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Reaction of Amide Homologs. XXIV.[1] Reactions of N-(N′,N′-Dialkylaminomethyl)amides with Grignard Reagents

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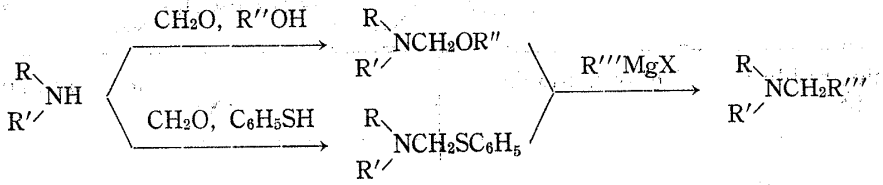
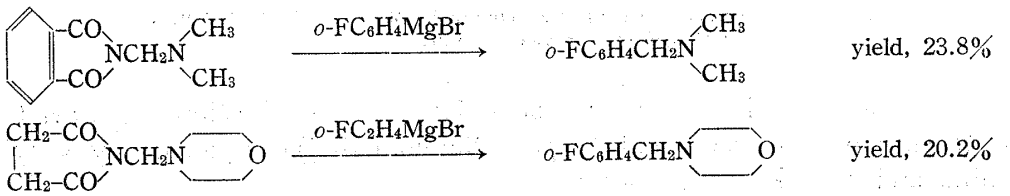
An investigation of Grignard reaction of N-(N′,N′-dialkylaminomethyl)amides (N-Mannich base) revealed that the phthalimide and succinimide derivatives underwent nucleophilic attack by Grignard reagent resulting in substitution of the amide residue with alkyls of Grignard reagent, to give tertiary amines in fair yields. These reactions have provided an practical means for preparation of tertiary amines from secondary amines through the N-Mannich bases. In these reactions it was also found that, when more than one molar equivalent amount of Grignard reagent was used, attacks to the amide moieties intially formed proceeded to give phthalimidine derivatives and γ-ketoamide respectively in the case of using N-(N′,N′-dialkylaminomethyl)phthalimide and N-(N′,N′-dialkylaminomethyl)succinimide. For identities of a series of the γ-ketoamides obtained discussions of their spectral data are also described.

The reaction of N,N-dialkylaminomethylethers (O-Mannich base) with Grignard reagents has very often been described in literature,[3] providing a useful means for preparation of tertiary amines from secondary amines through the compounds. Very recently there has been reported also the analogous reaction[4] with N,N-dialkylaminomethylthioethers (S-Mannich base).



However, on survey of the literature as for Grignard reaction of N,N-dialkylaminomethyl-substituted amide (N-Mannich base) there has been reported no more than the reactions of N-(N′,N′-dimethylaminomethyl)phthalimide and of N-(morpholinomethyl) succinimide with *o*-fluorophenylmagnesium bromide, which proceed in the same fashion, however, resulting in poor yields.[3e]



While no systematic study has been made of effects of varying structure and reaction condition, we conducted extensive related investigations on this type of Grignard reaction with a view to revealing its scope and natures.

1) Part XIII: M. Sekiya and H. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 42 (1969).
2) Location: *160, Oshika, Shizuoka.*
3) *a*) C.M. Robinson and R. Robinson, *J. Chem. Soc.*, **1923**, 532; *b*) A. Pollard and R. Robinson, *ibid.*, **1927**, 2770; *c*) J.P. Mason and M. Zief, *J. Am. Chem. Soc.*, **62**, 1450 (1940); *d*) M. Nomura, K. Yamamoto and R. Oda, *Kogyo Kagaku Zasshi*, **57**, 219 (1954); *e*) H. Hellmann and W. Unseld, *Ann.*, **631**, 95 (1960); *f*) I. Iwai and Y. Yura, *Chem. Pharm. Bull.* (Tokyo), **11**, 1049 (1963).
4) I.E. Pollak, A.D. Trifunac and G. F. Grillof, *J. Org. Chem.*, **32**, 272 (1967).

I Reactions with One Molar Equivalent of Grignard Reagent

We began with an investigation of the Grignard reaction of N-(N′,N′-dialkylaminomethyl)-amides with a view to revealing effect of variation of their amide residue. Some N-(piperidinomethyl) amides varying the amide residue were used as substrates and 2-phenylethylmagnesium bromide was selected as a model reagent. The reactions were carried out under the following uniform condition: the ethereal Grignard reagent prepared generally from 1.2-folds molar equivalent amount of the starting bromide was added dropwise to a refluxing suspension of the substrate in ether and the refluxing was continued for 30 minutes. Hydrolysis of the reaction solution was made by treatment with 30% aqueous potassium hydroxide and followed by isolation procedure of amine product from the ethereal layer.

The results of the experiments are summarized in Table I. As can be seen, in the cases of succinimide, phthalimide and *p*-toluenesulfonamide residues, nucleophilic substitution reaction of the reagent was shown to proceed to give N-(3-phenylpropyl)piperidine and, in comparison of the yields, greater efficiency was shown in the cases of succinimide and phthalimide residues.

