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REVISED STRUCTURE OF PHYSOPERUVINE, AN ALKALOID OF *PHYSALIS PERUVIANA* ROOTS

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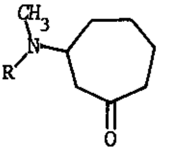
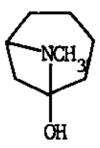
Abstract — The previously reported physoperuvine, an alkaloid isolated from the roots of *Physalis peruviana*, has been found to be a hydrochloride and its structure has been settled as 3 by X-ray analysis. The forms of existence of physoperuvine, a free base, and its hydrochloride have been studied, revealing that while the salt remains exclusively in the amino-alcohol form (3), the free base is an equilibrium mixture of the amino-alcohol (1) and the amino-ketone (2), the equilibrium being shifted toward the former.

"Physoperuvine", the major alkaloid of the roots of *Physalis peruviana* Linné (Solanaceae), was earlier formulated as 3-methylaminocycloheptanone (5) by Ray and co-workers on the basis of chemical and physical evidence.[1] A need for the revision of the structure of "physoperuvine" was initially felt from analysis of its IR spectrum which exhibited no carbonyl absorption band and its ^{13}C NMR spectrum which indicated the presence of a potential rather than an intact carbonyl carbon in the molecule. Consequently, a reexamination of the spectra of "physoperuvine" and its derivatives was taken up.

"Physoperuvine", m.p. 153°, $[\alpha]_D$ $-0.8°$ (*c* 1.00, MeOH), was now shown to possess the following spectral properties: an ion peak at *m/z* 141.1123 (*m/z* 141.1154 calcd. for $C_8H_{15}NO$) in the high resolution mass spectrum, a band at 3200 cm^{-1} attributed to a hydroxyl/amino group but no band associated with carbonyl group in the IR spectrum (KBr) and eight carbon signals in the ^{13}C NMR spectrum taken in CD_3OD (δ 18.5 t, 24.1 t, 29.9 t, 30.5 t, 37.6 t ($-CH_2-$ × 5), 33.5 q (CH_3-N), 64.8 d (>CH-N) and 99.2 s (O-C<N)). In accord with the ^{13}C NMR data, the ^{1}H NMR spectrum ($C_5D_5N+CD_3OD$) showed a signal attributed to hydrogen on carbon carrying nitrogen at δ 3.88 (1H broad, >CH-N) along with signals at δ 1.4-2.6 (10H m, $-CH_2-$ × 5) and 2.89 (3H s, CH_3-N). The foregoing data taken together with the double bond equivalence of the molecule demanded "physoperuvine" to be bicyclic.

In order to clarify the nature of the hydroxyl/amino group, "physoperuvine" was subjected to benzoylation with benzoyl chloride in the presence of triethylamine to give "N-benzoylphysoperuvine", $C_{15}H_{19}NO_2$ (HRMS: m/z 245.1408 (M^+)) which displayed IR bands at 1700 and 1628 cm^{-1} assigned to a carbonyl group in a six- or larger-membered ring and an amide group, respectively. The ^1H NMR spectrum ($CDCl_3$) of this benzoyl derivative disclosed signals at δ 1.4-2.2 (6H m, $-CH_2- \times 3$), 2.2-2.7 (4H m, $-CH_2- \times 2$), 2.82 (3H s, CH_3-N-C=O), 4.60 (1H broad, >CH-N-C=O) and 7.36 (5H m, aromatic H). These findings demonstrated that "physoperuvine" possessed a >CH-N(CH_3)-C<OH system and, on benzoylation, furnished a >CH-N(CH_3)-COC_6H_5 and a >C=O system. Furthermore, on treatment with deuterium oxide in the presence of alkali, "N-benzoylphysoperuvine" gave a tetradeuterio-derivative, "N-benzoylphysoperuvine-d_4" (HRMS: m/z 249.1664 (M^+)), the ^1H NMR spectrum of which differed from that of the former only in the absence of four hydrogen signals at δ 2.2-2.7, indicating that two α-methylene groups were present next to the carbonyl group in "N-benzoylphysoperuvine". The high resolution mass spectrum of "N-benzoylphysoperuvine" showed, in addition to the molecular ion peak at m/z 245.1408 (rel. int. 86%), a base peak at m/z 136.0762 corresponding to the elemental composition $C_8H_{10}NO$ and assignable to the protonated acylamine peak $C_6H_5CON^+H_2CH_3$, while in the spectrum of its tetradeuterio-derivative, the protonated acylamine peak appeared at m/z 137.0826 (rel. int. 52%) which corresponds to the elemental composition C_8H_9DNO. This shift of the protonated acylamine peak by one mass unit is a characteristic feature of α,α-dideuteriocycloalkylamides.[2] Consequently, "N-benzoylphysoperuvine" was thought to have the structure **6** and "physoperuvine" the bridged amino-alcohol structure **7**. However, the structure of "physoperuvine" (**7**), made up of a four-membered ring system was much strained and, therefore, considered unlikely. The improbability of the bridged amino-alcohol structure (**7**) became more apparent from the observation that the band width at half height of the broad signal for the lone methine hydrogen in the ^1H NMR spectrum of "N-benzoylphysoperuvine" was found to be the same as that of "N-benzoylphysoperuvine-d_4", inspite of the fact that the four-methylene hydrogens next to the carbonyl in the former are replaced by heavy hydrogens in the latter. These results indicated that "physoperuvine" is probably a bridged amino-alcohol derivable from 4-methylaminocycloheptanone rather than 3-methylaminocycloheptanone as was earlier deduced.


