[Chem. Pharm. Bull. 22(5)1119—1125(1974)]

UDC 547.783.04

On Behaviors of N-(Dialkylaminomethyl)imides and -amides toward Nucleophiles

Osamu Matsuda, Keiichi Ito, and Minoru Sekiya

Shizuoka College of Pharmacy[1]

(Received September 5, 1973)

On the reaction of N-(dialkylaminomethyl)imides and -amides with nucleophiles the previous papers have exhibited the substitution of the imide or the amide residue and that of the dialkylamine residue. Although the actual substitution has been shown to depend on the substrate and the reaction condition, preferential substitution site of the substrate and how this is influenced by the reaction condition have been still in the dark. In pursuit of the substitution reaction of N-(piperidinomethyl)phthalimide, -succinimide and -benzamide it has been presumed that the substitution of the imide or amide residue is processed directly and the substitution of the piperidine residue is processed by succeeding secondary substitution or through elimination of piperidine, if possible, followed by addition of nucleophiles.

There has been reported the substitution reaction of N-(dialkylaminomethyl)amides with a variety of nucleophiles. Hellmann's works which appear in most of these previous papers have exhibited the substitutions of the dialkylamine residue of N-(dialkylaminomethyl)benzamides with the nucleophiles such as active methylene compounds,[2,3] sulfides,[4] amines[5,6] and amides,[5] known as his "amidomethylation",[7] which are effected normally under refluxing in toluene or xylene in the presence of sodium hydroxide.

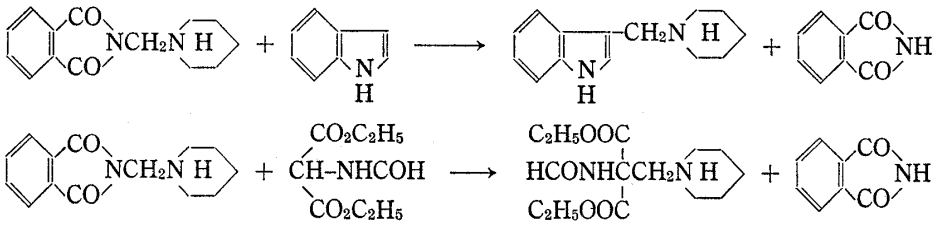
$$C_6H_5CONHCH_2\overset{R'}{\underset{R''}{N}} + X^- \longrightarrow C_6H_5CONHCH_2X + \overset{R'}{\underset{R''}{N}}{}^- \qquad (1)$$

Contrary to this reaction mode, several papers have reported the substitutions of the amide and imide residue of N-(dialkylaminomethyl)amides and -imides, which are shown to proceed exceedingly with sulfides[8] and cyanide[8] in methanol under refluxing and with Grignard reagents in ether[9] or tetrahydrofuran.[10]

$$RCON(I)CH_2\overset{R'}{\underset{R''}{N}} + Y^- \longrightarrow YCH_2\overset{R'}{\underset{R''}{N}} + RCON(I)^- \qquad (2)$$

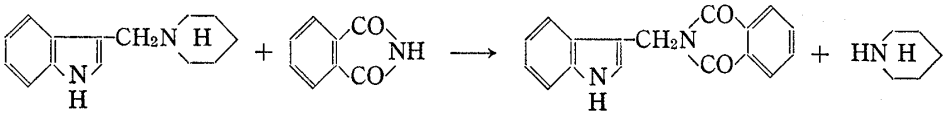
The substitution of the imide residue (Eq. 2) under the Hellmann's condition has also been reported[11] in the reactions of N-(piperidinomethyl)phthalimide with indole and with ethyl formamidomalonate as shown in the following.

