

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

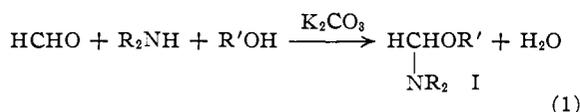
Synthesis and Reactions of α -Dialkylaminobenzyl Butyl Ethers. Interactions with Grignard Reagents to Form Tertiary Amines¹

BY A. THEODORE STEWART, JR., AND CHARLES R. HAUSER

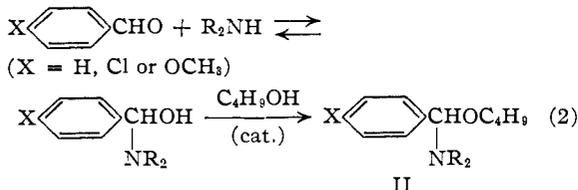
RECEIVED SEPTEMBER 7, 1954

Several methods have been developed for the synthesis of α -dialkylaminobenzyl *n*-butyl ethers and select derivatives from aromatic aldehydes, aliphatic secondary amines and butanol-1. The parent compound, $C_6H_5CH(NR_2)OC_4H_9$, was shown to be readily interconvertible with the diamine, $C_6H_5CH(NR_2)_2$, but not with the acetal, $C_6H_5CH(OC_4H_9)_2$. A series of amino ethers were treated with Grignard reagents to form tertiary amines of the type $C_6H_5CH(NR_2)R'$, many of which are difficult to prepare by more common methods. This displacement with a Grignard reagent is freer of side reactions than that of aminonitriles, $C_6H_5CH(NR_2)CN$, which have been employed previously for preparing such tertiary amines. A representative amino ether was reduced by *t*-butylmagnesium chloride and by catalytic hydrogenation. Some theoretical aspects of the formation of amino ethers and of their reactions with organomagnesium compounds are considered.

McCleod and Robinson² showed that formaldehyde reacts with aliphatic secondary amines and alcohols in the presence of potassium carbonate to form dialkylaminomethyl alkyl ethers (I) (equation 1). However, they reported that the corresponding reaction with benzaldehyde fails.²



We have succeeded in effecting the reaction with benzaldehyde and with certain substituted benzaldehydes to form amino ethers of type II by modifying the earlier conditions. The aldehyde presumably adds the amine to form an intermediate hydroxyamine which reacts with the alcohol (equation 2).



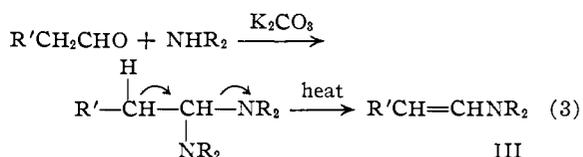
Whereas the earlier workers² used equimolar quantities of the three reactants, we employed a slight excess of the amine over the aldehyde and a large excess of butanol-1. The reaction was effected under three conditions: in method A, anhydrous potassium carbonate, usually equivalent to the aldehyde, was added to facilitate the condensation; in method B, a 25% aqueous solution of the amine was used and the reaction mixture subsequently supersaturated with potassium carbonate; while in method C, an anhydrous mixture of the three reactants was treated with a catalytic amount of mercuric chloride (or glacial acetic acid) and a substantial excess of Drierite. The results are summarized in Table I.

Our attempts to prepare the corresponding α -dialkylamino ethers from *n*-butyraldehyde, butanol-1 and dimethylamine or diethylamine were unsuccessful. It is possible that some of the prospective amino ether was formed but underwent thermal β -elimination of alcohol or amine during distillation to form an enamine III or vinyl ether,

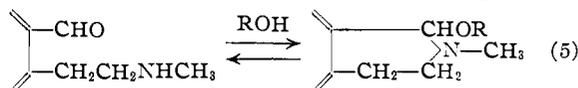
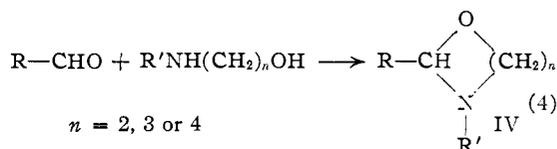
(1) Supported by the Office of Naval Research.

(2) C. M. McCleod and G. M. Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

similar to that observed with 1,1-diamines prepared from aldehydes having α -hydrogen and secondary amines (equation 3).³ The present methods failed also with methyl ethyl ketone or acetophenone and the lower aliphatic dialkylamines.



