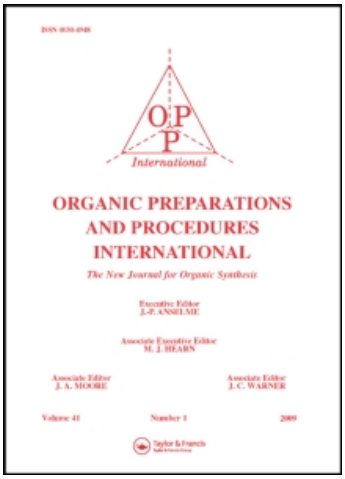

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SYNTHESIS OF STEREOISOMERIC 2-PHENYLIMINO-3,1-PERHYDRO-BENZOXAZINES AND 3,1-PERHYDROBENZOTHIAZINES†

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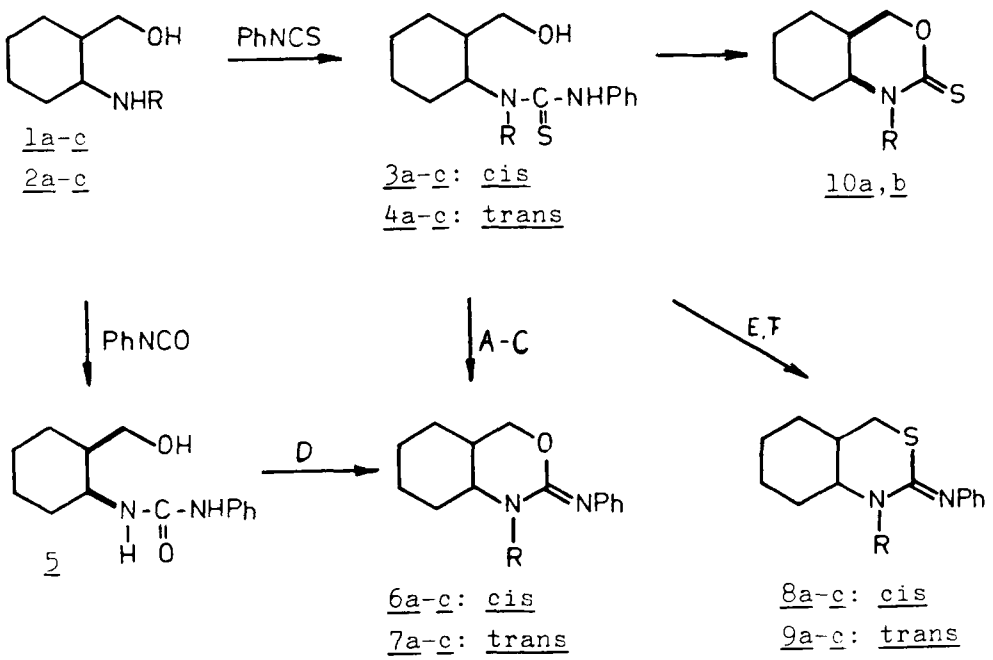
2-Imino-substituted 1,3-heterocycles with five- or six-membered rings have been extensively studied recently.[1-4] Their syntheses and the imino-amino tautomerism have been investigated by different methods.[5] This family of compounds is further interesting from a pharmacological aspect,[6] and some of the derivatives may be considered as potential drugs.[7]

As a continuation of our studies on the synthesis, reactions and conformational analysis of 1,3-heterocycles with condensed skeletons (see e.g.[8-13]), we now describe the synthesis of the title compounds 6-9. For the 1,3-oxazines and thiazines 6-9, it also seemed worthwhile to perform a comparative study of the influence of the configuration and the N-substituent of the starting aminoalcohols 1 and 2 on the cyclization. Another aim was to compare the different ring closure methods reported previously. The effects of the N-substituent on the predominant conformation of the cis isomers were discussed earlier.[10]

The synthesis of heterocycles 6a-c and 9a-c started from the adducts (3-5) of 2-hydroxymethylcyclohexylamines (1a-c and

2a-c)[11] with phenyl isothiocyanate or phenyl isocyanate, respectively (Scheme 1). The cyclization was performed by different routes. Treatment of thioureas (3a-c) with methyl iodide and 4a-c followed by alkali treatment led to the elimination of methyl mercaptan (Method A), to yield the oxazines 6a-c and 7a-c, in very high yields; in the case of 4a, the intermediate thiuronium salt could be isolated after treatment with methyl iodide. Cyclodesulfuration[14,15] of thiourea 3a using mercury(II) oxide (Method B) or N,N'-dicyclohexylcarbodiimide (Method C) resulted in oxazines 6a, but the purification of the products was cumbersome. The thionyl chloride ring closure[8] of 5 led to oxazine 6a in only moderate (46%) yield.



