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SYNTHESIS OF STEREOISOMERIC CONDENSED-SKELETON 2-IMINO-SUBSTITUTED 1,3-OXAZINES

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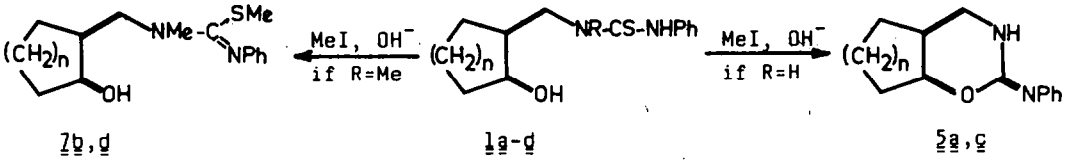
Abstract - Thiourea (1a-d, 2a-d) and urea (3a-d, 4a-d) derivatives have been prepared from cis- and trans-2-aminomethyl-1-cyclopentanols, and -1-cyclohexanols and their N-methyl derivatives with phenyl isothiocyanate and phenyl isocyanate, respectively. Treatment of 1 and 2 with methyl iodide and then with alkali furnished - with the exception of the cis-N-methyl derivative - 2-phenylimino-1,3-oxazines (5a,c, 6a-d). The remarkable fact that the ring closure of trans-2-aminomethyl-1-cyclopentanols gives 1,3-heterocycles with trans-anellation supports the assumption that the trans-1,2-disubstituted-1,3-difunctional cyclopentanes undergo ring closure when 1,3-heterocycles with a delocalized π bond system are formed. With thionyl chloride the cis-urea derivatives 3a-d afforded an elimination product (8), whereas the trans isomers 4 yielded the cis oxazines 5 by inversion. ^{1}H and ^{13}C NMR spectroscopic studies indicated that in 5a-d the "O-in" conformers are favoured (the methylene group of the hetero ring is equatorial, while the oxygen atom is axial) and all 3-unsubstituted-2-phenylimino-1,3-oxazines exist exclusively in the tautomeric form with an exo C=N bond.

The 2-imino-substituted 1,3-heterocycles, and particularly 1,3-thiazoles, 1,3-thiazines, 1,3-oxazoles and 1,3-oxazines, have been extensively studied in recent years.[2] Besides the synthetic investigations, the amino ⇌ imino tautomerism has also attracted attention. The high interest in this class of compounds is explained in part by pharmacological reasons too, for the cyclic guanidines and their hetero analogues have found wide-ranging application in therapy.[3-5]

In a continuation of our investigations on the synthesis and stereochemistry of fused 1,3-heterocycles,[6-8] our current aim was to elaborate the synthesis of the fused stereoisomers of 2-imino-1,3-oxazines (5, 6), which are interesting from both pharmacological and chemical aspects. The syntheses of 5a-d and 6a-d were planned *via* the ring closure of thiourea derivatives 1 and 2 and urea derivatives 3 and 4, respectively. Compounds 1-4 were synthesized from cis- and trans-2-aminomethyl-1-cyclopentanol[9] and cis and trans-2-aminomethyl-1-cyclohexanol[10] and their N-methyl derivatives[7,10] with phenyl isocyanate or phenyl isothiocyanate in good yields.

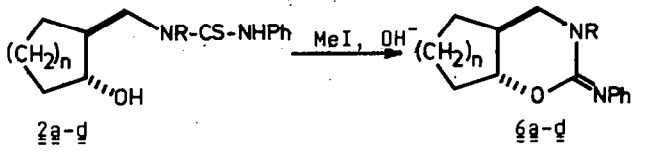
The preparations of 1,3-oxazoline and 1,3-oxazine from the isothiocyanate adducts of 1,2- and 1,3-aminoalcohols by treatment with methyl iodide and then with alkali, are known reactions.[11] Our investigations showed that only the unsubstituted cis-aminoalcohols 1a,c afforded the oxazines 5a,c, the analogues 1b,d

failing to undergo cyclization under similar conditions, but furnishing the isothiuronium derivatives (7b,d). Compounds 7b,d were not transformed into the desired compounds 5 even on heating with alkali, or on treatment with mercury(II) chloride or lead(II) nitrate.