It should be mentioned that cyclic α -amino ethers, such as IV, are produced readily from appropriate secondary amino alcohols and aliphatic, as well as aromatic, aldehydes (equation 4).⁴ Corresponding cyclic amino ethers have been prepared also from ketones.^{4a,b} Indeed, a cyclic α -amino ether was the first example reported, the preparation involving an intramolecular cyclization of cotarnine in an alcoholic medium (equation 5).⁵



The formation of the amino ether II presumably involves the ionization of the intermediate hydroxyamine to form a carbonium ion, $C_6H_5C^+=NR_2 \rightleftharpoons C_6H_5C^+-NR_2$, which reacts with the alcohol in a manner analogous to that generally postulated for acetal formation.⁶ Indeed, mercuric chloride, which is a well known acetalization catalyst, was found to implement markedly the formation of amino ethers (method C). However, the function of po-

(3) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).(4) (a) A. C. Cope and E. M. Hancock, *This Journal*, **64**, 1503 (1942); (b) E. M. Hancock and A. C. Cope, *ibid.*, **68**, 1738 (1946); (c) M. Senkus, *ibid.*, **67**, 1515 (1945); (d) L. H. Goodson and H. Christopher, *ibid.*, **72**, 358 (1950); (e) L. Knorr and H. Matthes, *Ber.*, **34**, 3484 (1901); (f) A. I. Kripianov and B. A. Rashkovan, *J. Gen. Chem.*, **7**, 1026 (1937); *C. A.*, **31**, 5357 (1937); (g) M. Bergmann, *et al.*, *Ber.*, **55**, 2796 (1922); (h) C. Mannich and H. Wieder, *ibid.*, **65B**, 385 (1932); (i) G. A. R. Kon and J. J. Roberts, *J. Chem. Soc.*, 978 (1950).(5) M. Freund and P. Bamber, *Ber.*, **35**, 1752 (1902).

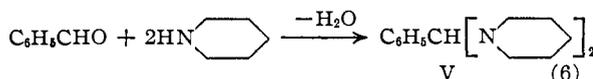
(6) E. R. Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 215.

TABLE I
 AMINO ETHERS OF TYPE II FROM AROMATIC ALDEHYDES, SECONDARY AMINES AND BUTANOL-1

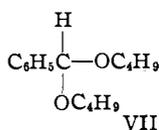
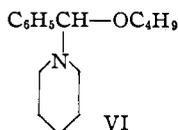
Amino ether X	R	Method	B.p.,		n_D^{25}	Yield, %	Carbon, %		Hydrogen, %		Nitrogen, %	
			°C.	Mm.			Calcd.	Found	Calcd.	Found	Calcd.	Found
H	CH ₃	A	109-110	1	1.4869 ^a	56 ^b	75.31	75.27	10.21	10.41	6.75	6.82
H	CH ₃	B	108-109	1		50						
H	C ₂ H ₅ ^c	A	122-123	1	1.4829 ^a	38 ^d	76.54	74.68	10.70	10.28	5.95	4.56
H	C ₂ H ₅	C	118-124	1		47 ^e						
H	-C ₆ H ₁₀ ^f	A	153-154	1	1.5069 ^a	67	77.68	77.51	10.19	10.25	5.66	5.76
H	-C ₆ H ₁₀ ^f	C ^g	148-149	1		80						
H	-C ₆ H ₈ O ^h	A	154-155	0.5	1.5108	44	72.25	72.26	9.30	9.37	5.62	5.67
Cl	CH ₃	B	123-125	1	1.5015	25 ⁱ	64.58	64.32	8.34	8.61	5.79	5.80
Cl	-C ₆ H ₁₀ ^f	A	169-172	1	1.5320	55	68.19	69.00	8.58	8.83	4.97	7.32
OCH ₃	-C ₆ H ₁₀ ^f	A	174-177	1	1.5228	61 ^j	73.60	73.43	9.81	9.72	5.05	5.17

^a An average from several preparations the maximum deviation from which was ± 0.001 . ^b Conversion was 75-80%. ^c Although analyses are unsatisfactory, this amino ether gave a good yield of tertiary amine X with benzylmagnesium chloride (see Table II). ^d Conversion was 43%. ^e Conversion was 58%. ^f Piperidyl. ^g When 0.1 mole of glacial acetic acid was substituted for the mercuric chloride catalyst, the yield was 44%. ^h Morpholino. ⁱ Conversion was 43%. ^j Conversion was 86%.

tassium carbonate (methods A and B) is not explained as readily. It may serve only as a desiccant. This is apparently its function in the corresponding formation of 1,1-diamines from aldehydes and secondary amines (see equation 3), since certain of these reactions may be effected in the absence of a catalyst if the by-product water is removed as a suitable azeotrope. For example, N,N'-benzylidenebis-piperidine (V) was prepared from benzaldehyde and piperidine in this manner (equation 6).

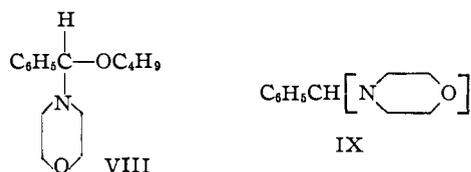


It is possible that 1,1-diamines, such as V, are formed as intermediates in the preparation of the amino ethers II. For example, α -N-piperidylbenzyl butyl ether (VI) might have arisen in this manner through diamine V. Thus, not only was diamine V simply prepared from benzaldehyde (equation 6), but it was converted to amino ether VI on refluxing with butanol-1, benzaldehyde and potassium carbonate. However, under the usual conditions, the amino ether most likely originates through direct reaction of the intermediate carbonium ion with the alcohol which is present in large excess. The amino ethers definitely did not arise through benzaldehyde dibutylacetal (VII), since not only was none of this acetal found in the preparations of the amino ethers (II, X = H), but it was largely recovered after refluxing with piperidine in the presence of mercuric chloride or potassium carbonate, or with benzene in the absence of a catalyst.