1) Location: *2-2-1 Oshika, Shizuoka.*
2) H. Hellmann and G. Haas, *Chem. Ber.*, **90**, 1357 (1957).
3) R.O. Atkinson, *J. Chem. Soc.*, **1954**, 1329.
4) H. Hellmann and G. Haas, *Chem. Ber.*, **90**, 444 (1957).
5) H. Hellmann and G. Haas, *Chem. Ber.*, **90**, 50 (1957).
6) H. Hellmann and G. Haas, *Chem. Ber.*, **90**, 53 (1957).
7) H. Hellmann, *Angew. Chem.*, **69**, 463 (1957).
8) H. Sakai, K. Ito, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **21**, 2257 (1973).
9) M. Sekiya and Y. Terao, *Chem. Pharm. Bull.* (Tokyo), **18**, 947 (1970).
10) H. Hellmann and W. Unseld, *Ann.*, **631**, 95 (1960).
11) H. Hellmann, I. Löschmann, and F. Lingens, *Chem. Ber.*, **87**, 1690 (1954).



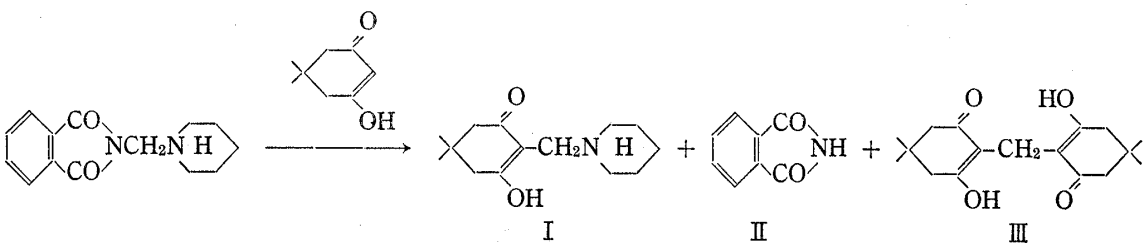
On inspection of all previously reported data, in every reaction of N-(dialkylaminomethyl)-phthalimides or -succinimides the substitution of the imide residue (Eq. 2) is favored under any condition. Besides, the substitution of the amine residue (Eq. 1) has been shown by the use of N-(dialkylaminomethyl)benzamides only under the Hellmann's condition. It can be said that these previously reported behaviors of N-(dialkylaminomethyl)amides and -imides toward nucleophiles remain unsolved on mechanistic ground.

Hellmann, *et al.* have also described[11] in the above-mentioned reaction of N-(piperidinomethyl)phthalimide with indole that for prolonged reaction period N-(3-indolylmethyl)phthalimide is obtained instead of 3-(piperidinomethyl)indole. This fact is suggestive of the formation of N-(3-indolylmethyl)phthalimide caused by successive interaction between 3-(piperidinomethyl)indole and phthalimide initially formed.



It was then inferred that the substitution of the amine residue of N-(dialkylaminomethyl)-imides, when caused, is not effected directly but indirectly.

Experiments to corroborate this assumption have now been provided in this laboratory on carrying out the reaction of N-(piperidinomethyl)phthalimide with dimedone(5,5-dimethyl-1,3-cyclohexanedione). The reaction between them was carried out under the two conditions; refluxing the solution in aromatic hydrocarbon in the presence (Hellmann's condition) and in the absence of powdered sodium hydroxide. The reactions in benzene resulted in the formation of 2-(piperidinomethyl)dimedone (I), phthalimide (II) and 2,2′-methylenebisdimedone (III) in the yields given in Table I (Runs 1 and 2).



When at higher temperature and for longer reaction period the reactions were carried out in toluene, N-[(4,4-dimethyl-2,6-dioxocyclohexyl)methyl]phthalimide (IV) was obtained in addition to the above products (Runs 3, 4 and 5). The formation of IV was supposed to be brought about by interaction of I and II initially formed. This was substantiated by the fact that IV was obtained by reacting I with II under the same condition (Runs 6, 7 and 8).

