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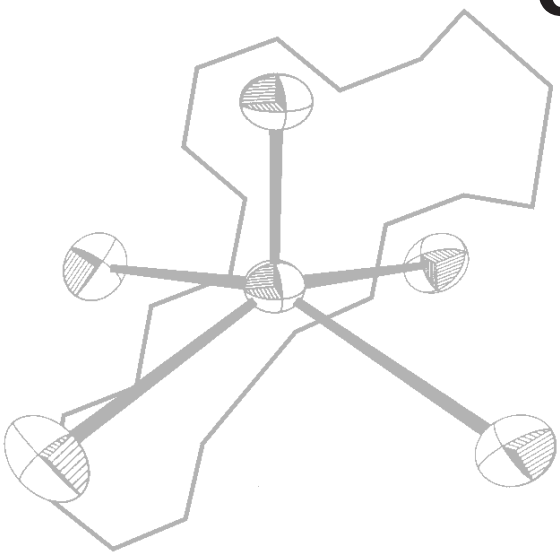

Volume 52, 1999

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Aust. J. Chem., 1999, **52**, 841–849

Phenyl Chloro(thionoformate): a New Dealkylating Agent of Tertiary Amines

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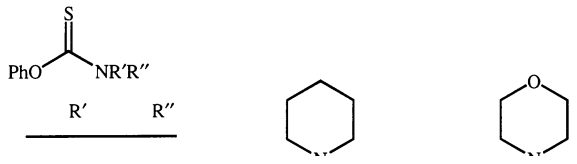
Phenyl chloro(thionoformate) reacts rapidly with unhindered tertiary aliphatic amines at 20° to give a thiocarbamate and an alkyl chloride. Dialkylcyclohexylamines react surprisingly rapidly to form predominantly cyclohexene. The thiocarbamates are converted into the secondary amine salt by treatment with dimethyl sulfate, followed by hydrolysis with water. Rates of reaction and alkyl group cleavage selectivity in amines were found to be superior or comparable to those previously reported with chloroformates.

Introduction

We have previously[1] reported a preliminary account of our study of the dealkylation of tertiary aliphatic amines with phenyl chloro(thionoformate) (1). The reactivity and selectivity of this reagent was found to be superior to that of a number of previously used methods, such as the von Braun[2] reaction or the use of ethyl chloroformate[3] and phenyl chloroformate.[4] The latter reagents produce products (Scheme 1) which are difficult to hydrolyse, and accordingly were replaced by 1-chloroethyl chloroformate,[5] 2,2,2-trichloroethyl chloroformate[6] and vinyl chloroformate.[7] We have found that chloro(thionoformates) are even more reactive toward amines than are chloroformates, but the ease and selectivity of the analogous second dealkylation step in Scheme 1 required elaboration.



Charles[8] has shown that the ease of cleavage of alkyl groups from tertiary amines with chloroformates is benzyl > allyl > methyl > alkyl, and in our preliminary communication we determined a similar pattern of reactivity for the chloro(thionoformate) reagents.

In this paper we aim to ascertain more definitively the relative rates of cleavage of alkyl groups with phenyl chloro(thionoformate), and to determine the scope of its effectiveness as a dealkylating agent of tertiary aliphatic amines.

Results and Discussion

The accepted pathway[9] for dealkylation of tertiary amines with chloroformates involves the rate determining decomposition of the salt (2) by chloride, forming the carbamate (3) and an alkyl chloride (Scheme 1). In a general way this appears also to be the case with chloro(thionoformates). The reaction of unhindered tertiary amines with phenyl chloro(thionoformate) was very rapid at 20° in chlorinated solvents. When the reaction of triethylamine with 1 equiv. of (1) was followed by ^{1}H n.m.r. analysis, the ammonium salt appeared to form instantly (δ CH_2 4.35), and the chloroethane formation could be followed to completion over the next 30 min. As shown in Table 1,[10–14] the reaction of most unhindered tertiary amines also went to completion within 1 h.

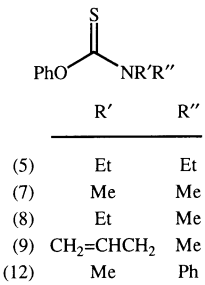
Olofson[7] has used *N*-ethylpiperidine as the benchmark for the determination of rate and selectivity of the dealkylation of tertiary amines by vinyl chloroformate, cyanogen bromide, phenyl chloroformate, ethyl chloroformate, 2,2,2-trichloroethyl chloroformate and benzyl chloroformate. The use of vinyl chloroformate gave the deethylated product in 90% yield but a period at 80° was required to effect decomposition of the intermediate salt. The use of phenyl chloroformate resulted in dealkylation at 20°, while the other chloroformates effected the conversion in, at best, 10% yield, under similar conditions. Cyanogen bromide showed low selectivity, giving cyanamide (18) (54%), accompanied by the ring-opened cyanamide (19) (28%). Olofson[5] reported that the reaction of 1-chloroethyl chloroformate with *N*-ethylpiperidine afforded the carbamate (20) in quantitative yield at 80°. By contrast, phenyl chloro(thionoformate) cleanly converted *N*-ethylpiperidine into the corresponding thiocarbamate (4) at room temperature in dichloromethane within 1 h. Together with the direct competition experiment of phenyl chloroformate and phenyl chloro(thionoformate) towards triethylamine, cited previously,[1] this demonstrates that the reactivity of phenyl chloro(thionoformate) with tertiary amines is superior to that of vinyl chloroformate and 1-chloroethyl chloroformate.

Manuscript received 18 September 1998 10.1071/CH98147 0004-9425/99/090841

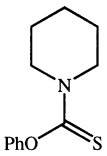
Table 1. Dealkylation of tertiary amines with (1)

Amine	Conditions	Product(s)	Yield (%)
N-Ethylpiperidine	CH_2Cl_2, 1 h, 20°	(4)[10]	98[A]
Triethylamine	CH_2Cl_2, 1 h, 20°	(5)[11]	93[A]
N,N-Diethylbenzylamine	CH_2Cl_2, 1 h, 20°	(5)	97[A]
N-Methylmorpholine	CH_2Cl_2, 1 h, 20°	(6)[10]	73[A]
N-(3-Phenylprop-2-enyl)dimethylamine	CH_2Cl_2, 1 h, 20°	(7)[12]	71[A]
N,N-Dimethyl-t-butylamine	CH_2Cl_2, 2 h, 40°	(7)	36[A,B]
N,N-Diethylmethylamine	CH_2Cl_2, 1 h, 20°	(8)+(5)	(44+12)[A]
N-Allyl-*N*-t-butylbenzylamine	neat, 16 h, 120°	[C]	
N-t-Butyl-*N*-methylbenzylamine	neat, 16 h, 120°	[C]	
N-Allyl-*N*-methylbenzylamine	CH_2Cl_2, 1 h, 20°	(9)	97[A]
N-Allyl-*N*-methylbenzylamine[D]	CH_2Cl_2, 1 h, 20°	(10)[13]	98[E]
N′-Benzyl-*N*-t-butyl-*N,N′*-dimethylpropane-1,3-diamine	CH_2Cl_2, 1h, 20°	(11)	77[A]
N-t-Butyl-*N*-methylallylamine	$Cl(CH_2)_2Cl$, 16 h, 83°	(9)	39[A]
N,N-Dimethylaniline	neat, 24 h, 130°	(12)[14]	60[A]
N,N-Dimethylaniline/$TiCl_4$	CH_2Cl_2, 1 h, 40°	(12)	9[A]
Quinuclidine	CH_2Cl_2, 1 h, 20°	(13)	95[A]
Tropine	CH_2Cl_2, 1 h, 20°	(14)+(15)[F]	>95[G]
Tropine acetate	CH_2Cl_2, 1 h, 20°	(16)	96[A]
Bicuculline	CH_2Cl_2, 1 h, 20°	(17)[H]	87[A]

[A] Isolated yield, chromatographically pure. [B] Yield of crude material was 76%. [C] No reaction. [D] Reaction of amine with cyanogen bromide (CH_2Cl_2, 1 h, 20°). [E] Yield based on unrecovered starting material. [F] Relative ratio of products in mixture 66 : 34. [G] Yield of crude material. [H] Ratio of *erythro* to *threo* 3 : 1.



