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STRUCTURE AND SYNTHESIS OF PHYSOPERUVINE: X-RAY CRYSTAL AND MOLECULAR STRUCTURES OF THE N-BENZOYL DERIVATIVES OF (±)-3- AND (+)-4-METHYLAMINOCYCLOHEPTANONE

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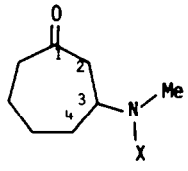
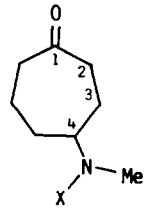
Abstract - Single-crystal X-ray analyses have defined the structures and solid-state conformations of (±)-*N*-benzoyl-3-methylaminocycloheptanone [(±)-3] and (+)-*N*-benzoyl-4-methylaminocycloheptanone [(+)-4]. Resolution of (±)-[4-methylaminocycloheptanone ⇌ 1-hydroxytropane] to yield the (+)-enantiomer, identical in all respects with the free base from natural (+)-physoperuvine, was achieved *via* the di-*p*-toluoyl-(+)-tartrate salt.

Physoperuvine, an alkaloid occurring as its (+)-form (and possibly also as its racemate) in the leaves and roots of the Indian plant *Physalis peruviana* L., was earlier assigned structure 1, *i.e.* 3-methylaminocycloheptanone, by Ray *et al.*[1,2] on the basis of chemical and spectroscopic studies. Recently, one of us[3] presented detailed evidence of a similar character which indicated that this formulation would have to be revised, most probably to 4-methylaminocycloheptanone 2. A re-investigation of this structural problem by Ray *et al.*,[4] chiefly *via* an X-ray crystallographic analysis, revealed that (+)-physoperuvine was, in reality, a hydrochloride salt with an absolute configuration represented by 6. Base treatment of this salt generated the



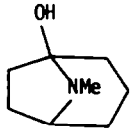
1 X = H

3 X = PhCO



2 X = H

4 X = PhCO



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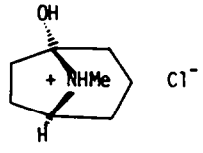

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free base, m.p. 68 - 70 °C, which on benzoylation yielded an *N*-benzoyl derivative apparently identical with the previously described *N*-benzoylphysoperuvine, m.p. 136 - 137 °C.

We here present the results of our X-ray diffraction studies on the *N*-benzoyl derivatives of 3 and 4, which led us independently to conclude that the structure of the free base is as shown (2⇌5), and describe the total synthesis of the optically-active base from which natural physoperuvine is derived.

Syntheses of racemic 3 and 4 have been described elsewhere.[3] A single-crystal X-ray analysis not only served to confirm the structure assigned to (±)-3, which crystallizes in the monoclinic system, space group $P2_1/c$, but also revealed that crystals of this product differed from either of the samples provided by Professor Ray which, although designated (±)- and (+)-4, were found to be identical on the basis of their X-ray diffraction data (*vide infra*).

The crystal structure of (±)-3 was solved by direct methods.[5] Full-matrix least-squares adjustment of atomic positional[6] and thermal parameters converged to $R^7 = 0.050$ over 1552 reflections. A view of the solid-state conformation is provided in Figure 1 along with interatomic distances and angles. Bond lengths and angles are close to expected values. Analysis of the endocyclic torsion angles indicates that the cycloheptanone ring is best described as a slightly skewed chair form with an approximate C_s symmetry plane passing through C(4) and the mid-point of the C(1)-C(7) bond. The pseudo-equatorial *N*-benzoyl substituent, with C(2)-C(3)-N(9)-C(10) and C(4)-C(3)-N(9)-C(10) torsion angles of -53.5 and 72.8°, respectively, is disposed so that the oxygen atom in the planar amide moiety is rotated by only 9.7° from that orientation in which it would eclipse the hydrogen atom at the ring carbon atom bearing this substituent [C(3)].

