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THE STEREOCHEMISTRY OF REACTION OF 2-BENZYLIDENECYCLOHEXANONE WITH DITHIOCARBAMIC ACID

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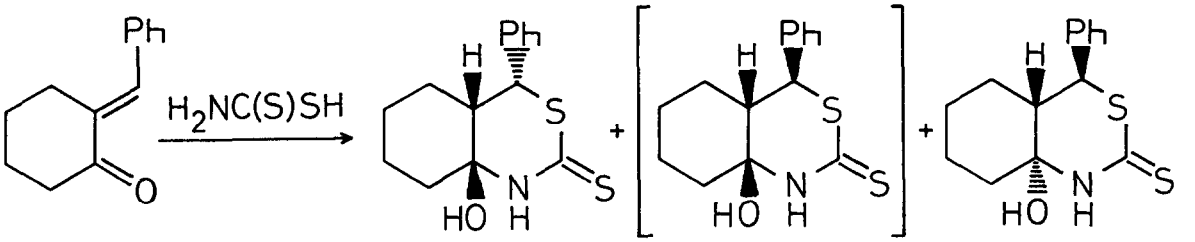
Abstract: The title reaction furnished stereoisomeric 2H-3,1-benzothiazine-2-thione derivatives (2-4), whose stereochemistry was determined by ^{1}H-NMR spectroscopy.

In an earlier study[1] we reported a stereospecific addition of dithiocarbamic acid to 2-arylidenecyclopentanones. In the present work we describe the reaction of 2-benzylidenecyclohexanone (1) with dithiocarbamic acid. In this reaction stereoisomeric 4-phenyl-8a-hydroxy-4,4a,5,6,7,8,8a-octahydro-2H-3,1-benzothiazine-2-thiones (2-4) were formed depending on the reaction conditions[2] (Scheme).[3]



1 2 3 4

Under the condition described in Method A 1 afforded an approximately 1:1 mixture of 3 and 4[4]. The ^{1}H-NMR data[5,8] showed the compounds to be epimers of C-8a. This was supported by the fact, that 3 could easily be converted into the trans-fused 4. Thus only 4 (m.p. 224-227°C)[6] could be isolated as a homogeneous product, because the interconversion had already been taken place under the crystallization of the crude product.

The interconversion is acid catalysed, so if the conditions were changed - longer reaction time or more hydrochloric acid was used (Method B) - only the formation of the more stable 4 could be detected. These experimental results can be well interpreted by the rapid epimerization of the kinetic product 3.

Drastic change could be observed in the isomeric composition of the reaction product by increasing of the hydrochloric acid employed. If we use only a quarter equivalent hydrochloric acid compared to the ammonium salt of dithiocarbamic acid (Method C), we could observe only the formation of the cis-fused 2 (m.p.

186-189°C)[6]. Its stereochemistry was deduced from the analysis of the H-4, H-4a, and OH signs[7], which was also supported by ^{1}H-^{1}H 1D NOE difference experiments[8]. This diastereomer - in contrast to 3 - was configurationally stable, even under the condition in Method B indicated.

Changing the quantity of hydrochloric acid used between the values in Methods C and B indicated, the formation of all the three isomers could be observed in different quantities depending on the hydrochloric acid actually used. The aromatic substitution of 1 (4-OMe, 4-Me, 4-Cl) practically did not change the isomeric composition of the reaction products.

References and Notes

1. Gy. Argay, A. Kálmán, P. Perjési, and D. Szabó, Acta Crystallogr. Sect. C, accepted for publication.
2. General procedure for addition reactions: To a solution of 0.175 mol of ammonium dithiocarbamate dissolved in 150 ml of 50% methanol, and cooled to -5°C, 25 ml (Method A), 40 ml (Method B), or 6.5 ml (Method C) of 6.5 N hydrochloric acid, cooled previously to -5°C was added dropwise, with stirring. Cooling and stirring was continued, and 0.03 mol of unsaturated ketone in methanol solution, previously cooled to -5°C, was added dropwise to the reaction mixture, which was then further stirred at this temperature for 3-4 hours. After completing the reaction (TLC), the mixture was diluted with water, the forming precipitate was filtered off, washed with water, dried, and purified by recrystallization from ethanol.
3. Although the compounds obtained are racemates, only one enantiomer is shown.
4. The crude product was analysed by ^{1}H-NMR spectroscopy in every case. The isomeric composition was deduced from the ratio of H-4 signals.
5. 3; ^{1}H-NMR (DMSO-d_6, 200 MHz; from the mixture of 3 and 4) δ 10.40 (1H, s, NH), 7.38-7.13 (5H, m, Ph), 6.20 (1H, d, $^4J_{OH,8(ax)}$=1.5Hz, OH), 4.83 (1H, d, $^3J_{4,4a}$=11.3Hz, H-4), 2.31 (1H, ddd, $^3J_{4a,5(ax)}$=$^3J_{4a,5(eq)}$=3Hz, H-4a), 1.87-0.90 (8H, m, aliphatic). 4; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 10.68 (1H, s, NH), 7.50-7.25 (5H, m, Ph), 6.29 (1H, d, $^4J_{OH,4a}$=1.2Hz, OH), 4.38 (1H, d, $^3J_{4,4a}$=11.7Hz, H-4), 2.17 (1H, m, H-8(eq)), 2.04 (1H, ddd, $^3J_{4a,5(ax)}$=11Hz, $^3J_{4a,5(eq)}$=4Hz, H-4a), 1.68-0.95 (7H, m, aliphatic).
6. Satisfactory elemental analyses, IR, and mass spectral data were obtained for this compound.
7. 2; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 10.93 (1H, s, NH), 7.50-7.25 (5H, m, Ph), 6.50 (1H, s, OH), 5.24 (1H, d, $^3J_{4,4a}$=3.5Hz, H-4), 2.28 (1H, m, H-8(eq)), 1.88 (1H, ddd, $^3J_{4a,5(ax)}$=11.5Hz, $^3J_{4a,5(eq)}$=3.5Hz, H-4a), 1.63-1.08 (7H, m, aliphatic).
8. ^{1}H-^{1}H 1D NOE difference data -H_{irr}(H_{obs}/NOE%/)- for 2: H-4(OH/8/,H-4a/6/), OH(H-4/6/), NH(H-8(eq)/3/); for 3: H-4(H-5(eq)/6/), OH(NH/5/,H-4a/14/), NH(OH/8/,H-5(eq)/4/); for 4: H-4(OH/6/), OH(H-4/6/), NH(OH/5/,H-8(eq)/5/).

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