7b,d 1a-d 5a,c

	R = H	R = Me
n = 1	a	b
n = 2	c	d



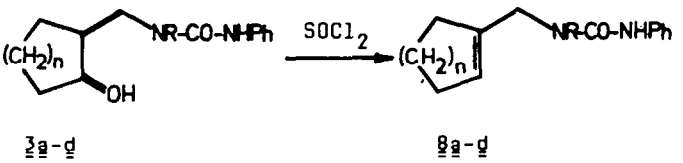
2a-d 6a-d

The treatment of trans-thiourea derivatives 2a-d with methyl iodide gave trans-1,3-oxazines 6a-d, irrespective of the ring size and the substituent R. The fact that the ring closure of both cis- and trans-thioureas to 1,3-oxazines proceeds with retention is in agreement with the mechanism suggested earlier[11] (formation of thiuronium salt, nucleophilic attack of oxygen on the positive carbon atom of the salt).

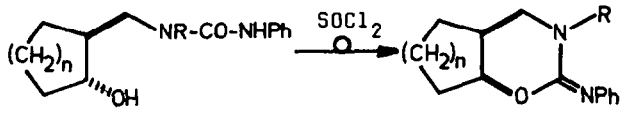
It is of particular interest that thiourea derivatives with a cyclopentane skeleton (2a,b) undergo facile cyclization, leading to the corresponding trans-1,3-oxazines 6a,b. It was established that the trans-1,3-disubstituted 1,3-difunctional cyclopentanes differ considerably in reactivity from the corresponding cis isomers, or higher homologous cis and trans isomers;[12-17] e.g. trans-cyclopentane-1,3-aminoalcohols,[13] -2-hydroxy-1-carboxamides[14] and 1,3-diols[15] cannot be cyclized to trans-trimethylene-1,3-oxazine, 1,3-oxazin-4-one or dioxan derivatives, whereas the corresponding cis isomers undergo a facile reaction. This has been utilized for the separation of the cyclopentane cis and trans isomers.[15,16] The N→O acyl migration of trans-2-aminomethyl-1-cyclopentanol and trans-2-hydroxymethyl-1-cyclopentylamine, which proceeds via a trans-trimethylene-1,3-oxazine transition state, is slower by several orders of magnitude,[9,17] than the reaction of the corresponding cis isomer.

In contrast with the earlier unsuccessful attempts to achieve the ring closure of trans-1,2-disubstituted 1,3-difunctional cyclopentane derivatives, we recently succeeded in obtaining the corresponding trans-trimethylene-2-oxo- and 2-thioxo-1,3-oxazine[12] derivatives from trans-2-aminomethyl-1-cyclopentanol. X-ray diffraction study of the product, trans-5,6-trimethylene-3,4,5,6-tetrahydro-2-thioxo-1,3-oxazine, indicated that the O-CS-N atoms formed a delocalized $p\pi$-$p\pi$ bond system, and the C_5-C_6 bond in the ring annelation was considerably shortened[12] (1.448 Å). These observations provided a good explanation for the trans ring closure.

We believe that the ring closure of 1,2-trans-cyclopentane thioureas 2a,b to trans-annelated 1,3-oxazines 6a,b can also be explained by delocalization of the N=C=N-Ph moiety, with consequent formation of a nearly planar hetero ring. The conclusion is obvious that the ring closure of the cyclopentane trans-1,2-disubstituted 1,3-difunctional compounds is feasible only when a hetero ring is formed which contains a delocalized $p\pi$ bond system, and hence has a nearly planar structure.