	R′	R″
(5)	Et	Et
(7)	Me	Me
(8)	Et	Me
(9)	CH_2=$CHCH_2$	Me
(12)	Me	Ph



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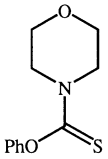

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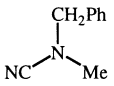

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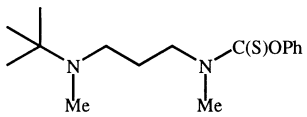

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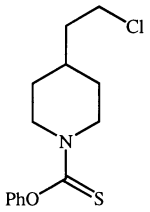

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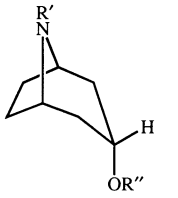
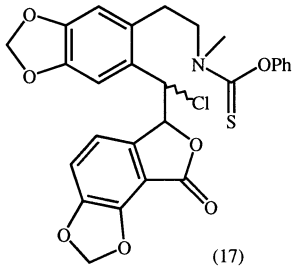


	R′	R″
(14)	Me	C(S)OPh
(15)	C(S)OPh	H
(16)	C(S)OPh	COMe



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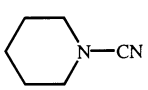

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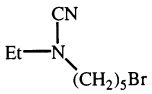

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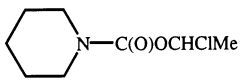
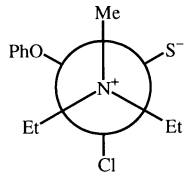


(20)

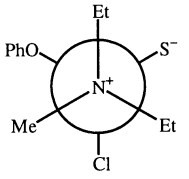
The selectivity of the cleavage of alkyl groups by phenyl chloro(thionoformate) was now investigated in greater detail. Reaction of *N,N*-diethylbenzylamine with (1) resulted only in debenzylation, as was expected.[6] While 1-methylmorpholine undergoes considerable ring opening on reaction with cyanogen bromide,[15] with phenyl chloro(thionoformate), as with 1-chloroethyl chloroformate,[5] only demethylation was observed. *N*-(3-Phenylprop-2-enyl)dimethylamine, prepared by the reaction of dimethylamine and cinnamyl chloride in ethanol, was cleaved totally to give the cinnamyl chloride. *N,N*-Dimethyl-t-butylamine was cleaved exclusively at the tertiary carbon centre when reacted with (1), as it did with vinyl chloroformate,[7] a result suggesting an S_N1 mechanism in this case.

The reaction of phenyl chloro(thionoformate) with *N,N*-diethylmethylamine resulted in the formation of the thiocarbamates (8) and (5), in a 7 : 1 ratio respectively; this corresponds to cleavage of ethyl to methyl of 7 : 2. The preference for ethyl group cleavage over methyl was totally unexpected, and clearly does not reflect the relative S_N2 reactivity of ethyl and methyl groups. The product ratios may be partially rationalized by consideration of the conformations of the initial conjugate formed on attack of the amine upon the chloroformate.

It is suggested that reestablishment of the thiocarbonyl group from the intermediates (21a) and (21b) releases chloride, which undergoes essentially a concerted S_Ni reaction in an ion pair with the most accessible alkyl group on nitrogen. Assuming that the lowest energy conformation involves the large sulfur anion flanked by a methyl and an ethyl group (conformer (21a)), rather than two ethyl groups (conformer (21b)), the observed ratio requires only a difference in free energy between (21a) and (21b) of 2.9 kJ mol^{-1} K^{-1}, which appears quite reasonable.[16] Support for the intermediacy of the salt (21) comes from monitoring the reaction of *N,N*-diethylmethylamine with (1) by ^{1}H n.m.r. spectroscopy. The amine disappeared totally in less than 1 min, and was being replaced by a salt in which the two ethyl groups were non-equivalent (CH_2 groups were apparent sextets at δ 4.28 and 4.88), as might be expected with the presence of a chiral carbon as in (21), and the hydrogens within each CH_2 group were also non-equivalent. The alternative ammonium salt, equivalent to (2), would be unlikely to show such striking non-equivalence in the ethyl groups, as rotation around carbon–nitrogen bonds is not significantly restricted.

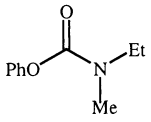


(21a)



(21b)

Since this rationalization departs from what has long been accepted for chloroformates (Scheme 1), a number of additional experiments were performed. When phenyl chloroformate was reacted with *N,N*-diethylmethylamine, a similar result to that above was observed in that again deethylation was more prevalent than demethylation, giving a ratio of (22) to (23) of 3 : 1, although the reaction was slower than that with (1).



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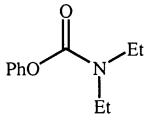


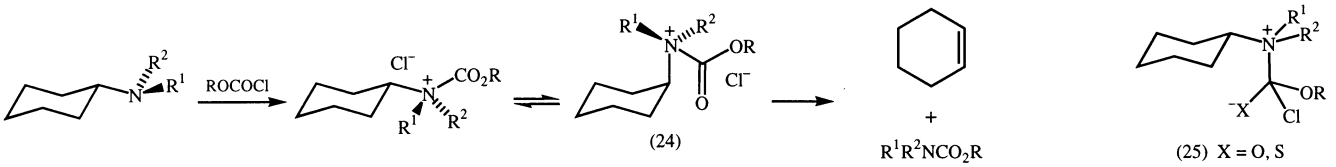
(23)

When *N,N*-diethylmethylamine was treated with (1) in acetone the reaction proceeded to completion more rapidly than in dichloromethane, but deethylation, leading to (8), still predominated over demethylation, giving (5). Reaction in acetone containing lithium bromide, in an attempt to promote S_N2 reactions on a possible thioacylammonium intermediate, gave essentially the same ratio of products, again favouring our S_Ni mechanism proposal.

The work of Charles[8] on the reaction of various chloroformates with dialkylcyclohexylamines suggested that, unless the alkyl groups were benzyl or allyl, such compounds underwent exclusive elimination (Scheme 2) to give cyclohexene. We have similarly found that *N,N*-dimethylcyclohexylamine reacts with (1) to give cyclohexene (61%) and the thiocarbamate (7) (82%). However, ^{1}H n.m.r. analysis showed the presence of chloromethane (18%) and *O*-phenyl *N*-cyclohexyl-*N*-methylthiocarbamate (18%), and the presence of the latter was confirmed by g.c.–m.s. The disparity between the yield of cyclohexene (61%) and the thiocarbamate (82%) suggested that the presence of chlorocyclohexane should be expected, but no spectroscopic or g.c.–m.s. evidence for its formation could be found. While Charles[8] has suggested that the elimination to cyclohexene is likely to be an *E*2 elimination from conformer (24) (Scheme 2), with chloride as the base, we believe a *syn* elimination from (25) appears more plausible.

In an attempt to ascertain the relative ease of cleavage of allyl, benzyl and tertiary alkyl groups, *N*-allyl-*N*-t-butylbenzylamine was synthesized from *N*-t-butylbenzylamine by reaction with allyl bromide and solid potassium carbonate. Unfortunately, the amine was too hindered for any reaction to occur, even after heating the amine with the chloro(thionoformate) for 16 h at 120° in the absence of a solvent. Likewise, *N*-t-butyl-*N*-methylbenzylamine[17] was also totally unreactive, even after prolonged heating in the absence of a solvent. It was concluded that only small alkyl groups would be tolerated on the nitrogen in the presence of a tertiary centre. *N*-Allyl-*N*-methylbenzylamine was synthesized in 84% yield from *N*-allylbenzylamine by reaction with formaldehyde and formic acid. The amine reacted readily with (1) at 20°, giving the debenzylated product (9) in 97% yield. Exclusive debenzylation was also observed when *N*-allyl-*N*-methylbenzylamine was treated with ethyl chloroformate.[8] By contrast, we have found that cyanogen bromide effects deallylation of *N*-allyl-*N*-methylbenzylamine in essentially quantitative yield, affording cyanamide (10).