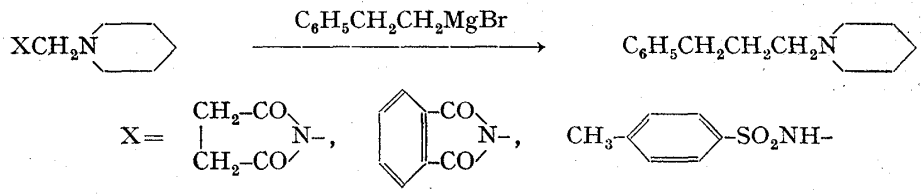
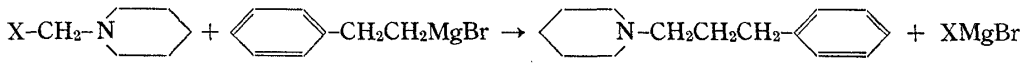
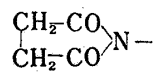
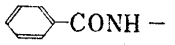
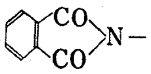
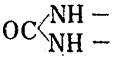
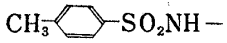


Table I. Effect of Variation of Amide Residue of N-(N′,N′-Dialkylaminomethyl)amide on the Grignard Reaction[a]



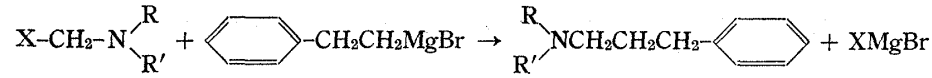
Amide residue (X)	Yield of *tert*-amine (%)	Amide residue (X)	Yield of *tert*-amine (%)
	80		0
	70		0
	35		

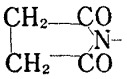
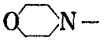
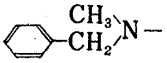
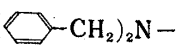
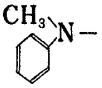
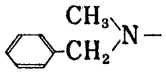
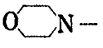
a) General procedures are given in Experimental. Means of using 30% KOH was adapted for hydrolysis of the reaction mixture.

Recognizing the reactivities from the above data, we then developed the reactions with respect to N-(succinimidomethyl) and N-(phthalimidomethyl) compounds by varying their amine residue and the Grignard reagent.

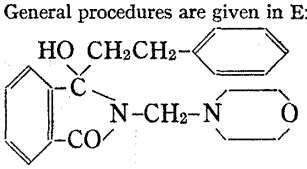
The results of the experiments by varying the amine residue are summarized in Table II. Also in these cases, the reactions were carried out under the foregoing standard condition, using 2-phenylethylmagnesium bromide as a model Grignard reagent. Yields of the tertiary amine products were varied in rather wide range, but higher yields were shown mostly in the cases of amine residues possesing rather strong basicity. Using N-(piperidinomethyl)succinimide and -phthalimide, the results of experiments with varying Grignard reagents are summarized in Table III. As can be seen, rather fair yields were obtained in most of the reactions. Regarded from the above findings, a method through the N-(succinimidomethyl) and N-(phthalimidomethyl) compound appears to be a convenient and general one for preparation of relatively strong basic aliphatic tertiary amines.

Table II. Effect of Variation of Amine Residue of N-(N′,N′-Dialkylaminomethyl)amide on the Grignard Reaction[a]



Amide residue (X)	Amine residue ($\begin{pmatrix}R\\R'\end{pmatrix}$N–)	Yield of tert. amine (%)
		80
	$(C_2H_5)_2N-$	70
		73
		68
		83
		53
		37
		70
	$(C_2H_5)_2N-$	61
		57
		28[b]

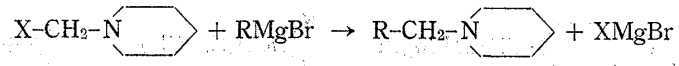
a) General procedures are given in Experimental.

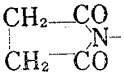
b)  I was isolated as a by-product.

From the reactions of N-(morpholinomethyl)phthalimide with 2-phenylethylmagnesium bromide and of N-(piperidinomethyl)phthalimide with benzylmagnesium bromide, as can be seen respectively in Table II and III, 2-(dialkylaminomethyl)-3-alkyl-3-hydroxy-phthalimidines were isolated as by-products, which were evidently referred to as those produced from the reaction of the phthalimide carbonyls of the substrates with the Grignard reagents. This reaction appeared to be in competition with the foresaid reactions forming tertiary amines. These by-products, 2-(morpholinomethyl)-3-hydroxy-3-(2-phenylethyl)phthalimidine (I) and 2-(piperidinomethyl)-3-benzyl-3-hydroxy-phthalimidine (II) were identified as follows. The IR absorptions of carbonyls in chloroform at 1702 cm^{-1}, 1692 cm^{-1} and the OH streching absorptions are suggestive of the 3-alkyl-3-hydroxy-phthalimidine structure with regard to our previous paper.[5] And the NMR signals of the bridged methylenes between nitrogens showed AB system, presumably owing to non equivalency of two hydrogen atoms of the methylene group, because the methylene hydrogens were fixed to the prefer conformation due to the influence of C_3-alkyl group. Selected I as a representative from the two analogous compounds, the structure of I was also confirmed from its chemical properties. When I was reduced over Raney nickel catalyst under high hydrogen pressure, 3-(2-phenylethyl)phthalimidine

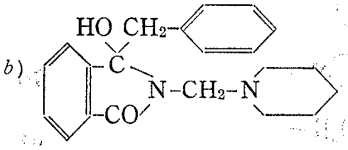
5) M. Sekiya and Y. Terao, *Yakugaku Zasshi*, **88**, 1085 (1968).

Table III. Effect of Variation of Grignard Reagent on the Grignard Reaction[a]

