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THE CONFIGURATIONS OF THE ISOMERIC 3,4-DIMETHYL-5-(1H)-2,2'-PYRROMETHENONES

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Pyrromethenones are known[1] to be essential partial structures of biologically relevant bile pigments (e.g. bilirubin) . According to our knowledge — apart from an "oxomethenone" structure[2] and several speculations — no configurational studies on the exocyclic double bond of this system have been published . In connection with studies on pyrrole pigments we have recently prepared the geometrical isomers of substituted benzal - pyrrolinones[3]. Their configurations were determined using Lanthanide Shift experiments (LIS) and Nuclear Overhauser Effect (NOE) measurements[3].

We are now reporting the assignments of configurations together with some conformational analyses of the geometrical isomers of a simple model compound : 3,4-Dimethyl-5-(1H)-2,2'-pyrromethenone (I) was obtained in the usual manner[4] by condensation of pyrrole-2-aldehyde and 3,4-dimethyl-Δ^3-pyrrolin-2-one ($CH_3OH/H_2O/NaOH$) in 70 % yield. The product is isomerically pure as evidenced by TLC . Mp.: 215^o ; MS : m/e = 188 (M^+) , fragmentation as well as elemental analysis is in accord with structure I ; NMR, 100MHz ($CDCl_3$, δ) 10.89 (s, H^1), 10.65 (broad s, $H^{1'}$), 7.04 (m, $H^{5'}$, $J_{5',3'}$ = 1.50 Hz, $J_{5',4'}$ = 2.50 Hz), 6.43 (m, $H^{3'}$, $J_{3',4'}$ = 3.50 Hz), 6.26 (m, $H^{4'}$), 6.14 (broad s, =CH-), 2.11 (broad s, CH_3^4), 1.85 (qu, CH_3^3 , $J_{CH_3^3,=CH-}$ = $J_{CH_3^3,CH_3^4}$ = 1.0 Hz) ppm. The coupling constants between $H^{1'}$ and $H^{3'}$, $H^{4'}$, $H^{5'}$ are in the order of 2. Hz, all further possible couplings are negligible (the signal assignments were deduced from decoupling experiments , Deuterium exchange and comparison with model compounds[3]).

The Z – Configuration of this isomer was independently derived from the following two experiments :

1. NOE measurements. Irradiation at the resonance frequency of the "4"-methyl group caused a thirty percent integral enhancement of the methine proton signal ($CDCl_3$/Argon). This result is well beyond the region documented[3] for the aforementioned benzal-condensates of Z - configuration (around twenty percent) — the corresponding E - isomers showing no detectable effect.

2. LIS measurements. LIS values in connection with a computer program (PDIGM)[5] which handles the geometrical problem, and an evaluation[6] of the confidence levels of the various hypotheses proved to be a valuable tool for configurational and conformational studies[3,7] of pyrrole compounds. The following data are shift values (Hz) of the NMR - resonances of I