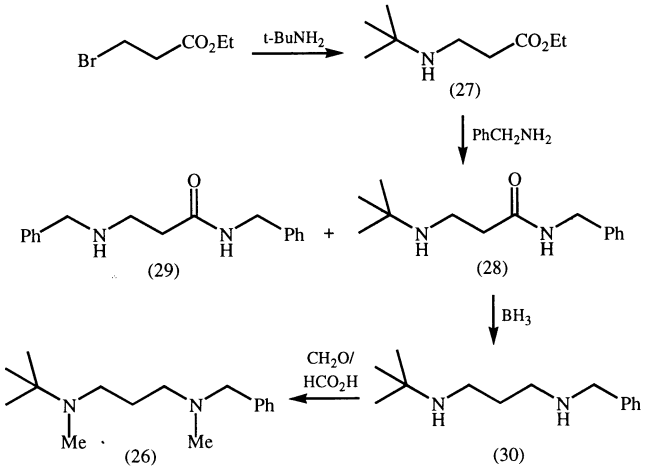
Since *N*-t-butyl-*N*-methylbenzylamine was too hindered to react with phenyl chloro(thionoformate), the relative ease of cleavage of t-butyl and benzyl groups was determined by an intermolecular competition reaction between *N,N*-dimethylbenzylamine and *N,N*-dimethyl-t-butylamine with 0.5 equiv. of the chloroformate. Although both amines could give the same product (7) after reaction with the chloro(thionoformate), the proportion of benzyl or t-butyl



Scheme 2

cleavage was ascertained by comparing the ratio of benzyl chloride and the thiocarbamate (7) in the reaction mixture. This ratio was determined spectroscopically and was found to be 1 : 2, respectively, a result which suggests that benzyl and t-butyl groups cleave with similar rates in boiling dichloromethane. However, it was found (Table 1) that cleavage of *N,N*-dimethyl-t-butylamine to the thiocarbamate required heating at 40° for 2 h, while benzyl cleavage of *N,N*-dimethylbenzylamine occurs at 20°. This reflects the differing ease of formation of the initial thioacylammonium salt. This implies that for synthetic purposes it is probable that a benzyl group will undergo cleavage in preference to a t-butyl group when the two are located on different tertiary nitrogens in the same molecule.

We investigated this hypothesis by synthesizing diamine (26) from ethyl 3-bromopropanoate, as shown in Scheme 3. G.c.–m.s. analysis of the intermediate (28), prepared as above, suggested that this product was contaminated by *N*-benzyl-3-(benzylamino)propanamide (29) which presumably arose by elimination of t-butylamine from (27) or (28), followed by conjugate addition of benzylamine. To improve the yield of the desired product (28), the mixture of (28) and (29) was heated in a sealed tube with t-butylamine which converted (29) into (28) (92%). The amide was then reduced with diborane affording the diamine (30), which was then methylated to give the diamine (26).



Scheme 3

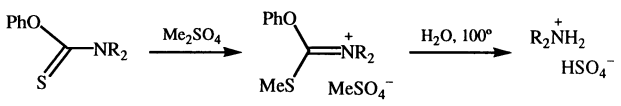
Reaction of amine (26) with phenyl chloro(thionoformate) at 20° for 1 h gave only the debenzylated thiocarbamate (11), which could be isolated in 77% yield; the same result was obtained in refluxing dichloromethane. We conclude that preferential cleavage of the benzyl group over the t-butyl group is probably due to the greater accessibility of the benzyl-substituted nitrogen to the chloroformate reagent.

The question of relative reactivity of t-butyl and allyl groups was easier to answer, by examining the reactivity of *N*-t-butyl-*N*-methylallylamine with phenyl chloro(thionoformate). The amine was synthesized in 79% yield by reacting t-butylamine with allyl bromide to form *N*-t-butylallylamine (63%), followed by methylation with formaldehyde/formic acid. To effect reaction of this amine with the reagent (1), reaction at 80° for 16 h was required, affording (9). Hence it can be concluded that a t-butyl group cleaves faster than an allyl group with this reagent. From the results above, it was concluded that the relative rate of cleavage of common alkyl groups from tertiary nitrogen centres was the following: benzyl ⩾ t-butyl > allyl > cyclohexyl > ethyl > methyl > carbocyclic ring.

We now turned our attention to the reactivity of (1) with amines that have been dealkylated by previous literature methods to compare their relative reactivites and selectivities. Demethylation of *N,N*-dimethylaniline with (1) was very slow, but the demethylated product (12) was isolated in 60% yield after reaction at 130° for 24 h; a similar reaction, with phenyl chloroformate,[4] gave an 80% yield at 100° after 60 h. It was hoped that addition of titanium tetrachloride to the reaction mixture would increase the reactivity of (1), but no synthetically useful improvement to the isolated yield was obtained after refluxing in dichloromethane for 16 h (Table 1).

The ring opening of quinuclidine to form (13) was achieved in 88% yield with phenyl chloroformate,[4] but in near quantitative yield with phenyl chloro(thionoformate). The amino alcohol tropine has been successfully demethylated only with vinyl chloroformate.[7] We found that with 1 equiv. of (1), tropine was converted into a 2 : 1 mixture of tropine thiocarbonate (14) and the demethylated thiocarbamate (15). Efficient demethylation of tropine with (1) required prior acetylation of the hydroxy group. Bicuculline gave a mixture of epimers (17) in high yield and ^{1}H n.m.r. experiments established that epimerization had occurred prior to nucleophilic attack by chloride anion, a result suggesting an S_N1 mechanism. The epimeric products were found to be configurationally stable under the reaction conditions. Treatment of bicuculline with phenyl chloroformate[18] under basic conditions gave a mixture of the enol lactone and the chlorinated species, while reaction[7] of hydrastine with vinyl chloroformate gave 88% of the enol lactone.

We conclude that phenyl chloro(thionoformate) is a useful dealkylating agent of tertiary amines, and appears to complement existing literature procedures. The intra- and inter-molecular competition reactions reported in this paper provide a basis for predicting the outcome of dealkylation from a tertiary amine with this reagent. While the dialkyl thiocarbamate resulting from the reaction of phenyl chloro(thionoformate) with a tertiary amine is readily hydrolysed by refluxing with aqueous acid or alkali, it is considerably more easily hydrolysed if the thiocarbamate is first methylated with dimethyl sulfate (Scheme 4), and the secondary amines are thus readily accessible.



Scheme 4

Experimental

General

^{1}H and ^{13}C n.m.r. spectra were recorded with a Varian Gemini spectrometer in $CDCl_3$ at 300 and 75.5 MHz respectively. Spectra were measured in (D)chloroform unless otherwise indicated and coupling constants were recorded in Hertz. Infrared spectra were recorded on a Perkin Elmer 1600 Fourier-transform i.r. spectrometer, with samples measured as a Nujol mull (solid) or as a neat film (oil). Mass spectra and high-resolution mass spectra were recorded on a Kratos MS25RF spectrometer operating at an electron ionizing energy of 70 eV. Melting points were determined on a Reichert hot-stage apparatus and remain uncorrected.

Analytical thin-layer chromatography (t.l.c.) was carried out with Merck silica gel 60 F_{254} aluminium-backed sheets. Radial chromatography was performed with silica gel PF254 coated glass rotors by using a Chromatotron 7924T. G.c.–m.s. analyses were performed on a Varian Saturn 4D instrument, with a J & W DB5 5% phenylmethylpolysiloxane column (30 m by 0.25 mm i.d.). The identity of previously prepared compounds was confirmed by direct comparison with an authentic compound or by comparison of spectroscopic data with those published. Where the isolation of only a single thiocarbamate is reported, n.m.r. analysis of the crude reaction mixture confirmed that no other thiocarbamate was produced.

The routine purification of reagents and solvents was carried out by standard laboratory procedures.[19] All organic extracts were dried with anhydrous sodium sulfate. Microanalyses were performed by Chemical and Micro Analytical Services, Melbourne.

Typical Reaction of a Tertiary Amine with (1): Reaction of N-*Ethylpiperidine*

Phenyl chloro(thionoformate) (1) (0.15 g, 0.12 ml, 0.88 mmol) was added to a solution of *N*-ethylpiperidine (0.1 g, 0.88 mmol) in dichloromethane (10 ml) and the solution stirred at 20° for 1 h. The solvent was evaporated affording a pale yellow oil which was purified by radial chromatography (dichloromethane–light petroleum, 1 : 4) on silica. The major fraction yielded a pale yellow oil, identified as *O*-phenyl piperidine-1-carbothioate[10] (4) (0.19 g, 98%) (Found: $M^{+\bullet}$, 221.0874. Calc. for $C_{12}H_{15}NOS$: $M^{+\bullet}$, 221.0874). ^{1}H n.m.r. δ 1.60–1.84, m, 6H; 3.84–3.98, m, 2H; 4.04–4.38, m, 2H; 7.03–7.10, m, 2H; 7.16–7.26, m, 1H; 7.36–7.44, m, 2H. ^{13}C n.m.r. δ 23.85, 24.92, 25.74, 47.15, 51.41, 122.63, 125.60, 128.94, 153.95, 186.15. ν_{max} 1593, 1504, 1489, 1444, 1289, 1268, 1243, 1203, 1168, 1147 cm^{-1}. Mass spectrum *m/z* 221 (M^+, 15%), 128 (52), 112 (100), 77 (14).

