form nearly to the boiling point. A white precipitate was formed which was filtered from the solution. This precipitate proved to be the hydrochloride of the original amino alcohol. The free benzoate remaining in solution was obtained by evaporating the chloroform. However, the ester proved to be a sticky oil which was analyzed as the dihydrochloride prepared by dissolving the ester in ethanol, adding an excess of concentrated hydrochloric acid and precipitating with ether. The salt was recrystallized from methanol in 77% yield, m. p. 228–230°. This salt is insoluble in water.

Anal. Calcd. for $C_{25}H_{28}N_2O_2Cl_2$: N, 6.09; Cl, 15.44. Found: N, 6.30; Cl, 15.16.

N-Phenyl-N'-β-*p*-tolyl-β-hydroxyethylpiperazine, (II).—This compound was prepared from the hydrochloride of N-phenyl-N'-*p*-methylphenacylpiperazine by Method A. Recrystallized from ethanol the yield was 80%, m. p. 127–128°. This amino alcohol is slightly soluble in ethanol, ether; soluble in chloroform and insoluble in water.

Anal. Calcd. for $C_{19}H_{24}ON_2$: N, 9.45. Found: N, 9.32.

Preparation of this amino alcohol by Method B gave a 77% yield, m. p. 127–128°.

The dihydrochloride of (II) was prepared as described above, yield 94%, m. p. 199–201°. This salt is soluble in water.

Anal. Calcd. for $C_{19}H_{26}ON_2Cl_2$: N, 7.59; Cl, 19.19. Found: N, 7.71; Cl, 18.78.

The dihydrochloride of the benzoate of (II) was prepared as described above. It was recrystallized from methanol in 80% yield, m. p. 219–221°. This salt is slightly soluble in methanol and insoluble in water.

Anal. Calcd. for $C_{26}H_{30}O_2N_2Cl_2$: N, 5.92; Cl, 14.98. Found: N, 6.20; Cl, 14.70.

N-Phenyl-N'-phenylethylpiperazine, (III).—This compound was prepared by refluxing molecular proportions of phenylethyl bromide and N-phenylpiperazine for five hours in butanol solution. The hydrobromide thus obtained was dissolved in hot water and the free base precipitated by the addition of sodium hydroxide. The yield after recrystallization from hexane was 74%, m. p. 77–78°. This compound is soluble in ethanol, chloroform: fairly soluble in ether and insoluble in water.

Anal. Calcd. for $C_{18}H_{22}N_2$: N, 10.74. Found: N, 10.58.

The dihydrochloride of (III) was prepared in 94% yield from 5 g. of the amine in the manner described above. It was recrystallized from ethanol, m. p. 220–222°. This salt is slightly soluble in water.

Anal. Calcd. for $C_{18}H_{24}N_2Cl_2$: N, 8.22. Found: N, 8.35.

Summary

Two new analogs of ephedrine which contain the N-phenylpiperazine nucleus have been synthesized.

The hydrochlorides and benzoates of these amino alcohols have been prepared.

GAINESVILLE, FLORIDA RECEIVED OCTOBER 11, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

New Alkaloids in Aconitum Napellus[1]

BY WERNER FREUDENBERG AND E. F. ROGERS

An investigation by Schulze and Berger[2] on congeners of aconitine resulted in the isolation and chemical study of a base $C_{32}H_{45}NO_8 \cdot 3H_2O$ which was named neopelline. The relationship of neopelline to aconitine was demonstrated by the fact that on alkaline hydrolysis it yielded an alkamine neoline, $C_{23}H_{39}NO_6$, in addition to one mole each of acetic and benzoic acids. Neither neopelline nor neoline could be obtained in the crystalline state. Neoline hydrobromide was the only crystalline derivative which could be used analytically to set up the empirical formula. Quantitative group determinations led Schulze and Berger to extend the neoline formula as follows: $C_{19}H_{25}O(OH)_2(OCH_3)_3(NCH_3)$.

It appeared promising to reinvestigate these findings inasmuch as neoline appears to be structurally related to aconitine[3–5] or its alkamine aconine. Furthermore its lower oxygen content (six), as compared to aconine (nine) should make neoline a good starting material for structural studies in the aconitine group.

We had available for this study a generous supply of so-called amorphous aconitine which is a mixture of residual bases obtained in the commercial preparation of crystalline aconitine from *tubera aconiti napelli* (Merck). Our procedure as outlined in the following flow sheet, is essentially identical with that of Schulze who used for his studies a similar starting material also secured from E. Merck.

