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REACTIONS OF Δ^1-PIPERIDEINE DERIVATIVES WITH HETEROCUMULENES

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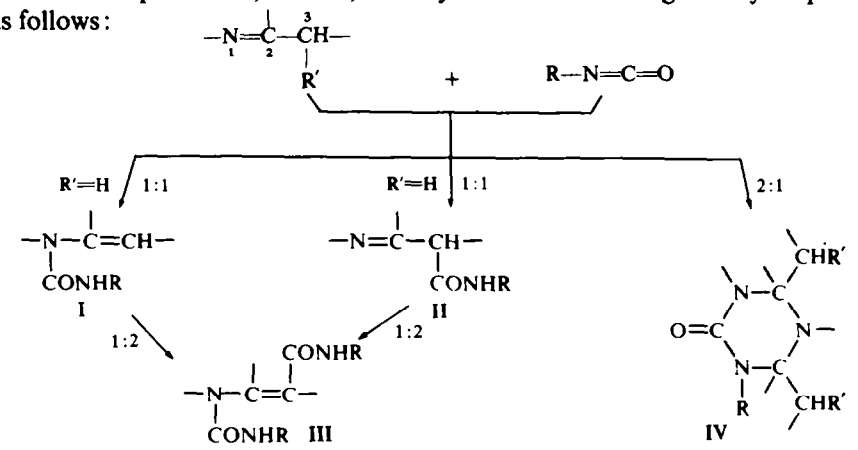
Abstract—The reactions of Δ^1-piperideine derivatives with various heterocumulenes afford the 1:1 or 2:1 adducts. The structures of the products were based on data obtained from NMR, IR, hydrolysis and the salt formation of the products. The results show that with few exceptions both isocyanates and isothiocyanates attack the C atom at 3-position of Δ^1-piperideine derivatives. The equimolar adducts from isocyanates have a Δ^1-structure while those from isothiocyanates a Δ^2-structure. It was found that the reaction with carbon disulfide gives a product with a cyclic structure different from the one reported.

INTRODUCTION

THE reaction of both aromatic and saturated heterocyclic compounds containing a N atom in a ring has been studied extensively but little work has been done with cyclic Schiff's bases which contain a C=N double bond in a ring. This situation has probably resulted from the difficult preparation of these substances, and their tendency to trimerize. Piperideine di- and trimers or their derivatives have been studied extensively by Schöpf *et al.*,[1] although little is known of the chemical and physical properties of piperideine monomers. This is also the case with 5-membered cyclic Schiff's bases.[2]

Recently, the cycloaddition of heterocumulenes to open-chain Schiff's bases[3] has received attention. Huisgen *et al.* have reported on the 1,4-dipolar cycloaddition of Schiff's bases to heterocumulenes (1:1 or 1:2 cycloadditions[4, 5]), and more recently, it was found that in the reactions of isocyanate with Schiff's bases having more than two H atoms on the C atom at 3-position, instead of cycloaddition apparent insertion of isocyanate to the C—H or N—H bond occurs.[6] This apparent insertion reaction would afford the products I, II or III, while cycloaddition would give only the products IV as follows:



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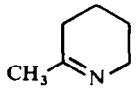
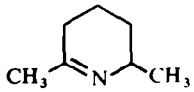
Recently, the author found that isocyanates and Δ^1-piperideine derivatives having no active hydrogen apparently, react very rapidly with each other to form new substances, which suggests that this reaction may be extended to a series of hetero-cumulenes.

As 6-membered cyclic Schiff's bases, Δ^1-2-methyl piperideine (V) and Δ^1-2,6-dimethyl piperideine (VI) were employed.



V



VI

RESULTS AND DISCUSSION

Reactions with isocyanates. The results of the reaction of selected piperideine derivatives with various isocyanates are shown in Table 1.

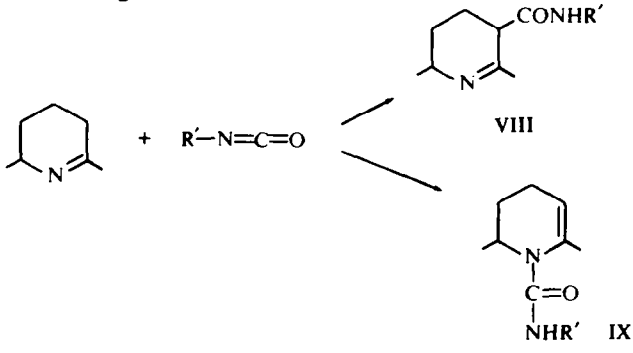
TABLE 1. REACTIONS OF PIPERIDEINES WITH ISOCYANATES

Piperideine	Isocyanate	Method*	Yield (%)	M.p. (°C)	Structure of the product	IR (cm^{-1})	
						$\nu_{C=O}$	$\nu_{C=N}$
2-Methyl	Phenyl	A	80	118	(VIIIa)	1640	1670
2-Methyl	p-Anisyl	B	99	126–127	(VIIIb)	1640	1667
2-Methyl	p-Nitrophenyl	B	92	151–153	(VIIIc)	1643	1670
2-Methyl	α-Naphthyl	A	61	114–116	(VIIId)	1640	1668
2-Methyl	Cyclohexyl	B	89	108–112	(IXa)	1615, 1630,	1661
2,6-Dimethyl	Phenyl	A	32	114–115	(VIIIe)	1640	1671

* A: Reacted for 20 min at 0°C.
B: Reacted for 20 min at 0°C and 12 hr at room temperature.