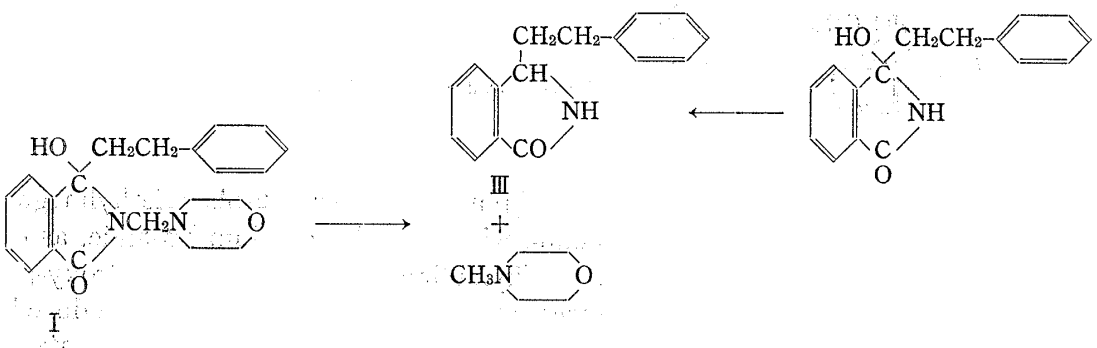


Amide residue (X)	Grignard reagent (R)	Yield of *tert*-amine (%)
	C_6H_5	74
	$C_6H_5CH_2$	73
	$C_6H_5CH_2CH_2$	80
	$CH_3(CH_2)_2CH_2$	76
	$(CH_3)_2CHCH_2$	55
	$(CH_3)_2CHCH_2CH_2$	70
	$C_{10}H_7$	71
	$C_6H_5C\equiv C$	76
	C_6H_5	68
	$C_6H_5CH_2$	38[b]
	$CH_3(CH_2)_2CH_2$	60
	$C_6H_5C\equiv C$	58

a) General procedures are given in Experimental.

b)  (II) was isolated as a by-product.

(III) and N-methylmorpholine were obtained in equimolar ratio, after uptake of two molar equivalents of hydrogen. The compound, III was confirmed to be identical with the one obtained from 3-hydroxy-3-(2-phenylethyl)phthalimidine, prepared by previously reported method[5], by the same hydrogenation procedure.



The same hydrogenolysis mode has previously generalized with the hydrogenation of the compounds having N-(morpholinomethyl) groups attached to the amide nitrogens.[6]

II Reaction with Two Molar Equivalents of Grignard Reagents

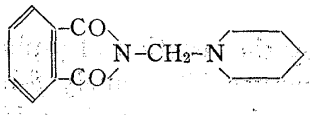
N-(N′,N′-Dialkylaminomethyl)phthalimides and -succinimides underwent nucleophilic attack by Grignard reagents resulting in substitutions of the amide groups with alkyls of Grignard reagents, as described section I. However, when enough amount of Grignard reagents were used, succeeding reactions were shown to proceed to give phthalimidine derivatives and γ-ketoamide in the case of using N-(N′,N′-dialkylaminomethyl)phthalimide and N-(N′,N′-dialkylaminomethyl)succinimide respectively. It is clearly evident from our earlier paper[5] that Grignard reagent, at first stage, reacts to form a possible salt-like phthalimidomagnesium

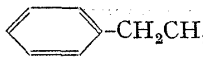
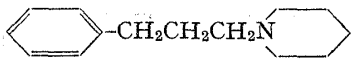
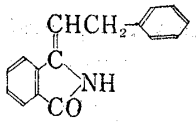
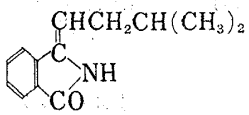
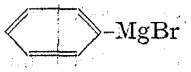
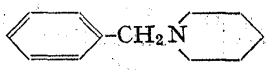
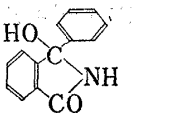
6) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **14**, 996 (1966).

bromide together with tertiary amine product and reacts further with this nitrogenanion intermediate, of which amide carbonyl appears most susceptible type.

Using 2.4-folds molar equivalent amount of Grignard reagents, the reactions with N-(piperidinomethyl)phthalimide, which was selected as a representative, were carried out in ethereal medium by similar manners as indicated in section I. Yield of both phthalimidine and tertiary amine products are recorded in Table IV. These phthalimidine derivatives were identical with those obtained by the reactions of potassium phthalimide with Grignard reagents reported in the previous work[5] by noting well correspondence of their physical data, melting points, infrared spectra and UV spectra. In comparison of the data between the reactions of N-(piperidinomethyl)phthalimide and of potassium phthalimide, generally higher yields can be seen in the former. In such phthalimidine formation reaction, which proceeds in suspending state of the salt of phthalimide in the ethereal reaction solution, this is presumably due to the more fain state of the magnesium salt-like intermediate in the reaction with N-(piperidinomethyl)phthalimide.

Table IV. Reaction[a] of N-(Piperidinomethyl)phthalimide with Two Molar Equivalent of Grignard Reagents

Substrate: 

Grignard reagent[b]	*tert*-Amine	Yield (%)	Phthalimidine	Yield (%)
		63		85
$(CH_3)_2CHCH_2CH_2MgBr$	$(CH_3)_2CHCH_2CH_2CH_2N$	71		63
		75		83

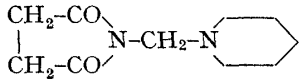
a) General procedure is given in Experimental.
b) molar ratio to sabstrate=1:2.4

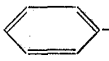
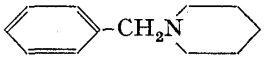
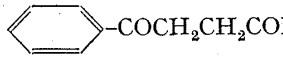
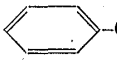
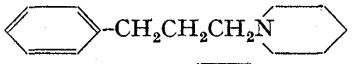
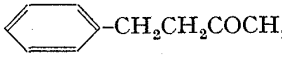
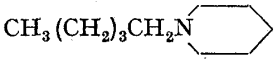
By the same manner as in the reaction with N-(piperdinomethyl)phthalimide, N-(piperidinomethyl)succinimide was affected by 2.4 molar equivalent amounts of Grignard reagents. By treatment of the reaction mixtures with ammonia-ammonium chloride solution γ-ketoamides and additionally tertiary amines were obtained. The γ-ketoamides are formed by the attack of Grignard reagent to the intermediates, succinimidomagnesium bromide. Result of these experiments are summarized in Table V.

Identities of the γ-ketoamides obtained are described in the following. Cromwell, *et al.*[7] investigated spectroscopically the structures of the ring-chain tautomers relating to β-benzoylpropionamides.