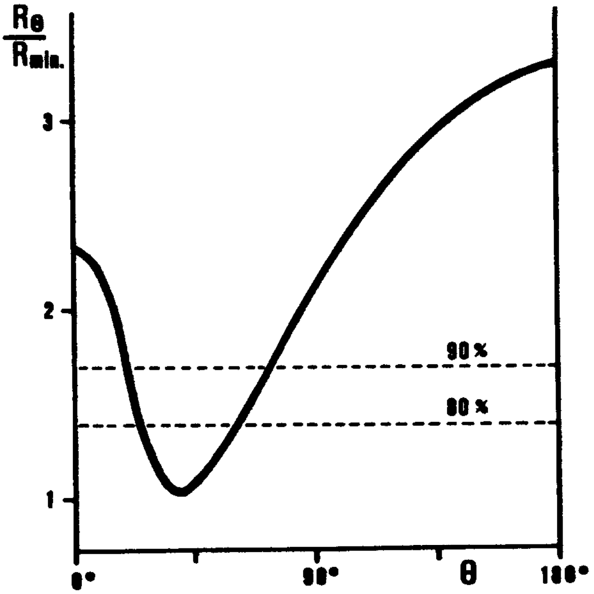

Fig. 1

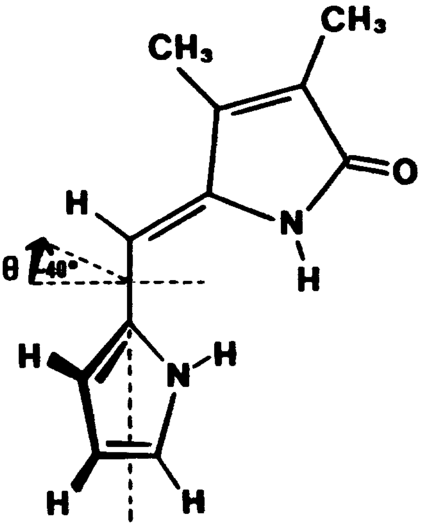

Fig. 2

($CDCl_3$; I : Tris-[dipivalomethanato]-Eu^{III} = 1 : 0.33 ; linear concentration dependence confirmed) : NH^1 107.0 , CH_3^3 124.5 , CH_3^4 48.0 , =CH- 24.0 , $NH^{1'}$ too broad for correct evaluation , $H^{3'}$ -30.0 , $H^{4'}$ -20.0 , $H^{5'}$ -33.5 , ± 0.3 Hz. Taking the carbonyl -O- atom as the coordination centre (justified by our previous LIS studies[3,7]) and including position averaged protons of the pyrrole ring the E configuration hypothesis can be rejected at a confidence level of 99 percent, as it is the case with those hypotheses concerning tautomeric structures of the system or alternative signal assignments.

Considering rotation around the pyrrole - methine bond (θ) a probability profile is obtained (Fig. 1. — the regions above the dashed lines represent conformational hypotheses which can be rejected at a confidence level of 80 and 90 percent resp., compared with the optimal one). The most probable conformation of Z-I ($R_{min.}$ = 0.078, φ = 130°, ϱ = 60°, r = 2.9 Å, compare[3,5,7]) is shown in Fig. 2 . A twisted syn conformation is thereby deduced.

Photoisomerization ("Hanau" TQ 150 lamp , Pyrex filter, CH_3OH, Argon, 4°C) affords after preparative TLC (Silica, $CHCl_3/CH_3OH$ = 20/1 ; R_f^{Z-I} = 0.6 , R_f^{E-I} = 0.2) the E-isomer of I : Mp.: 180° (accompanied by thermal isomerization) ; MS : m/e = 188 (M^+) ; NMR, 100MHz ($CDCl_3$, δ) : 10.62 (s, H^1) , 10.50 (broad s, $H^{1'}$) , 6.70 (m, $H^{5'}$) , 6.28 (m, $H^{3'}$) , 6.16 (m, $H^{4'}$) , 6.15 (s, =CH-), 2.09 (qu, CH_3^4) , 1.92 (s, CH_3^3) ppm , showing approximatly the same coupling characteristics as the Z-isomer.

The E-configuration was derived as before :

1 . NOE measurements. No NOE could be observed at the methine proton signal on irradiation at the "4"-methyl group frequency.

2 . LIS measurements. Application of the LIS method with the LIS values NH^1 124., CH_3^3 125., CH_3^4 49., =CH- 14., (±1 Hz) , $NH^{1'}$ 14., $H^{3'}$ 22., $H^{4'}$ 26., $H^{5'}$ 21., (±2 Hz) allowed the rejection of the corresponding Z configuration hypothesis at a confidence level of 98 percent. Because of the thermal instability (isomerization to the more stable Z-

isomer) in aprotic solvents the LIS values of E-I could not be determined with the accuracy needed for conformational analysis.

It has therefore been possible for the first time to isolate and characterize the geometrical isomers of a pyrromethenone as well as to allocate the preferred conformation of the Z-isomer. The thermal and photochemical isomerization and the correlation of conformation and configuration with the light absorbing properties are now being studied. The relevance of these findings to the chemistry and understanding of function and properties of bile pigments is evident.

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References

1. W.Rüdiger, Fortschr. Chem. Org. Naturst. 29, 61 (1971).
2. A.Gossauer and H.H.Inhoffen, Ann. Chem. 738, 18 (1970).
3. H.Falk, K.Grubmayr and O.Hofer, Mh.Chem. 106, in press.
4. H.Plieninger, H.Bauer and A.R.Katritzky, Ann.Chem. 654, 165 (1962).
5. M.R.Willcott III, R.E.Lenkinski and R.E.Davis, J.Am.Chem.Soc. 94, 1742 (1972).
6. W.C.Hamilton, Acta Cryst. 18, 502 (1965);
   R.E.Davis and M.R.Willcott III, J.Am.Chem.Soc. 94, 1744 (1972).
7. H.Falk, S.Gergely and O.Hofer, Mh.Chem. 105, 1004 (1974).