The reaction of Δ^1-piperideine derivatives is relatively slow with aliphatic isocyanate but very rapid with aromatic isocyanates. The activity of *p*-nitrophenyl isocyanate towards the Δ^1-piperideine was qualitatively much higher than that of *p*-anisyl isocyanate. Consequently, an electron-attracting substituent promotes the addition reactions described above. In other words, the isocyanates act as electrophilic reagents.

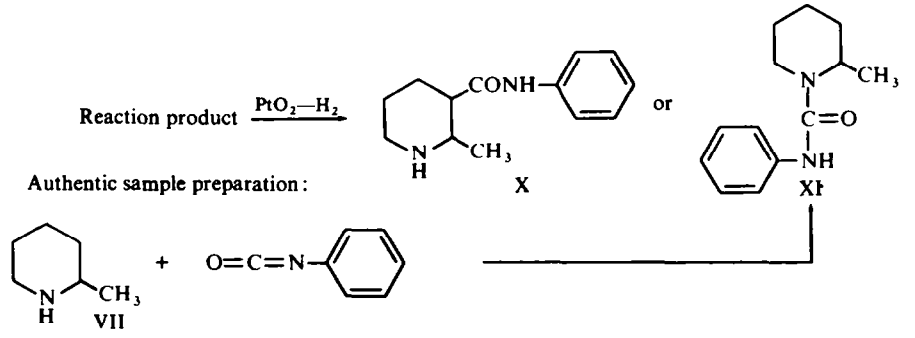
The products obtained were confirmed as adducts formed from equimolar amounts of isocyanate and the Δ^1-piperideine derivative. In this case, the following reactions are most probable although the other reaction also should be considered:



The spectroscopical analyses and the catalytic reduction of the addition products

were carried out in order to clarify the structure of the products and the pathway of the addition reaction.

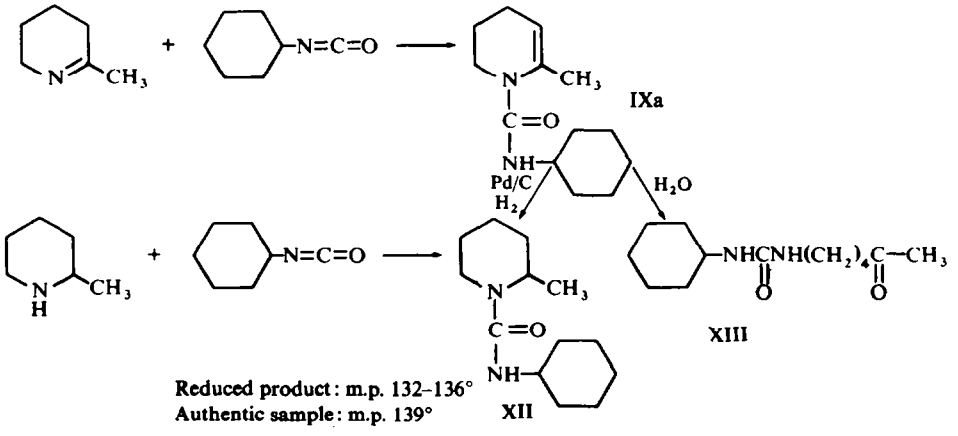
For example, NMR spectrum of the equimolar adduct of Δ^1-2-methyl piperideine and phenyl isocyanate involves three singlet peaks at $\tau = 3{\cdot}30$, 4·95 and 7·95 ppm due to N—H, methine and Me protons, respectively. The reduction of the product should afford the compound X or XI if the product is VIII or IX as follows:



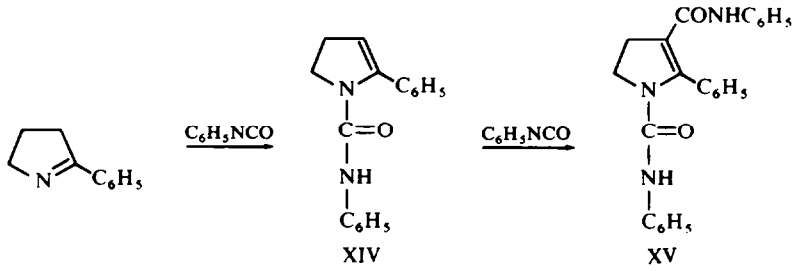
After reduction with platinum oxide–hydrogen, the IR absorption at 1670 cm^{-1} due to $\nu_{C=N}$ disappeared but the band due to $\nu_{C=O}$ remained, and the product differed in both IR spectrum and m.p. from the authentic sample (XI) which could be synthesized from α-pipecoline (VII) and phenyl isocyanate, analogous to the reaction of piperidine with isocyanate derivatives.[7] These results indicate that the equimolar adduct of Δ^1-2-methyl piperideine with phenyl isocyanate is Δ^1-2-methyl-3-(N-phenyl-carbamoyl) piperideine (VIIIa).