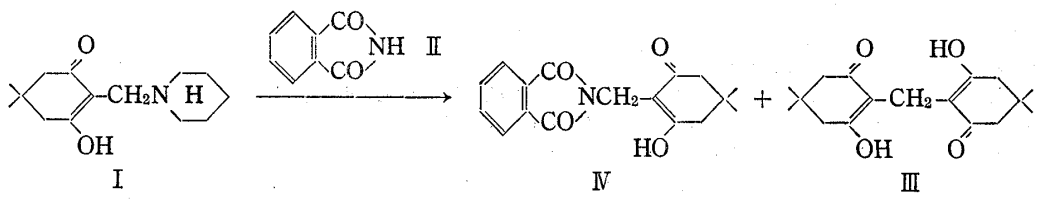
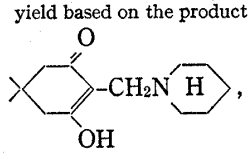
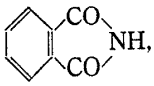
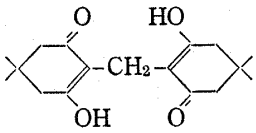
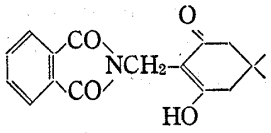


TABLE I

Run No.	Solvent	Additive	Reaction period (hr)	Yield[a] (%) of product[b] I	II	III	IV
A. Reaction[c] of N-(piperidinomethyl)phthalimide with dimedone							
1	benzene	NaOH[d]	4	27	93	58	0
2	benzene	none	4	66	86	14	0
3	toluene	NaOH[d]	10	30	78	52	9
4	toluene	NaOH[d]	10	65	79	15	7
5	toluene	none	10	68	84	14	5
B. Reaction[c] of 2-(piperidinomethyl)dimedone (I) with phthalimide (II)							
6	toluene	NaOH[d]	10	48[e]	75[e]	21	12
7	toluene	NaOH[f]	10	57[e]	72[e]	12	11
8	toluene	none	10	62[e]	79[e]	12	9

a) yield based on the product actually isolated

b) I:  , II:  , III:  , IV: 