Although diamine V was converted to amino ether VI as described above, the reverse conversion was realized more readily. Thus, amino ether VI produced some diamine V on standing overnight exposed to air, and a good yield of V was obtained on refluxing VI with piperidine in benzene. Even on standing in a stoppered flask for several days, pure α -(4-morpholino)-benzyl butyl ether (VIII)

deposited crystals of the corresponding diamine IX.



It can be seen from Table I that, in general, the yields of amino ethers II were good, and some assuredly are not the maximum obtainable. The secondary amines employed successfully were dimethylamine, diethylamine, piperidine and morpholine, but not methylaniline which was recovered from the reaction mixture of this amine, benzaldehyde, and butanol-1 under the conditions of method A. Although the amino ether from diethylamine (II, R = C₂H₅, X = H) failed to give a satisfactory analysis, it was probably nearly pure since it afforded a high yield of the corresponding tertiary amine when treated with benzylmagnesium chloride (see equation 7 and Table II). The refractive indices of freshly prepared samples of each of the first three amino ethers listed in Table I from several different experiments varied by as much as ± 0.001 . This may have been due to traces of benzaldehyde or the diamine. Most of the present amino ethers, which are liquids, are somewhat unstable, becoming colored on standing overnight or longer, although they usually are recoverable in a comparatively pure state by redistillation. Apparently, these compounds are converted slowly to the corresponding 1,1-diamines as pointed out above.

Reactions of Amino Ethers with Grignard Reagents.—Robinson and Robinson⁷ observed that the alkoxy group of type I amino ethers could be displaced by the hydrocarbon portion of Grignard reagents to form tertiary amines. We have effected the corresponding substitution reaction of type II amino ethers to produce type X tertiary amines (equation 7). The organomagnesium halide was employed in a maximum excess of 50% (see Experimental). The conversion of halides to the Grignard reagent was carried out in the presence

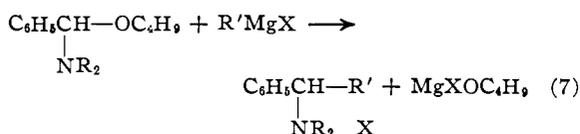
(7) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **123**, 532 (1923).

TABLE II
 TERTIARY AMINES X FROM AMINO ETHER II (X = H) AND GRIGNARD REAGENTS

Tertiary amine X R	R'	B.p. or m.p. °C.	Mm.	n_D^{20}	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH ₃	CH ₃	80-81	10	1.5000 ^a	56 ^b						
CH ₃	(CH ₃) ₂ CH	80.5	1	1.4996	61 ^c	81.30	81.11	10.80	10.92	7.90	7.99
CH ₃	C ₆ H ₅	M. 71 ^d			88-92 ^e						
CH ₃	C ₆ H ₅ CH ₂	142	1	1.5568	80-96 ^{f,g}	85.28	85.00	8.49	8.29	6.21	6.13
CH ₃	(C ₆ H ₅) ₂ CH	M. 126.5-127.5			50 ^{h,i}	87.66	87.66	7.69	7.63	4.65	4.74
C ₂ H ₅	C ₆ H ₅ CH ₂	148	1	1.5460	92 ^j	85.32	85.35	9.15	9.08	5.53	5.46
C ₆ H ₅ ^k	C ₆ H ₅	M. 74.5-75 ^l			99 ^m						
C ₆ H ₁₀ ^k	C ₆ H ₅ CH ₂	186-187 ⁿ	1	1.5662	88 ^o	60.72 ^p	60.78 ^p	5.30 ^p	5.27 ^p	11.33 ^p	11.50 ^p
C ₄ H ₉ O ^q	CH ₃				92 ^r						
C ₄ H ₉ O ^q	C ₆ H ₅	M. 75-75.5 ^s			65 ^t						