Other aromatic isocyanates were found to react with the Δ^1-piperideine to afford equimolar adducts having similar structures (VIIIa), confirmed by spectral data as shown in Table 1, the only exception being cyclohexyl isocyanate. In this case the equimolar adduct of Δ^1-2-methyl piperideine with cyclohexyl isocyanate is not 3-substituted but 1-substituted 2-methyl piperideine-Δ^2. This compound was very easily hydrolyzed to XIII during recrystallization from moist ethyl acetate, probably as is normal for compounds of this type.[2]

Recently, a similar case of nitrogen attack of isocyanate has been reported in the case of a 5-membered cyclic Schiff's base.[2]



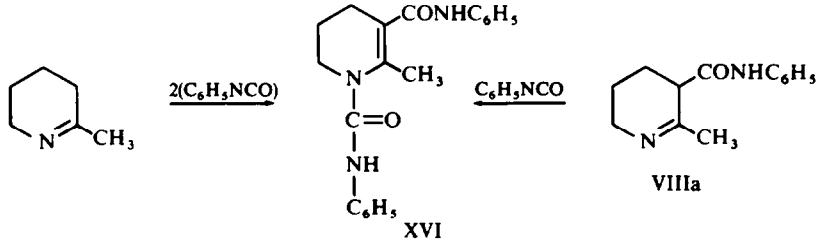
Love and Moore reported that one mole of Δ^1-2-phenyl pyrroline reacts with phenyl isocyanate to form Δ^2-1-(N'-phenylcarbamoyl)-2-phenyl pyrroline (XIV) but addition of one more mole phenyl isocyanate affords Δ^2-1,3-disubstituted-2-phenyl pyrroline (XV).



The compound XIV was found to be thermally unstable.[2]

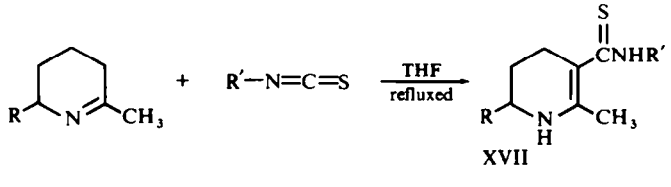
Although the difference in the mode of attack between aromatic and cyclohexyl isocyanates is unknown, the stability of the addition product may be the reason.

The 1:2 adduct (XVI) could be obtained either by the reaction of two moles of phenyl isocyanate and one mole of Δ^1-2-methyl piperideine at a temperature of 70° or by treatment of VIIIa with one more mole of phenyl isocyanate. Therefore, these findings support the view that the first phenyl isocyanate molecule adds to the C atom of Δ^1-2-methyl piperideine to form the equimolar adduct, whose N atom in the ring is successively attacked by the second isocyanate molecule.



Although there is no conclusive proof, imine–enamine tautomerism in the piperideine derivatives may play an important role in these reactions.

Reactions with isothiocyanates. Isothiocyanates are not so reactive as isocyanages towards piperideine derivatives, but a mixture of isothiocyanates and piperideines at about 70° affords Δ^2-3-substituted piperideine (XVII), in contrast with Δ^1-structure in the case of the reaction with isocyanates.



Results of the addition reaction of piperideines with various isothiocyanates are summarized in Table 2.

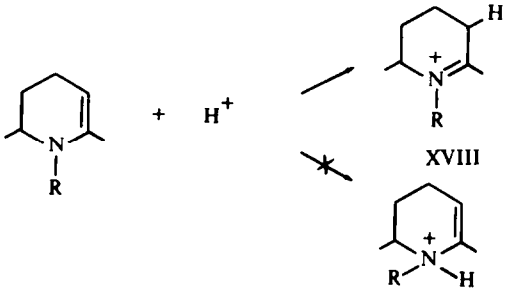
TABLE 2. REACTIONS OF Δ^1-PIPERIDEINE DERIVATIVES WITH ISOTHIOCYANATES

Δ^1-Piperideine	Isothiocyanate	Yield (%)	Structure of the product	M.p. (°C)	IR (cm^{-1})
2-Methyl	Phenyl	78	(XVIIa)	151–153	1597
2-Methyl	α-Naphthyl	71	(XVIIb)	114–116	1597
2-Methyl	Allyl	42	(XX) or (XXI)*	102–104	1636
2,6-Dimethyl	Phenyl	69	(XVIIc)	131–133	1560, 1582, 1598
2-Methyl	Phenyl		(XVIIIa)	180–182	1620, 1700
2,6-Dimethyl	Phenyl		(XVIIIb)	170–172	1595, 1680

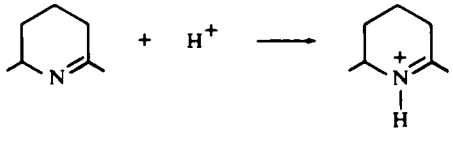
* The elemental analysis indicated $C_{16}H_{27}N_3S$ and 2:1 adduct.

The NMR spectrum of the addition product of Δ^1-2-methyl piperideine to phenyl isothiocyanate has two broad singlet peaks at $\tau = -0{\cdot}19$, and 3·72 ppm due to a proton of enamine and that of thioamide N—H, respectively.

The structure was confirmed by salt formation with hydrochloric acid since the protonation is known to transform Δ^2-structure of the piperideine to Δ^1-one as follows:[7]



On the other hand, direct protonation is known to take place in the Δ^1-structure so that an additional N—H proton peak should appear in the NMR spectrum.



As there is no additional peak due to an N—H proton in NMR spectrum of the hydrochloric acid salt, and since the IR spectrum of XVIIIa shows a new absorption at 1700 cm^{-1} due to $C{=}N^+$ stretching as shown in Fig. 1, Δ^2-structure of the product is confirmed.

As a secondary enamine is unstable,[9] these products should isomerize to an imine form, i.e., Δ^1-structure. Therefore, it is very interesting that Δ^2-3-thiocarbamoyl piperideine could be isolated. The stability is probably due to the great mesomeric effect of the thiocarbonyl group.