Reaction of Triethylamine with (1)

Phenyl chloro(thionoformate) (0.20 g, 0.16 ml, 1.19 mmol) was reacted with triethylamine (0.12 g, 0.17 ml, 1.19 mmol) at 20° for 1 h as above. Radial chromatography (dichloromethane–light petroleum, 1 : 4) on silica gave a pale yellow oil identified as *O*-phenyl *N,N*-diethylthiocarbamate[11] (5) (0.23 g, 93%) (Found: $M^{+\bullet}$, 209.0873. Calc. for $C_{11}H_{15}NOS$: $M^{+\bullet}$, 209.0874). ^{1}H n.m.r. δ 1.33, t, *J* 7.2 Hz, 6H; 3.70, q, *J* 7.2 Hz, 2H; 3.91, q, *J* 7.2 Hz, 2H; 7.05–7.09, m, 2H; 7.21–7.30, m, 1H; 7.36–7.43, m, 2H. ^{13}C n.m.r. δ 11.75, 13.44, 44.21, 48.35, 122.89, 125.93, 129.27, 154.13, 186.87. ν_{max} 1512, 1490, 1429, 1317, 1286, 1243, 1203, 1126 cm^{-1}. Mass spectrum *m/z* 209 (M^+, 17%), 116 (38), 100 (100), 94 (15), 88 (42), 77 (19).

Reaction of N,N-*Diethylbenzylamine with (1)*

Phenyl chloro(thionoformate) (0.11 g, 0.09 ml, 0.61 mmol) was reacted with *N,N*-diethylbenzylamine (0.10 g, 0.11 ml, 0.61 mmol) at 20° for 1 h as above. Radial chromatography on silica (dichloromethane–light petroleum, 1 : 4) gave a colourless oil (0.13 g, 97%) identical with the sample of (5) obtained above.

Reaction of N-*Methylmorpholine with (1)*

Phenyl chloro(thionoformate) (0.17 g, 0.14 ml, 0.99 mmol) and *N*-methylmorpholine (0.10 g, 0.99 mmol) were reacted as above. Radial chromatography on silica (dichloromethane–light petroleum, 1 : 4) yielded a pale yellow oil which was recrystallized from ether–light petroleum to give white cubes of *O*-phenyl morpholine-4-carbothioate[10] (6) (0.16 g, 73%), m.p. 120–122° (Found: C, 59.4; H, 5.9; N, 6.2%; $M^{+\bullet}$, 223.0667. Calc. for $C_{11}H_{13}NO_2S$: C, 59.2; H, 5.8; N, 6.3%; $M^{+\bullet}$, 223.0667). ^{1}H n.m.r. δ 3.74, t, *J* 4.6 Hz, 2H; 3.80, t, *J* 4.6 Hz, 2H; 3.95, t, *J* 5.1 Hz, 2H; 4.14, t, *J* 5.1 Hz, 2H; 7.01–7.10, m, 2H; 7.21–7.29, m, 1H; 7.32–7.44, m, 2H. ^{13}C n.m.r. δ 46.53, 49.92, 65.92, 66.14, 122.63, 125.98, 129.14, 153.75, 187.27. ν_{max} 1507, 1488, 1437, 1282, 1249, 1189, 1128 cm^{-1}. Mass spectrum *m/z* 223 (M^+, 26%), 130 (55), 114 (100), 94 (11), 86 (67), 77 (13).

N-*(3-Phenylprop-2-enyl)dimethylamine*

Cinnamyl chloride (5.00 g, 4.56 ml, 33 mmol) was added over 15 min at 20° to a stirred solution of 10 M dimethylamine (16.40 ml, 0.16 mol) in ethanol (50 ml). The reaction mixture was stirred for 7 h and then the solvent was evaporated. The residue was diluted with water (40 ml) and extracted twice with ether (50 ml) and the solvent dried and evaporated. The residue was distilled to give the title compound as a colourless oil (1.50 g, 28%), b.p. 200°C/25 mmHg (lit.[20] 137°C/18 mmHg) (Found: $M^{+\bullet}$, 161.1207. Calc. for $C_{11}H_{15}N$: $M^{+\bullet}$, 161.1204). ^{1}H n.m.r. δ 2.26, s, 6H; 3.05, d, *J* 6.6 Hz, 2H; 6.25, dt, *J* 15.9, 6.6 Hz, 1H; 6.50, d, *J* 15.9 Hz, 1H; 7.16–7.23, m, 1H; 7.24–7.33, m, 2H; 7.34–7.40, m, 2H. ^{13}C n.m.r. δ 45.08, 61.91, 126.25, 127.35, 127.39, 128.49, 132.47, 137.02. Mass spectrum *m/z* 161 (M^+, 99%), 146 (23), 117 (83), 115 (54), 91 (47), 84 (38), 70 (94), 58 (100).

Reaction of N-*(3-Phenylprop-2-enyl)dimethylamine with (1)*

Phenyl chloro(thionoformate) (0.11 g, 0.09 ml, 0.62 mmol) was reacted with *N*-(3-phenylprop-2-enyl)dimethylamine (0.10 g, 0.62 mmol) as above. Radial chromatography (dichloromethane–light petroleum, 1 : 19) on silica gave a pale yellow oil, identified as *O*-phenyl *N,N*-dimethylthiocarbamate[12] (7) (0.08 g, 71%). ^{1}H n.m.r. δ 3.32, s, 3H; 3.44, s, 3H; 7.04–7.12, m, 2H; 7.21–7.28, m, 1H; 7.34–7.44, m, 2H. ^{13}C n.m.r. δ 38.48, 43.01, 122.70, 125.81, 129.08, 154.04, 187.84. ν_{max} 2939, 1592, 1533, 1490, 1394, 1287 cm^{-1}. Mass spectrum *m/z* 181 (M^+, 28%), 94 (18), 88 (91), 72 (100).

Reaction of N,N-*Dimethyl-t-butylamine with (1)*

Phenyl chloro(thionoformate) (0.17 g, 0.14 ml, 0.99 mmol) was added to a solution of *N,N*-dimethyl-t-butylamine[21] (0.10 g, 0.99 mmol), prepared by the reaction of t-butylamine with formaldehyde and formic acid in dichloromethane (10 ml), and the solution refluxed for 2 h. The solvent was evaporated to give a yellow oil which was diluted with ether (20 ml) and washed twice with water (20 ml); solvent was dried and evaporated affording a pale yellow oil (0.14 g, crude yield 76%). The oil was purified by radial chromatography (ether–dichloromethane–light petroleum, 1 : 1 : 8) on silica to give a colourless oil which was identified as *O*-phenyl *N,N*-dimethylthiocarbamate (7) (0.065 g, 36%), with spectroscopic and analytical data identical to those obtained above.

Reaction of N,N-*Dimethylcyclohexylamine with (1)*

The reaction was performed in an n.m.r. tube with the amine (0.05 g, 0.06 ml, 0.39 mmol) dissolved in (D)chloroform (0.5 ml) to which was added phenyl chloro(thionoformate) (0.07 g, 0.06 ml, 0.39 mmol). The reaction was monitored by ^{1}H n.m.r. spectroscopy and after 30 min no further reaction occurred. The pale yellow solution was analysed by ^{1}H n.m.r. spectroscopy and g.c.–m.s. and was identified as a mixture of cyclohexene (61%), *O*-phenyl *N,N*-dimethylthiocarbamate (7) (82%) [mass spectrum *m/z* 180 (M^+–H), 88, 72], *O*-phenyl *N*-cyclohexyl-*N*-methylthiocarbamate (25) (18%) [mass spectrum *m/z* 250 (M^++H), 156, 140, 83, 74, 55], and chloromethane (18%). The above yields were based on reacted *N,N*-dimethylcyclohexylamine. Spectroscopic data for (7) were identical to those above.