1a-c
2a-c

3a-c: cis
4a-c: trans

10a,b

5

6a-c: cis
7a-c: trans

8a-c: cis
9a-c: trans

a: R = H; b: R = CH_3; c: R = CH_2Ph

Scheme 1

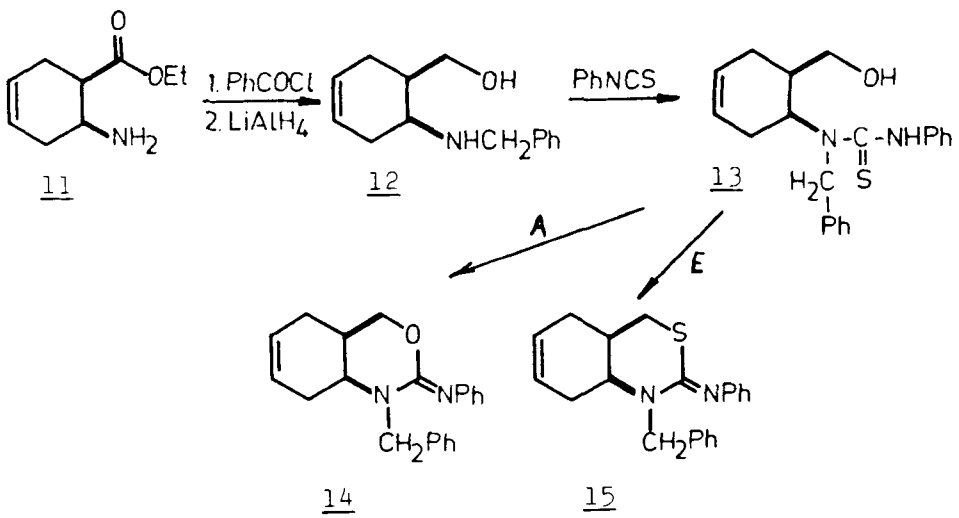
2-PHENYLIMINO-3,1-PERHYDROBENZOXAZINES AND 3,1-PERHYDROBENZOTHIAZINES

Treatment of thioureas 3a-c and 4a-c with ethanolic hydrogen chloride at reflux for a brief period of time, followed by basification (Method E) provided thiazines 8a-c and 9a-c in excellent yields; the reaction is independent of the nature of N-substituent and of the configuration. With aqueous hydrogen chloride (Method F), the yield of the conversion of 4a →9c was somewhat lower.

The thermal cyclization of thioureas of 1,3-aminoalcohols was described[2] recently, resulting in 1,3-oxazine-2-thiones through amine elimination. Since the available methods for the preparation of 1,3-oxazine-2-thiones with condensed skeletons resulted in very low yields,[17] the present method starting from 3a and 3b, was attempted but only afforded thioxo derivatives 10a and 10b in poor yields.

Since it is known that the 6,7-double bond has a considerable effect on the conformation of condensed-skeleton saturated 1,3-heterocycles,[13] the synthesis of 14 and 15 starting from 1-benzylamino-cis-2-hydroxymethyl-4-cyclohexene 12 (Scheme 2) proceeded without difficulties by methods A and F.

All of the compounds prepared gave spectral data (^{1}H and ^{13}C NMR at 400 MHz), which corresponded to the structures proposed. A detailed conformational analysis, determination of the conformational equilibria using dynamic NMR methods and a study of the tautomerism of these compounds will be reported in a forthcoming paper.[18]



11 12 13 14 15

Scheme 2

EXPERIMENTAL SECTION

Mps were determined with a Boetius micro melting point apparatus and are uncorrected. The physical properties, analyses and yields are listed in Tables 1 and 2.