3a-d 8a-d



4a-d 5a-d

	R = H	R = Me
n = 1	a	b
n = 2	c	d

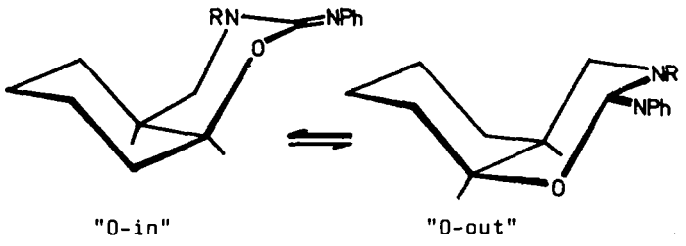
On treatment of the cyclohexane cis-urea derivatives 3c,d with thionyl chloride, trans elimination of water took place from the ring, affording the cyclohexene derivatives 8a,d. In the cases of cyclopentane ureas 3a,b, however, rather heterogeneous products were obtained. TLC and NMR spectroscopy of the crude product demonstrated the elimination product of type 8 and 1,3-oxazine (5).

The treatment of trans-ureas 4a-d with thionyl chloride resulted in the formation of the desired 1,3-oxazines. As in the case of the formation of 1,3-oxazolines and dihydro-1,3-oxazines, the reaction proceeded by an inversion mechanism.[18,19] The cis isomers 5b,d could also be synthesized in this way.

Spectroscopic investigations

The basic principles of the configurational and conformational studies on oxazine derivatives 5a-d and 6a-d were described in detail earlier.[20-22] Accordingly, we restrict ourselves here only to the most important facts.

The presence of the NH and the attached phenyliminoether function is unambiguously proved by the diffuse νNH band (3300-2500 cm^{-1}), the group frequencies of νC=N, νC-N and νC-O character of the conjugated urea group in the intervals 1670-1620, 1585-1950 and 1020-1090 cm^{-1}, and the characterictic $\gamma C_{Ar_1}\text{-}H\text{-}\gamma C_{Ar}C_{Ar}$ band pair of monosubstituted benzene derivatives (754-766 and 692-698 cm^{-1}).



"O-in" "O-out"

Fig. 1. The possible conformation of compounds 5c,d

In agreement with our earlier experience, of the two relatively stable chair conformations ("O-in", "O-out") of cis-fused oxazines 5a-d, that conformer is favoured in which the oxygen atom is axial with respect to the alicyclic ring, and the 4-methylene moiety is in the equatorial position ("O-in", Fig. 1). The NMR spectroscopic data support a conformationally pure, quasi-rigid system, irrespective of the size of the alicyclic ring and the substitution on the nitrogen atom. The chemical shift and the band-width of the H-6 adjacent to the oxygen atom give evidence of this. A comparison of the data on cis-fused isomers 5a-d with those on their trans counterparts in which H-6 is undoubtedly axial, revealed a characteristic difference. The chemical shift is about 0.6 ppm higher (from 3.82 ppm, the mean value for the trans isomers is increased to 4.42 ppm), while the band-width is decreased from 28 to 12 Hz, which is unambiguous evidence of the equatorial position of H-6 in the cis isomer.

Table 1. ^{1}H NMR data on compounds 5a-d, 6a-d, 7b,c, and 8c,d (δ_{TMS} = 0 ppm, coupling constants in Hz) in $CDCl_3$ solution at 250 MHz[a]