Fraction Ib which corresponds to Schulze's

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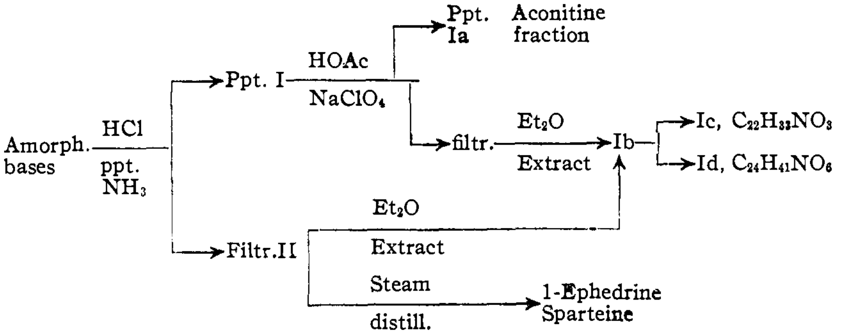
[1] Fourth communication on aconite alkaloids. Presented at the Rochester meeting of the American Chemical Society, Sept., 1937.

[2] Schulze and Berger, *Arch. Pharm.*, **262**, 553 (1924).

[3] Jacobs and Elderfield, THIS JOURNAL, **58**, 533 (1936).

[4] Freudenberg, *Ber.*, **69**, 1962 (1936).

[5] Majima and Tamura, *Ann.*, **526**, 116 (1936).



neopelline is a practically colorless amorphous product; its solutions are only slightly yellow. Repeated nitrogen determinations on this material, obtained from three different preparations of amorphous aconitine, gave consistent values of 3.2%. The molecular weight, therefore, could not be greater than 450, while neopelline even in its anhydrous form has a molecular weight of 539. Furthermore, negative acetyl determinations on fraction Ib indicated the absence of any ester group.

Napelline.—After several unsuccessful attempts to purify and crystallize fraction Ib, we succeeded in fractionating it in the following way. The entire material was dissolved in the minimum amount of 0.1 normal acid. Upon addition of the equivalent of 0.1 normal sodium hydroxide a precipitate formed which after filtration was neutralized with dilute hydrobromic acid. The resulting hydrobromide was crystallized from a mixture of methyl alcohol and ether. It darkens at 200° and melts with decomposition at 229°; $[\alpha]^{23}\text{D}$ $-42.72°$ (H$_2$O; $c = 5$). The composition $C_{22}H_{33}NO_3HBr$, compares favorably with the analytical results. Additional support for its correctness was secured by analyses of the hydrochloride, hydroiodide and of the free base.

For the new base we wish to suggest the name napelline. The possible relationship of napelline and luciculine, an alkaloid $C_{22}H_{35}NO_3 \cdot H_2O$ obtained by Majima and Morio[6] from *aconitum lucidusculum*, Nakei, will be discussed in a forthcoming communication.

Neoline.—The filtrate obtained from the napelline preparation upon ether extraction yielded a base which was isolated as the crystalline hydrobromide. Its physical properties and analyses are compared below with those of neoline hydrobromide as reported by Schulze and Berger. The data presented appear sufficiently convincing to establish the identity of the two products; Schulze's formula, however, $C_{23}H_{39}NO_6 \cdot HBr$ must be changed to $C_{24}H_{41}NO_6 \cdot HBr$.

TABLE I

Neoline·HBr	M. p., °C.	Cryst.	Spec. rot.	%C	%H	%N	%Br
Schulze + Berger	200–210, dec.	Needles	−4.31°[a]	55.42	8.26	2.95	15.93
				55.34	7.97	2.83	15.92
Our product	214, dec.	Needles	+2.10°	55.34	8.34	2.80	15.36
				55.38	8.29	2.79	15.35
$C_{24}H_{41}NO_6 \cdot HBr$ calculated				55.37	8.13	2.69	15.36
$C_{23}H_{39}NO_6 \cdot HBr$ calculated				54.52	7.96	2.77	15.78

[a] Schulze and Berger's reported specific rotation is −43.17°; this must be a typographical error as their reported values for concentration, length of tube and observed rotation calculate to −4.31°.

Additional support for the new neoline formula has been attained by isolation of neoline hydrochloride and the free base in crystalline form analyzing almost theoretically for $C_{24}H_{41}NO_6 \cdot HCl$ and $C_{24}H_{41}NO_6$, respectively.