General Method for the Preparation of Urea Derivatives (3-5 and 13).- To a solution of 10 mmol aminoalcohol 1, 2 or 12 in 20 ml ether, was added phenyl isothiocyanate or phenyl isocyanate (11 mmol). The solution became turbid within several minutes and the crystalline product separated out. After 3 hrs the products were collected and recrystallized.

Preparation of 2-Phenylimino-1,3-oxazines (6, 7 and 14)

Method A.- To a solution of thiocarbamide 3, 4 or 13 (5 mmol) in methanol (10 ml) was added methyl iodide (1 ml) and the solution was stirred for 2 hrs. After evaporation of the solvent, the

Table 1. Analytical data on starting urea derivatives

Compound	Mp.[a] °C	Yield %	Formula M.w.	Analysis: Calculated / Found % C	H	N	S
3a	171-173	90	$C_{14}H_{20}N_2OS$	63.39	7.63	10.60	12.13
			264.39	63.89	7.75	10.37	12.30
3b	126-128	89	$C_{15}H_{22}N_2OS$	64.70	7.97	10.06	10.52
			278.42	65.65	8.23	9.94	10.87
3c	134-135	92	$C_{21}H_{22}N_2OS$	71.14	7.39	7.90	9.05
			354.51	71.03	7.60	8.01	9.39
4a	157-158	75	$C_{14}H_{20}N_2OS$	63.59	7.63	10.60	12.13
			264.39	63.60	7.85	10.48	12.43
4b	183-185	82	$C_{15}H_{22}N_2OS$	64.70	7.97	10.06	10.52
			278.42	64.52	8.25	10.10	10.77
4c	159-161	88	$C_{21}H_{22}N_2OS$	71.14	7.39	7.90	9.05
			354.51	71.28	7.45	7.75	9.27
5	137-139	85	$C_{14}H_{20}N_2O_2$	67.71	8.13	11.28	-
			248.32	67.39	8.46	11.30	-
13	129-131	80	$C_{21}H_{24}N_2OS$	71.75	6.86	7.95	9.10
			352.49	71.53	7.03	7.95	9.45

[a] All compounds were recrystallized from ethanol.

residue was stirred in 3 N methanolic potassium hydroxide (20 ml) for 2-4 hrs. After evaporation, the residue was dissolved in water (30 ml) and extracted with chloroform (3x20 ml). After drying and evaporation of the solvent, the oxazine was obtained. Treatment of 4a with methyl iodide, gave the yellow crystalline thiuronium intermediate which was recrystallized from ethanol, mp. 141-144°.

Anal. Calcd. for $C_{22}H_{29}IN_2OS$: C, 53.22; H, 5.89; N, 5.64

Found: C, 53.37; H, 6.13; N, 5.36%.

Method B.- To thiocarbamide 3a (5 mmol, 1.32 g) in a mixture of benzene (40 ml) and ethanol (20 ml), was added mercury(II) oxide (8 g). After 8 hrs stirring under reflux, the mixture was treated with activated carbon and filtered. Evaporation of the filtrate gave oxazine 6a.

Method C.- Thiocarbamide 3a (5 mmol, 1.32 g) was dissolved in ethanol (30 ml) and N,N'-dicyclohexylcarbodiimide (7.5 mmol, 1.55 g) was added. After 1 hrs stirring at room temperature, the mixture was refluxed for 4 hrs and left overnight at room temperature, the precipitate was filtered off and the filtrate was evaporated. The oily residue was purified via the picrate salt. After recrystallization of the picrate, the base 6a was liberated with potassium hydroxide.

Method D.- Carbamide derivative 5 (5 mmol, 1.24 g) was dissolved in dry chloroform (20 ml) and thionyl chloride (1 ml) was added. After standing for 5 hrs at room temperature, the mixture was evaporated and the residue was basified with sodium hydrogen carbonate; after extraction with ethyl acetate, oxazine 6a was obtained.

Preparation of 2-Phenylimino-1,3-thiazines (8, 9 and 15)

Method E.- Thiocarbamide 3a (5 mmol, 1.32 g) was refluxed for 25 min in ethanol containing 10% dry hydrogen chloride. After evaporation, the residue was neutralized with aqueous potassium carbonate and the solution was extracted with chloroform (3x30 ml). Drying and evaporation of the organic layer resulted in thiazine 8a as white crystals.