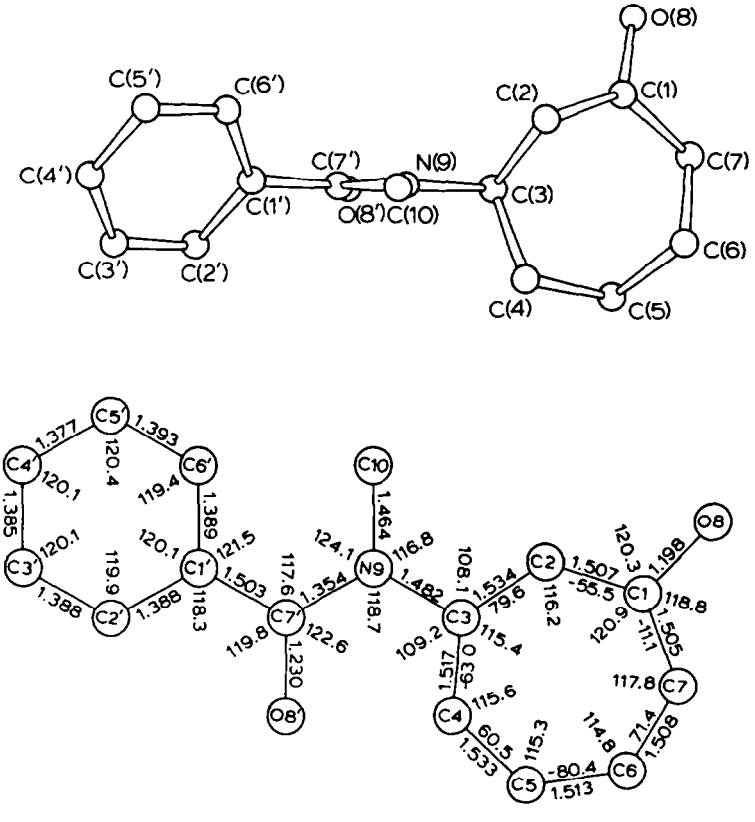

Figure 1. Solid-state conformation, bond lengths (σ 0.003-0.005 Å), bond angles (σ 0.2-0.3°), and cycloheptanone ring torsion angles (σ 0.3°) in (±)-3.

Crystallization of synthetic (±)-4 from several solvent systems consistently yielded extremely thin plates belonging to space group $Pna2_1$ of the orthorhombic system; no evidence for polymorphism was found. Since both enantiomers must be present in these crystals, we concluded that (±)-4 is not resolved spontaneously upon recrystallization. Consequently, the samples provided by Professor Ray, which proved to be identical on the basis of their X-ray diffraction patterns, must have been either mislabelled or misidentified and both were really (+)-4 which also crystallizes in the orthorhombic system, but in this case the space group is $P2_12_12_1$ with four molecules of one enantiomer per unit cell.[8] Crystals of (+)-4 yielded X-ray data superior to those from synthetic (±)-4, and so we elected to settle the structural issue by performing an analysis of the chiral *N*-benzoyl derivative provided by Professor Ray.

Solution of the crystal structure of (+)-4 was effected by direct methods.[5] Refinement of non-hydrogen atom positional[6] and thermal parameters converged to $R^7 = 0.078$ over 678 reflections. Interatomic distances and angles are provided in Figure 2 which also shows the solid-state conformation of 4. These results unequivocally established that 4 correctly represents *N*-benzoylphysoperuvine from which it follows that (2⇌5) must represent the free base. Bond lengths in 4 are normal and close to corresponding values in 3. The substitution pattern in 4 yields torsion angles in the cycloheptanone ring which are related by an approximate C_2 axis passing through C(1) and the mid-point of the C(4)-C(5) bond, and the ring has a twist-chair form. Here, as in (±)-3, the torsion angles associated with the orientation of the pseudo-equatorial *N*-benzoyl substituent [C(3)-C(4)-N(9)-C(10) 73.6°; C(5)-C(4)-N(9)-C(10) -55.0°] indicate that the car-

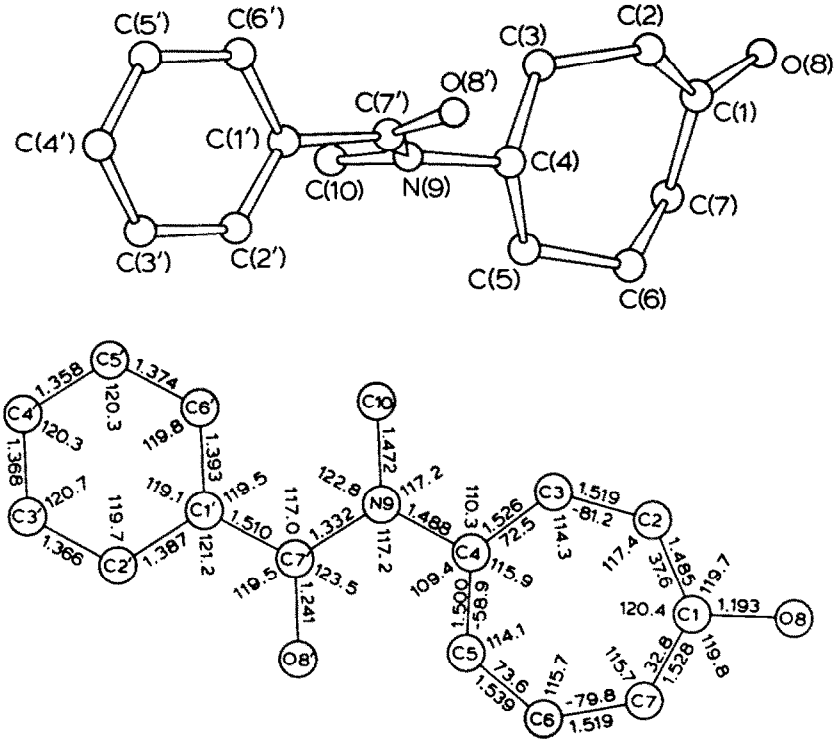

Figure 2. Solid-state conformation, bond lengths (σ 0.009-0.018 Å), bond angles (σ 0.6-1.1°), and cycloheptanone ring torsion angles (σ 0.8-0.9°) in (+)-4.

