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ACYCLIC STEREOSELECTION. ERYTHROSELECTIVE ALDOL CONDENSATION OF 4-ACYL-2,3-DIHYDRO-4H-1,4-BENZOTHIAZINE AND 10-ACYLPHENOTHIAZINE.

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Summary The title amides undergo aldol-type cross-condensation providing aldols of exclusive erythro configuration.The preferred *cis* geometry of the precursor amide enolate is likely to be at the origin of the erythro selection

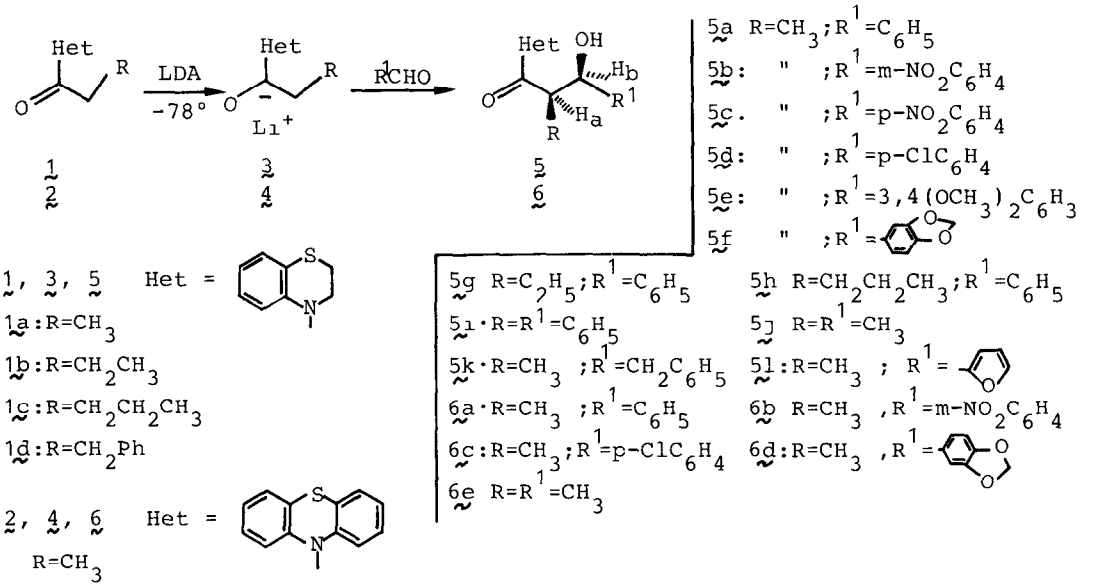
The stereochemistry of the aldol-type cross-condensation reaction of carboxylic acid derivatives has been investigated.Thus esters undergo aldol condensation with either threo[1] or erythro[2] stereoselectivity,whereas erythro selection has been observed for thiolesters,[3] lactones,[4] and thioamides.[5] The stereochemistry of the aldol product is closely bound up with the stereostructure of the enolate precursor such that *cis* enolates lead predominantly to erythro aldols and *trans* enolates provide mainly threo isomers.[1]

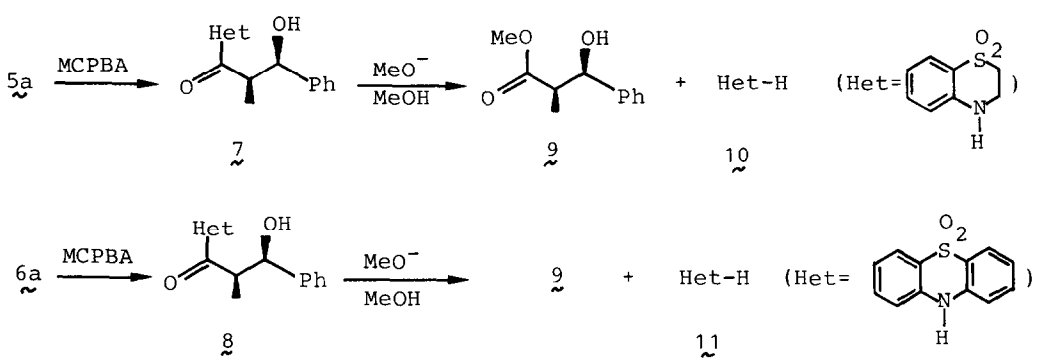
Despite its interest in biosynthesis,the stereochemistry of the aldol condensation of carboxamides has not much been explored;it has only been shown that N,N-dimethylpropionamide[5] and N,N-diisopropylpropionamide[6] do not exhibit any significant selectivity.The lack of stereoselection of these amides might likely be ascribed to the fact that related amide enolates may not have any preference for a *cis* or *trans* geometry.