^a Reported n_D^{20} 1.500, A. C. Cope, T. T. Foster and P. H. Towle, *THIS JOURNAL*, **71**, 3929 (1949). ^b Picrate (recrystallized from methanol) m.p. 139.5-140°; reported m.p. 140-140.5°, A. C. Cope and co-workers (see note a). ^c Picrate, m.p. 156-157°. ^d Reported m.p. 72°, E. Stoelzel, *Ber.*, **74B**, 982 (1941); m.p. 68.5-70° (ref. 16). ^e Picrate, m.p. 197-198°; reported m.p. 196° (ref. 12). ^f Picrate, m.p. 159-160°; reported m.p. 156-157°, T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 1932 (1932). ^g Hydrochloride (recrystallized from methanol-ether) m.p. 188-191° and 208-210°; reported m.p. 187-188° (ref. 23), m.p. 187° and 210-211° (ref. 4d). ^h Picrate (recrystallized from methanol) m.p. 226-227° dec. *Anal.* Calcd. for C₂₀H₂₆N₄O₇: N, 10.56. Found: N, 10.61. ⁱ Hydrochloride (recrystallized from acetone-benzene) m.p. (slowly) 243-244°; m.p. (rapidly) 260°. *Anal.* Calcd. for C₂₂H₂₄NCl: N, 4.15. Found: N, 4.00. ^j Picrate m.p. 125-126°. *Anal.* Calcd. for C₂₄H₂₈N₄O₇: C, 59.74; H, 5.43. Found: C, 59.97; H, 5.46. ^k Piperidyl. ^l Reported m.p. 75° (ref. 11e); m.p. 73-74° (ref. 16). ^m Hydrochloride (recrystallized from acetone-benzene) m.p. slowly, 239-240°; m.p. (rapidly) 249° (see ref. 11e). ⁿ Reported b.p. 198-200° at 18 mm. (ref. 11e). ^o Picrate (recrystallized twice from methanol) m.p. 167-168°. ^p Analysis of picrate. ^q Morpholino. ^r Isolated as the hydrochloride (recrystallized from ethanol-ethyl acetate) m.p. 209-210° dec.; reported m.p. 211-212°, M. T. Leffler and E. H. Volwiler, *THIS JOURNAL*, **60**, 896 (1938). ^s Reported m.p. 76-78°, N. H. Cromwell, *THIS JOURNAL*, **69**, 1857 (1947). ^t Hydrochloride, m.p. 227° dec. (darkens at 215°).

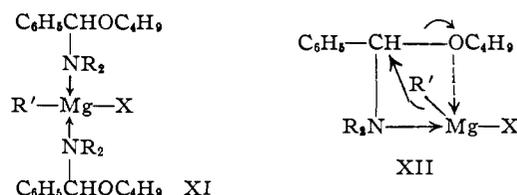
of excess magnesium to avoid the possible reaction of unchanged halide with the tertiary amines X being prepared. The results are presented in Table II.



The reaction of type II amino ethers with Grignard reagents is rapid and vigorous. It is sufficiently exothermic to reflux the ether used as the solvent; this is remarkable since the two closely related compounds, acetals⁸ and 1,1-diamines,^{4d} react with these reagents only sluggishly or not at all under the same conditions.⁹

In the usual method of preparation, in which the amino ether was added to the Grignard reagent, an immediate precipitation occurred. This precipitate, nevertheless, quickly redissolved in an excess of the reagent. However, when a solution of phenylmagnesium bromide of known molarity was added to amino ether II (R = CH₃, X = H), a precipitate formed which accumulated until approximately one-half equivalent of the Grignard reagent had been added. When a second half equivalent (plus 17%) was introduced the precipitate dissolved and, subsequently, there was obtained an 87% yield of tertiary amine X (R' = C₆H₅, R = CH₃), which is comparable to that (90%) produced by the usual procedure. It is postulated that coordination complex XI, consisting of two molecules of the amino ether to one of the Grignard

reagent, is first formed and that it reacts with a second molecule of the Grignard reagent to form the tertiary amine X. Although complex XI may react directly with the Grignard reagent to form tertiary amine X, it could engender a complex, XII, comprising one molecule each of the amino ether and organomagnesium halide, which undergoes internal displacement. The importance of the formation of coordination complexes is exemplified by the following observations: (1) phenyllithium gave only a 39% yield with amino ether II (R = CH₃, X = H) compared to the 90% yield obtained with phenylmagnesium bromide; (2) sodium diphenylmethide (in liquid ammonia) or potassium diphenylmethide in ether¹⁰ failed to react with this amino ether while benzhydrylmagnesium chloride produced 50% of the desired amine.



It may be seen from Table II that most of the yields of tertiary amines X from amino ethers and Grignard reagents are excellent. This method is considered generally preferable to an earlier one involving the analogous substitution reaction of α -aminonitriles XIII with Grignard reagents (equation 8)^{4d,11} in which large excesses (100-500%) of the reagents appear to be required for maximum yields. The aminonitriles have usually been prepared from aldehydes, secondary amines and potas-

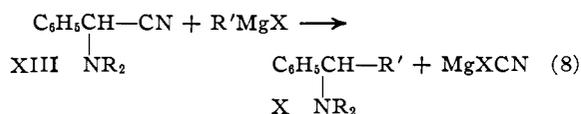
(8) (a) A. E. Tschitschibabin and S. A. Jelgasin, *Ber.*, **47**, 48 (1914); (b) E. Späth, *Monatsh.*, **35**, 331 (1914); **36**, 1 (1915); (c) J. Gard, *Compt. rend.*, **189**, 925 (1929).

(9) Ordinary acetals fail to react appreciably with Grignard reagents in ethyl ether; indeed, acetals are produced from the reaction of orthoformic esters with these reagents. However, acetals have been shown to react with Grignard reagents at higher temperatures (120-130°) to form ethers (ref. 8).

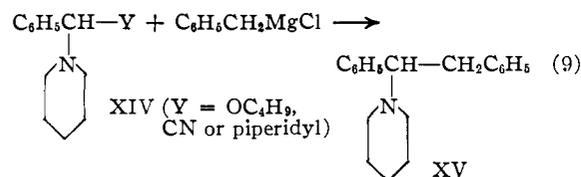
(10) This reagent was prepared as a suspension in ethyl ether as described by R. S. Yost and C. R. Hauser, *THIS JOURNAL*, **69**, 2325 (1947).