Fraction Ib represents approximately 30% of the starting material.

Precipitate Ia consists of a mixture of bases forming water-insoluble perchlorates, which were not investigated further.

Filtrate II, finally, also contains neoline in appreciable quantities but very little napelline. They can be isolated as indicated in Chart I by ether extraction of filtrate II. It is, however, not advisable to combine this extract with fraction Ib because the presence of traces of two further bases in this extract were ascertained; they were identified as *l*-ephedrine and sparteine. A mixture of the two volatile bases was obtained on steam distillation. Their separation depended upon the insolubility of ephedrine hydrochloride in alcohol–acetone and the relative insolubility of sparteine in water. Both alkaloids could be identified by a number of characteristic derivatives, which were found identical with authentic samples.

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[6] Majima and Morio, *Ber.*, **65**, 599 (1932).

The identified fractions (II, Ib and Ic) account for approximately 60% of the entire mixture of residual bases.

Our previous statement[7] that *l*-ephedrine is a degradation product of napellus alkaloids must be revised. One can assume that both ephedrine and sparteine are present in the plant as such.

The bases which have been isolated from *aconitum napellus* in pure form and which must, therefore, be considered as genuine aconitum alkaloids are, in addition to the already recognized aconitine,[8] mesaconitine,[9] hypaconitine[10] and neopelline,[2] *l*-ephedrine and sparteine and the newly discovered and described neoline and napelline.

Experimental Part

Reprecipitation.—One hundred grams of amorphous aconitine was dissolved in 360 cc. of 0.6 *N* hydrochloric acid. When the alkaloid was completely dissolved, 360 cc. of 3 *N* ammonium hydroxide (5 equiv.) was added with constant stirring. The voluminous precipitate (I) after filtration and drying *in vacuo* over sulfuric acid, weighed 70 g. The mother liquor was extracted exhaustively with ether and then rejected. The ether solution, after drying over anhydrous sodium carbonate and evaporation *in vacuo*, yielded 18–20 g. of alkaloid (II).

Perchlorate Treatment of I.—Seventy grams of I was dissolved in 200 cc. of 10% acetic acid and to the solution obtained, 200 cc. of 10% sodium perchlorate solution was added. The resulting brown gummy precipitate has not been examined further. The filtrate was made alkaline with sodium carbonate, exhaustively extracted with ether and then discarded. The ether extract was dried with sodium carbonate, concentrated under reduced pressure to about 150 cc. and saved for fractionation of Ib. Complete removal of the solvent gave 30–32 g. of amorphous slightly yellow hygroscopic powder. It was easily soluble in alcohol, ether, chloroform and benzene, insoluble in petroleum ether and partly soluble in water. Its rotation determined in alcohol ($c = 5$) was $-13.5°$. *Anal.* N, 3.25, 3.19, 3.20, 3.28; CH_3CO,[11] nil; mol. wt. (based on average nitrogen percentage), 435.

Fractionation of Ib.—The ethereal solution of Ib in a separatory funnel was made acid to litmus with 0.1 *N* hydrochloric acid added carefully with repeated shaking. To the aqueous solution after separation and removal of the ether *in vacuo* its own volume of 0.1 *N* sodium hydroxide was added with constant stirring. The precipitated alkaloid (Ic) was filtered off and dissolved in the minimum amount of 10% acetic acid. After chilling, a 10% sodium perchlorate solution was added until no further precipitation was noticed. The mother liquor was then separated and made distinctly alkaline with sodium carbonate and exhaustively extracted with ether. The dried ether extract gave crude napelline (Ic).

Napelline Hydrobromide.—The dried fraction (Ic) was dissolved in alcohol, neutralized to litmus with dilute hydrobromic acid and the solution evaporated under reduced pressure. After taking up the amorphous material in little methyl alcohol and filtration, ether was added until faint cloudiness remained. The solution was then warmed until clear and placed in the ice box. The crystals obtained were recrystallized in the same way giving small rosets, darkening at 200°, melting at 229° (dec.); yield 8%; $[\alpha]^{23}\mathrm{D}$ $-42.7°$ (H_2O, $c = 6$).

Anal. Calcd. for $C_{22}H_{33}NO_3HBr$: C, 59.99; H, 7.76; N, 3.18; Br, 18.14. Found: C, 59.93, 59.91, 60.14, 59.72; H, 7.82, 8.25, 7.75, 7.8; N, 3.19, 3.29; Br, 17.87. 18.24.