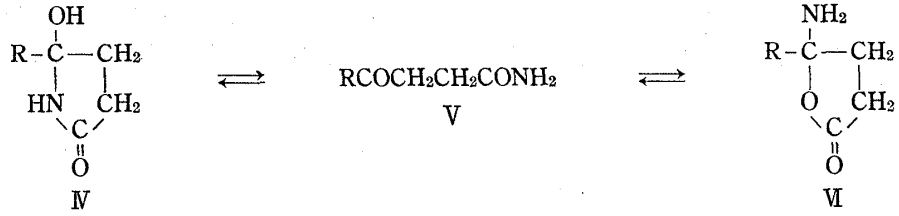
7) N.H. Cromwell and K.E. Cook, *J. Am. Chem. Soc.*, **80**, 4573 (1958).

Table V. Reaction[a] of N-(Piperidinomethyl)succinimide with Two Molar Equiv. of Grignard Reagents

substrate: 

Grignard reagent[b]	*tert*-Amine	Yield (%)	γ-Ketoamide	Yield (%)
 -MgBr		83		61
 -CH_2CH_2MgBr		83		35
$CH_3(CH_2)_2CH_2MgBr$	$CH_3(CH_2)_3CH_2N$ 	76	$CH_3(CH_2)_2CH_2COCH_2CH_2CONH_2$	33

a) General procedure is given in Experimental. b) molar ratio to substrate=1:2.4



For the compound produced by the reaction of γ-phenyl-$\Delta^{\beta\gamma}$-butenolide with ammonia, they decided open-chain amide structure (V), namely β-benzoylpropionamide. The material obtained by the reaction with phenylmagnesium bromide was shown to be the same one as they obtained; melting point and UV and IR spectra corresponded well with those reported, as shown in Table VI.

Table VI. Spectral Data of γ-Ketoamide Derivatives and Related Compounds

Compound	mp (lit., mp) (°C)	UV λ_{max}^{MeOH} mμ	ε	IR cm^{-1} Band assign.	KBr disk	$CHCl_3$ soln.	Dioxane soln.	
$C_6H_5COCH_2CH_2$-$CONH_2$	122—123 (123—125)[a]	241.5	1.31×10^4	NH	3362	3350 [b]	3425	3440 [b]
		279	1.04×10^3		3184	3172	3338	3350
		242	1.32×10^4 [b]	ketone C=O amide C=O	1678	1675	1688	1687
		280	1.20×10^3 [b]	amide II	1626	1625	1618	1620
				phenyl	1598	1594	1600	1600
$C_6H_5CH_2CH_2$-$COCH_2CH_2$-$CONH_2$	85— 86			NH	3362	3522	3440	
					3179	3402	3335	
				ketone C=O	1711	1713	1715	
				amide C=O	1654	1681	1693	
$CH_3(CH_2)_2$ $COCH_2CH_2$-$CONH_2$	114—116			NH	3372	3512	3438	
					3185	3400	3339	
				ketone C=O	1712	1707	1716	
				amide C=O	1661	1689	1692	
cf.								
$C_6H_5COC_2H_5$		241.5	1.27×10^4	ketone C=O			1693	
		279	1.00×10^3	phenyl			1598	
$CH_3CH_2CONH_2$				NH	3362	3497	3449	
					3193	3380	3353	
				amide C=O	1660	1675	1694	
				amide II	1631		1618	

a) E. Walton, *J. Chem. Soc.*, **1940**, 438 b) lit.[7]

The UV spectrum of this compound in methanol has maxima at 241.5 mμ and 279 mμ, which are consistent with the presence of alkyl phenyl ketone system because of well agreement of the locations and the intensities of these maxima with those of propiophenone. An examination of IR spectra in comparison with those of propiophenone and propionamide are very informative for assigned structure. The IR spectra in the solid and solution states shows the absorption bands of carbonyl, amide carbonyl and amide-NH_2 similar to those of both propiophenone and propionamide as shown in Table VI. Cromwell, *et al.*[7] assigned the band at 1620 cm^{-1} to the amide carbonyl in their paper, but it is evident from the data that the amide carbonyl and ketone carbonyl bands should be overlapped each other and the band at 1620 cm^{-1} is then assigned to amide II band.

The IR spectra of the materials obtained by the reactions with 2-phenylethylmagnesium bromide and butylmagnesium bromide are also suggestive of the γ-ketoamide structure; amide carbonyl band (cm^{-1}) 1654, 1661 (KBr disk), 1681, 1689 ($CHCl_3$), 1693, 1692 (dioxane) and amide-NH_2 bands 3362, 3179 and 3372, 3185 (KBr disk), 3522, 3402 and 3512, 3400 ($CHCl_3$). These absorption bands are similar to those of propionamide, and ketone carbonyl bands each appeared at 1711, 1712 (KBr disk), 1713, 1707 ($CHCl_3$) and 1715, 1716 (dioxane).

Thus, the present work has also paved a way for preparation of γ-ketoamide through the reaction of N-(N′,N′-dialkylaminomethyl)succinimide with Grignard reagent, which has not been known.

Experimental[8]

Preparation of N-(N′,N′-Dialkylaminomethyl)amides——Among N-(N′,N′-dialkylaminomethyl)amides used for the present work, those which have not been known previously were prepared as follows.

N,N′-Di(piperidinomethyl)urea——In 100 ml of EtOH 9 g of urea, 24.4 g of 37% CH_2O and 25.5 g of piperidine were dissolved and the solution was refluxed for 1 hr. Concentration of the reaction solution under reduced pressure gave a crystalline residue, which was collected by filtration and washed with petr. ether. Yield, 14.5 g (62%). Recrystallization from EtOH gave needles, mp 125—126°. IR ν_{max}^{KBr} cm^{-1}: 3461 (NH), 1636, 1591 (HNCONH). *Anal.* Calcd. for $C_{13}H_{26}ON_4$: C, 61.38; H, 10.30; N, 22.03. Found: C, 61.47; H, 10.26; N, 21.67. Perchlorate: Needles (from EtOH), mp 158—159°. *Anal.* Calcd. for $C_{13}H_{28}O_9N_4Cl_2$: C, 34.26; H, 6.19; N, 12.30. Found: C, 34.34; H, 6.36; N, 12.20.