c) substrate: 0.05 mole, reagent: 0.05mole, solvent: 100 ml

d) 0.05 mole

e) recovery of the starting material

f) 0.005 mole

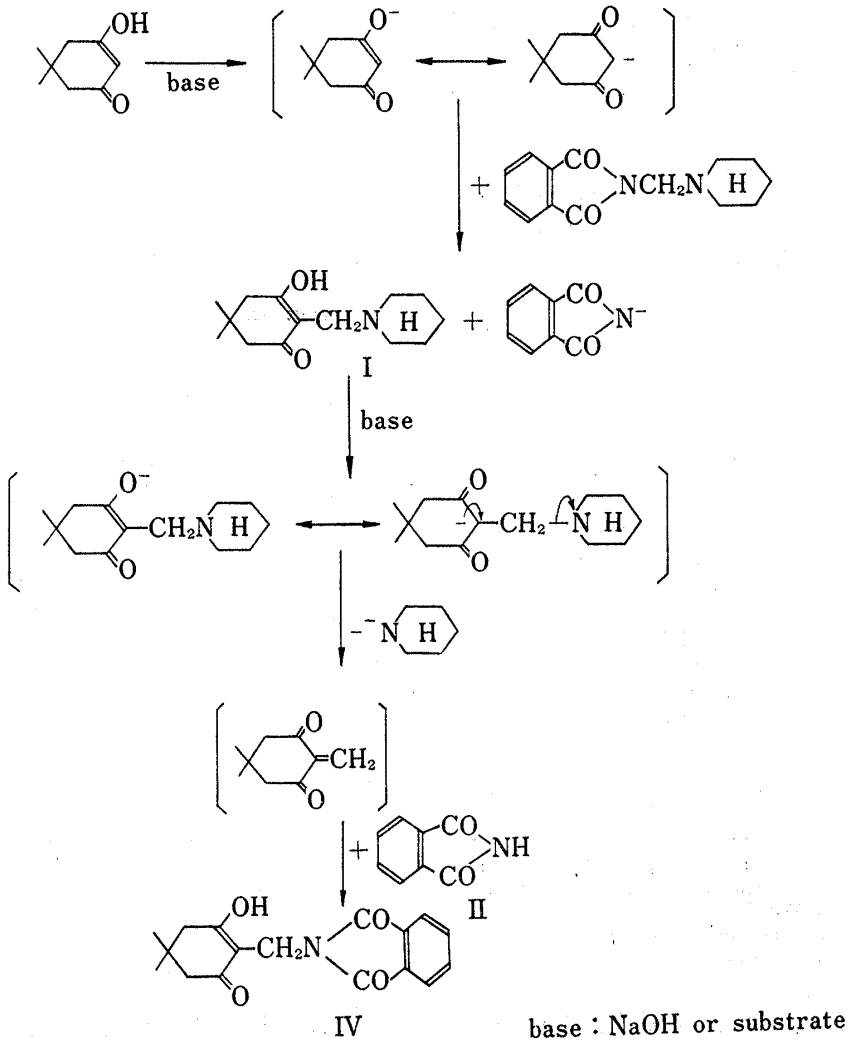


Chart 1

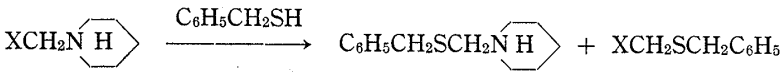
Likely reaction course can be described as shown in Chart 1, where the nucleophilic substitution converting to I is initiated and the formation of IV succeeds probably through 2-methylenedimedone. As shown in Table I the by-product III was produced in the two reactions, A and B. Its greater formation in the former is supposed to be brought about by an interaction between dimedone and the intermediate 2-methylenedimedone to that extent.

As stated above, the substitution of the amine residue of N-(piperidinomethyl)phthalimide (abnormal fashion) observed in the reaction with dimedone and with indole is clarified to involve a secondary stage after the substitution of the phthalimide residue. Thus, it can be said as for the reaction of N-(dialkylaminomethyl)imides with nucleophiles that a general understanding is established, in which the substitution of the imide residue is always favored preferentially.

However, in what course the substitution of the amine residue of N-(dialkylaminomethyl)-benzamide widely shown under the Hellmann's condition does occur is another problem to be solved. N-(Dialkylaminomethyl)benzamide possesses a secondary amide residue which appears likely to behave in a different reaction mode.

Previously it has been reported[8] in this laboratory that N-(piperidinomethyl)benzamide reacts with benzyl mercaptan on heating in toluene suspended with sodium hydroxide (Hellmann's condition) to give N-[(benzylthio)methyl]piperidine (V) and N-[(benzylthio)methyl]-benzamide (VI) in 51% and 23% yield, respectively, indicating the occurrence of the substitutions of both the benzamide and piperidine residues. Contrary to this fact, N-(piperidinomethyl)succinimide was shown to react with benzyl mercaptan under the same condition to give only V in 85% yield. These data together with additional related ones are shown in Table II.

Table II. Reaction[a] of N-(Piperidinomethyl)benzamide and -succinimide with Benzyl Mercaptan



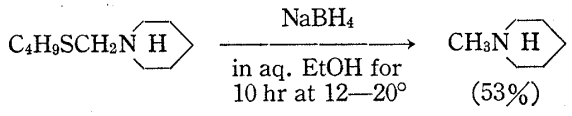
V VI

Run No.	X	Additive	Yield[b] (%) of product V	VI
1	C_6H_5CONH-	NaOH[c]	66	10
2[d]	C_6H_5CONH-	NaOH[e]	51	23
3	C_6H_5CONH-	none	38	42
4		NaOH[c]	83	0
5		NaOH[e]	85	0
6		none	84	0

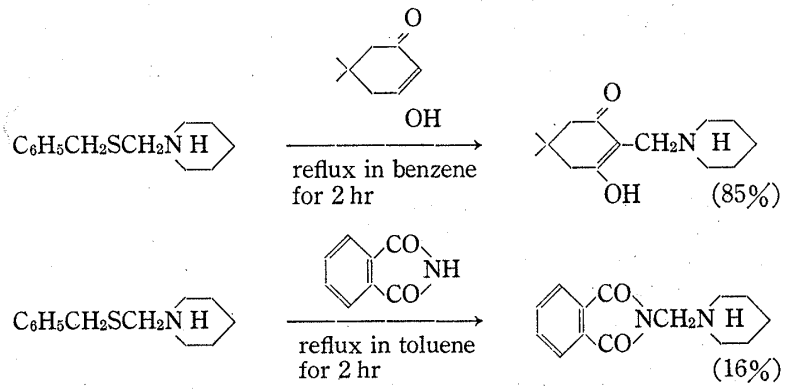
a) substrate: 0.05 mole, benzyl mercaptan: 0.055 mole, solvent: toluene 90 ml, reaction period: 4 hr
b) yield based on the product actually isolated
c) 0.055 mole
d) datum quoted from ref. 8
e) 0.0055 mole