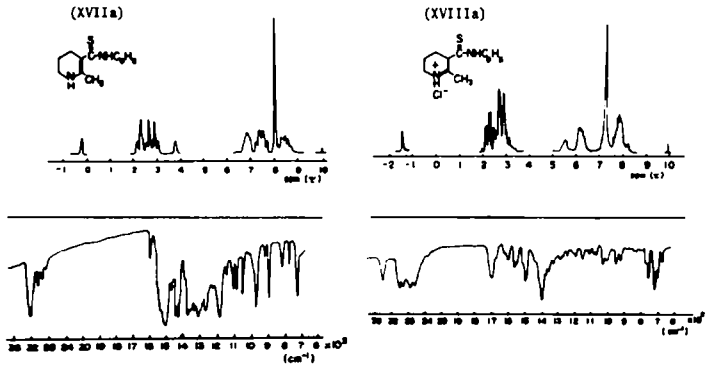
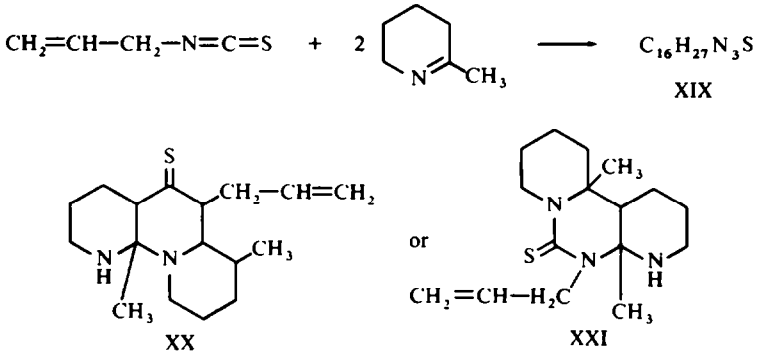


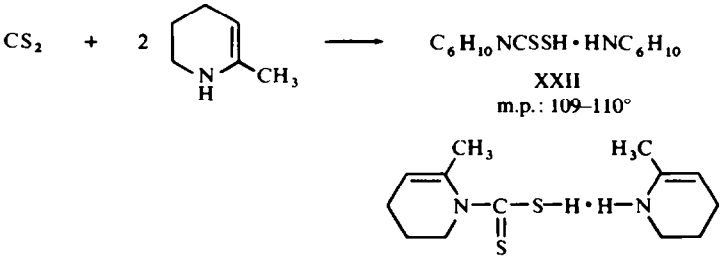
FIG. 1 IR and NMR spectra of Δ^2-2-methyl-3-(N-phenyl thiocarbamoyl) piperideine (XVIIa) and its hydrochloric acid salt (XVIIIa).

The reaction of allyl isothiocyanate with Δ^1-2-methyl piperideine affords a white 1:2 adduct of unknown structure even if equimolar amounts are used. This 1:2 adduct should be a cycloadduct such as XX or XXI because the IR spectrum shows of no absorption of C=N or C=C (enamine) stretching.



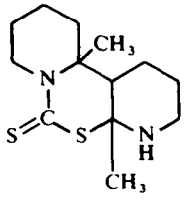
The reaction of cyclohexyl isothiocyanate with Δ^1-2-methyl piperideine gave a yellow semi-solid which could not be purified.

Reaction with carbon disulfide. In 1896, Lipp[10] reported that the 1:2 adduct of carbon disulfide and Δ^2-2-methyl piperideine is an enamine salt of dithiocarbamate as shown:

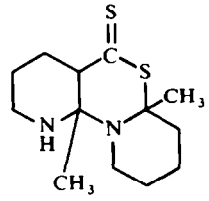


At that time, Δ^2-2-methyl piperideine was considered to have an enamine structure, although it is now known to have an imine structure. The formation of a 2:1 adduct

was confirmed but it was found that this adduct is not the salt of dithiocarbamic acid (XXII) because it has neither ammonium bands nor double bonds stretching absorption in the IR region. As the NMR spectrum shows a triplet peak at $\tau = 6{\cdot}4$ ppm due to a N—H proton, this 1:2 adduct probably has a cyclic structure such as XXIII or XXIV.

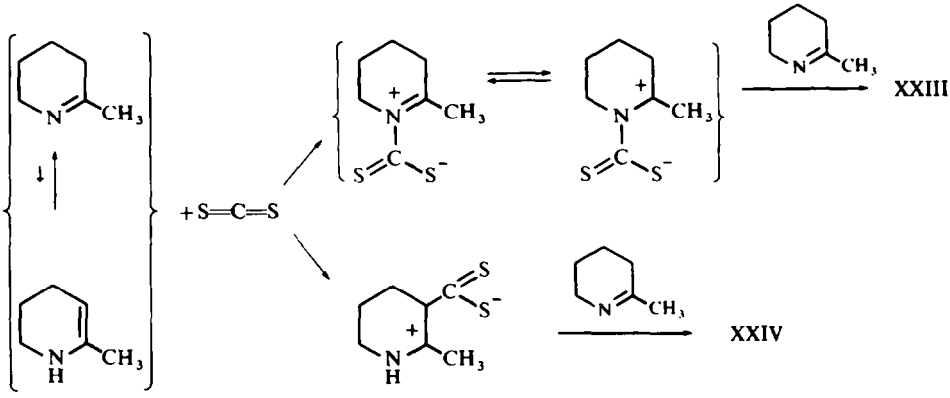


XXIII



XXIV

If these structures are correct, the reaction mechanism can be speculated on the basis of strong nucleophilicity at 1 and 3 positions as follows:



EXPERIMENTAL

The following abbreviations have been used—NMR: s, singlet; d, doublet; t, triplet; m, multiplet; IR: s, strong; m, medium; w, weak.