5: R=H
6: R=COC_6H_5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For unambiguous elucidation of the structure of "physoperuvine", it was subjected to an X-ray crystallographic analysis and, to our surprise, it was revealed to be a hydrochloride. In agreement of this observation, the result of elemental analysis of "physoperuvine" also matched with the molecular formula, $C_8H_{15}NO \cdot HCl$. The crystals of "physoperuvine", characterized as the monohydrochloride, belong to the orthorhombic space group $P2_12_12_1$, cell dimensions are a=10.282 (1), b=10.026 (1) and c=8.900 (1) Å, and the calculated density is 1.249 g/cm^3 for Z=4 (M=177.67; $C_8H_{15}NO \cdot HCl$). A total of 872 independent reflections within $2\theta=135°$ (Cu-K_α radiation) were collected using a computer-controlled diffractometer. The structure was solved by the direct method. Approximate coordinates of non-hydrogen atoms were refined by the block-diagonal least-squares method with anisotropic temperature factors to reduce the R-factor of 0.09. All the hydrogen atoms were located in the difference Fourier map and included further refinement with isotropic temperature factors. The final R-factor is 0.086.

A stereoscopic view of the molecule is shown in Fig. 1, and bond lengths for non-hydrogen atoms are shown in Table I.

They are all normal for the expected structure. The six-membered ring is in a chair conformation and the seven-membered ring in a boat conformation. In the crystalline state, the chloride atom is involved in N-H- - -Cl and O-H- - -Cl hydrogen bonding interactions in the

Table I. Bond lengths (Å)

C(1) – C(2)	1.567(7)	C(1) – N	1.567(6)
C(2) – C(3)	1.566(7)	C(5) – N	1.536(6)
C(3) – C(4)	1.569(7)	N – C(8)	1.513(7)
C(4) – C(5)	1.512(7)	N- - -Cl	3.08
C(5) – C(6)	1.541(7)	N-H- -Cl	2.05
C(6) – C(7)	1.564(7)	O- - -Cl	3.04
C(7) – C(1)	1.558(7)	N-H- -Cl	2.08

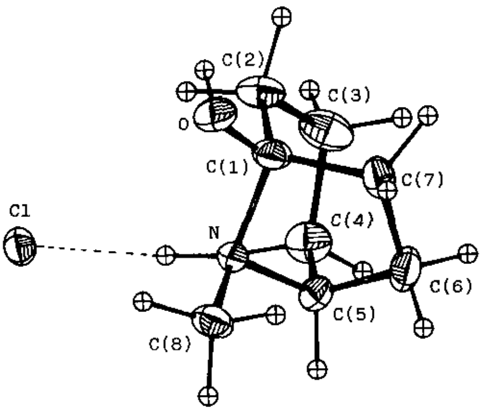


Fig. 1 ORTEP drawing of physoperuvine monohydrochloride

Supplementary Material; Atomic coordinates

Atom	x/a	y/b	z/c
Cl(1)	0.7889	0.7135	–0.6858
C(6)	0.7021	0.6729	–0.0896
C(7)	0.6199	0.7997	–0.1292
C(1)	0.6588	0.8347	–0.2936
N(1)	0.6991	0.6944	–0.3564
C(4)	0.7861	0.6414	–0.2290
C(3)	0.9151	0.7123	–0.2379
C(2)	0.8950	0.8658	–0.2097
C(7)	0.7813	0.9193	–0.3087
O(1)	0.5603	0.8889	–0.3814
C(8)	0.5834	0.6044	–0.3903
H(5)	0.810	0.537	–0.231
HN	0.750	0.696	–0.462
H(61)	0.763	0.690	0.003
H(62)	0.633	0.589	–0.061
H(71)	0.516	0.781	–0.115
H(72)	0.643	0.882	–0.048
H(41)	0.960	0.693	–0.355
H(42)	0.986	0.668	–0.150
H(31)	0.985	0.923	–0.232
H(32)	0.874	0.883	–0.087
H51	0.817	0.920	–0.432
H52	0.761	1.024	–0.275
H(81)	0.499	0.610	–0.296
H(82)	0.613	0.506	–0.402
H(83)	0.540	0.632	–0.495
HO	0.595	0.948	–0.400

adjacent molecules and the net work of the hydrogen bonds are made in the direction of c axis.