Napelline Hydroiodide.—The substance melts at 181–185° (dec.) after crystallization and recrystallization as described under napelline hydrobromide.

Anal. Calcd. for $C_{22}H_{33}NO_3{\cdot}HI$: C, 54.21; H, 7.03; N, 2.87; I, 26.04. Found: C, 53.80, 53.88; H, 7.28, 7.10; N, 2.86; I, 25.93.

Napelline Hydrochloride.—M. p. 220–222° (dec.) $[\alpha]^{22}\mathrm{D}$ $-93.9°$ (H_2O, $c = 5$).

The compound seems to crystallize with solvent of crystallization. It was dried *in vacuo* over phosphorus pentoxide at 100°.

Anal. Calcd. for $C_{22}H_{33}NO_3{\cdot}HCl$: Cl, 8.97. Found: Cl, 8.90.

Napelline.—The free base crystallizes in rectangular plates from a mixture of ether and petroleum ether or from acetone containing a little water. The crystallization is very difficult.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.81. Found: C, 73.58, 73.47; H, 8.97, 9.19; N, 3.89.

Neoline Hydrobromide.—The base Id was neutralized with hydrobromic acid and crystallized from a mixture of methanol and ether as small needles melting at 215° (dec.), $[\alpha]^{23}\mathrm{D}$ $+2.10°$ (H_2O, $c = 5$).

Anal. Calcd. for $C_{24}H_{41}NO_6HBr$: C, 55.35; H, 8.13; N, 2.69; Br, 15.35. Found: C, 55.34, 55.38; H, 8.35, 8.29; N, 2.80, 2.79; Br, 15.36, 15.35.

Neoline Hydrochloride.—The base recovered by alkali treatment from the crystalline hydrobromide was neutralized with hydrochloric acid and crystallized from a mixture of methyl alcohol and ether; decomposition point 178–180°.

Anal. Calcd. for $C_{24}H_{41}NO_6{\cdot}HCl$: C, 60.55; H, 8.68; N, 2.94; Cl, 7.45. Found: C, 60.41, 60.88; H, 8.81, 8.41; N, 3.03; Cl, 7.37

Neoline.—A sample of dry amorphous base recovered from the pure crystalline hydrobromide was dissolved in the minimum amount of ether. The ether solution was covered with a layer of petroleum ether, then cooled on ice. After a few hours of standing crystallization appeared complete. Small prisms were obtained, somewhat soluble in ether and water, very soluble in alcohol, chloroform, benzene and insoluble in petroleum ether. The base melts at 153–154°; $[\alpha]^{23}\mathrm{D}$ $+9.7$ (alcohol, $c = 10.0$).

Anal. Calcd. for $C_{24}H_{41}NO_6$: C, 65.57; H, 9.40; N, 3.19. Found: C, 65.74, 65.65; H, 9.39, 9.33; N, 3.20, 3.30,

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(7) Freudenberg and Rogers, THIS JOURNAL, **58**, 533 (1936).

(8) Geiger and Hesse, *Ann.*, **7**, 269 (1833).

(9) Morio, *ibid.*, **476**, 181 (1929).

(10) Majima and Morio, *ibid.*, **476**, 171 (1929).

(11) Elek and Harte, *Ind. Eng. Chem., Anal. Ed.*, **8**, 267 (1937).

Isolation of *l*-Ephedrine.—The material obtained on exhaustive ether extraction of the mother liquors (II) could be shown to contain neoline and a small amount of napelline. The mother liquors were made strongly alkaline and steam distilled until the distillate no longer reacted alkaline. The distillate was neutralized carefully with hydrochloric acid, concentrated to a small volume, filtered and evaporated to dryness. The residue was taken up in the minimum volume of boiling alcohol and 5 to 6 volumes of acetone was then added with good shaking. In a few seconds needles began to appear. After several hours of standing in the ice box the material was filtered off and recrystallized in the same way; yield 0.68 g. The filtrate from the first crystallization was saved for the isolation of sparteine. The substance melted at 217–218°; $[\alpha]^{23}\mathrm{D}$ −33.0° (H_2O, c = 6.0).

Anal. Calcd. for $C_{10}H_{15}NO{\cdot}HCl$: C, 59.61; H, 8.00; N, 6.95; Cl, 17.61. Found: C, 59.59, 59.98; H, 7.84, 8.27; N, 6.97, 7.05; Cl, 17.57, 17.59.