Compound	NCH_2 2xdd	(2x1H)[b]	OCH m(1H)	$\Delta\nu$[c]	OCH m(1H)	n CH_2 (alicycles)[d] overlapping m's (6 or 8H)	NH/NCH_3/OH s(1/3H)
5a	3.21	3.52	4.55	12	2.25	1.6-2.0 (6H)	~6.35[e]
5b	2.93	3.33	4.50	15	2.45	~1.55 (2H), ~1.8 (4H)	3.00[f]
5c	3.16	3.48	4.33	12	1.95	1.25-1.85 (8H)	~6.7[e]
5d	2.95	3.48	4.31	10	1.95	1.25-1.80 (8H)	3.06[f]
6a	3.17	3.62	3.88	30	2.10	~1.2 (1H), 1.6-2.0 (5H)	~4.5[e]
6b	3.18	3.42	3.94	27		~1.3 (1H), 1.55-2.1 (6H)	3.08[f]
6c	2.98	3.36	3.78	25	2.05	~0.98 (1H), ~1.35 (3H), ~1.8 (4H)	~6.15[e]
6d	2.93	3.17	3.70	30	~2.00	1.05 (1H), ~1.25 (3H), ~1.75 (4H)	3.02[f]
7b	3.05	4.18	4.12	12	2.10	1.4-2.0 (9H)[g]	~6.3[h] 3.23[f]
7d	2.78	4.09	3.82	10	2.00	1.2-1.8 (11H)[g]	~5.9[h] 3.16[f]
8c	3.66 s(2H)		5.55 ~s(1H)[i]			1. 65 m (4H) 1.90 m (4H)	~5.7[e] ~5.6[e]
8d	3.80 s(2H)		5.48 ~s(1H)[i]			1.65 m (4H), 1.95 m (2H), 2.05 m (2H)	~6.7[e] 2.97[f]

[a] The partly overlapping multiplet of the aromatic protons appear in the interval 6.90-7.30 ppm (5H); [b] A and B parts of an ABX spin system, J(A,B): 13.8-14.2 (5a,c, 6c, 7b,d) and 10.8-11.9 Hz (5b,d, 6b,d), J(A,X): 5.3-6.8 (5a-d, 6a-d) 11.7 (7b) and 11.9 Hz (7d), J(B,X): 2.5-5.5 (6a-d, 7b,d) and 10.7-11.1 Hz (6b-d); [c] half-width of the signal in Hz; [d] n = 3 (5a,b and 6a,b) or n = 4 (5c,d, 6c,d, 7b,d and 8c,d); [e] NH signal; [f] NCH_3 signal; [g] overlapping with the SCH_3 signal s (3H) at 1.90 ppm; [h] OH signal; [i] H-6 signal of the =C(6)H olefinic group.

The assumed conformation for the cis isomers is confirmed independently by the values of the vicinal coupling constants of the 4-methylene protons. The H-4a,H-5-coupling is considerably higher in the trans isomers (~11 Hz) than in the cis analogues (~6 Hz). The former value suggests a diaxial, and the latter an axial-equatorial interaction.[23a] Since H-5 in the "O-in" conformation is equatorial, whereas in the "O-out" structure it is axial, the predominance of the former conformation is unambiguously proved.

It should be noted that the general empirical rule for cyclohexanes and their hetero analogues, that the axial protons are more shielded than the equatorial protons,[23b] is not valid for the cis isomers. This can be explained by the deshielding anisotropic effect[23c] of the phenyl ring, forced into coplanarity with H-4a in the crowded molecule, and can thus be regarded as additional proof of the conformation.

In the ^{13}C NMR spectra the chemical shifts of C-2 and C-4 are sensitive to N-substitution: the β-effect of the methyl group[23d] is manifested in downfield shifts of 5.6 and 5.8 ppm, respectively (Table 2).

As further support of the "O-in" conformation in the cis-trans pairs of cyclohexanes, a considerable steric compression shift,[24] i.e. upfield shift, can be observed for the C-8 and C-10 signals of the cis isomers (4.2 and 3.4 ppm, respectively, for the 6c-5c pair, and 3.9 and 3.1 ppm, respectively, for the 6d-5d pair), whereas this effect is smaller (1.8, 1.2, 1.6 and 0.7 ppm, respectively)

for the C-7 and C-9 lines. In the "O-in" conformation C-8 and C-10, and in the "O-out" species C-7 and C-9 are in the sterically unfavourable "endo" position. Thus, the steric effect observed for the former signals provides evidence of the "O-in" species.