As part of our researches concerning the condensation reactions of carboxamides[7] and lactams[8] we report here our results of the stereochemistry of the aldol condensation of 4-acyl-2,3-dihydro-4H-1,4-benzothiazine 1 and 10-acylphenothiazine 2.

Treatment of amides 1 and 2 with lithium diisopropylamide(LDA) in THF at -78° gives stable lithium enolates 3 and 4 respectively.Addition of aldehydes to 3 and 4 results in the ready formation of aldols 5 and 6(see Table).[9] All of the reactions of 1 and 2 proceed with virtually complete stereoselectivity The rather low values of the ^{1}H NMR coupling constants between H_a and H_b seem to indicate an erythro stereostructure for the aldols 5 and 6;however,unequivo-

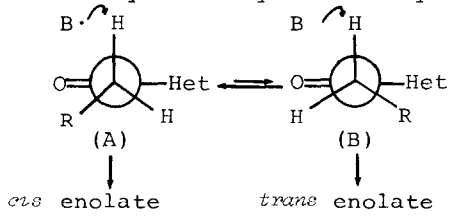
cal assignment of structure on this basis was not feasible, since we could not have in hand the related diastereomers of 5 and 6. Stereostructure was established by an indirect way deblocking of the heterocyclic moiety of 5 and 6 on oxidation to the corresponding sulfones 7 and 8 and subsequent treatment with methanolic sodium methoxide[10] afforded the known erythro β-hydroxy ester 9.[2]

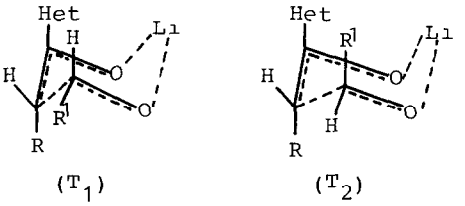




The stereochemistry does not change on varying the experimental conditions (i.e.: temperature, reaction time and reactants ratio) and aldols 5 and 6 do not isomerize to the corresponding threo diastereomers[11]. It is likely that enolates 3 and 4 adopt a *cis* geometry, as the partial double bond character of the C-N bond of amides makes conformer A energetically more stable than conformer B, which experiences a large steric interaction between the methyl and heterocyclic groups. Abstraction of the α-proton perpendicular to the sp^2 plane of the amide function would generate *cis* and *trans* enolates from conformer A and B

respectively[12]. In this view the observed erythro stereoselectivity may be explained in terms of ordered transition state energy. Six-centre chair-like transition state T_1, that would lead to the erythro product, is energetically more favored than transition state T_2 that would precede the threo aldol formation, as the latter maximizes the pseudo axial interactions between the R^1 group and the bulky heterocyclic moiety[13].





The present communication therefore reports the first examples of stereoselective aldol condensation of carboxamides, providing aldols of potential utility in medicinal chemistry. The preference of the precursor amide enolate to adopt a *cis* geometry and the lower steric interaction in the transition state that goes to the erythro aldol are likely to be at the origin of the erythro stereoselectivity of the above mentioned amides.

Table. Aldols 5 and 6 from enolates 3 and 4.

Aldol	Yield[a] %	mp °C (solvent)[b]	^{1}H NMR ($CDCl_3/D_2O$) δ (ppm) H_b[c]
5a	85	102-103 (A)	4.8 (d, J=4.5 Hz)
5b	76	92-93 (B)	4.9 (d, J=5.0 Hz)
5c	90	111-112 (A)	4.9 (d, J=4.0 Hz)
5d	75	145-147 (C)	4.85 (d, J=4.5 Hz)
5e	86	143-145 (A)	4.6 (d, J=5.0 Hz)
5f	90	118-119 (C)	4.7 (d, J=5.5 Hz)
5g	78	77-79 (D)	5.0 (d, J=4.0 Hz)
5h	60	oil	4.9 (d, J=4.0 Hz)
5i	45	149-150 (E)	5.0 (d, J=5.5 Hz)
5j[16]	66	127-129 (A)	4.1 (m, J=4.0, 7.0 Hz)
5k	75	oil	4.0 (m, J=3.5, 6.0 Hz)
5l	83	oil	4.9 (d, J=5.2 Hz)
6a	80	136-137 (A)	5.1 (d, J=3.0 Hz)
6b	85	139-140 (A)	5.05 (d, J=3.5 Hz)
6c	80	175-176 (C)	5.0 (d, J=3.0 Hz)
6d	85	147-148 (A)	4.9 (d, J=3.5 Hz)
6e	75	137-138 (A)	4.1 (m, J=3.5, 7.0 Hz)