The mere formation of V in the reaction with N-(piperidinomethyl)succinimide shows no occurrence of the secondary substitution such as shown in the reaction of N-(piperidino-

methyl)phthalimide with dimedone, but the formation of VI in the reaction with N-(piperidinomethyl)benzamide offers a problem in what course this is produced, in secondary substitution or others. Possibility of the secondary substitution of V inferred for the formation of VI is, however, excluded by the following features of V. Substitution reaction of N-[(alkylthio)-methyl]amine with nucleophiles has been exhibited[12] by the reaction with sodium borohydride to proceed as follows.



Further examination was made by the use of dimedone and phthalimide as nucleophiles giving the following results.



Behavior of N-[(alkylthio)methyl]amine toward nucleophile becomes clear from the above facts to bring about exceedingly the substitution of alkylthio residue, which proceeds directly. This alkylthio-substitution behavior of N-[(alkylthio)methyl]amine makes the formation of VI from V impossible, excluding the possibility of this stage presumed above as secondary reaction.

The formation of VI in the reaction of N-(piperidinomethyl)benzamide with benzyl mercaptan would be induced by a characteristic course. Difference from the reaction of N-

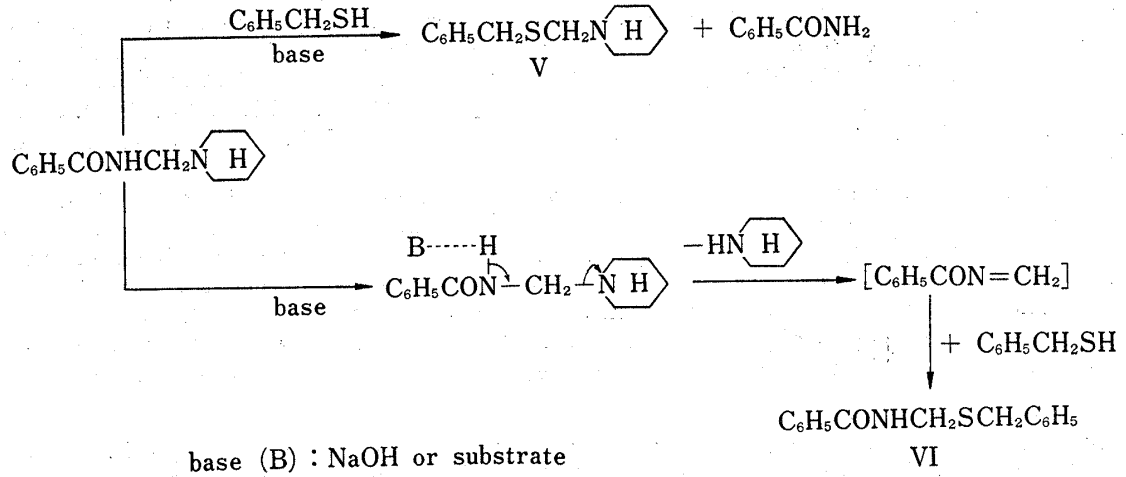


Chart 2

12) K. Shimizu, K. Ito, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), "in press."

(piperidinomethyl)succinimide appears to depend on the hydrogen-possessing secondary amide residue. When we speculate on a mechanism, the formation of VI may proceed by initial elimination of piperidine catalyzed by the base, sodium hydroxide or the substrate, followed by addition of benzyl mercaptan as shown in Chart 2.