(11) (a) P. Bruylants, *Bull. acad. roy. Belg.*, **10**, 126 (1924); (b) **11**, 261 (1925); (c) P. Bruylants, *Bull. soc. chim. Belg.*, **33**, 467 (1924); (d) **35**, 139 (1926); (e) A. Christiaen, *ibid.*, **33**, 483 (1924).

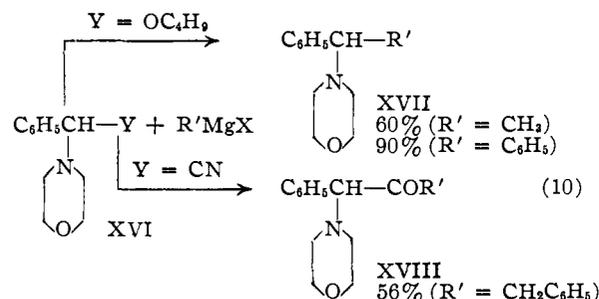
sium cyanide, and employed with Grignard reagents for the preparation of tertiary amines X when the more common techniques, such as alkylation, were unsatisfactory.



Several tertiary amines of type X have been obtained in much better yields from amino ethers than from aminonitriles. For example, tertiary amine XV was obtained in 90% yield from amino ether XIV ($\text{Y} = \text{OC}_4\text{H}_9$) and benzylmagnesium chloride, and in only 32% yield^{4d} from aminonitrile XIV ($\text{Y} = \text{CN}$) and this Grignard reagent (equation 9). The over-all yields from benzaldehyde were 70 and 30%, respectively. Tertiary amine XV also has been prepared from diamine XIV ($\text{Y} = \text{piperidyl}$) and the Grignard reagent but the yield was only 19%.^{4d} It should be pointed out that the common method of alkylation, employing 1,2-diphenylethyl bromide and piperidine, has produced less than a 10% yield of tertiary amine XV, the predominant reaction being dehydrohalogenation (β -elimination) to form stilbene.^{4d}

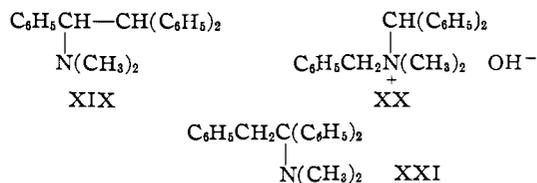


The general superiority of the present method is illustrated especially well by the reactions of the morpholino compounds XVI with Grignard reagents (equation 10). Thus, whereas the amino ether XVI ($\text{Y} = \text{OC}_4\text{H}_9$) gave good yields of the corresponding tertiary amine XVII with methylmagnesium iodide and with phenylmagnesium bromide, the aminonitrile XVI ($\text{Y} = \text{CN}$) resulted in a different product, ketone XVIII, with benzylmagnesium chloride.^{4d} It is obvious that the latter type of reaction, which involves the common addition of the Grignard reagent to the nitrile group, is always possible with the aminonitriles but not with the amino ethers.

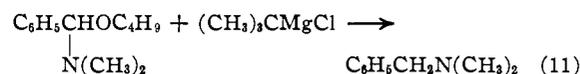


It should be pointed out that tertiary amine XIX, produced from amino ether II ($\text{R} = \text{CH}_3$, $\text{X} = \text{H}$) and benzhydrylmagnesium chloride, is identical with the tertiary amine obtained previously from the Stevens rearrangement of quaternary ammonium hydroxide XX, which was assumed to have

structure XXI.¹² This was established not only by the present unequivocal synthesis of XIX, but also by the synthesis of tertiary amine XXI by an unequivocal method which was carried out in this Laboratory in connection with another investigation.

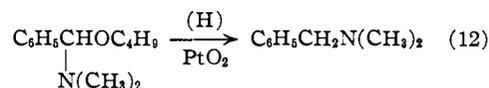


In contrast to the Grignard reagents listed in Table II, *t*-butylmagnesium chloride reduced amino ether II ($\text{R} = \text{CH}_3$, $\text{X} = \text{H}$) to benzyltrimethylamine in 70% yield (equation 11). This product most likely results from a hydride ion reduction, which, although quite common with carbonyl compounds, apparently has not been observed earlier in a saturated system.



Other Reactions of Amino Ethers.—McCleod and Robinson² showed that amino ethers of type I undergo hydrolysis particularly readily in the presence of acid. We have confirmed this rapid hydrolysis with amino ether II ($\text{R} = \text{CH}_3$, $\text{X} = \text{H}$). Thus, on shaking 1 ml. of the amino ether with 3 ml. of 10% hydrochloric acid, complete solution was first achieved; however, within 30 seconds the contents of the test-tube solidified. This slowly reverted (five minutes) to liquid as benzaldehyde separated from the aqueous phase. The nature of the precipitate was not determined.