The field effect is also observable on the C-4,5,6 signals, and it is particularly large in the case of annelated C-5,6 (5.7, and 5.3, 5.0, and 4.6 ppm for the pairs 6c-5c and 6d-5d, respectively), as is general for cis- and trans-annelated ring systems.[23e]

In the five-membered alicyclic ring, due to the ring-strain in the trans-fused skeleton, the situation is reversed: the field effect reveals in the upfield shifts of C-5,6,7,8,9 signals of the trans isomers. For C-8 and C-6 this is partly or fully overcompensated by the more crowded structure of the cis isomer, as concerns C-5, however, a marked increase of shielding can be observed in 5a,b relative to trans pair 6a,b (2.7 and 4.5 ppm, respectively). This reversed effect is again evidence of the "O-in" species, since this atom would be in sterically hindered endo position in the "O-out" form.

Since C-4 is unaffected by the ring-strain, it is obvious that a similar upfield shift to those observed in cyclohexanes can be detected (7.5 and 4.4 ppm increase of shielding for 5a,b, compared to trans compounds 6a,b).

In the N-unsubstituted compounds 5a,c and 6a,c there is a possibility for tautomerism involving a shift of an exo-endo C=N bond. The identical values of IR-frequencies of the conjugated C=N bond, of the ^{1}H and ^{13}C NMR signals of the aromatic rings, suggest a practically pure tautomeric species with an exo C=N bond for all four compounds. This is supported by the fully different spectroscopic data on the analogous compounds 8c,d containing a phenylamino moiety.

Table 2. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds 5a-d, 6a-d, 7b,d and 8c,d in $CDCl_3$ solution[a] at 20 MHz[b]

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	NCH_3
5a	142.8	42.0	36.5	80.0	32.8	21.7	27.3	-	-
5b	148.1	49.2	37.1	80.6	32.9	22.4	28.6	-	38.2
5c	142.2	46.2	31.9	73.6	29.7	19.9	23.9	24.9	-
5d	148.5	52.3	32.7	73.8	29.4	20.0	24.0	25.5	37.6
6a	144.0	49.5	41.0	81.0	29.8	20.2	25.8	-	-
6b	148.4	53.6	39.8	80.6	28.2	20.2	24.9	-	38.3
6c	142.2	47.6	37.6	78.9	31.5	24.1	25.1	28.3	-
6d	148.7	53.3	37.7[c]	78.4	31.0	23.9	24.7	28.6	37.7[c]
7b	158.0	51.7	44.9	71.3	33.5	21.9	26.7	-	37.7
7d	157.8	53.9	39.3	63.7	31.9	19.9	24.2	25.6	37.1
8c	156.9	46.7	137.4	122.6	26.1	23.8[d]	23.9[d]	27.8	-
8d	155.9	55.5	134.4	124.1	25.0	22.3[d]	22.4[d]	26.0	35.0

[a] In DMSO-d_6 solution for 6a and 8c; [b] C-1': 148.3-150.8 (8c: 142.3, 8d: 139.5), C-2',6': 119.4-123.9, C-3',5': 127.4-130.2, C-4': 120.3-122.7 ppm, SCH_3: 16.0 (7b) and 15.6 (7d); [c] overlapping lines; [d] assignment may be reversed.

The structure of compounds 7b,d is supported by the νOH (3150 and 3190 cm^{-1}) and νC-O (1144-1119 and 1084 cm^{-1}) IR bands (the latter are typical of secondary alcohols[25a]), the NMR signals of the characteristically shielded[23f] protons of the methylmercapto moiety and those of the methyl carbon atom (1.90 ppm, and 16.0 or 15.6 ppm, respectively), the upfield shift of about 9.5 ppm observed for the "C-6" signal* (as a consequence of the disappearance of the β-effect of the "C-2" substituent[23d]), the downfield shift of the "C-2" signal owing to the sulphur-substitution,[23g] and naturally the unaltered pattern of the spectrum signals characteristic of the skeleton (IR bands and NMR signals of the alicyclic and phenyl rings and the N-methyl group).