N-(Diethylaminomethyl)succinimide——In 80 ml of MeOH 14.9 g of succinimide, 12.2 g of 37% CH_2O and 10.9 g of diethylamine were dissolved. The solution was refluxed for 1 hr. The residue obtained on removal of the solvent was distilled under reduced pressure. bp 120—122° (1 mmHg). Yield, 21 g (75%). IR $\nu_{max}^{liq.}$ cm^{-1}: 1759, 1694, (C=O). *Anal.* Calcd. for $C_9H_{16}O_2N_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.23; H, 8.42; N, 14.84.

N-(Pyrrolidinomethyl)succinimide——A solution of 14.9 g of succinimide, 12.2 g of 37% CH_2O and 10.9 g of pyrrolidine dissolved in 80 ml of MeOH refluxed for 1 hr. Concentration of the reaction solution under reduced pressure gave the product, Yield, 13.1 g (60%). Plates (from isopropylether), mp 53—54°. IR ν_{max}^{KBr} cm^{-1}: 1769, 1690 (C=O). *Anal.* Calcd. for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.47; N, 15.37. Found: C, 59.17; H, 7.74; N, 14.70.

N-(N′-Methylbenzylaminomethyl)succinimide——A solution of 14.9 g of succinimide, 12.2 g of 37% CH_2O and 18.1 g of N-benzylmethylamine dissolved in 80 ml of MeOH was refluxed for 30 min. On cool, the crystaline solid deposited was collected by filtration. Concentration of the filtrate under reduced pressure gave further amount of the product. Total yield, 29.8 g (93%). Plates (from MeOH), mp 72°. IR ν_{max}^{KBr} cm^{-1}: 1764, 1685 (C=O). *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.17; H, 6.89; N, 11.83.

N-(Dibenzylaminomethyl)succinimide——To 100 ml of MeOH 14.9 g of succinimide, 12.2 g of 37% CH_2O and 19.7 g of dibenzylamine were added, whereupon the reaction set in immediately. After refluxing for 10 min the crystals deposited in the reaction mixture. After cool, the crystals were collected by filtration. Yield, 28.4 g (92%). Plates (from MeOH), mp 122—123°. IR ν_{max}^{KBr} cm^{-1}: 1714, 1688 (C=O). *Anal.* Calcd. for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.99; H, 6.57; N, 9.03.

N-(Diethylaminomethyl)phthalimide——A solution of 14.1 g of phthalimide, 8.2 g of 37% CH_2O and 7.6 g of diethylamine dissolved in 200 ml of EtOH was refluxed for 1 hr. The residue obtained on removal of the solvent was distilled under reduced pressure to give pale yellow oil, bp 127—129° (0.03 mmHg). Yield,

8) All melting points are uncorrected.

17.2 g (74.1%). IR $\gamma_{max}^{liq.}$ cm^{-1}: 1755, 1695 (C=O). *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.84; H, 6.78; N, 11.62.

Reactions with One Molar Equiv. of Grignard Reagents General Procedure——To a refluxing suspension of 0.06 mole of pulverized N-(N',N'-dialkylaminomethyl)amide in 100 ml of dry ether was added dropwise an ethereal solution of Grignard Reagent (prepared by usual means from 0.08 mole of magnesium, 0.072 mole of alkyl halide and 100 ml of dry ether) with thorough stirring, and the refluxing and the stirring were continued for further 30 min. By means of hydrolysis by addition of 40 ml of 30% KOH to the reaction mixture in ice-bath, the tertiary amine product was allowed to pass into the ethereal layer. In the case of using phthalimide analog, proceeding treatment with 50 ml of 12% HCl was convenient for isolation of phthalimide, which deposited on cool, and follwed by addition of KOH for isolation of the amine product. The extracted ethereal solution of the amine product was dried over K_2CO_3. After removal of ether, the residue was distilled under reduced pressure to give tertiary amine. Yields of the tertiary amine products are shown in Table I, II, and III, and identities of those products and side reaction products are described in the following.

1-(3-Phenylpropyl)piperidine——Obtained by the reaction of N-(piperidinomethyl)succinimide, N-(piperidinomethyl) phthalimide and N-(piperidinomethyl)-*p*-toluenesulfoneamide with 2-phenylethylmagnesium bromide: bp 153—154° (7 mmHg) (lit.,[3b] bp 272—274°). *Anal.* Calcd. for $C_{11}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.51; H, 10.35; N, 6.80. Perchlorate: Needles (from EtOH). mp 112—113°. *Anal.* Calcd. for $C_{14}H_{22}O_4NCl$: C, 55.34; H, 7.39; N, 4.76. Found: C, 55.28; H, 7.35; N, 4.54. Picrate: Yellow plates (from EtOH) mp 101—102° (lit.,[3b] mp 99—100°).

N,N-Diethyl-(3-phenylpropyl)amine——Obtained by the reaction of N-(diethylaminomethyl)succinimide and N-(diethylaminomethyl)phthalimide with 2-phenylethylmagnesium bromide: bp 83—84° (1 mmHg) [lit.,[9] bp 137—139° (22 mmHg)]. *Anal.* Calcd. for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.49; H, 10.72; N, 7.20. Picrate: Yellow needles (from EtOH), mp 84—85°. *Anal.* Calcd. for $C_{19}H_{24}O_7N_4$: C, 54.28; H, 5.75; N, 13.33. Found: C, 54.64; H, 5.94; N, 13.30.

