Communications to the Editor

[Chem. Pharm. Bull. 30(10)3856—3859(1982)]

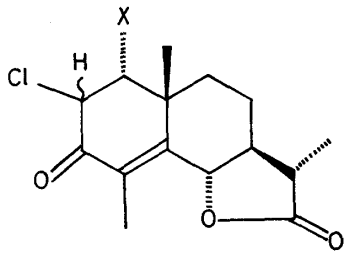
CONFORMATION OF CHLORODIHYDROSANTONINS

Seiichi Inayama,*[a] Nobuko Shimizu,[a] Hitoshi Hori,[a] Tetushi Ohsaka,[a] Tadaaki Hirose,[a] Tetsuichi Shibata,[a] and Yoichi Iitaka[b]
Pharmaceutical Institute, School of Medicine, Keio University,[a] 35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan
and Faculty of Pharmaceutical Sciences, University of Tokyo[b] 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

The structure and conformation of newly obtained 2β-chloro-1,2-dihydro-ℓ-α-santonin (1) were elucidated in comparison with those of 2α-chloro-1,2-dihydro- (2) and 1α,2β-dichloro-1,2-dihydro-ℓ-α-santonin (3) and firmly characterized by IR, NMR, MS and CD spectrometry and X-ray crystallographic analysis. While both 2β-chloro- (1) and 1α,2β-dichloroenone (3) were found to take a half-boat conformation (A), 2α-chloroisomer (2) was shown to be in the inverted half-chair conformation (B).

KEYWORDS——2α-chloro-1,2-dihydro-ℓ-α-santonin; 2β-chloro-1,2-dihydro--ℓ-α-santonin; 1α,2β-dichloro-1,2-dihydro-ℓ-α-santonin; 2-chloro-4β,5αH-dihydro-ℓ-α-santonin; 2-chloro-4α,5βH-dihydro-ℓ-α-santonin; half-chair conformation; half-boat conformation; stereoviews; NMR; IR; UV; CD; X-ray diffraction

In the course of our continuing studies on biologically active substances in santonin derivatives, we isolated a new 2-chloro-1,2-dihydro-ℓ-α-santonin along with the stereo isomer previously obtained.[1,2] Among four possible stereo stereostructures these two chloroenones are considered to be either the 2β-equatorial chloro isomer in a half-chair form or the 2β-equatorial chloro isomer in a half-boat form rather than the corresponding one of 2α-axial or 2β-axial chloro isomer. However, it is not so easy to determine properly whether a half-boat or a half-chair form is favored by the two conformational isomers in question, even though one of them is now in hand as the first instance of isolation of a half-boat form in a fused cyclohexenone system. Hendrickson and Bogard deduced that "santonindichloride" (mp 172-173°C) prepared by chlorination of ℓ-α-santonin[1] is shown to be 1β,2α-dichloro-1,2-dihydrosantonin by a simple conformation analysis.[2] Ogura et al. have recently suggested that the configuration should be revised to be 1α,2β based on the coupling constant between vicinal protons at the C(1) and C(2) positions in the proton magnetic resonance spectrum (NMR) and the X-ray diffraction data of 1α,2β,4α,5β-tetrachlorotetrahydrosantonin.[3] However, the conformation with a crowded surrounding highly substituted by the chlorine atoms seems not to parallel those of the foregoing less substituted 2-chloro- (1 and 2) and 1,2-dichloro-1,2-dihydro-4-en-3-ones (3) as mentioned below. When "dihydrosantonin oxide" (4α,5α-epoxy-3-one) derived from "santoninoxide"[1] was treated with cold concentrated hydrochloric aicd, a new levorotatory 2-chloro-4-en-3-one (1) with a higher melting point, $C_{15}H_{19}O_3Cl$ (1), mp 194-196°C,