[a] Yield determined on isolated, purified aldols. [b] Crystallisation solvents A, ethanol, B, ether, C, methanol, D, ether-petroleum ether, E, dichloromethane-petroleum ether [c] Other ^{1}H NMR data fit the assigned structures

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References and Notes

1. C.H.Heathcock, M.C.Pirrung, S.H.Montgomery and J.Lampe, Tetrahedron, 37, 4087, (1981) and Refs therein.
2. C.H.Heathcock, C.T.Buse, W.A.Kleschick, M.C.Pirrung, J.E.Sohn and J.Lampe, J. Org.Chem., 45, 1066 (1980); C.Heathcock, M.C.Pirrung, J.Lampe, C.T.Buse and S.D.Young, ibid., 46, 2290 (1981).
3. D.E. Van Horn and S.Masamune, Tetrahderon Lett., 2229 (1979); M.Hirama, D.S Garvey, L.D.-L Lu and S.Masamune, ibid., 3937 (1979).
4. H.M.Shieh and G.D.Prestwich, J.Org.Chem., 46, 4319 (1981).
5. Y.Tamaru, T.Harada, S.Nishi, M.Mizutani, T.Hioki and Z.Yoshida, J.Am.Chem.Soc. 102, 7806 (1980).
6. W.A.Kleschick, C.T.Buse and C.H.Heathcock, J Am.Chem.Soc., 99, 247 (1977).
7. F.Ciminale, L.Di Nunno and S.Florio, Tetrahedron Lett., 21, 3001 (1980), F.Babudri, F.Ciminale, L.Di Nunno and S.Florio, Tetrahedron, 38, 557 (1982).
8. F.Babudri, L.Di Nunno and S.Florio, Synthesis, 488 (1982); Tetrahedron, 38, 3059 (1982).
9. The general experimental procedure for the aldol condensation is as follows: A solution of 1 (or 2), 6mmol in 30mL of dry THF is added to a THF stirred solution of LDA (6.2 mmol) prepared in situ from n-BuLi in hexane (6.2 mmol) and diisopropylamine (6.2 mmol) in THF (10 mL) under nitrogen at -78°C The mixture is stirred for about 15 min at -78°C; then a THF (10 mL) solution of the aldehyde (6 mmol) is added dropwise. The mixture is kept at -78°C for 30 min; then allowed to warm to room temperature. Quenching with sat NH_4Cl (20 mL), and usual work-up leaves the crude aldol product which is purified by crystallisation or by column chromatography.
10. Deblocking of the heterocyclic moiety has been carried out as described for 5a: m-chloroperbenzoic acid (2 mmol) in 20mL CH_2Cl_2 is added to 5a (1 mmol) in 15mL CH_2Cl_2 at 0°C and the mixture kept at this temperature overnight. Washing with aqueous 5% $NaHCO_3$, 5% $Na_2S_2O_3$, drying over Na_2SO_4 and removal of the solvent leaves sulfone 7a. The so obtained sulfone (1 mmol) is treated with sodium methoxide (1 mmol) in 30mL of MeOH Reaction is over in 30 min and TLC shows the presence of two products that can be separated by column chromatography (ether as eluent). The first eluted component corresponds to 9. The second eluted compound corresponds to 10.[14] In the case of 6a the second eluted component is compound 11.[15]
11. Attempted isomerization of both 5a and 6a on treatment with sodium methoxide in methanol at RT or with LDA in THF at -78°C failed.
12. Similar considerations have been made for the deprotonation of amides and thioamides, see references 5.
13. For the 1,3-like interaction in the transition states preceding the aldol product formation, see. D.A.Evans, E.Vogel and J.V.Nelson, J.Am.Chem Soc., 101, 6120 (1979) and Refs. therein.
14. S.Florio, J.L.Leng and C.J.M.Stirling, J.Heterocyclic Chem., 19, 237 (1982).
15. K.Toei, Chem.Abstr., 52, 9611 (1958).
16. Amide 1a readily condenses stereoselectivity also with other aliphatic aldehydes but the assignment of the structure for the aldol is difficult since the Hb proton lies just underneath the CH_2 belonging to the heterocyclic ring.

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