1-(3-Phenylpropyl)pyrrolidine——Obtained by the reaction of N-(pyrrolidinomethyl)succinimide with 2-phenylethylmagnesium bromide: bp 144—145° (16 mmHg). *Anal.* Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.60; H, 9.97; N, 7.42. Picrate: Yellow needles (from EtOH), mp 115—116°. *Anal.* Calcd. for $C_{19}H_{22}O_7N_4$: C, 54.54; H, 5.30; N, 13.39. Found: C, 54.90; H, 5.37; N, 13.08.

4-(3-Phenylpropyl)morpholine——Obtained by the reaction of N-(4-morpholinomethyl)succinimide and N-(4-morpholinomethyl)phthalimide with 2-phenylethylmagnesium bromide: bp 126—127° (4 mmHg) [lit.,[10] bp 120—130° (0.5 mmHg)]. *Anal.* Calcd. for $C_{13}H_{19}ON$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.10; H, 9.38; N, 6.47. Picrate: Yellow needles (from EtOH), mp 129—130°. *Anal.* Calcd. for $C_{19}H_{22}O_8N_4$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.46; H, 5.20; N, 12.78.

N-Methyl-N-(3-phenylpropyl)benzylamine——Obtained by the reaction of N-(N'-methylbenzylaminomethyl)succinimide and N-(N'-methylbenzylaminomethyl)phthalimide with 2-phenylethylmagnesium bromide: bp 151—152° (4 mmHg). *Anal.* Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84; N, 5.85. Found: C, 85.83; H, 8.97; N, 5.38. Picrate: Yellow plates (from EtOH), mp 107—108°. *Anal.* Calcd. for $C_{23}H_{24}O_7N_4$: C, 58.97; H, 5.16; N, 11.96. Found: C, 58.88; H, 5.08; N, 11.83.

N-(3-Phenylpropyl)dibenzylamine——Obtained by the reaction of N-(dibenzylaminomethyl)succinimide with 2-phenylethylmagnesium bromide: bp 180—181° (0.4 mmHg). *Anal.* Calcd. for $C_{23}H_{25}N$: C, 87.57; H, 7.99; N, 4.44. Found: C, 87.54; H, 8.00; N, 4.36. Picrate: Yellow granules (from EtOH), mp 102—103.° *Anal.* Calcd. for $C_{29}H_{28}O_7N_4$: C, 63.97: H, 5.18; N, 10.29. Found: C, 63.99; H, 5.23; N, 10.31.

N-Methyl-N-(3-phenylpropyl)aniline——Obtained by the reaction of N-(N'-methylanilinomethyl)succinimide with 2-phenylethylmagnesium bromide: bp 146—147° [lit.,[11] bp 182—184° (4 mmHg)]. *Anal.* Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 84.73; H, 8.69; N, 5.86. Picrate: Yellow needles (from EtOH), mp 132—133° (lit.,[11] mp 133—134°).

1-Benzylpiperidine——Obtained by the reaction of N-(piperidinomethyl)succinimide and N-(piperidinomethyl)phthalimide with phenylmagnesium bromide: bp 81—82° (2 mmHg) [lit.,[12] bp 120—124° (14 mmHg)]. *Anal.* Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.19; H, 9.60; N, 7.77. Picrate: Yellow plates (from iso-BuOH), mp 183—184° (lit.,[12] mp 183—184°).

1-(2-Phenylethyl)piperidine——Obtained by the reaction of N-(piperidinomethyl)succinimide and N-(piperidinomethyl)phthalimide with benzylmagnesium bromide: bp 102—103° (3 mmHg) [lit.,[13] bp 138—139° (14 mmHg)]. *Anal.* Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.81; H, 9.92; N, 6.94. Picrate: Yellow needles (from EtOH), mp 148—149° (lit.,[3b] mp 144—145°).

1-Pentylpiperidine——Obtained by the reaction of N-(piperidinomethyl)succinimide and N-(piperidinomethyl)phthalimide with butylmagnesium bromide: bp 78—79° (7 mmHg) [lit.,[3a] bp 80° (8 mmHg)].

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10) P.L. Bennenville, U.S. Patent 2578787 (1953) [*C. A.*, **46**, 9578 (1953)].
11) D.A. Archer and H. Booch, *J. Chem. Soc.*, **1963**, 322.
12) B. William and J.R. Wright, *J. Org. Chem.*, **27**, 1042 (1962).
13) C. Mannich and H. Davidson, *Chem. Ber.*, **69**, 2106 (1936).

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.35; H, 13.63; N, 9.02. Found: C, 77.29; H, 13.27; N, 8.88. Picrate: Yellow needles (from EtOH), mp 107—108° (lit.,[3a] mp 108°).

1-Isopentylpiperidine——Obtained by the reaction of N-(piperidinomethyl)succinimide with isobutylmagnesium bromide: bp 73—74° (15 mmHg) (lit.,[14] bp 186°). *Anal.* Calcd. for $C_{10}H_{21}N$: C, 77.35; H, 13.63; N, 9.02. Found: C, 77.54; H, 13.60; N, 8.68. Picrate: Yellow needles (from EtOH), mp 134—135° (lit.,[15] mp 134°).

1-Isohexylpiperidine——Obtained by the reaction of N-(piperidinomethyl)succinimide with isopentylmagnesium bromide: bp 87—89° (13 mmHg) [lit.,[16] bp 63—65° (3 mmHg)]. *Anal.* Calcd. for $C_{11}H_{21}N$: C, 78.03; H, 13.69; N, 8.27. Found: C, 78.06; H, 13.49; N, 8.09. Picrate: Yellow plates (from EtOH), mp 105—106°. *Anal.* Calcd. for $C_{17}H_{26}O_7N_4$: C, 51.25; H, 6.58; N, 14.06. Found: C, 51.62; H, 6.68; N, 14.11.