bonyl oxygen atom in the planar amide moiety nearly eclipses (Δ = 9.3°) the ring hydrogen atom at the carbon atom [C(4)] bearing this substituent. The occurrence of this common conformational feature in the absence of any strong inter- or intramolecular interactions in crystals of both (±)-3 and (+)-4 indicates that it must be preferred by such systems.

After several unsuccessful attempts to resolve (±)-2 *via* its salts with (+)-camphor-10-sulfonic acid, (+)- and (-)-α-bromocamphor-π-sulfonic acids, (+)-tartaric acid, and (+)- and (-)-mandelic acid, and also *via* its semioxamazone using (+)-α-phenethylsemioxamazide,[9] a partial resolution was achieved *via* its acid salt with di-*p*-toluoyl-(+)-tartaric acid.[10] Crystallization of this salt from hot acetone furnished a very sparingly soluble fraction which proved to be identical with the acid salt derived from the same acid and a sample of the free base of natural (+)-physoperuvine supplied by Professor Ray. The salt was basified in aqueous solution, and the free base was isolated by continuous ether extraction. The base, purified by vacuum sublimation and crystallization from dry acetone, had m.p. 47-48 °C, alone or mixed with an authentic sample[11] (m.p. 47 - 48 °C) of the free base of natural physoperuvine. The optical rotation of our product was too small to measure reliably, so the free base was *N*-benzoylated to 4 which proved to be identical in all respects with (+)-*N*-benzoylphysoperuvine.[1-3] Evidently, the resolution yielded the base corresponding to natural (+)-physoperuvine. Attempts to extend the fractional crystallization of this salt to achieve separation of the salt of the enantiomeric base were unsuccessful.

EXPERIMENTAL

Crystal Data. — (±)-*N*-Benzoyl-3-methylaminocycloheptanone (±)-3, $C_{15}H_{19}NO_2$, M = 245.32, Monoclinic, a = 12.943(5), b = 13.705(6), c = 7.557(3) Å, β = 102.59(2)°, U = 1308.3 Å^3, Z = 4, D_c = 1.245 g cm^{-3}, μ(Cu-K_α, λ = 1.5418 Å) = 6.7 cm^{-1}. Space group $P2_1/c$ (C_{2h}^5) uniquely from systematic absences: $0k0$ when $k \neq 2n$; $h0l$ when $l \neq 2n$.

(+)-*N*-Benzoyl-4-methylaminocycloheptanone (+)-4, $C_{15}H_{19}NO_2$, M = 245.32, Orthorhombic, a = 10.225(4), b = 20.612(8), c = 6.423(3) Å, U = 1353.7 Å^3, Z = 4, D_c = 1.204 g cm^{-3}, μ(Cu-K_α) = 6.4 cm^{-1}. Space group $P2_12_12_1$ (D_2^4) uniquely from systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$.

(±)-*N*-Benzoyl-4-methylaminocycloheptanone (±)-4, $C_{15}H_{19}NO_2$, M = 245.32, Orthorhombic, a = 6.43(1), b = 20.61(2), c = 10.38(1) Å, U = 1376 Å^3, Z = 4, D_c = 1.184 g cm^{-3}, μ(Cu-K_α) = 6.3 cm^{-1}. Space group $Pna2_1$ (C_{2v}^9) or $Pnma$ (D_{2h}^{16}), with b and c axes interchanged, from systematic absences: $0kl$ when $k + l \neq 2n$, $h0l$ when $h \neq 2n$; with Z = 4, an ordered structure requires $Pna2_1$ since 4 lacks either $\bar{1}$ or m point symmetry.