Reaction of N,N-*Dimethylethylamine with (1)*

(i) Phenyl chloro(thionoformate) (0.40 g, 0.32 ml, 2.30 mmol) was added to a solution of *N,N*-diethylmethylamine (0.2 g, 2.30 mmol) in dichloromethane (10 ml) and the solution stirred at 20° for 3 h. The

solvent was evaporated affording a pale yellow oil that contained, by ^{1}H n.m.r. spectroscopy, thiocarbamate material and *N,N*-diethylmethylamine hydrochloride (30%). Water (10 ml) was added, the mixture was extracted twice with ether (20 ml) and the extract dried and evaporated affording a pale yellow oil (0.45 g). Radial chromatography on silica (dichloromethane–light petroleum, 1 : 9) afforded a pale yellow oil identified as a mixture of *O*-phenyl *N,N*-diethylthiocarbamate (5) (12%) and *O*-phenyl *N*-ethyl-*N*-methylthiocarbamate (8) (44%) (0.25 g). The spectroscopic data for (5) were identical to those above. O-*Phenyl* N-*ethyl*-N-*methylthiocarbamate* (8) (Found: $M^{+\bullet}$, 195.0712. $C_{10}H_{13}NOS$ requires $M^{+\bullet}$, 195.0718). ^{1}H n.m.r. (rotamer 1) δ 1.28, t, *J* 7.2 Hz, 3H; 3.25, s, 3H; 3.92, q, *J* 7.2 Hz, 2H; 7.03–7.09, m, 2H; 7.20–7.27, m, 1H; 7.34–7.42, m, 2H. ^{1}H n.m.r. (rotamer 2) δ 1.28, t, *J* 7.2 Hz, 3H; 3.39, s, 3H; 3.73, q, *J* 7.2 Hz, 2H; 7.03–7.09, m, 2H; 7.20–7.27, m, 1H; 7.34–7.42, m, 2H. ^{13}C n.m.r. (rotamer 1) δ 10.85, 35.73, 49.94, 122.69, 125.67, 128.95, 153.98, 187.10. ^{13}C n.m.r. (rotamer 2) δ 12.60, 40.77, 46.29, 122.58, 125.67, 129.01, 153.89, 187.28.

(ii) The above reaction was repeated except that acetone replaced dichloromethane. After 1 h at 20° a 6 : 1 mixture of thiocarbamates (8) and (5), respectively, was obtained, as determined by ^{1}H n.m.r. analysis.

(iii) Reaction (ii) was repeated except that lithium bromide (1.0 g, 0.015 mol) was present before addition of (1). After 1 h at 20° the mixture was added to water (10 ml) and extracted twice with ether (20 ml), affording a pale yellow oil (0.344 g) which was identified as a 6 : 1 mixture of thiocarbamates (8) and (5), respectively, by ^{1}H n.m.r. analysis.

Reaction of Phenyl Chloroformate with N,N-*Diethylmethylamine*

A solution of *N,N*-diethylmethylamine (0.1 g, 1.15 mmol) in dichloromethane (10 ml) was added to phenyl chloroformate (0.18 g, 0.14 ml, 1.15 mmol) and the solution stirred at 20° for 3 h. The solvent was evaporated affording a colourless oil containing carbamate material (41%) and ammonium salts (59%). Water (10 ml) was added to the residue, the mixture extracted twice with ether (20 ml) and the extracts dried and evaporated affording a pale yellow oil (0.17 g). Radial chromatography on silica (ether–dichloromethane, 1 : 4) gave a pale yellow oil identified as a mixture of *O*-phenyl *N,N*-diethylcarbamate[22] (23) (10%) and *O*-phenyl *N*-ethyl-*N*-methylcarbamate (22) (32%) (0.09 g).

O-Phenyl *N,N*-diethylcarbamate (23) (Found: $M^{+\bullet}$, 193.1105. Calc. for $C_{11}H_{15}NO_2$: $M^{+\bullet}$, 193.1103). ^{1}H n.m.r. δ 1.23, m, 6H; 3.40, m, 4H; 7.09–7.22, m, 3H; 7.30–7.39, m, 2H. ^{13}C n.m.r. δ 13.24, 14.09, 41.81, 42.14, 121.85, 125.13, 129.28, 151.68, 154.41.

O-*Phenyl* N-*ethyl*-N-*methylcarbamate* (22) (Found: $M^{+\bullet}$, 179.0950. $C_{10}H_{13}NO_2$ requires $M^{+\bullet}$, 179.0946). ^{1}H n.m.r. (rotamer 1) δ 1.20, m, 3H; 2.97, s, 3H; 3.41, m, 2H; 7.07–7.22, m, 3H; 7.30–7.39, m, 2H. ^{1}H n.m.r. (rotamer 2) δ 1.20, m, 3H; 3.04, s, 3H; 3.41, m, 2H; 7.07–7.22, m, 3H; 7.30–7.39, m, 2H. ^{13}C n.m.r. (rotamer 1) δ 12.30, 33.65, 41.78, 121.62, 125.00, 129.05, 151.37, 156.50. ^{13}C n.m.r. (rotamer 2) δ 13.04, 34.08, 42.11, 121.62, 125.00, 129.05, 151.37, 156.50.

N-*Allyl*-N-*t-butylbenzylamine*

To a solution of potassium carbonate (4.66 g, 0.034 mol) in ethanol (50 ml) were added *N*-t-butylbenzylamine[21] and allyl bromide (3.71 g, 2.65 ml, 0.03 mol) and the solution was refluxed for 16 h. The solvent was evaporated, the mixture diluted with water (50 ml) and extracted with ether (50 ml). The extract was evaporated and distilled to give a colourless oil (4.84 g, 78%), b.p. 67°/0.5 mmHg (lit.[23] 63–65°/0.5 mmHg) (Found: $M^{+\bullet}$, 203.1675. Calc. for $C_{14}H_{21}N$: $M^{+\bullet}$, 203.1674). ^{1}H n.m.r. δ 1.13, s, 9H; 3.20, d, *J* 6.3 Hz, 2H; 3.68, s, 2H; 4.86–5.02, m, 2H; 5.74–5.90, m, 1H; 7.12–7.39, m, 5H. ^{13}C n.m.r. δ 27.61, 52.43, 52.50, 54.95, 115.10, 126.20, 127.98, 128.14, 138.80, 143.03. Mass spectrum *m/z* 203 (M^+, 9%), 188 (79), 148 (15), 91 (100).

N-*Allyl*-N-*methylbenzylamine*

A mixture (10 g) of *N*-allylbenzylamine[24] (79%) and *N,N*-diallylbenzylamine (21%), prepared by the reaction of benzylamine and allyl bromide, was added to a solution of 40% formalin (15.32 g, 14.15 ml, 0.20 mol) and 97% formic acid (15.66 g, 12.83 ml, 0.34 mol) with cooling in an ice bath. The solution was then refluxed for 16 h. The mixture was poured into ice-cold water (50 ml), basified (solid NaOH), and the solution extracted twice with ether (60 ml). The extracts were dried and evaporated affording a colourless oil (10.57 g). The yield of title compound (83%) was calculated from the ^{1}H n.m.r. spectrum. The product was fractionally distilled, a process giving several fractions boiling in the range 60–72°/1 mmHg, all of which contained some *N,N*-diallylbenzylamine (*c*. 17%) and the title compound.[25] ^{1}H n.m.r. δ 2.18, s, 3H; 3.02, dt, *J* 6.6, 1.2 Hz, 2H; 5.10–5.24, m, 2H; 5.80–5.98, m, 1H; 7.18–7.35, m, 5H. ^{13}C n.m.r. δ 41.94, 60.46, 61.59, 117.42, 126.95, 128.23, 129.07, 136.01, 139.10. Mass spectrum *m/z* 161 (M^+), 143, 91.

N,N-diallylbenzylamine: ^{1}H n.m.r. δ 3.06, dt, *J* 6.3, 1.2 Hz, 4H; 3.56, s, 2H; 5.10–5.24, m, 4H; 5.80–5.98, m, 2H; 7.18–7.35, m, 5H. ^{13}C n.m.r. δ 56.23, 57.37, 117.26, 127.00, 128.13, 128.83, 135.89, 139.43. Mass spectrum *m/z* 187 (M^+), 172, 160, 146, 110, 91.