1-(Naphthylmethyl)piperidine——Obtained by the reaction of N-(piperidinomethyl)succinimide with 1-naphthylmagnesium bromide: bp 128—129° (0.3 mmHg) [lit.,[17] bp 128—130° (0.2 mmHg)]. *Anal.* Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 84.98; H, 8.50; N, 5.93. Picrate: Yellow needles (from EtOH), mp 202—203°. *Anal.* Calcd. for $C_{22}H_{22}O_7N_4$: C, 58.18; H. 4.88; N, 12.28. Found: C, 58.39; H, 4.92; N, 12.39.

1-(3-Phenyl-2-propynyl)piperidine——Obtained by the reaction of N-(piperidinomethyl)succinimide and N-(piperidinomethyl)phthalimide with phenylethynylmagnesium bromide:[18] bp 125—127° (0.3 mmHg) [lit.,[19] bp 170—180° (18 mmHg)]. UV λ_{max}^{EtOH} mμ: 239.8 (log ε=4.28), 250.2 (log ε=4.23). *Anal.* Calcd. for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.30. Found: C, 84.24; H, 8.69; N, 6.99. Picrate: Yellow needles (from EtOH), mp 161—162°. *Anal.* Calcd. for $C_{20}H_{20}O_7N_4$: C, 56.07; H, 4.71; N, 13.08. Found: C, 56.29; H, 4.79; N, 12.88.

2-(Morpholinomethyl)-3-hydroxy-3-(2-phenylethyl)phthalimidine——In the run with the reaction of N-(morpholinomethyl)phthalimide 2-phenylethylmagnesium bromide this compound was obtained by treatment of the precipitates, which were deposited after hydrolysis of the reaction mixture, with 5% KOH. Yield: 45%. prisms (from EtOH), mp 161—162°. IR cm^{-1}: ν_{OH} 3348 (KBr), 3345 ($CHCl_3$), $\nu_{C=O}$ 1702 (KBr), 1675 ($CHCl_3$). NMR (10% solution in $CDCl_3$) τ: 7.25—8.1 (multiplet, 8H, morpholine ring protones and $-CH_2CH_2-$), 6.28—6.43 (multiplet, 4H, morpholine ring protones), 6.16 and 5.41 (2 doublets, J=12 cps, 2H, $N-CH_2-N$), 4.07 (broad, 1H, -OH), 2—3.2 (multiplet, 9H, aromatic protones). *Anal.* Calcd. for $C_{21}H_{24}O_3N_2$: C, 71.57; H, 6.86; N, 7.95. Found: C, 72.04; H, 6.78; N, 7.74.

2-(Piperidinomethyl)-3-benzyl-3-hydroxy-phthalimidine——In the run with the reaction of N-(piperidinomethyl)phthalimide with benzylmagnesium bromide, this compound was obtained as crystals which were precipitated on cool of the residue obtained by concentration of the extracted ethereal layer as described in general procedure. Yield, 18%. Prisms (from EtOH), mp 164—165°. IR cm^{-1}: ν_{OH} 3200 (broad, KBr), 3200 (broad, $CHCl_3$), $\nu_{C=O}$ 1681 (KBr), 1692 ($CHCl_3$). NMR (10% solution in $CDCl_3$) τ: 8.2—8.8 and 7.2—7.5 (multiplet, 10H, piperidine ring protones), 6.56 (singlet, 2H, $-CH_2-$), 6.03 and 5.26 (2 doublets, J=12.3 cps, 2H, $N-CH_2-N$), 2.2—2.3 (multiplet, 10H, aromatic ring protones and -OH). *Anal.* Calcd. for $C_{21}H_{24}O_2N_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.17; H, 7.00; N, 8.13.

Reactions of N-(Piperidinomethyl)phthalimide with Two Molar Equiv. Grignard Reagents General Procedure——To a refluxing suspension of 0.06 mole of N-(piperidinomethyl)phthalimide in 100 ml of dry ether was added dropwise an ethereal solution of Grignard reagent (prepared by usual means from 0.155 mole of magnesium, 0.144 mole of alkyl halide and 200 ml of dry ether) with vigorous stirring. The refluxing and the stirring were continued for further 30 min. The reaction mixture was hydrolyzed by addition of 50 ml of 15% HCl in an ice-bath. In runs with phenylmagnesium bromide and 2-phenylethylmagnesium bromide, most part of the phthalimidine product was precipitated and the other part was obtained by evaporation of thee thereal layer. In the case of isopentylmagnesium bromide, whole phthalimidine product was obtained by evaporation of the ethereal layer. Basification of the aqueous layer with KOH followed by extraction of benzene gave the tertiary amine product, which was identified by noting exact correspondences of IR spectrum with the specimen obtained by foregoing reaction with one molar equiv. of Grignard reagent. The following is identities of the phthalimidine products.

3-Hydroxy-3-phenylphthalimidine——This was obtained together with 1-benzylpiperidine by the reaction of N-(piperidinomethyl)phthalimide with phenylmagnesium bromide. Recrystallization from AcOEt, needles, mp 164—165°. IR cm^{-1}: $\nu_{OH,NH}$ 3541, 3409 (CH_2Cl_2), $\nu_{C=O}$ 1714 (dioxane). This was identical with that obtained in the previous paper[5] by noting exact correspondences of the spectral data and no depression in the melting point by admixture.

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15) D.T. Gibson and A.K. Macbeth, *J. Chem. Soc.*, **119**, 437 (1921).
16) I.N. Nazorov, R.I. Kruglikova and G.M. Nikolaev, *Zur Obshchi Khim.*, **30**, 462 (1960) [*C. A.*, **54**, 22633 (1961)].
17) A.M. Akkerman, P.K. de Jongh and H. Veldstra, *Rect. Trav. Chim.*, **70**, 899 (1951).
18) J.W. Kroeger and J.A. Nieuwland, *J. Am. Chem. Soc.*, **58**, 1861 (1936).
19) C. Mannich and F.T. Chang, *Chem. Ber.*, **66**, 415 (1933).