Crystallographic Measurements.— Preliminary unit-cell parameters and space group information were obtained from oscillation and Weissenberg photographs (Cu-K_α radiation) recorded from crystals of dimensions *ca.* 0.05 x 0.14 x 0.50 mm for (±)-3, 0.04 x 0.22 x 0.30 mm for (+)-4, and 0.01 x 0.20 x 0.50 mm for (±)-4. Intensity data, measured on an Enraf-Nonius CAD-3 automated diffractometer as described previously[12] (Ni-filtered Cu-K_α radiation; θ-2θ scans, θ_{max} = 67°) yielded 1442 [(±)-3] and 678 [(+)-4] observed [$I > 2.0\sigma(I)$] reflections out of totals of 2341 and 1301 independent measurements, respectively. The observed data were corrected in the usual way for Lorentz and polarization effects. Refined unit-cell parameters for (±)-3 and (+)-4 were derived by least-squares treatment of the diffractometer setting angles for 40 high order (28° < θ < 55°) reflections widely separated in reciprocal space; for (±)-4 only 24 reflections (21° < θ < 30°) were used.

Structure Analyses.- Both crystal structures were solved by direct methods by use of MULTAN76.[5] Full-matrix least-squares adjustment of atomic positional[6] and thermal parameters [anisotropic C, N, O; isotropic H for (±)-3, fixed H contributions for (+)-4] converged to R = 0.050 for (±)-3 and R = 0.078 for (+)-4.

Atomic scattering factors used in the structure-factor calculations were those for oxygen, nitrogen, and carbon from ref. 13, and for hydrogen from ref. 14. In the least-

squares iterations, $\sum w\Delta^2$ ($\Delta = ||F_o| - |F_c||$) was minimized with weights, w, assigned as follows: $\sqrt{w} = 1$ for $|F_o| \leq 12.0$, and $\sqrt{w} = 12.0/|F_o|$ for $|F_o| > 12.0$; this scheme showed no systematic dependence of $\langle w\Delta^2 \rangle$ when analyzed in ranges of $|F_o|$ and $\sin\theta$.

Resolution of 4-Methylaminocycloheptanone (1-Hydroxytropane) (2⇌5). - The racemic base was synthesized as described earlier[3] [m.p. 75 °C, ν_{max}(KBr disc) 3120 cm^{-1} (OH), virtually no C=O band]. When the base (1.41 g, 0.10 mol) in dry ether (25 ml) was cooled and mixed with di-*p*-toluoyl-(+)-tartaric acid monohydrate (4.05 g, 0.10 mol) in dry ether (25 ml), the salt was precipitated immediately. The suspension was kept at 0 °C overnight, then filtered, and the salt was washed thoroughly with dry ether, then dried *in vacuo* (yield 5.25 g, 100%). The salt separated from dry acetone as glistening feathery needles, m.p. 143 - 144 °C (decomp.), with shrinking from 120 °C (Found: C, 63.6; H, 6.4. $C_{28}H_{33}NO_9$ requires C, 63.7; H, 6.3%). This salt (4.0 g) was boiled under reflux with dry acetone (240 ml) for several minutes, then the suspension was filtered hot. The residue was washed with a little hot acetone, then dried *in vacuo*; yield 0.64 g, m.p. 184 - 185 °C (decomp.) alone or mixed with the salt [m.p. 185 °C (decomp.)] prepared from (+)-physoperuvine base and the same acid (Found: C, 63.55; H, 6.3%). This salt (0.60 g) was dissolved in warm water (100 ml) and the solution cooled during the addition of solid KOH, with continual agitation, until strongly basic. The solution was subjected to continuous ether extraction for 24 h. The extract was dried (K_2CO_3) and concentrated, leaving a crystalline residue (0.22 g, 100%) of the resolved base. Purification of the base was effected by vacuum sublimation [75 - 80 °C (bath)/ 0.03 mm Hg] and crystallization from dry acetone, from which it separated as elongated prisms, m.p. 47 - 48 °C, alone or mixed with an authentic sample (m.p. 47 - 48 °C) of the base derived from natural (+)-physoperuvine (Found: C, 68.1; H, 10.5; N, 10.0. $C_8H_{15}NO$ requires C, 68.0; H, 10.7; N, 9.9%). G.l.c., t.l.c., and i.r. comparisons revealed that the two bases were identical in all respects except, possibly, optical rotation. The resolved base was *N*-benzoylated as described previously[3] and the product crystallized from light petroleum (b.p. 60-90 °C)-benzene (3:2) as needles, m.p. 135-136 °C alone or mixed with an authentic sample of the amide (m.p. 136 °C) derived from the free base of natural (+)-physoperuvine: $[\alpha]_D^{24}$ +93.6° (*c* 1.3, $CHCl_3$) (lit.,[2] +95.6°). Spectral and t.l.c. comparisons confirmed the identity of the two amides. Thus, resolution yielded the enantiomer identical in all respects with the 'natural' base.

Attempts to separate the di-*p*-toluoyl-(+)-tartrate salt remaining in the mother liquors into fractions, one of which might lead to the enantiomeric base, were unsuccessful.

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7. $R = \sum||F_o| - |F_c||/\sum|F_o|$.
8. Mixed m.p. comparisons made earlier (ref. 3) are probably invalid.
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