 g (1.25 mmol) of **10** (oxalic acid salt) were dissolved in 10 ml water, the solution adjusted to pH 10 with 10 % NaOH and then extracted three times with 10 ml of chloroform. The combined chloroform extracts were dried over Na_2SO_4 and filtered. Yellow mercuric oxide (1.5 g) was added to the filtrate and the suspension was shaken for 2 h during which time a black colour (Hg) developed. The suspension was centrifuged and the chloroform supernatant was evaporated to yield 0.31 g (82 %) of **11** as a semi solid mass which was shown to be virtually pure (TLC, NMR, MS). The compound was hygroscopic and a satisfactory elemental analysis could not be obtained.

TLC: Rf_{11} = 0.57, system (i). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.22–6.71 (m, 8 ArH); 6.15 (AB; J = 8 Hz, CH_2=N), 4.62–3.81 (m, CH_2–CH); 1.47 (d, J = 6 Hz, CH_3). – MS (70 eV): m/e = 284 (11 % M^+), 268 (14 %), 255 (7 %), 240 (14 %), 239 (77 %), 238 (15 %), 214 (6 %), 213 (19 %), 212 (100 %), 200 (14 %), 199 (76 %), 198 (57 %), 180 (57 %), 179 (12 %), 167 (32 %), 166 (15 %), 154 (13 %), 77 (8 %), 69 (10 %).

b) By reaction of **9** with formaldehyde: **9** was liberated from 0.5 g (1.38 mmol) of the oxalic acid salt as described in a). 0.5 ml of a 40 % solution of formaldehyde (0.2 g, 5 mmol) was added to the chloroform solution of **9** and stirred for 2 h. The mixture was dried over Na_2SO_4 filtered and the solvent removed by rotary evaporation. An oil was left which was shown by NMR, MS and TLC characteristics to consist mainly of the nitrone **11** (see a) for spectral data).

10-(2-Hydroxypropyl)phenothiazine **(12)**

The lithium salt **5** in ether was prepared as described above from 10 g (0.05 mol) phenothiazine and 25 ml of the solution of CH_3Li in ether. 5 g (0.086 mol) of propylene oxide (BDH) was added at once to the reaction mixture and stirring was continued for 1 h at room temp. The mixture was then poured into 100 ml of water, the organic layer was separated, dried over $CaCl_2$ and the ether removed by rotary evaporation to yield an oily mass. After standing overnight waxy crystals were formed; they were pulverized and dried under low vac. to yield 11.8 g (92 %) of an almost white crystalline solid. m.p. 78° (lit.[11] b.p. 192–196° (0.3–0.5 mm)). – GLC: R_{t4} = 1.6 min., R_{t12} = 3.8 min. – IR (KBr): 3500–3200 (b, OH). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.20–6.64 (m, 8 ArH); 4.22–3.82 (m, CH); 3,70 (d, CH_2); 3.05 (s, OH); 1.16 (d, CH_3). – MS (70 eV): m/e = 258 (8 %), 257 (38 % M^+), 213 (8 %), 212 (100 %), 199 (5 %), 198 (13 %), 181 (7 %), 180 (45 %), 179 (8 %), 58 (5 %), 45 (5 %), 40 (5 %). $C_{15}H_{15}NOS$ (257.4) Calc. C 70.0 H 5.87 N 5.4 S 12.5 Found C 70.0 H 5.79 N 5.4 S 12.2

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ortho-Effekte in 1-(o-Aminomethylaryl)-buten(1)-3-onen und ihren Hydrierungsprodukten, 5. Mitt.[9]

MS-Untersuchungen an Modellsubstanzen des Alkaloids Vinceten

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Eingegangen am 11. November 1980

Die Modellsubstanzen **3–14** des Dihydro-Vincetens **(2)** wurden ms untersucht. Wichtige Fragmentierungsfolgen und -mechanismen wurden mit Hochauflösung, ^{2}H-Markierung und Analyse metastabiler Ionen aufgeklärt.

Ortho Effects in 1-(*o*-Aminomethylaryl)-1-buten-3-ones, V: MS Investigations on Model Compounds of the Alkaloid Vinceten

Compounds **3–14**, model compounds of dihydrovinceten **(2)**, were investigated by mass spectrometry. Main fragmentation pathways and mechanisms were elucidated by high resolution measurements, ^{2}H-labelling and analysis of metastable ions.

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