3-(2-Phenylethylidene)phthalimidine——This was obtained together with 1-(3-phenylpropyl)piperidine by the reaction of N-(piperidinomethyl)phthalimide with 2-phenylethylmagnesium bromide. Needles (from EtOH), mp 163—164°. IR ν_{max}^{KBr} cm^{-1}: 3449, 3185 (NH), 1703 (C=O). This was identical with that obtained in the previous paper.[5]

3-(Isopentylidene)phthalimidine——This was obtained together with 1-isohexylpiperidine by the reaction of N-(piperidinomethyl)phthalimide with isopentylmagnesium bromide. Plates (from AcOEt), mp 114—115° (lit.,[20] mp 115°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3451, 3193 (NH), 1702 (C=O). This was identical with that obtained in the previous paper.[5]

Reactions of N-(Piperidinomethyl)succinimide with Two Molar Equiv. Grignard Reagents General Procedure——N-(Piperidinomethyl)succinimide was allowed to react with two molar equiv. Grignard reagent according to the procedure described in the phthalimide analogs. The reaction mixture was hydrolyzed with 100 ml of aqueous NH_4Cl–NH_3 solution (0.4 mole of NH_4Cl in 100 ml of 3% aq. NH_3) in an ice bath. The γ-ketoamide products were precipitated in part [in runs with β-benzoylpropionamide and β-(β-phenylpropionyl)propionamide]or passed into the ethereal layer (in the case of β-pentoylpropionamide). The aqueous layer was extracted with ether, and the combined ether solution was dried over $MgSO_4$ and concentrated. The deposited crystlas of γ-ketoamide in the resulting residue on cool were collected by filteration and washed with dry petr. ether. The tertiary amine was obtained by distillation of the residue obtained by removal of petr. ether from the washing solution. Identities of tertiary amines were conduted by comparison of IR spectrum with those of the specimen obtained in the foregoing. The followings are identities of the γ-ketoamides. IR and UV spectra of these compounds are shown in Table VI.

β-Benzoylpropionamide——Obtained together with 1-benzylpiperidine by the reaction of N-(piperidinomethyl)succinimide with phenylmagnesium bromide. Recrystallization from EtOH, needles, mp 122—123°. *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.58; H, 6.30; N, 7.67.

β-(β-Phenylpropionyl)propionamide——Obtained together with 1-(3-phenylpropyl)piperidine by the reaction of N-(piperidinomethyl)succinimide with 2-phenylethylmagnesium bromide. Leaflets (from benzene), mp 85—86°. *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.06; H, 7.30; N, 6.77.

β-Pentoylpropionamide——Obtained together with 1-pentylpiperidine by the reaction of N-(piperidinomethyl)succinimide with butylmagnesium bromide. Plates (from benzene), mp 114—116°. *Anal.* Calcd. for $C_8H_{15}O_2N$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.07; H, 9.59; N, 8.87.

Hydrogenolysis of 3-Hydroxy-3-(2-phenylethyl)phthalimidine——In an autoclave 12.3 g (0.04 mole) of 3-hydroxy-3-(2-phenylethyl)phthalimidine, 100 ml of EtOH and Raney nickel catalyst freshly prepared from 2 g of 50% alloy, was added under 80 kg/cm² (at room temperature) of hydrogen, the whole was preheated and constant shaking was started at 130—135°. It took 4 hr untill drop of hydrogen pressure was ceased, and then shaking and heating at this temperature were continued for further 30 min. The uptake of hydrogen was calculated at nealy one molar equivelent. After removal of catalyst by filteration EtOH was evaporated from hydrogenation solution. The residual liquid was washed with petr. ether to give crystalline solid. Yield, 7.8 g (81.3%). Recrystallyzation from EtOH, prisms, mp 140—141°. IR ν_{max}^{KBr} cm^{-1}: 3284, 3163 (NH), 1673 (C=O). NMR (10% solution in $CDCl_3$) τ: 7—8.35 (multiplet, 4H, $-CH_2CH_2-$), 5.34 (multiplet, 1H, –CH–), 2.73 (singlet, 5H, aromatic ring H), 1.98—2.65 (multiplet, 4H, aromatic ring H), 1.2—1.4 (broad, 1H, NH). *Anal.* Calcd. for $C_{16}H_{15}ON$: C, 80.98; H, 6.37; N, 5.53. Found: C, 80.52; H, 6.36; N, 5.53.

Hydrogenolysis of 2-(Morpholinomethyl)-3-hydroxy-3-(2-phenylethyl)phthalimidine——In an autoclave a mixture of 14. 1g (0.04 mole) of 2-(morpholinomethyl)-3-hydroxy-3-(2-phenylethyl)phthalimidine and 100 ml of EtOH was hydrogenated at 130—135° over Raney nickel catalyst, prepared from 2 g of 50% alloy, under high pressure (initial hydrogen pressure: 80 kg/cm² at room temperature). Uptake of nearly two molar equiv. of hydrogen was ceased after 4.5 hr. After removal of catalyst by filteration, solvent was distilled off from filtrate under reduced pressure, whereupon N-methylmorpholine was vaporized along with EtOH. To remove the amine completely, alternate addition of H_2O followed by steam distillation was necessary. The distillate was treated with ethanolic picric acid solution as usual. N-Methylmorpholine was obtained its picrate which was weighed. Yield, 11.3 g (92.6%) and identified with authentic sample by the mixed melting point test. The distilled residue was solidified by washing with small amount of petr. ether. Yield, 8.2 g (87%). Recrystallization from EtOH, prisms, mp 140—141°, undepressed by admixture with a sample prepared by the above method.

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20) C. B'eis, *Compt. Rend.*, **1904**, 138, 987.