The derivatives described below were prepared by standard methods, using the hydrochloride as starting material. They all appeared identical with the corresponding derivatives prepared from synthetic *l*-ephedrine (Merck).

Ephedrine Hydrobromide.—Needles, m. p. 206°, $[\alpha]^{21}\mathrm{D}$ −28.1° (H_2O, c = 4.0).

Anal. Calcd. for $C_{10}H_{15}NO{\cdot}HBr$: C, 48.80; H, 6.55; N, 5.68; Br, 32.46; (N)CH_3, 6.09. Found: C, 49.01, 48.82; H, 6.20, 6.21; N, 5.59, 5.64; Br, 31.91; (N)CH_3, 5.66, 5.50.

Ephedrine Oxalate.—Needles, m. p. 245°.

Anal. Calcd. for $(C_{10}H_{15}NO)_2{\cdot}H_2C_2O_4$: N, 6.66. Found: N, 6.67.

Ephedrine *p*-Toluenesulfonate.—M. p. 126°.

Anal. Calcd. for $C_{10}H_{14}NOSO_2C_7H_7$: N, 4.38. Found: N, 4.40.

Isolation of Sparteine.—The mother liquor from the first crystallization of ephedrine hydrochloride was evaporated to dryness. The residue was taken up in water, an excess of sodium hydroxide was added and the basic material extracted with ether. The dried and filtered ether extract was evaporated in a small centrifuge tube. On complete removal of the ether about 200 mg. of yellow-brown oil remained. In order to remove the ephedrine present, the filtrate was shaken with four successive 2-cc. portions of water. After each treatment the mixture was centrifuged and the water drawn off. The base was then dissolved in ether and the solution dried. The filtered solution was transferred to a Craig micro-still and, after removal of the ether, distilled at 1 mm. The fraction distilling between 120–130° (bath temp.) was examined. This was a clear yellow oil which became brown on standing. The odor resembled that of authentic sparteine: b. p. above 250°, $[\alpha]^{23}\mathrm{D}$ −14.4° (EtOH, c = 5.5); $n^{24}\mathrm{D}$ 1.528.

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 76.87; H, 11.18; N, 11.95. Found: C, 77.06; H, 11.05; N, 12.07.

Sparteine Picrate.—M. p. 208°.

Anal. Calcd. for $C_{15}H_{26}N_2(C_6H_2(OH)(NO_2)_3)_2$: N, 16.17. Found: N, 16.24.

Acknowledgments.—The authors desire to express their appreciation to E. Merck for the starting material, to Merck and Co., Inc., Rahway, N. J., for a grant to one of us (E. F. R.). The micro-analyses were carried out in this Laboratory by Mr. J. F. Alicino.

Summary

The fractionation of the ether soluble alkaloids contained in the residual bases of *aconitum napellus* yielded two new alkaloids, neoline, $C_{24}H_{41}NO_6$, and napelline, $C_{22}H_{33}NO_3$, as the main constituents together with traces of *l*-ephedrine and sparteine. All four alkaloids must be considered as genuine aconitum alkaloids.

NEW YORK, N. Y. RECEIVED OCTOBER 15, 1937

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Some Derivatives of Monothiophloroglucinol

BY C. M. SUTER AND GEORGE A. HARRINGTON

Previous investigations in this Laboratory[1] and elsewhere[2] have shown that hydroxyaryl alkyl sulfides exhibit strong germicidal properties. In the present paper are reported the synthesis and phenol coefficients of a series of alkyl sulfides derived from monothiophloroglucinol.

Synthesis of Sulfides

The starting material for the preparation of the sulfides was *sym*-benzenetrisulfonic acid. This was obtained in good yields by sulfonating sodium *m*-benzenedisulfonate in the presence of a mercury catalyst by a modification of the procedure of Behrend and Mertelsmann.[3] Fusion of sodium *sym*-benzenetrisulfonate with six times its weight of sodium hydroxide at 240–250° gave a 77% yield of sodium 3,5-dihydroxybenzenesulfonate.[4] When less alkali was employed a mixture of products was obtained from which none of the dihydroxysulfonate could be isolated.

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[1] Suter and Hansen, THIS JOURNAL, **54**, 4100 (1932); Suter and McKenzie, *ibid.*, **56**, 2470 (1934).

[2] Miller and Read, *ibid.*, **55**, 1244 (1933).

[3] Behrend and Mertelsmann, *Ann.*, **378**, 352 (1910).

[4] Senhofer, *Sitzber. K. Akad. Wiss. Wien*, **78**, II, 678 (1879).