Δ^1-*2-Methyl piperideine* (V). This material was prepared by a modification of the published procedure.[11] α-Pipecoline was chlorinated with 10% NaOCl aq to give N-chloro-α-pipecoline. The latter was dehydrochlorinated in NaOH–MeOH and subsequently acidified with HCl. The soln of salt of V was concentrated and extracted with ether under alkaline conditions and then subjected to distillation, b.p. 135·0–135·5° (lit.[11] 78°C/222 mmHg). (Found: C, 74·33; H, 11·33; N, 14·53. Calc. for $C_6H_{11}N$: C, 74·17; H, 11·41; N, 14·42%); NMR (neat) τ ppm: 6·5 (m, 2H); 7·85 (m, 2H); 8·15 (t, 3H, $J = 1{\cdot}7$ Hz); 8·2–8·5 (m, 4H); IR (20 vol % in CCl_4): 3300 (w); 1665 (s, C=N).

Δ^1-*2,6-Dimethylpiperideine* (VI). The preparation was similar to that of V, b.p. 70·0°C/66 mmHg (lit.[11] 38–42°C/66 mmHg). (Found: C, 75·87; H, 11·79; N, 12·59. Calc. for $C_7H_{13}N$: C, 75·61; H, 11·79; N, 12·60%); NMR (neat) τ ppm: 2·5–3·3 (m, 0·2H); 6·5–7·2 (s, broad, 0·8H); 7·7 (s, 1H); 8·3 (two singlet, ~ 3H); 8·85 (two doublets, 3H, 6-methyl). The spectrum was so complicated that complete assignments were difficult; IR (20 vol % in CCl_4): 3210 (w); 1655 (s, C=N); 1593 (s); 1581 (s).

Δ^1-*2-Methyl-3-phenylcarbamoylpiperideine* (VIIIa). To a soln of 14·3 g (0·15 mol) Δ^1-2-methyl piperideine in 75 ml abs ether, 18·0 g (0·15 mol) phenyl isocyanate was added dropwise within 5 min at 0°. A white solid separated immediately. After 20 min, the mixture was filtered off, and 26·0 g (80%) of a white crystalline product was obtained. After recrystallization from acetone, the m.p. was 118°. (Found: C, 72·19; H, 7·46; N, 12·95. Calc. for $C_{13}H_{16}N_2O$: C, 72·15; H, 7·42; N, 13·00%); NMR ($CDCl_3$) τ ppm: 2·5–3·1 (m, 5H,

aryl); 3·3 (s, broad, 1H, NH); 4·85 (s, broad, 1H, H_3); 4·4 (t, J = 5 Hz, 2H, H_6); 7·95 (s, 3H, CH_3); 7·9–8·4 (m, 4H, H_4 and H_5); IR (KBr) cm^{-1}: 3280 (s, NH); 1670 (s, C=N); 1640 (s, amide carbonyl); 940 (m). UV (EtOH), λ_{max}, 256 mμ; ε, 94400.

Δ¹-2-Methyl-3-(p-methoxyphenylcarbamoyl) piperideine (VIIIb). After mixing *p*-anisyl isocyanate (8·00 g, 0·0536 mol) and Δ¹-2-methyl piperideine (5·23 g, 0·0549 mol) in 25 ml abs ether at 0°, the mixture was allowed to stand for 12 hr at room temp. The white crystalline product was washed with light petroleum: yield, 13·06 g (0·0534 mol), 99%. After recrystallization from EtOAc, the m.p. was 126–127°. (Found: C, 68·27; H, 7·38; N, 11·29. Calc. for $C_{14}H_{18}N_2O_2$: C, 68·27; H, 7·37; N, 11·37%); NMR ($CDCl_3$) τ ppm: 2·7–3·3 (m, 4H, aryl); 3·4 (s, broad, 1H, NH); 4·95 (s, broad, 1H, H_3); 6·25 (s, 3H, OCH_3); 6·45 (t, J = 5 Hz, 2H, H_6); 7·95 (s, 3H, α-CH_3); 7·7–8·7 (m, 4H, H_4 and H_5); IR (KBr) cm^{-1}: 3280 (s, NH); 1667 (m, C=N); 1640 (s, amide carbonyl); 940 (m).

Δ¹-2-Methyl-3-(p-nitrophenylcarbamoyl) piperideine (VIIIc). The preparation was similar to that used for VIIIb, yield, 92%. The reaction was more vigorous than in preparation of VIIIa and VIIIb. After recrystallization from EtOAc, yellow prisms, m.p. 151–153° were obtained. (Found: C, 59·61; H, 5·80; N, 16·10. Calc. for $C_{13}H_{15}N_3O_3$: C, 59·76; H, 5·79; N, 16·08%); NMR ($CDCl_3$–DMSO-d_6, 1:1) τ ppm: 0·43 (s, 1H, NH); 1·8–2·4 (m, 4H, aryl); 5·02 (s, 1H, H_3); 6·4 (t, J = 5 Hz, 2H, H_6); 7·45 (m, 2H); 8·0 (s, 3H, CH_3); 7·8–8·4 (m, 2H); IR (KBr) cm^{-1}: 3300 (m, NH); 1670 (m, C=N); 1643 (s, amide carbonyl); 1619, 1599 (s, arom); 940 (m).