Reaction of N-*Allyl*-N-*methylbenzylamine (and* N,N-*Diallylbenzylamine) with (1)*

The above mixture of *N*-allyl-*N*-methylbenzylamine (83%) and *N,N*-diallylbenzylamine (17%) (0.1 g) was reacted with a solution of phenyl chloro(thionoformate) (0.11 g, 0.09 ml, 0.62 mmol) in dichloromethane (5 ml) at 20° for 1 h. The resultant pale yellow oil (0.19 g) was analysed by g.c.–m.s. The oil was found to contain *O*-phenyl *N*-allyl-*N*-methylthiocarbamate (9) (89.2%) [mass spectrum *m/z* 207 (M^+), 179, 148, 114, 98], *O*-phenyl *N,N*-diallylthiocarbamate (9.5%) [mass spectrum *m/z* 233 (M^+), 124, 98, 91, 77], *O*-phenyl *N*-benzyl-*N*-methylthiocarbamate (1.2%) [mass spectrum *m/z* 257 (M^+), 163, 147, 109, 91, 77], and *O*-phenyl *N*-allyl-*N*-benzylthiocarbamate (0.1%) [mass spectrum *m/z* 283 (M^+), 193, 131, 109, 91, 77]. The oil was purified by radial chromatography on silica (dichloromethane–light petroleum, 1 : 4) to give O-*phenyl* N-*allyl*-N-*methylthiocarbamate* (9) (0.1 g, 97% based on the *N*-allyl-*N*-methylbenzylamine present in the starting material) as the major fraction (Found: $M^{+\bullet}$, 207.0715. $C_{11}H_{13}NOS$ requires $M^{+\bullet}$, 207.0718). ^{1}H n.m.r. (rotamer 1) δ 3.24, s, 3H; 4.24–4.32, m, 2H; 5.14–5.34, m, 2H; 5.80–6.00, m, 1H; 7.00–7.12, m, 2H; 7.20–7.30, m, 1H; 7.32–7.44, m, 2H. ^{1}H n.m.r. (rotamer 2) δ 3.40, s, 3H; 4.48–4.56, m, 2H; 5.14–5.34, m, 2H; 5.80–6.00, m, 1H; 7.00–7.12, m, 2H; 7.20–7.30, m, 1H; 7.32–7.44, m, 2H. ^{13}C n.m.r. (rotamer 1) δ 35.87, 57.55, 118.50, 122.70, 125.85, 129.08, 131.02, 153.99, 188.21. ^{13}C n.m.r. (rotamer 2) δ 41.02, 53.60, 117.67, 122.66, 125.85, 129.10, 131.42, 154.03, 187.84. ν_{max} 1592, 1513, 1490, 1400, 1299, 1247, 1201, 1135 cm^{-1}. Mass spectrum *m/z* 207 (M^+, 11%), 114 (20), 98 (65), 41 (100).

Reaction of N-*Allyl*-N-*methylbenzylamine (and* N,N-*Diallylbenzylamine*) *with Cyanogen Bromide*

The above mixture (0.2 g) was treated with a solution of cyanogen bromide (0.13 g, 1.24 mmol) in dichloromethane (5 ml). After 1 h at 20° the reaction mixture was analysed by g.c.–m.s. The oil was found to contain a mixture of (1 : 12) *N,N*-diallylcyanamide [mass spectrum *m/z* 122 (M^+), 107, 94, 81, 68, 55] and *N*-allyl-*N*-benzylcyanamide [mass spectrum *m/z* 172 (M^+), 91, 77, 65] from reaction of the *N,N*-diallylbenzylamine, and only *N*-benzyl-*N*-methylcyanamide[13] (10) [mass spectrum *m/z* 146 (M^+), 131, 91, 65] from reaction of the *N*-allyl-*N*-methylbenzylamine.

Competition Between N,N-*Dimethylbenzylamine and* N,N-*Dimethyl-t-butylamine for (1)*

To a refluxing solution of *N,N*-dimethylbenzylamine (0.13 g; 0.99 mmol) and *N,N*-dimethyl-t-butylamine (0.1 g, 0.99 mmol) in dichloromethane (5 ml) was added phenyl chloro(thionoformate) (0.09 g, 0.07 ml, 0.50 mmol) dropwise. The solution was refluxed for 2 h and the solvent evaporated at 20°/20 mmHg affording a pale yellow oil which was analysed by ^{1}H n.m.r. spectroscopy; this suggested the presence of *O*-phenyl *N,N*-dimethylthiocarbamate (7) (67%) and benzyl chloride (33%), which were identified by direct comparison with authentic samples.

Ethyl 3-(t-Butylamino)propanoate (27)

Ethyl 3-bromopropanoate (20 g, 0.11 mol) and t-butylamine (16.16 g, 23.22 ml, 0.22 mol) in ethanol (50 ml) were refluxed for 16 h under nitrogen. The solvent was evaporated, water (50 ml) and 10 M NaOH (5 ml) were added, and the mixture was extracted twice with ethyl acetate (60 ml). The extracts were dried and evaporated affording a pale brown oil identified spectroscopically as the title compound[26] (27) (9.53 g, 50%). The oil was used without further purification (Found: $M^{+\bullet}$, 173.1415. Calc. for $C_9H_{19}NO_2$: $M^{+\bullet}$, 173.1416). ^{1}H n.m.r. δ 1.11, s, 9H; 1.27, t, *J* 7.0 Hz, 3H; 2.16, br s, 1H; 2.50, t, *J* 6.7 Hz, 2H; 2.83, t, *J* 6.7 Hz, 2H; 4.14, q, *J* 7.0 Hz, 2H. ^{13}C n.m.r. δ 13.98, 28.60, 35.16, 37.78, 50.43, 60.11, 172.58. Mass spectrum *m/z* 173 (M^+, 1%), 158 (100), 112 (17), 86 (42), 70 (90).

N-*Benzyl-3-(t-butylamino)propanamide (28)*

The ester (27) obtained above (8.0 g, 0.05 mol) was dissolved in benzylamine (20 ml) and heated at 130° for 16 h. Excess benzylamine was removed under vacuum and the residue transferred to a sealed tube containing t-butylamine (5 ml) and the mixture heated at 130° for 4 h. Excess t-butylamine was evaporated affording a thick brown oil which was triturated with ether–light petroleum. The brown solid obtained was recrystallized from ethanol–ether affording a white powder identified as the *title compound* (28) (10 g, 92%), m.p. 172–174° (Found: $M^{+\bullet}$, 234.1727. $C_{14}H_{22}N_2O$ requires $M^{+\bullet}$, 234.1732). ^{1}H n.m.r. δ 1.38, s, 9H; 2.99, t, *J* 6.6 Hz, 2H; 3.11, t, *J* 6.6 Hz, 2H; 4.04, br s, 1H; 4.33, d, *J* 6.0 Hz, 2H; 7.14–7.40, m, 5H; 8.26, br s, 1H. ^{13}C n.m.r. δ 25.76, 31.01, 38.02, 43.15, 57.08, 127.17, 127.82, 128.47, 138.23, 170.23. ν_{max} 3265, 2463, 1642, 1559 cm^{-1}.

N-*Benzyl*-N′-*t-butylpropane-1,3-diamine (30)*

Diborane (10 M in dimethyl sulfide) (3.21 ml, 0.03 mol) was added to a solution of the amide (28) (1.5 g, 6.41 mmol) in tetrahydrofuran (30 ml) and the solution was refluxed for 16 h. HCl (6 M, 5 ml) was added dropwise and the mixture stirred for 20 min. The solvent was evaporated and the residue made alkaline (10 M NaOH) and extracted twice with ether (60 ml). The solvent was dried and evaporated affording a colourless oil which was distilled (Kugelrohr) to give the title compound[27] (30) as a colourless oil (0.68 g, 48%), b.p. 100°/2 mmHg (Found: $M^{+\bullet}$, 220.1940. $C_{14}H_{24}N_2$ requires $M^{+\bullet}$, 220.1939). ^{1}H n.m.r. δ 1.08, s, 9H; 1.66, m, *J* 6.7 Hz, 2H; 1.84, br s, 1H; 2.61, t, *J* 6.7 Hz, 2H; 2.69, t, *J* 6.7 Hz, 2H; 3.54, br s, 1H; 3.77, s, 2H; 7.20–7.40, m, 5H. ^{13}C n.m.r. δ 28.82, 30.91, 40.95, 47.93, 50.05, 53.88, 126.67, 127.91, 128.17, 140.29.