(1) x= H, 2αH (2) x= H, 2βH (3) x= Cl, 2αH

$[\alpha]_D^{20}$ -82.9° ($CHCl_3$, c 0.97),[4] was obtained along with a small amount of dextrorotatory "2α"-chloro-1,2-dihydro-ℓ-α-santonin (2) with a lower melting point, $C_{15}H_{19}O_3Cl$ (2), mp 171-173°C, $[\alpha]_D^{20}$ +11.9° ($CHCl_3$, c 1.00) [mp 168-170°C[2]], the latter being almost exclusively produced at elevated temperatures. Here we report the elucidation of unique half-boat conformations of the new 2β-chloroenone (1) and the related 1α,2β-dichloroenone (3) in comparison with an ordinary half-chair form of the 2α-chloroisomer (2) on the basis of X-ray diffrection of 1 and 3 as well as their chemical and spectral data described below.

Both chloroenones 1 and 2 were equally reduced to 1,2-dihydro-ℓ-α-santonin (4) with zinc dust in acetic acid. The same UV ($\lambda_{max}^{CHCl_3}$ 245 and 318 nm) and IR ($\nu_{max}^{CHCl_3}$ 1697 cm^{-1}) absorption in 1 as in 2 indicate the presence of equivalent α,β-unstaturated α'-chloroketone. The increment of IR carbonyl stretching of 1 compared to that of 4 (Δ~30 cm^{-1}) suggests that the halogen atom next to the ketone is equatorially oriented as in 2.[5] For comparison, 2-chloro-4β,5αH-dihydro- (5), $C_{15}H_{19}O_3Cl$, mp 162-164°C, $[\alpha]_D^{24}$ +18.0° ($CHCl_3$, c 0.10) (mp 150°C, prepared from 1,2-dichloro-4,5-dihydrosantonin)[2] and 2-chloro-4α,5βH-dihydro-ℓ-α-santonin (6), $C_{15}H_{19}O_3Cl$, mp 260-262°C, $[\alpha]_D^{24}$ -41.0° ($CHCl_3$, c 0.10) were prepared in reasonable yield by dehydrochlorination of 2,2-dichloro-4β,5αH-tetrahydro- (7) and 2,2-dichloro-4α,5βH-tetrahydro-ℓ-α-santonin (8)[6] with lithium bromide and lithium carbonate in dimethylformamide at 120°C, respectively. Although there is not discrepancy in the π-π* absorption (245 nm) between 2-chloro-4-en-3-ones (1 and 2) and 2-chloro-1-en-3-ones (5 and 6), NMR signals for the methyl at C(4) are illustrative with respect to the location of the olefin. In the former cases those appear as singlets in the lower field at 2.07 in 1 and 2.08 ppm in 2 both with a narrow spacing (2.0 Hz), corresponding to vinylogous methyl, whereas, in the latter case, they absorb as doublets in the higher field at 1.42 in 5 and 1.32 ppm in 6 both with a coupling constant of 6.0 Hz indicating the secondary methyl group. In comparison of the above-mentioned data for 1, 2, 5 and 6, the double bonds

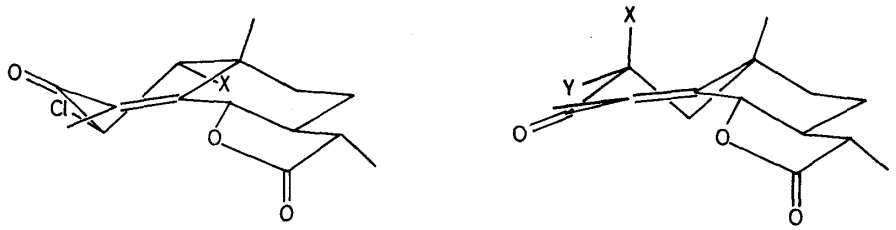


Fig. 1. (a) Conformation A (X= H, Cl) (b) B (X= Cl, Y= H; X= H, Y= Cl)

in the chloroenones in question (1 and 2) are definitely proved to locate between C(4) and C(5).