Δ¹-2-Methyl(α-naphthylcarbamoyl) piperideine (VIIId). The preparation was similar to that of VIIIa. The white solid product could not be obtained in crystalline form, yield, 61%, m.p. 114–116° (dec). Recrystallization from moist EtOAc gave only the hydrolysed product, m.p. 132–133°. (Found: C, 76·93; H, 6·61; N, 10·23. Calc. for $C_{17}H_{18}N_2O$: C, 76·66; H, 6·81; N, 10·52%); NMR ($CDCl_3$): a clear spectrum was not observed; IR (KBr) cm^{-1}: 3220 (m, NH); 1668 (s, C=N); 1640 (s, amide carbonyl); 1600 (m, arom); 940 (m).

The hydrolysis product of VIIId. (Found: C, 71·80; H, 7·07; N, 9·67. Calc. for $C_{17}H_{20}N_2O_2$: C, 71·80; H, 7·09; N, 9·85%); IR (KBr) cm^{-1}: 3320 (m, NH); 1710 (s, ketone carbonyl); 1633 (s, urea carbonyl).

Δ¹-2,6-Dimethyl-3-(phenylcarbamoyl) piperideine (VIIIe). The preparation was similar to that of VIIIa, yield, 32%. Recrystallization from toluene gave white crystals, m.p. 114–115°. (Found: C, 72·99; H, 7·89; N, 12·07. Calc. for $C_{14}H_{18}N_2O$: C, 73·01; H, 7·88; N, 12·17%); NMR ($CDCl_3$) τ ppm: 2·6–3·1 (m, 5H, aryl); 3·4 (s, broad, 1H, NH); 4·4 (s, broad, 1H, H_3); 5·5 (m, 1H, H_6); 7·96 (s, 3H, 2-CH_3); 8·83 (d, 3H, J = 3·3 Hz, 6-CH_3); 7·7–9·0 (m, 4H); IR (KBr) cm^{-1}: 3280 (s, NH); 1671 (m, C=N); 1640 (s, amide carbonyl); 1600 (m, arom); 1570 (m, NH).

2-Methyl-3-(phenylcarbamoyl) piperidine (X)—*hydrogenation product of* VIIIa. To a soln of 1·0 g of VIIIa in abs THF, 0·3 g of $PtO_2 \cdot H_2O$ was added and this mixture was shaken in a hydrogen atmosphere until 140 ml H_2 had been absorbed. After removal of the THF, 0·98 g of crystalline X was obtained. Recrystallization from ligroin gave white crystals, m.p. 109–112°. (Found: C, 71·22; H, 8·33; N, 12·85. Calc. for $C_{13}H_{18}N_2O$: C, 71·52; H, 8·31; N, 12·84%); NMR ($CDCl_3$) τ ppm: 2·5–3·1 (m, 5H, aryl); 3·15 (s, broad, 1H); 5·1 (m, broad, 1H); 6·1 (m, broad, 1H); 7·1 (m, broad, 1H); 8·42–9·00 (s, broad, 6H); 8·82 (d, 3H, J = 7 Hz, CH_3); IR (KBr) cm^{-1}: 3280 (m, NH); 1630 (s, amide); 1600 (s, arom); 1535 (s, NH).

2-Methyl-1-(phenylcarbamoyl) piperidine (XI). This was prepared from phenyl isocyanate and α-pipecoline, m.p. 145–147°; NMR ($CDCl_3$) τ ppm: 2·5–3·1 (m, 5H, arom); 3·45 (s, broad, 1H, NH); 5·5–6·0 (m, 2H); 8·3–9·0 (m, 7H); 8·74 (d, 3H, J = 7 Hz, CH_3); IR (KBr) cm^{-1}: 3280 (m, NH); 1630 (s, urea carbonyl); 1600 (s, arom); 1500–1530 (s, NH). The IR spectrum of XI did not agree with that of X in the 1100–1400 cm^{-1} region.

Δ²-2-Methyl-1,3-di(phenylcarbamoyl) piperideine (XVI). A soln of 4·76 g (0·05 mol) Δ¹-methyl piperideine and 11·91 g (0·1 mol) phenyl isocyanate in 50 ml abs THF was allowed to stand overnight and then heated under reflux for 4 hr. The mixture was poured into light petroleum and the resulting solid was collected by filtration and dried. Treatment with toluene at 100° gave 6·7 g (40%) of insoluble crystalline material. After recrystallization from EtOAc, white woolly crystals were obtained, m.p. 157–158°. (Found: C, 71·61; H, 6·31; N, 12·53. Calc. for $C_{20}H_{21}N_3O_2$: C, 71·33; H, 6·31; N, 12·46%); NMR (DMSO-d_6) τ ppm: 0·55 (s, 1H, NH); 1·53 (s, 1H, NH); 2·2–3·2 (m, 10H, arom); 6·37 (t, 2H, J = 5 Hz, H_6); 7·5–8·4 (m, 4H, H_5 and H_6); 7·8 (s, 3H, CH_3); IR (KBr) cm^{-1}: 3300 (s, NH); 1660 (s); 1630 (s); 1598 (s).

Δ²-2-Methyl-1-(cyclohexylcarbamoyl) piperideine (IXa). The preparation was similar to that of VIIIb, yielding white prisms in 89% yield which after recrystallization from EtOAc had m.p. 108–112°. (Found: C, 70·52; H, 10·21; N, 12·65. Calc. for $C_{13}H_{22}N_2O$: C, 70·23; H, 9·97; N, 12·60%); NMR (DMSO-d_6) τ ppm; 3·95 (d, 1H, J = 8 Hz, NH); 5·23 (s, broad, 1H); 6·56 (t, 2H, J = 5 Hz, H_6); 7·43 (m, 1H); 7·9–9·0 (m, 14H); 8·03 (s, 3H, CH_3); IR (KBr) cm^{-1}: 3286 (m, NH); 1661 (m); 1630 (sh); 1615 (s); 945 (m).