N-*Benzyl*-N′-*t-Butyl*-N,N′-*dimethylpropane-1,3-diamine (26)*

Formic acid (90%, 0.58 g, 0.48 ml, 0.01 mol) was added to a mixture of the amine (28) (0.5 g, 2.27 mmol) and 40% formalin (0.51 g, 0.47 ml, 6.82 mmol) and the solution heated at 90° for 16 h. The mixture was poured onto water (20 ml), basified (10 M NaOH) and extracted twice with ether (60 ml). The extracts were dried and evaporated affording the title compound (26) as a colourless *oil* (0.45 g, 79%) which was used without further purification (Found: $M^{+\bullet}$, 248.2259. $C_{16}H_{28}N_2$ requires $M^{+\bullet}$, 248.2252). ^{1}H n.m.r. δ 1.05, s, 9H; 1.67, m, *J* 7.8 Hz, 2H; 2.17, s, 3H; 2.20, s, 3H; 2.34–2.42, m, 4H; 3.47, s, 2H; 7.17–7.33, m, 5H. ^{13}C n.m.r. δ 25.89, 27.25, 35.03, 42.04, 48.89, 53.93, 55.54, 62.10, 126.64, 127.96, 128.83, 139.13.

Reaction of N-*Benzyl*-N′-*t-butyl*-N,N′-*dimethylpropane-1,3-diamine (26) with (1)*

Phenyl chloro(thionoformate) (0.07 g, 0.06 ml, 0.40 mmol) was reacted with the amine (26) (0.1 g, 0.40 mmol) as above. Radial chromatography on silica (methanol–ethyl acetate, 1 : 1) of the product afforded a pale yellow oil identified as O-*phenyl* N-*(3-[t-butyl(methyl)amino]propyl)*-N-*methylthiocarbamate* (11) (0.09 g, 77%) as the major fraction (Found: $M^{+\bullet}$, 294.1760. $C_{16}H_{26}N_2OS$ requires $M^{+\bullet}$, 294.1766). ^{1}H n.m.r. (rotamer 1) δ 1.14, s, 9H; 1.98, m, *J* 7.3 Hz, 2H; 2.31, s, 3H; 2.56, t, *J* 7.3 Hz, 2H; 3.43, s, 3H; 3.77, t, *J* 7.3 Hz, 2H; 7.01–7.08, m, 2H; 7.21–7.29, m, 1H; 7.35–7.43, m, 2H. ^{1}H n.m.r. (rotamer 2) δ 1.28, s, 9H; 2.20, m, *J* 7.3 Hz, 2H; 2.48, s, 3H; 2.79, t, *J* 7.3 Hz, 2H; 3.34, s, 3H; 3.96, t, *J* 7.3 Hz, 2H; 7.01–7.08, m, 2H; 7.21–7.29, m, 1H; 7.35–7.43, m, 2H. ^{13}C n.m.r. (rotamer 1) δ 25.52, 26.44, 34.60, 41.45, 47.88, 49.71, 55.97, 122.52, 125.70, 128.94, 153.70, 187.31. ^{13}C n.m.r. (rotamer 2) δ 24.07, 25.05, 34.36, 36.74, 47.96, 52.90, 58.96, 122.52, 125.70, 128.94, 153.70, 187.81. ν_{max} 3429, 2974, 1519, 1490, 1404, 1204, 1135 cm^{-1}.

When the reaction was repeated at 50° for 1 h the same result was obtained, as determined by ^{1}H n.m.r. spectroscopy.

N-*t-Butyl*-N-*methylallylamine*

N-t-Butylallylamine[28] (5 g, 0.04 mol), made from the reaction of allyl bromide with t-butylamine in ethanol, was added to 40% formalin (9.96 g, 9.2 ml, 0.133 mol) and 90% formic acid (11.31 g, 9.27 ml, 0.22 mol) and the solution heated at 90° for 16 h. The mixture was poured onto water (20 ml), basified (10 M NaOH), extracted twice with ether (60 ml) and the extracts were dried and evaporated. The oil was distilled to give the title compound as a colourless *oil* (4.46 g, 79%), b.p. 42°/25 mmHg (Found: $M^{+\bullet}$, 127.1370. C_8H_7N requires $M^{+\bullet}$, 127.1361). ^{1}H n.m.r. δ 1.09, s, 9H; 2.17, s, 3H; 3.02, d, *J* 6.3 Hz, 2H; 5.05–5.20, m, 2H; 5.80–5.95, m, 1H. ^{13}C n.m.r. δ 25.77, 34.32, 54.04, 54.13, 116.49, 137.53.

Reaction of N-*t-Butyl*-N-*methylallylamine with (1)*

To a solution of *N*-t-butyl-*N*-methylallylamine (0.1 g, 0.79 mmol) in 1,2-dichloroethane (10 ml) was added phenyl chloro(thionoformate) (0.14 g, 0.11 ml, 0.79 mmol) and the solution refluxed for 16 h. The solvent was evaporated affording a pale brown solid identified as a mixture of thiocarbamate material (40%) and *N*-t-butyl-*N*-methylallylamine hydrochloride (60%). The solid was chromatographed on silica by radial chromatography (dichloromethane–light petroleum, 1 : 1) affording a pale brown oil identified as *O*-phenyl *N*-allyl-*N*-methylthiocarbamate (9) (0.06 g, 39%), with spectroscopic data identical to those obtained above.

Reaction of N,N-*Dimethylaniline with (1)*

(i) Phenyl chloro(thionoformate) (1) (0.29 g, 0.23 ml, 1.65 mmol) was added to *N,N*-dimethylaniline (0.2 g, 1.65 mmol) and the solution heated at 130° under a nitrogen atmosphere for 24 h. A blue oil was obtained which was purified by radial chromatography (dichloromethane–light petroleum, 1 : 4) on silica. The major fraction yielded a pale yellow solid which was recrystallized from ether–light petroleum affording pale yellow needles, identified as *O*-phenyl *N*-methyl-*N*-phenylthiocarbamate (12) (0.24 g, 60%), m.p. 102° (lit.[14] 103°) (Found: $M^{+\bullet}$, 243.0710. Calc. for $C_{14}H_{13}NOS$: $M^{+\bullet}$, 243.0718). ^{1}H n.m.r. δ 3.72, s, 3H; 6.95–7.50, m, 10H. ^{13}C n.m.r. δ 44.53, 122.5, 125.60, 125.88, 127.67, 129.12, 129.40, 143.53, 154.05, 188.08. ν_{max} 1591, 1491, 1455, 1381, 1210 cm^{-1}. Mass spectrum *m/z* 243 (M^+, 17%), 214 (12), 150 (59), 134 (100), 109 (19), 94 (19), 77 (61).

(ii) To a solution of *N,N*-dimethylaniline (0.2 g, 1.65 mmol) in dichloromethane (5 ml) was added phenyl chloro(thionoformate) (0.29 g, 0.23 ml, 1.65 mmol) followed by titanium tetrachloride (0.31 g, 0.18 ml, 1.65 mmol) and the solution refluxed for 16 h. The reaction mixture was washed twice with water (60 ml) and the solvent dried and evaporated affording a dark blue oil (0.362 g). The oil was purified by radial chromatography on silica (dichloromethane–light petroleum, 1 : 4) to give *O*-phenyl *N*-methyl-*N*-phenylthiocarbamate (12) as a pale yellow oil (0.04 g, 9%) with spectroscopic properties identical to those obtained above.

When the reaction was carried out with excess phenyl chloro(thionoformate) and excess titanium tetrachloride an intractable black tar was obtained.

Reaction of Quinuclidine with (1)

Phenyl chloro(thionoformate) (0.16 g, 0.12 ml, 0.90 mmol) was reacted with quinuclidine (0.10 g, 0.90 mmol) as above. The product

was purified by radial chromatography (dichloromethane–light petroleum, 1 : 1) on silica. The major fraction yielded O-*phenyl 4-(2-chloroethyl)piperidine-1-carbothioate* (13) (0.24 g, 95%) as an orange oil (Found: $M^{+\bullet}$, 283.0803. $C_{14}H_{18}{}^{35}ClNOS$ requires $M^{+\bullet}$, 283.0798). ^{1}H n.m.r. δ 1.18–1.45, m, 2H; 1.69–1.94, m, 5H; 2.96–3.21, m, 2H; 3.57, t, *J* 6.6 Hz, 2H; 4.77, d, *J* 13.3 Hz, 1H; 5.09, d, *J* 13.3 Hz, 1H; 7.02–7.10, m, 2H; 7.20–7.27, m, 1H; 7.34–7.42, m, 2H. ^{13}C n.m.r. δ 30.48, 31.31, 32.48, 38.10, 41.95, 46.05, 50.37, 122.57, 125.62, 128.92, 153.83, 186.17. ν_{max} 2932, 1592, 1504, 1489, 1284, 1193 cm^{-1}. Mass spectrum *m/z* 283 (M^+, 7%), 192 (14), 190 (34), 174 (100), 94 (46), 77 (32).