The new chloroenone (1) is thus clearly defined as the configurational isomer of 2 with respect to the C(2) chlorine atom and is formulated as 2β-chloro-1,2-dihydro-ℓ-α-santonin, whether the C(2) chlorine of 2 properly takes an α-configuration as stated in reference[7] or not. The former isomer (1) was equilibrated to the latter (2) with conc. hydrochloric acid in the warm condition, e·g· (1):(2)= ca. 40:60 at 70-90°C for 15 min. It seems reasonable to assume that 1 in a half-boat form A (X=H) could initially cause the inversion of its cyclohexenone ring leading to an unstable intermediate in half-chair form B (X= Cl, Y= H), which should be converted to the most stable 2α-equatorial chloroisomer (2) in the form B (X= H, Y= Cl) by epimerization at C(2), in order to release the non-bonded steric interaction between the 2β-axial chlorine atom and the 10β-methyl group. The C(2)-H NMR signal of 1 and 2 appeared at δ 4.58 (dd, J = 7.0, 11.0 Hz) and 4.72 (dd, J = 8.0, 12.0 Hz), respectively. From these coupling constants, the dihedral angle[8] between 2-H and 1α-H in 1, and that between 2-H and 1β-H in 2, are estimated to be nearly 40° and 160°, respectively. Therefore, the chlorine atoms at C(2) of both 1 and 2 are equatorially oriented in harmony with the aforementioned IR data, without regard to the conformation of the cyclohexenone ring. In fact, the chemical shift for the singlet angular methyl in 1 and 2 appeared at 1.37 and 1.45 ppm, respectively, owing to the anisotropic effect of the C(3) carbonyl. In the case of dichlorodihydrosantonin (3), the signal due to C(1)-H, C(2)-H and C(15)-H appeared at δ 4.20 (d, J = 11.0 Hz), 4.66 (d, J = 11.0 Hz) and 1.34(s), respectively. It is self-evident that 3, possessing diequatorial chlorines in a half-boat conformation (A), must be formed in a similar manner to 1 from a half-chair form (B) having 1α,2β-diaxial chlorines, which were originally produced under kinetically controlled conditions.

Since 2 and 4 exhibited negative CD Cotton effects, these are shown to be in a half-chair conformation (B) with respect to the cyclohexenone ring according to the inverse rule for α,β-unstaturated ketones in the CD spectrum.[9] On the other hand, the positive Cotton effects for 1 and 3 suggest that the new monochloro- (1) and dichloroenone (3) adopt a half-boat conformation (A) in solution, which has been confirmed by the X-ray analyses mentioned below. The absolute configuration of 1, 2 and 3 thus established accords with that deduced from their structural relationship to 4.

Recrystallization of 1 and 3 from ethyl acetate afforded coloress prisms, respectively, with crystal data as follows: $C_{15}H_{19}O_3Cl$ (1), M.W. 282.8, orthorhombic, a= 8.426, b= 22.859, c= 7.596 Å, U= 1463.1 Å^3, z= 4, Dc= 1.284 g·cm^{-3}, space group