The axial position of the OH group is supported by the H-6 signal width similar to that found for the cyclic cis derivatives (12 and 10 Hz). The chemical non-equivalence of the "4"-methylene protons and the large difference between their vicinal coupling constants indicate a considerable barrier for rotation around the C_4-C_5 axis, which is due partly to the crowded structure, and partly to the presence of a six-membered cyclic intramolecular hydrogen-bond between the sp^3 nitrogen and the OH group. This type of association is indicated by the relatively sharp νOH IR band.[25b]

The NMR signals of the olefinic protons and those of the two unsaturated carbon atoms (5.55 and 5.48 ppm /"H-6"/, and 137.4 and 134.4 ppm /"C-5"/, and 122.6 and 124.1 ppm /"C-6"/, respectively, the lack of the νC-O IR band and of the "H-5" signal as well as the singlet "4"-methylene signal confirm the formation of the cyclohexene derivatives 8c,d.

The "C-2" signal is of course shifted downfield (~10 ppm) to the region of urea-carbonyls. The "C-7" signal is more shielded, due to the β-effect of the olefinic carbon, which is smaller than that of a quaternary carbon.[23h] For the signal of the substituted carbon atom in the phenyl ring, an upfield shift (~10 ppm) can be observed relative to that for the cyclic compound, in agreement with the smaller α-effect of the sp^2 nitrogen which replaces the sp^3 nitrogen atom with its larger α-effect (cf. e.g. Ref.[23i]). The β-effect of the N-methyl substituent gives rise to a downfield shift of ~9 ppm in the "C-4" signal for compound 8d with respect to that for the unsubstituted analogue 8c.

Acknowledgements

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EXPERIMENTAL

The IR spectra were run in KBr discs on an Aspect 2000 computer-controlled Bruker IFS-113v FT-spectrometer.

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature on a Bruker WM-250 or WP-80-SY FT-spectrometer at 250.13 and 20.14 MHz, respectively, using the ^2H signal of the solvent as the lock and TMS as internal standard. The most important recording parameters of the ^1H and ^{13}C NMR spectra were as follows: sweep width, 5 kHz, pulse width, 1 and 3.5 μs (ca. 20° and 30° flip angle, respectively); acquisition time, 1.64 s, number of scans, 8 and 1-4 K; computer memory 16 K. Complete proton noise decoupling (ca. 1.5 W) for the

*Retaining the original numbering of oxazines.

^{13}C spectra, and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width 0.7 and 1.0 Hz).

General method for the preparation of urea derivatives 1a-d 4a-d

0.01 mole 2-Aminomethyl-1-cycloalkane was dissolved in 25 ml dry ether, and 0.011 mole phenyl isocyanate or phenyl isothiocyanate was added. The reaction mixture soon became turbid and the crystalline product separated out. In some cases the precipitation of crystals was completed by addition of a small quantity of petroleum ether. M.p.s, recrystallisation solvents, formulas are as follows: 118-120, ethyl acetate, $C_{13}H_{18}N_2OS$ (1a); 139-140, ethyl acetate, $C_{14}H_{20}N_2OS$ (1b); 157-158, ethanol, $C_{14}H_{20}N_2OS$ (1c); 157-158, ethanol, $C_{15}H_{22}N_2OS$ (1d); 90-93, ethyl acetate petroleum ether, $C_{13}H_{18}N_2OS$ (2a); 79-84, ethyl acetate petroleum ether, $C_{14}H_{20}N_2OS$ (2b); 103-105, benzene n-hexane, $C_{14}H_{20}N_2OS$ (2c); 122-124, benzene, $C_{15}H_{22}N_2OS$ (2d); 151-154, ethyl acetate, $C_{13}H_{18}N_2O_2$ (3a); 114-117, ethyl acetate petroleum ether, $C_{14}H_{20}N_2O_2$ (3b); 141-143, ethyl acetate petroleum ether, $C_{14}H_{20}N_2O_2$ (3c); 119-121, benzene, $C_{15}H_{22}N_2O_2$ (3d); 145-147, ethyl acetate, $C_{13}H_{18}N_2O_2$ (4a); 88-91, ethyl acetate petroleum ether, $C_{14}H_{20}N_2O_2$ (4b); 142-143, ethyl acetate, $C_{14}H_{20}N_2O_2$ (4c); 124-125 °C, diisopropyl ether, $C_{15}H_{22}N_2O_2$ (4d). All compounds gave satisfactory microanalyses.