Reaction of Tropine with (1)

Reaction of tropine (0.1 g, 0.71 mmol) with (1) (0.12 g, 0.098 ml, 0.71 mmol) as above gave a creamy white solid which was diluted with water (10 ml) and the mixture basified with 20% sodium carbonate solution. The mixture was extracted twice with ether (40 ml) and the solvent dried and evaporated affording a light brown solid which was separated on silica by radial chromatography (dichloromethane). This afforded a colourless oil which later solidified and was identified as the *carbothioate** (15) (0.014 g, 8%), m.p. 128–130° (Found: $M^{+\bullet}$, 263.0984. $C_{14}H_{17}NO_2S$ requires $M^{+\bullet}$, 263.0980). ^{1}H n.m.r. δ 1.88, t, *J* 16.5 Hz, 2H; 2.07–2.20, m, 2H; 2.22, t, *J* 4.5 Hz, 1H; 2.27, t, *J* 4.5 Hz, 2.30–2.46, m, 2H; 2.49, t, *J* 4.5 Hz, 1H; 2.54, t, *J* 4.5 Hz, 1H; 4.23, t, *J* 4.8 Hz, 1H; 4.90, m, 2H; 7.05–7.12, m, 2H; 7.24–7.29, m, 1H; 7.35–7.44, m, 2H. ^{13}C n.m.r. δ 26.71, 28.11, 37.72, 39.61, 55.34, 58.66, 64.91, 122.88, 125.96, 129.33, 153.73, 182.17. ν_{max} 3278, 1482, 1456, 1191, 1165, 1084 cm^{-1}. Mass spectrum *m/z* 263 (M^+, 12%), 170 (30), 154 (79), 110 (15), 93 (100).

The aqueous solution was evaporated, the residue extracted with ethyl acetate (50 ml) and the solvent dried and evaporated affording a white solid (0.144 g) identified as tropine.

The above reaction was repeated in an n.m.r. tube with tropine (0.02 g, 0.14 mmol) dissolved in (D)chloroform followed by addition of phenyl chloro(thionoformate) (0.024 g, 0.02 ml, 0.14 mmol). After 30 min a mixture (34 : 66) of compound (15) (spectroscopically identical with that above) and the carbothioate† (14) was obtained. For (14): ^{1}H n.m.r. δ 2.00–3.00, m, 8H; 3.85, s, 3H; 5.05, br s, 2H; 5.66, br s, 1H; 7.20–7.60, m, 5H.

Reaction of O-*Acetyltropine with (1)*

Reaction of *O*-acetyltropine (0.1 g, 0.55 mmol) with (1) (0.09 g, 0.08 ml, 0.55 mmol) as above gave a pale yellow solid which was recrystallized from ether–dichloromethane–light petroleum affording colourless needles of the *carbothioate*‡ (16) (0.16 g, 96%), m.p. 159–161° (Found: C, 62.9; H, 6.3; N, 4.6%; $M^{+\bullet}$, 305.1083. $C_{16}H_{19}NO_3S$ requires C, 63.0; H, 6.3; N, 4.6%; $M^{+\bullet}$, 305.1086). ^{1}H n.m.r. δ 1.90, t, *J* 14.7 Hz, 2H; 2.02–2.32, m, 8H; 2.08, s, 3H; 2.50, t, *J* 4.2 Hz, 2.55, t, *J* 4.2 Hz, 1H; 4.90, d, *J* 13.2 Hz, 2H; 5.15, t, *J* 4.8 Hz, 1H; 7.05–7.16, m, 2H; 7.20–7.30, m, 1H; 7.31–7.49, m, 2H. ^{13}C n.m.r. δ 21.20, 26.24, 27.73, 34.42, 36.51, 54.62, 58.01, 67.06, 122.63, 125.79, 129.00, 153.41, 170.02, 182.23. ν_{max} 1729, 1481, 1243, 1189, 1035, 769 cm^{-1}. Mass spectrum *m/z* 305 (M, 1%), 150 (11), 134 (19), 124 (31), 94 (100).

Reaction of (+)-*Bicuculline with (1)*

Reaction of (+)-bicuculline (0.1 g, 0.27 mmol) with (1) (0.05 g, 0.04 ml, 0.27 mmol) as above gave a yellow solid (0.15 g) which was purified by radial chromatography on silica (ether–dichloromethane, 1 : 19) affording a fluorescent yellow solid. This was recrystallized from ether–dichloromethane as a fluorescent yellow powder, containing a mixture of epimers (*erythro/threo*, 3 : 1) of the *isobenzofuran derivative*§ (17) (0.13 g, 87%), m.p. 182–184° (Found: C, 60.0; H, 4.1; N, 2.5. $C_{27}H_{22}{}^{35}ClNO_7S$ requires C, 60.0; H, 4.1; N, 2.6%). The tentative assignment of stereochemistry is based on the coupling constants.

Erythro: ^{1}H n.m.r. δ 2.89–3.02, m, 1H; 3.18–3.32, m, 1H; 3.24, s, 3H; 3.78–3.92, m, 2H; 5.70, d, *J* 3.7 Hz, 1H; 5.84, d, *J* 3.7 Hz, 1H, CH; 5.98, s, 2H; 6.18, s, 2H; 6.72, s, 1H; 6.95, d, *J* 7.8 Hz, 1H; 7.00–7.12, m, 3H; 7.20, s, 1H; 7.24–7.35, m, 1H; 7.36–7.50, m, 2H. ^{13}C n.m.r. δ 29.32, 38.17, 57.26, 59.10, 83.02, 101.62, 103.55, 109.03, 109.49, 109.80, 113.97, 116.05, 122.89, 126.21, 129.15, 129.31, 129.97, 139.03, 145.07, 147.28, 148.52, 149.83, 153.94, 166.71, 188.00.

Threo: ^{1}H n.m.r. δ 2.89–3.02, m, 2H; 3.41, s, 3H; 3.92–4.06, m, 2H; 5.36, d, *J* 5.7 Hz, 1H; 5.67, d, *J* 5.7 Hz, 1H; 5.98, s, 2H; 6.19, s, 2H; 6.46, d, *J* 7.9 Hz, 1H; 6.65, s, 1H; 6.85, d, *J* 7.9 Hz, 1H; 7.00-7.12, m, 2H; 7.24-7.35, m, 2H; 7.36-7.50, m, 2H. ν_{max} 1749, 1488, 1468, 1037 cm^{-1}. Mass spectrum *m/z* 503 (M^+ – HCl, 11%), 161 (72), 117 (87), 91 (100), 70 (99).

Hydrolysis of (5)

(i) The thiocarbamate (5) (0.07 g, 0.33 mmol) was added to a solution of 10 M HCl (5 ml) in ethanol (5 ml) and refluxed for 16 h. The solvent was evaporated affording a white solid which was identified by its spectroscopic properties as diethylamine hydrochloride (0.04 g, 95%).

(ii) The thiocarbamate (5) (0.08 g, 0.38 mmol) was added to a solution of 10 M NaOH (5 ml) in ethanol (5 ml) and refluxed for 16 h. The solution was acidified with 10 M HCl and the solvent evaporated affording a white solid which was extracted twice with chloroform (40 ml). The solvent was dried and evaporated affording a white solid identified as diethylamine hydrochloride (0.04 g, 84%).

(iii) The thiocarbamate (5) (0.2 g, 0.96 mmol) and dimethyl sulfate (0.24 g, 0.18 ml, 1.91 mmol) were refluxed under nitrogen for 2 h in dichloromethane (10 ml). The solvent was evaporated affording a green oil which was washed twice with ether (20 ml) to give the iminium salt as a pale green oil (0.32 g). The salt (0.1 g, 0.28 mmol) was dissolved in water (5 ml) and refluxed for 2 h. Excess water was evaporated under reduced pressure to afford diethylamine hydrogen sulfate as a spectroscopically pure orange oil (0.04g, >95%).

Acknowledgments

The authors are grateful to the Australian Research Council for support of this work. D.S.M. acknowledges an Australian Postgraduate Award.

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* *O*-Phenyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carbothioate.
† *O*-Phenyl 3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-3-carbothioate.
‡ *O*-Phenyl 3-*O*-acetyl-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carbothioate.
§ *O*-Phenyl *N*-[2-[2-[chloro(4,5-methylenedioxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl]-4,5-methylenedioxyphenyl]ethyl]-*N*-methylthiocarbamate.

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