Cope and Hancock^{4a} and Senkus^{4c} hydrogenated cyclic amino ethers to form substituted ethanolamines. We have prepared dimethylbenzylamine in 76% yield by hydrogenating amino ether II ($\text{R} = \text{CH}_3$, $\text{X} = \text{H}$), the reduction being effected under relatively mild conditions (equation 12).



Earlier workers have reported quaternization⁷ and Mannich-type condensations² with simple amino ethers of type I. As yet, we have been unable to isolate distinct compounds in the analogous reactions of type II amino ethers.

Experimental¹³

Preparation of Dialkylaminobenzyl Butyl Ethers (II) (Table I). Method A.—To a 500-ml. three-neck flask fitted with a mechanical stirrer and a reflux condenser capped with a drying tube were added 0.2 mole of aldehyde, 0.22–0.24 mole of amine, 0.2 mole of anhydrous potassium carbonate and 1.0 mole of butanol-1. With the exception of dimethylamine experiments, which were done at room temperature, the reactants were stirred for 24 hours¹⁴ at an outside temperature of 80–100°. After cooling to room tem-

(12) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 69 (1933).

(13) Melting points (taken on an electrically heated Fisher block) and boiling points are uncorrected. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

(14) Mr. Wallace R. Brasen of this Laboratory increased the yield of amino ether II ($\text{R} = \text{CH}_3$, $\text{X} = \text{H}$) from 56 to 75% by stirring the reaction mixture at room temperature for only 10 hours.

perature, the potassium carbonate was separated by filtration and the filtrate stripped of excess reactants under reduced pressure. The residue, which consisted mainly of the desired amino ether, was purified by distillation through a 20-cm. Vigreux column at a pressure of 1 mm. or below. When conversion percentages were desired, the filtrate was fractionated carefully at higher pressures and unreacted aldehyde recovered.

Method B.—To a 500-ml. three-neck flask equipped as described in method A were added 0.2 mole of aldehyde, 0.24–0.26 mole equivalent of amine as a 25% aqueous solution and 1.0 mole of butanol-1. To this well stirred solution was added sufficient potassium carbonate to cause separation into two layers, with an excess remaining undissolved in the aqueous phase. The reaction was allowed to proceed 24 hours. The mixture was filtered and the organic layer separated and dried with anhydrous potassium carbonate. After stripping off butanol-1 the product was purified by distillation as described above.

Method C.—To apparatus assembled as in method A were introduced 0.2 mole of aldehyde, 0.22 mole of amine, 0.0074 mole of mercuric chloride, 1.0 mole of butanol-1 and 100 g. of anhydrous calcium sulfate (Drierite). After stirring 24 to 48 hours at room temperature, several milligrams of solid phenolphthalein were added, followed by enough freshly prepared sodium methoxide solution to render the mixture strongly basic. After removing the dehydrating agent by vacuum filtration the basic solution was distilled to obtain the pure amino ether.

N,N'-Benzylidenebispiperidine (V).—In a 300-ml. one-neck flask equipped for azeotrope separation were placed 21.2 g. (0.2 mole) of benzaldehyde, 21.0 g. (0.247 mole) of piperidine and 150 ml. of dry benzene. These were refluxed overnight and the water removed. Excess reactants were discharged under aspirator pressure; the residue was diluted with 200 ml. of 30–60° petroleum ether and cooled on solid carbon dioxide, yielding 37.2 g. (72%) of the diamine V, m.p. 80.5–81°; reported m.p. 80–81°.¹⁵

Conversion of Diamine V to Amino Ether VI.—A mixture of 12.9 g. (0.05 mole) of diamine V, 5.3 g. (0.05 mole) of benzaldehyde, 25.0 g. (0.3 mole) of butanol-1 and 6.4 g. (0.05 mole) of anhydrous potassium carbonate was refluxed for 24 hours and let stand an equal period of time at room temperature. The potassium carbonate was separated and the filtrate stripped of butanol-1. The residue was distilled *in vacuo* to give a forerun of 1.2 g., b.p. 58–140° at 1.5 mm., and 14.0 g. (57%) of α -N-piperidylbenzyl butyl ether (VI), b.p. 140–155° at 1.5 mm., essentially at 152–155°.

The product was identified as VI by treating a sample of it with an excess of phenylmagnesium bromide (as described below) to give N-benzohydrilpiperidine, m.p. 73–73.5°; reported m.p. 75°,^{11e} 73–74°.¹⁶

Benzaldehyde Dibutylacetal (VII).—In a 300-ml. flask equipped for azeotrope separation were placed 50.0 g. (0.47 mole) of benzaldehyde, 150 g. (2.0 moles) of butanol-1, 1.0 g. (0.091 mole) of calcium chloride and 100 ml. of dry benzene. The reactants were refluxed 27 hours, cooled rapidly, and solid phenolphthalein added followed by sufficient freshly prepared sodium methoxide solution to make the solution basic. After removing alcohol and benzene by stripping to 66° at 3 mm., the acetal VII (77.5 g., 70%) was obtained as a water-white liquid boiling at 138–138.5° at 3 mm., n_D^{20} 1.4732; reported b.p. 149–150° at 15 mm., n_D^{19} 1.4790.¹⁷

Non-conversion of Acetal VII to Amino Ether VI.—The acetal (23.6 g., 0.1 mole) and piperidine (14.0 g., 0.165 mole) were refluxed 48 hours in the presence of 13.8 g. (0.1 mole) of anhydrous potassium carbonate. When heating was terminated the reactants were pale yellow. The potassium carbonate was removed by filtration and washed with 25 ml. of anhydrous ether. After stripping off the ether and excess amine, 94% of the acetal was recovered.