Table 3. Analytical data on products 5-8 prepared by Methods A and B

Compound	M.p. °C	Yield % (Method)	Found % C	H	N	Formula (M.w.)	Calculated % C	H	N
5a	100-101[a]	70 (A) 36 (B)	72.44	7.60	12.82	$C_{13}H_{16}N_2O$ (216.28)	72.19	7.46	12.96
5b[b]	143-145[c]	50 (B)	52.39	4.80	14.96	$C_{20}H_{21}N_5O_8$ (259.41)	52.28	4.61	15.25
5c	122-123[d]	70 (A) 48 (B)	73.12	7.97	12.40	$C_{14}H_{18}N_2O$ (230.30)	73.01	7.88	12.17
5d[e]	177-180[c]	12 (B)	64.36	7.61	9.82	$C_{15}H_{21}ClN_2O$ (280.80)	64.16	7.54	9.98
6a	122-124[f]	84 (A)	72.22	7.72	12.70	$C_{13}H_{16}N_2O$ (216.28)	72.19	7.46	12.96
6b	94-96[g]	72 (A)	73.17	7.60	12.15	$C_{14}H_{18}N_2O$ (230.30)	73.01	7.88	12.17
6c	142-144[d]	75 (A)	72.86	7.96	12.02	$C_{14}H_{18}N_2O$ (230.30)	73.01	7.88	12.17
6d	97-98[d]	78 (A)	73.49	8.39	11.60	$C_{15}H_{20}N_2O$ (244.33)	73.73	8.25	11.47
7b	103-105[d]	71 (A)	64.88	7.85	10.34	$C_{15}H_{22}N_2OS$ (278.42)	64.70	7.97	10.06
7d	119-123[a]	86 (A)	65.66	8.52	9.72	$C_{16}H_{24}N_2OS$ (292.44)	65.71	8.27	9.58
8c	147-150[a]	64 (B)	73.12	7.98	12.20	$C_{14}H_{18}N_2O$ (230.30)	73.01	7.88	12.17
8d	119-121[a]	73 (B)	73.72	8.45	11.66	$C_{15}H_{20}N_2O$ (244.34)	73.73	8.25	11.47

[a] Ethyl acetate; [b] picrate salt; [c] ethanol - ether; [d] n-hexane; [e] HCl salt; [e] ethanol; [g] ether

Reaction of thioureas 1a-d and 2a-d with methyl iodide (Method A)

5 mmole N-Phenylthiocarbamoyl derivative (1, 2) was stirred for 2 h with 3 ml methyl iodide. The excess methyl iodide was removed under reduced pressure, and 30 ml 15% methanolic potassium hydroxide was then added. After stirring at room temperature for 3 h, the reaction mixture was evaporated to dryness, 20 ml ice-water was added and the mixture was extracted with 3x25 ml chloroform. After drying (Na_2SO_4) of the combined extracts and removal of the solvent by evaporation, the residue was crystallized by trituration with ether.

Reaction of urea derivatives 3a-d and 4a-d with thionyl chloride (Method B)

A mixture of 5 mmole N-phenylcarbamoyl derivative (3, 4) in 30 ml dry ether and 2.2 ml (0.03 mole) thionyl chloride was boiled for 1 h. After evaporation of the

reaction mixture, 30 ml 10% sodium carbonate was added to the residue under ice-cooling, and the mixture was then extracted with 4x20 ml ether. Evaporation of the combined extracts after drying yielded a crystalline product. In the cases of 4b and 4d, oily products were obtained after evaporation; these were purified in the form of picrate or hydrochloride salts. For the NMR investigations the bases liberated from the salts were used.

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