Hydrogenation of IXa. Hydrogenation of IXa was similar to that of VIIIa, except that Pd-C was used in place of $PtO_2 \cdot H_2O$. Recrystallization from EtOAc–light petroleum gave white crystals, m.p. 132–136°. (Found: C, 69·48; H, 10·54; N, 12·23. Calc. for $C_{13}H_{24}N_2O$: C, 69·60; H, 10·78; N, 12·49%); IR (KBr) cm^{-1}: 3315 (m, NH); 1613 (s, C=C); 1530 (s, NH).

The authentic sample (XII). This material was synthesized from cyclohexyl isocyanate and α-pipecoline, m.p. 139°. The IR spectrum of the authentic sample was identical with that of the hydrogenated product of IXa.

1-*Cyclohexyl*-3-(1-(4-*acetyl*) *butyl*) *urea* (XIII). To a soln of 0·75 g of IXa in 20 ml MeOH, 20 ml water containing very small amount of HCl was added. After 3 hr, white needles (XIII) separated and these were washed with water, yield, 0·5 g (66%); m.p. 115–116°. (Found: C, 64·80; H, 9·83; N, 11·44. Calc. for $C_{13}H_{24}N_2O_2$: C, 64·96; H, 10·07; N, 11·66%); NMR ($CDCl_3$) τ ppm: 4·5–5·0 (m, 2H, NH); 6·4–7·0 (m, 3H); 7·3–7·7 (m, 2H); 7·85 (s, 3H, CH_3); 8·0–9·0 (m, 14H); IR (KBr) cm^{-1}: 3358, 3310 (s, NH); 1710 (s, ketone); 1623 (s, urea carbonyl); 1570 (s, NH).

Δ^2-2-*Methyl*-3-(*phenylthiocarbamoyl*) *piperideine* (XVIIa). A soln of 5·42 g (0·04 mol) phenyl isothiocyanate and 4·70 g (0·04 mol) Δ^1-2-methyl piperideine in 15 ml THF was heated under reflux for 40 min. An orange colour was developed. The mixture was poured into ether–light petroleum and the solid formed was collected and dried, yield, 78%. After recrystallization from EtOH, yellow needles, m.p. 151–153° were obtained. The compound (XVIIa) could not be reduced with $PtO_2 \cdot H_2O$ and only an oily product was recovered. (Found: C, 67·48; H, 7·06; N, 12·00; S, 13·77. Calc. for $C_{13}H_{16}N_2S$: C, 67·20; H, 6·94; N, 12·06; S, 13·80%); NMR (DMSO-d_6) τ ppm: −0·19 (s, 1H, enamine NH); 2·1–3·1 (m, 5H, arom); 3·72 (s, broad, 1H, thioamide NH); 7·0 (m, 2H); 7·5 (m, 2H); 8·01 (s, 3H, CH_3); 8·3 (m, 2H); IR (KBr) cm^{-1}: 3200 (s, NH); 1599 (m, arom); 1500 (s); 1185 (s); 960 (s); UV (C_2H_5OH) λ_{max} mμ: 222·5; 314 (ε, 41,800); 362 (ε, 44,300).

Hydrochloric acid salt of XVIIa (XVIIIa). Dry HCl gas was bubbled into a soln of XVIIa in chloroform and the soln was poured into light petroleum to afford a yellow oily product. The resulting oil was again dissolved in EtOH and reprecipitated by addition of light petroleum. Recrystallization from EtOH–light petroleum gave yellow crystals, m.p. 180–182°. (Found: C, 58·15; H, 6·24; N, 10·63; S, 11·92; Cl, 13·02. Calc. for $C_{13}H_{17}N_2SCl$: C, 58·09; H, 6·37; N, 10·42; S, 11·93; Cl, 13·19%); NMR (DMSO-d_6) τ ppm: −1·40 (s, 1H, N^+H); 2·1–3·0 (m, 5H, aryl); 5·52 (s, broad, 1H, NH); 6·30 (m, 2H, H_6); 7·40 (s, 3H, CH_3); 7·7–8·3 (m, 5H); IR (KBr) cm^{-1}: 3440 (m, NH); 2760, 2680 (s, ammonium); 1700 (m, C=N^+); 1620 (m, arom); 1420 (s).

Δ^2-2-*Methyl*-3-(α-*naphthylthiocarbamoyl*) *piperideine* (XVIIb). The preparation was similar to that of XVIIa, yield, 71%, after recrystallization from EtOH, m.p. 114–116°. (Found: C, 72·52; H, 6·66; N, 9·76; S, 11·30. Calc. for $C_{17}H_{18}N_2S$: C, 72·32; H, 6·43; N, 9·92; S, 11·33%); NMR (DMSO-d_6) τ ppm: 0·6 (s, 1H, NH); 2·0–2·7 (m, 7H, aryl); 6·6 (s, broad, 1H, NH); 6·9 (m, 2H); 7·4 (m, 2H); 7·78 (s, 3H, CH_3); 2·2 (m, 2H); IR (KBr) cm^{-1}: 3200 (s, NH); 1597 (m, arom); 1520 (s, NH); 1193 (s); 960 (s).