Similarly, when dibutylbenzal (0.1 mole), piperidine (excess) and mercuric chloride (0.037 mole) were refluxed 12 hours without solvent, 76% of the acetal was recovered. The acetal was regained quantitatively when a benzene solution of it and excess piperidine was refluxed 48 hours.

Conversion of Amino Ethers to Diamines. (A) VI to V.— α -N-Piperidylbenzyl butyl ether (VI) (24.7 g., 0.1 mole)

and piperidine (14.0 g., 0.165 mole) were refluxed in 150 ml. of dry benzene for 12 hours, and held just below the boiling point for an additional 36 hours. By twice cooling the benzene solution, filtering the precipitate and washing it with cold 30–60° petroleum ether, there was isolated 14.7 g. (60%) of N,N'-benzylidenebispiperidine (VI), m.p. 80.5–81°. This melting point was not depressed by admixture with a sample of the diamine prepared as described above.

(B) VIII to IX.—Pure amino ether VIII, on standing several days in a closed flask deposited an appreciable quantity of crystals. These were separated and recrystallized from 30–60° petroleum ether to give N,N'-benzylidenebismorpholine (IX), m.p. 105.5–106°; reported m.p. 101–101.5°,¹⁸ 102°.¹⁹

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.46; H, 8.21; N, 10.72.

Reaction of Amino Ethers with Grignard Reagents (Table II). (A) **General Procedure.**—A 500-ml. three-neck flask equipped with a sealed stirrer, an efficient reflux condenser closed by a drying tube, and a liquids addition funnel, was dried by a bunsen flame while being flushed by a rapid stream of dry nitrogen. After cooling under positive nitrogen pressure there were added 4.8 g. (0.2 g.-atom) of magnesium turnings and 200 ml. of anhydrous ether, followed by 0.15 mole of the selected halide, added at such a rate as to maintain a continuous reflux of the solvent. After the addition was complete, the reactants were stirred 1.5 hours at room temperature. The amino ether (0.1 mole) in an equal volume of dry ether then was added slowly. In every reaction performed in this investigation a curdy precipitate was observed as the amino ether first contacted the Grignard solution.

After stirring 12–24 hours at room temperature the product was isolated in one of two ways: (1) If the amine was known to be solid the solution was poured onto several equivalents of concentrated hydrochloric acid mixed with an approximately equal weight of cracked ice. The amine hydrochloride was filtered and the amine liberated by shaking with an aqueous sodium carbonate-sodium hydroxide solution. It was then, most often, recrystallized from 30–60° petroleum ether. (2) If the amine was unknown or known to be a liquid the Grignard solution was poured onto a 1:1 mixture of ammonium chloride and cracked ice. After all reaction ceased, sodium hydroxide solution was added until magnesium hydroxide began to precipitate. The layers were separated and the aqueous solution extracted thoroughly with ether; the ethereal extracts were combined and dried over Drierite. After removing the solvent the amine was distilled under reduced pressure.

(B) **Inverse Addition Procedure.**—In an apparatus assembled and dried as described in the general procedure, was placed 20.7 g. (0.1 mole) of α -dimethylaminobenzyl butyl ether in 100 ml. of anhydrous ether. To this solution was added slowly 100 ml. of 1.17 M phenylmagnesium bromide solution analyzed by the method of Gilman.²⁰ The addition was accompanied by exothermic reaction and the accumulation of a white precipitate where the Grignard reagent entered the solution. Despite vigorous stirring the precipitate increased in volume until approximately 50 \pm 5 ml. of the Grignard reagent was introduced. As further additions were made the amount of precipitate visibly decreased until, at the equivalence point, the only solid noticeable was that on the stem of the stirrer. When the addition was complete and the stirrer stopped, permitting the solution to contact the material it retained, complete solution resulted.

After stirring at room temperature overnight, the reaction mixture was decomposed on an ammonium chloride-ice mixture, the pH adjusted to approximately eight with sodium hydroxide solution, and the amine extracted with ether. After drying, and removal of the solvent, there was obtained 29.9 g. of crude amine which was induced to solidify on solid carbon dioxide. It was collected from 30–60° petroleum ether in two crops, 18.4 g. (87%), of white to pale yellow crystals, m.p. 70–71°. A mixed melting point with a more completely identified product made earlier showed no depression.

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Reduction of α -Dimethylaminobenzyl Butyl Ether. (A) With *t*-Butylmagnesium Chloride.—In apparatus identical to that described in the general procedure were placed 10 g. (0.41 g.-atom) of magnesium turnings and 100 ml. of anhydrous ether. Several milliliters of *t*-butyl chloride (total 27.7 g., 0.3 mole) were added and the reaction initiated with a few drops of methyl iodide. The halide, in 100 ml. of dry ether, was added slowly, according to the observations of Whitmore²¹ for maximum yields with this material, and stirred an additional 3 hours.