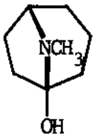
The absolute configuration was determined by using the anomalous dispersion of chlorine and oxygen atoms for Cu-K_α radiation. For the application of the Bijvoet method, 12 sets of (hkl), $(h\bar{k}\bar{l})$, $(\bar{h}\bar{k}l)$ and $(hk\bar{l})$ reflections with large values of ΔFc/<Fc> were selected. The signs of the corresponding ΔFo and ΔFc values are in good agreement with each other for all 12 reflections, thus indicating that the actual absolute configuration corresponds to that shown in the figure. As a result, the absolute stereostructure of "physoperuvine" has been elucidated as that represented by formula **3**.

The CD spectrum of "N-benzoylphysoperuvine" showed a positive Cotton effect at 288 nm ([θ] +7809, MeOH) which was opposite to that of R-(–)-4-methylcycloheptanone ($[\alpha]_{307}^{\mathrm{trough}}$ –2150°, $[\alpha]_{258}^{\mathrm{peak}}$ +1549°, MeOH),[3] also demonstrating the absolute configuration at C-5 of "physoperuvine" to be S. This conclusion from the CD spectrum matched with that by the X-ray crystallographic analysis.

The free base, physoperuvine, m.p. 68–70°, derived from the hydrochloride was shown to have the following spectral properties: HRMS: m/z 141.1172 (M^+); IR (KBr): 3100 (hydroxyl) and 1702 cm^{-1} (cycloheptanone); ^1H NMR ($CDCl_3$) δ 1.0–2.2 (10H m), 2.36 (3H s), 3.15 (1H broad) and 3.40 (1H broad, disappeared with D_2O); ^{13}C NMR (C_5D_5N): δ 19.3 t, 24.8 t, 25.6 t, 31.2 q, 32.1 t, 35.6 t, 59.9 d and 79.7 s. Benzoylation of the free base gave the N-benzoate (**4**) which was found identical with the previous "N-benzoylphysoperuvine".

The form of existence of physoperuvine remained to be clarified. In the ^{13}C NMR spectrum of physoperuvine, no signal due to carbonyl carbon was observed but that due to carbon bonded to nitrogen and oxygen was found at δ 79.7. However, because a very weak absorption band for carbonyl group was seen at 1702 cm^{-1} in the IR spectrum of physoperuvine, the possibility of ring-chain tautomerization may also be considered. This assumption gained credence from a weak positive Cotton effect ($[\theta]_{288}$ +174 (MeOH)) displayed by physoperuvine compared to that of

N-benzoylphysoperuvine ($[\theta]_{288}$ +7809 (MeOH)) which is exclusively in the amino-ketone form (**4**). The data further indicated that the proportion of the amino-ketone form (2) and the bridged amino-alcohol form (1) are in the ratio of 1:45, provided that the molecular ellipticity of physoperuvine in the amino-ketone form (2) is the same as that of N-benzoylphysoperuvine (**4**). On the other hand, it is concluded that physoperuvine hydrochloride exclusively exists in the amino-alcohol form (**3**) in the crystalline state as has been revealed by the X-ray analysis. Furthermore, no Cotton effect was observed in the CD spectrum of physoperuvine hydrochloride which showed that physoperuvine hydrochloride is present only in the amino-alcohol form (**3**) also in solution.



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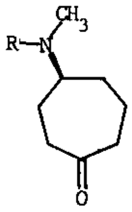
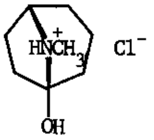


2: R=H
4: R=COC$_6$H$_5$



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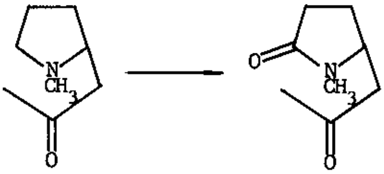
Erroneous conclusion previously drawn for the structure of physoperuvine is due to the anomalous fragmentation behavior of N-benzoylphysoperuvine under electron impact and improper assumption of identity of N,N-dimethylphysoperuvinium iodide with the methiodide of synthetic 3-dimethylaminocycloheptanone. N,N-dimethylphysoperuvinium iodide gave m.p. 266-268° and ^{1}H NMR data (δ 3.16 (9H s, CH_3-N), 3.52 (1H m, >CH-N), $CDCl_3$), while the methiodide from the synthetic 3-dimethylaminocycloheptanone afforded m.p. 200-203° and ^{1}H NMR data (δ 3.18 (9H s, CH_3-N), 3.88 (1H m, >CH-N), $CDCl_3$).

The revised structure of physoperuvine fits well the present-day knowledge of the biogenesis of tropane bases.[4] The intermediate, hygrine (**8**) formed from ornithine and a C_3-unit may, on oxidation, give rise to a pyrrolidone derivative (**9**) and subsequently the bridged carbinolamine derivative related to physoperuvine by aldol condensation.



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It is worth mentioning in this connection that the acute toxicity in mice (Std:ddY strain, 21-25 g, i.p., up-and-down method) was weaker in the hydrochloride (887 mg/kg) than in the free base (284 mg/kg).

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