Table 2. Analytical data on oxazines and thiazines

Compound	Mp. °C	Yield %	Formula M.w.	Analysis: Calculated Found C	H	N	% S
6a	144-146[b]	82 (A) 65 (B) 47 (C) 46 (D)	$C_{14}H_{18}N_2O$ 230.30	73.01 73.17	7.88 8.08	12.17 12.34	- -
6b	91-93[c]	74 (A)	$C_{15}H_{20}N_2O$ 244.33	73.73 73.41	8.25 8.26	11.47 11.68	- -
6c	oil	76 (A)	$C_{21}H_{24}N_2O$ 320.42	78.71 78.90	7.55 7.74	8.74 8.49	- -
7a	134-136[b]	78 (A)	$C_{14}H_{18}N_2O$ 230.30	73.01 73.40	7.88 8.10	12.17 11.76	- -
7b	107-109[c]	70 (A)	$C_{15}H_{20}N_2O$ 244.33	73.73 73.93	8.25 8.17	11.47 11.62	- -
7c	oil	68 (A)	$C_{21}H_{24}N_2O$ 320.42	78.71 78.53	7.55 7.70	8.74 8.67	- -
8a	187-188[b]	80 (E)	$C_{14}H_{18}N_2S$ 246.37	68.25 68.53	7.36 7.47	11.37 11.26	13.02 12.74
8b	107-109[d]	76 (E)	$C_{15}H_{20}N_2S$ 260.40	69.18 69.45	7.74 7.64	10.76 10.93	12.31 12.09
8c	135-136[c]	81 (E)	$C_{21}H_{24}N_2S$ 336.49	74.95 74.83	7.19 7.20	8.33 8.26	9.53 9.72
9a	195-196[b]	78 (E)	$C_{14}H_{18}N_2S$ 246.37	68.25 68.01	7.36 7.53	11.37 11.60	13.02 13.41
9b	116-118[c]	71 (E)	$C_{15}H_{20}N_2S$ 260.40	69.18 68.98	7.74 7.86	10.76 10.88	12.31 12.27
9c	125-127[c]	79 (E) 74 (F)	$C_{21}H_{24}N_2S$ 336.49	74.95 75.20	7.19 7.43	8.33 8.78	9.53 9.68
14	89-91[c]	70 (A)	$C_{21}H_{22}N_2O$ 318.49	79.21 79.37	6.97 6.93	8.80 9.11	- -
15	91-93[c]	78 (E)	$C_{21}H_{22}N_2S$ 334.48	75.40 75.58	6.63 6.39	8.38 8.27	9.59 9.40

[a] The method used is given in brackets. [b] From ethanol. [c] From petroleum ether. [d] From diisopropyl ether.

Method F.- Thiocarbamide 4c (5 mmol, 1.77 g), was refluxed for half an hour, in 36% aqueous hydrogen chloride solution, and the solution was then neutralized with aqueous sodium hydroxide under cooling. The mixture was extracted with chloroform (4x20 ml), and, after drying and evaporation, thiazine 9c was obtained.

Perhydro-3,1-benzoxazine-2-thiones 10a,b.- Thiocarbamide 3a or 3b (5 mmol) was refluxed in toluene (20 ml) for 30 hrs. After evaporation of the solvent, the residue was recrystallized from ethanol, resulting in thioxo derivatives 10a,b.

10a: mp. 191-192°, lit.[17] mp. 191-192°; yield 43%.

10b: mp. 94-96°, lit.[17] mp. 95-96°; yield 31%.

1-Benzylamino-cis-2-hydroxymethyl-4-cyclohexene 12.- Ethyl 1,2,3,6-tetrahydroanthranilate[13] was treated with benzoyl chloride in the Schotten-Baumann procedure, and the carboxamide formed was reduced, without purification, with lithium aluminum hydride by the procedure described earlier.[11] The aminoalcohol 12 (1.01 g, 46%) was recrystallized from hexane, mp. 71-73°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45

Found: C, 77.44; H, 8.89; N, 6.29%.

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