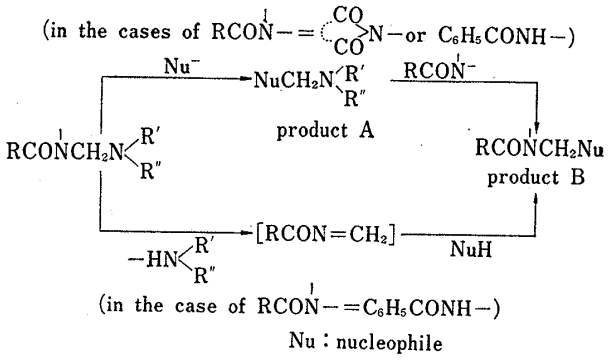


Chart 3

Thus, the mechanistic difference has now been pointed out between the substitutions of the piperidine residue of N-(piperidinomethyl)phthalimide and N-(piperidinomethyl)benzamide. The mechanistic behavior of N-(piperidinomethyl)benzamide resulting the substitution of the piperidine residue would be suggestive for all this type of the reaction under the Hellmann's condition. Extensively speaking, the general scheme shown in Chart 3 can be described.

Experimental[13]

Reaction of N-(Piperidinomethyl)phthalimide with Dimedone——A refluxing solution of 12.2 g (0.05 mole) of N-(piperidinomethyl)phthalimide and 7.0 g (0.05 mole) of dimedone in 100 ml of dry benzene or toluene suspended with appropriate amount of powdered NaOH was stirred for 4—10 hr (see Table I). The reaction mixture was treated as in the following.

In the runs using NaOH as an additive (Runs 1, 3 and 4 in Table I), the paste insoluble in the reaction solution was dissolved into cold H_2O and CO_2 was saturated, while crystals were deposited. These crystals were shown to be a mixture of phthalimide (II) and 2,2′-methylenebisdimedone (III). Separation from the mixture was made by fractional recrystallization from EtOH. III was crystallized in EtOH as prisms, mp 190—191° (lit.[14] mp 191—191.5°), showing no depression of the melting point on admixture with an authentic sample.

Usually in all the runs, from the hot reaction solution II was deposited on cool. Filtration followed by concentration gave additional II and III as crystals deposited. After removal by filtration the solvent was thoroughly evaporated from the filtrate. The resulting solid residue was shown to be 2-(piperidinomethyl)-dimedone(I) in the Runs 1 and 2, but in the other runs, a mixture of I and N-[(4,4-dimethyl-2,6-dioxocyclohexyl)methyl]phthalimide (IV). From the latter mixture separation of the two products was performed by fractional recrystallization from AcOEt. 2-(Piperidinomethyl)dimedone (I), pale yellow prisms from AcOEt, mp 164—166°. IR ν_{max}^{KBr} cm^{-1}: 1586 (CO). UV λ_{max}^{EtOH} mμ (log ε): 277.5 (3.14). NMR (in $CDCl_3$) τ: 0.21—0.49 (1H, m, enolic OH), 6.14 (2H, s, bridged CH_2), 6.66—7.46 and 7.94—8.68 (10H, m, piperidine ring protons), 7.18 (4H, s, ring CH_2), 8.95 (6H, s, CH_3). *Anal.* Calcd. for $C_{14}H_{23}O_2N$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.81; H, 9.62; N, 5.84. N-[(4,4-Dimethyl-2,6-dioxocyclohexyl)methyl]phthalimide (IV), prisms from EtOH, mp 189—191° (lit.[15] mp 189—193°). IR ν_{max}^{KBr} cm^{-1}: 1592, 1642, 1724, 1780 (CO). UV λ_{max}^{EtOH} mμ (log ε): 221 (4.68), 261 (3.83), NMR (in $CDCl_3$) τ: 0.23—0.43 (1H, m, enolic OH), 1.93—2.43 (4H, m, aromatic protons), 5.39 (2H, s, bridged CH_2), 7.62 and 7.77 (2×2H, 2s, ring CH_2), 8.95 (6H, s, CH_3). *Anal.* Calcd. for $C_{17}H_{17}O_4N$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.23; H, 5.56; N, 4.62. Yields of the products in each run are recorded in Table I.

Reaction of 2-(Piperidinomethyl)dimedone (I) with Phthalimide (II)——A refluxing solution of 11.9 g (0.05 mole) of 2-(piperidinomethyl)dimedone (I) and 7.4 g (0.05 mole) of phthalimide (II) in 100 ml of dry toluene suspended with appropriate amount of powdered NaOH was stirred for 10 hr. Isolation and identification of the products were made by the same manner as described for the reaction of N-(piperidinomethyl)-phthalimide and dimedone. Yields of the products in each run are recorded in Table I.