To the stirred *t*-butylmagnesium chloride solution was added 20.7 g. (0.1 mole) of α -dimethylaminobenzyl butyl ether in an equal volume of dry ether. The reaction mixture was stirred 2 hours at room temperature, refluxed 4 hours, cooled, and poured onto an ammonium chloride-ice mixture. The amine was taken up in ether, the ether dried, removed, and the residue distilled. There was obtained 10.7 g. (80%) of benzyldimethylamine boiling at 76–78° at 20 mm., n_D^{20} 1.4986 (reported n_D^{20} 1.5000²²). The picrate

of this product, recrystallized from ethanol, melted at 96–97°; reported m.p. 94°.²³

Anal. Calcd. for $C_{15}H_{18}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.35; H, 4.57; N, 15.42.

(B) With Hydrogen.—The amino ether (20.7 g., 0.1 mole), was dissolved in 300 ml. of commercial absolute ethanol contained in a 500-ml. erlenmeyer flask. Several milligrams of Adams catalyst was added and the flask attached to an atmospheric, buret-type hydrogenator; agitation was provided by a magnetic stirrer. Over an 8-hour period, at room temperature, the hydrogen uptake was greater than 0.096 mole.

The catalyst was removed by filtration and the solvent distilled at atmospheric pressure. The remaining material was fractionated *in vacuo* to give 6 g. of impure butanol-1 and 10.2 g. (75%) of benzyldimethylamine, b.p. 79–83° at 28 mm., essentially at 82–83°, n_D^{20} 1.5003. The picrate, after three recrystallizations from methanol, melted at 95–95.5°; reported m.p. 94°.²³

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[CONTRIBUTION FROM THE ROHM AND HAAS Co.]

Reactive Nitrile Groups. I. The Reaction of α,ω -Dinitriles with Aqueous Amines¹

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RECEIVED OCTOBER 7, 1954

Acetonitrile, *n*-butyronitrile and benzonitrile failed to react at 100° with aqueous solutions of such amines as methylamine, benzylamine, morpholine and piperidine. However, under the same conditions, malononitrile, succinonitrile and glutaronitrile were converted to the corresponding N,N' -disubstituted amides by reaction with aqueous methylamine, *n*-butylamine, *n*-octylamine, benzylamine and morpholine. Phthalonitrile reacted similarly. Adiponitrile did not react. Exceptions to the general reaction were the reactions of succinonitrile with aniline, which failed, and with piperidine and 1,1,3,3-tetramethylbutylamine, respectively, which gave the corresponding amine salts of succinamic acid.

The reaction of a nitrile with an amine to yield the N -substituted amidine, or with aqueous amine to yield the N -substituted amide customarily does not proceed at any obvious rate. A reaction with aqueous ammonia has been observed in a few special cases.^{2,3} It is demonstrated here, for example, that butyronitrile can be recovered almost quantitatively after a long refluxing period with aqueous morpholine, and even with so strong a base as aqueous piperidine. Aqueous methylamine does not convert acetonitrile to the amide, nor does aqueous benzylamine convert benzonitrile to the amide, at 100° and at reflux, respectively. For the lack of any direct route, therefore, the conventional methods used have entailed the conversion of the nitrile to an intermediate, such as the imino-ester hydrochloride.⁴ Recently, N -arylamidines were prepared by the severe conditions of the use of sodium amide⁵ or similar strong base catalyst.

It has been observed in concurrent work by Elvidge and Linstead⁶ that succinonitrile shows remarkable reactivity toward ammonia. Thus, Elvidge and Linstead were able to prepare 2,5-diphenyliminopyrrolidine by reaction of succinonitrile

with ammonia to yield succinimidine, followed by reaction with aniline. Further reaction with water gave succinamide. Both succinonitrile and phthalonitrile have been observed to react rapidly with aniline hydrochloride.^{6,7} Couch and Krewson² obtained succinamide by reaction of succinonitrile with aqueous ammonia at high temperatures.

In our own work, we had early arrived at the same observations of the unique reactivity of succinonitrile from the reaction of that dinitrile with aqueous solutions of primary aliphatic amines. It seemed most likely that the reactions of succinonitrile involved cyclization to some form of succinimide intermediate. Since it was also possible that the reactivity of dinitriles could result simply from inductive effects transmitted through the chain, our studies have taken the course of a general investigation of the reaction of α,ω -dinitriles with a variety of amines in water solution.

The reaction of two moles of most primary amines with one mole of dinitrile in the presence of two to six moles of water yielded N,N' -disubstituted amides in the cases of malononitrile, succinonitrile and glutaronitrile. Phthalonitrile also gave a diamide under similar conditions. Adiponitrile was found to be unreactive. In most cases, temperatures of 100° or reflux (usually about 100°) were necessary for a reasonable reaction rate. It may be deduced from yield data and the necessary conditions of reaction, that the reactivity of succino-

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