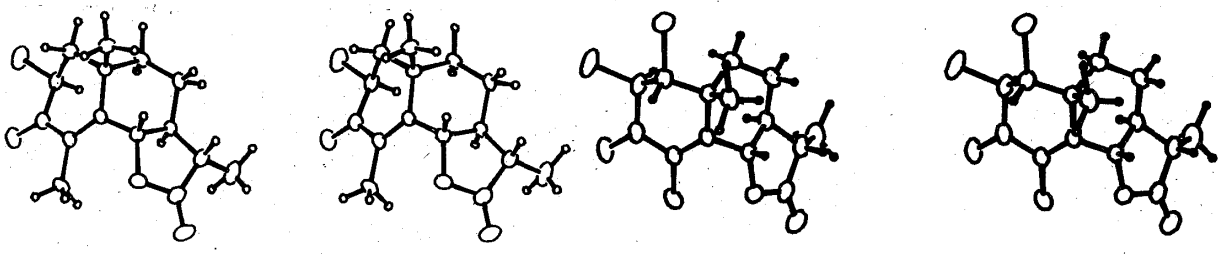


Fig. 2. (a) Stereoview of 1 (b) Stereoview of 3

$P2_12_12_1$. 987 Intensities were measured with a four-circle diffractometer with graphite monochromated Cu-Kα radiation. The crystal structures was solved by the heavy atom method and anisotropic refinement by block-diagonal least-squares, excluding hydrogen atoms, giving a final R value of 0.0493. A stereoview of the molecular structure is shown in Fig. 2(a). $C_{15}H_{18}O_3Cl_2$(3), M.W. 317.2, orthorhombic, a= 11.849, b= 12.903, c= 9.993 Å, U= 1527.8 $Å^3$, z= 4, Dc= 1.379 $g \cdot cm^{-3}$, space group $P2_12_12_1$. Some 1636 intensities were measured and calculated as mentioned above, and the final R value was shown to be 0.0582. A stereoview of 3 thus determined is illustrated in Fig. 2(b). It is now confirmed that the half-boat (A) and half-chair (B) conformation of each cyclohexenone ring, possessing all the equatorial configurations of every chlorine atom in 1 (or 3) and 2, agrees with those deduced from the NMR, IR and CD spectrometric evidence, respectively. Lastly a plausible reaction mechanism of formation of chloroenone (1) from α-epoxydihydrosantonin through 2,4-cyclopropan-3-one intermediate[10] is tentatively suggested. Further studies on the equilibration between 1 and 2 as well as their thermodynamic stabilities will be reported in a following paper.

ACKNOWLEDGEMENTS

One of the authors (S.I.) acknowledges in part an academic prize from the Miyata Foundation for this work. The authors' thanks are due to Miss S. Takei and Mr. K. Chiba of the Joint Laboratory of the school of Medicine, Keio University, for IR and MS measurements, respectively, as well as to Mr. Y. Okano of our Laboratory for his excellent technical assistance.

REFERENCES AND NOTES

1) E. Wedekind and K. Tettweiler, Ber., 64, 387 (1931).
2) J.B. Hendrickson and T.L. Bogard, J. Chem. Soc., 1962, 1678.
3) H. Ogura, H. Takayanagi, A. Yoshino and T. Okamoto, Chem. Pharm. Bull., 22, 1433 (1974).
4) Satisfactory UV, IR, NMR and EI, CI (isobutane)-MS spectrometric and elemental analysis data were obtained for all new and related compounds.
5) S. Inayama, Pharm. Bull., 4, 198 (1956).
6) 2,2-Dichloro derivative (7 and 8) [mp 200°C (dec) and mp 208°C (dec)] was newly obtained by chlorination of 4β,5αH-tetrahydro- and 4α,5βH-tetrahydro-ℓ-α-santonin with sulfuryl chloride, respectively.
7) Since the so-called "2α"-chloroenone (mp 168-170°C)[2] was prepared by the action of cold HCl and dihydrosantonin epoxide and assigned without unambiguous stereochemical evidence, it may be said to be coincident with our higher melting isomer (mp 196°C), i.e. 2β-chloroenone (1) based on its apparent formation in the same cold condition as in references,[1,2] even though the melting point of the stated compound happened to be similar to that of our lower melting isomer (mp 173°C), i.e. 2α-chloroenone (2) formed only in a warm condition.
8) R.J. Abraham and J.S.E. Holker, J. Chem. Soc., 1963, 806.
9) G. Snatzke, Tetrahedron, 21, 413, 421 (1965).
10) M. Yanagita and S. Inayama, J. Org. Chem., 19, 1423 (1954); references loc. cit.

(Received August 16, 1982)