Reaction of N-(Piperidinomethyl)benzamide and N-(Piperidinomethyl)succinimide with Benzyl Mercaptan——A refluxing solution of 0.05 mole of N-(piperidinomethyl)benzamide or -succinimide and 6.8 g

13) All melting and boiling points are uncorrected. Infrared (IR) and ultraviolet (UV) spectra were recorded on a Hitachi EPI-G2 grating spectrophotometer and a Hitachi EPS-3T spectrophotometer, respectively. Nuclear magnetic resonance (NMR) spectra were taken with a JEOL JNM-C-60H spectrometer using tetramethylsilane as internal standard.

14) E.C. Horning and M.G. Horning, *J. Org. Chem.*, **11**, 95 (1946).

15) H. Hellmann, G. Aichinger, and H.P. Wiedemann, *Ann.*, **626**, 35 (1959).

(0.055 mole) of benzyl mercaptan in 90 ml of dry toluene suspended with appropriate amount of powdered NaOH (see Table II) was stirred for 4 hr. After filtration of the hot reaction mixture the filtrate was concentrated under reduced pressure. The resulting residue was extracted with dry petr. ether. N-[(Benzylthio)methyl]piperidine (V), bp 146—148° (4 mmHg), was obtained from the petr. ether extract. The residue insoluble in petr. ether was further subjected to extraction with dry ether. N-[(Benzylthio)methyl]-benzamide (VI), needles from ether-petr. ether (1: 1), mp 74—75°, in the runs with N-(piperidinomethyl)-benzamide was isolated from the ether extract. From the residue insoluble in ether benzamide or succinimide was obtained. Yields of the products for each run are recorded in Table II. Identities of the products V and VI were made by noting good correspondence of their IR and NMR spectra with those of the samples prepared previously.[8]

Reaction of N-[(Benzylthio)methyl]piperidine (V) with Dimedone——A solution of 11.1 g (0.05 mole) of N-[(benzylthio)methyl]piperidine (V) and 7.0 g (0.05 mole) of dimedone dissolved in 100 ml of dry benzene was refluxed for 2 hr with stirring. Crystals deposited on cool were collected by filtration, which were shown to be 6.8 g of 2-piperidinomethyldimedone (I), prisms from AcOEt, mp 164—166°. The filtrate was concentrated and the residue was triturated with a small amount of dry benzene. Filtration gave additional 3.3 g of I. Total yield, 10.1 g (85%). After concentration of the filtrate distillation of the residue under reduced pressure gave 4.4 g (71%) of benzyl mercaptan, bp 94—100° (23 mmHg), and 0.7 g (6%) of recovered V. These products were identified by comparison of their IR and NMR spectra with those of authentic samples and by mixed melting point test.

Reaction of N-[(Benzylthio)methyl]piperidine (V) with Phthalimide (II)——A refluxing solution of 11.1 g (0.05 mole) of N-[(benzylthio)methyl]piperidine (V) and 7.4 g (0.05 mole) of phthalimide (II) in 100 ml of dry toluene was stirred for 2 hr. Crystals, 5.0 g, deposited on cool were shown to be unreacted II. The concentration residue of the above filtrate was extracted with dry petr. ether. From the petr. ether extract 0.9 g (15%) of benzyl mercaptan, bp 98—100° (20 mmHg), and 8.3 g (75%) of recovered V was obtained by fractional distillation under reduced pressure. The residue insoluble in petr. ether was further subjected to extraction with dry ether several times, and 2.0 g (16%) of N-(piperidinomethyl)phthalimide, mp 117°, was obtained from the combined extracts. Additional 0.6 g of unreacted II was recovered from the residue insoluble in ether. Total recovery of II, 5.6 g (76%). These products were identified by comparison of their IR and NMR spectra with those of authentic samples and by mixed melting point test.

Acknowledgement The authors are indebted to the members of the Analysis Center of this college for microanalyses and for spectral measurements.