Δ^2-2,6-*Dimethyl*-3-(*phenylthiocarbamoyl*) *piperideine* (XVIIc). The preparation was similar to that of XVIIa, yield, 69%, after recrystallization from EtOAc, m.p. 131–133°. (Found: C, 68·06; H, 7·36; N, 11·20; S, 12·84. Calc. for $C_{14}H_{18}N_2S$: C, 68·27; H, 7·37; N, 11·37; S, 13·00%); NMR ($CDCl_3$) τ ppm: 1·46 (s, broad, 1H, NH); 2·5–3·0 (m, 5H, aryl); 6·02 (s, broad, 1H, NH); 6·7 (m, 1H, H_6); 7·2–7·6 (m, 2H); 8·00 (s, 3H, 2-CH_3); 8·0–8·8 (m, 2H); 8·83 (d, 3H, J = 6·2 Hz, 6-CH_3); IR (KBr) cm^{-1}: 3200 (s, NH); 1560, 1582, 1598 (m); 1500 (vs).

Hydrochloride salt of XVIIc (XVIIb). The preparation was similar to that of XVIIIa, m.p. 170–172°. (Found: C, 59·19, H, 6·73; N, 9·76; S, 11·34; Cl, 12·79. Calc. for $C_{14}H_{19}N_2SCl$: C, 59·45; H, 6·77; N, 9·91; S, 11·34; Cl, 12·54%); NMR (DMSO-d_6) τ ppm: − 3·0 (d, 1H, J = 6 Hz, NH); 1·9–2·8 (m, 5H, aryl; 5·12 (s, broad, 1H, NH); 7·46 (s, 3H, 2-CH_3); 6·0 (m, 2H); 7·5–8·3 (m, 4H); 8·54 (d, 3H, J = 6 Hz, 6-CH_3); IR (KBr) cm^{-1}: 3400 (w, NH); ~ 2700 (s, ammonium); 1680 (m); 1595 (m); 1538 (m); 1410 (s).

The adduct (2:1) *of* Δ^2-2-*methyl piperideine and allyl isothiocyanate* (XIX). A soln of 4·96 g (0·05 mol) allyl isothiocyanate and 4·76 g (0·05 mol) Δ^1-2-methyl piperideine in 25 ml THF was heated under reflux for 1 hr and the solvent evaporated to dryness in vacuum. The residue was treated with hot ligroin and the soln was cooled. White crops were obtained after 24 hr, 42% yield (3·1 g). After recrystallization from ligroin, m.p. 102–104°. (Found: C, 65·13; H, 9·11; N, 14·20; S, 11·45. Calc. for $C_{16}H_{27}N_3S$: C, 64·58; H, 9·27; N, 14·32; S, 10·93%); IR (KBr) cm^{-1}: 3240 (w, NH); 1636 (w, allyl, C=C); 1430 (s); 1350 (s); 1255 (s); 915 (m). It was assumed that this adduct was not the normal type (XVII) but a cyclo-adduct because of the absence of C=N or enamine C=C stretching absorption in the IR.

Reaction of Δ^1-2-*methyl piperideine with carbon disulfide.* The reaction was similar to that reported.[10]

The product showed a m.p. 105·0–105·5° (lit.[10] 109–110°). (Found: C, 57·93; H, 8·35; N, 10·48; S, 23·83. Calc. for $C_{13}H_{22}N_2S_3$: C, 57·73; H, 8·20; N, 10·26; S, 23·71%); NMR ($CDCl_3$) τ ppm: 4·35 (t, 1H, J = 13 Hz); 7·1 (m, 2H); 7·7 (s, 2H); 7·5–8·5 (m, 17H); IR (KBr) cm^{-1}: 3280 (m, NH); 1467 (s); 1450 (s); 1420 (s); 1260 (s); 1240 (s); 1162 (s); 1130 (s); 990 (s). UV (C_2H_5OH) λ_{max} mμ: 255 (ε, 24,300); 292 (ε, 35,800).

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REFERENCES

[1] For example, C. Schöpf and W. Merkel, *Liebigs Ann.* **701**, 180 (1967).
[2] For example, S. J. Love and J. A. Moore, *J. Org. Chem.* **33**, 2361 (1968).
[3] H. Ulrich, *Cycloaddition Reactions of Heterocumulenes*. Academic Press, New York. London (1967).
[4] R. Huisgen, M. Morikawa, D. S. Breslow and R. Grashey, *Chem. Ber.* **100**, 1602 (1967).
[5] R. Huisgen, K. Herbig and M. Morikawa, *Ibid.* **100**, 1107 (1967).
[6] For examples, J. Moszew and A. Inasiński, *Roczniki Chem.* **34**, 1173 (1960); J. Goerdeler and U. Keuser, *Chem. Ber.* **97**, 2209 (1964); J. P. Chupp and E. R. Weiss, *J. Org. Chem.* **33**, 2357 (1968).
[7] C. W. van Hoogstraten, *Rec. Trav. Chim.* **51**, 414 (1932); M. J. Gelcleren, *Ibid.* **52**, 976 (1933).
[8] N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.* **76**, 2781 (1954).
[9] For example, K. Bláha and O. Červinka, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritzky and A. J. Boulton) Vol. 6, p. 147. Academic Press, New York. London (1966).
[10] A. Lipp, *Liebigs Ann.* **289**, 173 (1896).
[11] M. F. Grundon and B. E. Reynolds, *J. Chem. Soc.* 2445 (1964).