[Chem. Pharm. Bull. 17(1) 32—35 (1969)]

UDC 547.554.07

Reaction of Amide Homologs. XXIII.[1] Syntheses of α-Amidobenzylamines

Minoru Sekiya and Hideo Sakai

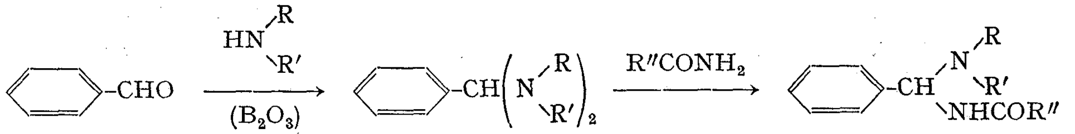
Shizuoka College of Pharmacy[2]

(Received February 7, 1968)

A variety of N-α-amidobenzyl compounds attached to secondary amines have been newly prepared advantageously by reactions of N,N'-benzylidenebisamines with amides. Also the known procedures for preparation of N,N'-benzylidenebisamines from benzaldehyde was best improved in yield using a dehydrating agent, boron trioxide.

Recently in our laboratory a need arose to prepare N-α-amidobenzyl derivatives attached to aliphatic secondary amines in order to investigate their chemical properties, in continuation of our studies on the reaction of N-amidomethylamines (N-Mannich base). Although the syntheses of the compounds of this type have been carried out in several ways,[3-6] the methods appear not to be sufficiently appropriate for their preparation; the direct synthesis[3] from aromatic aldehyde, aromatic amide and secondary amine, in which paper yields are not described, was repeated with some materials giving very poor yields in general and the other methods seemed rather laborious.

We have now found a new general synthetic route advantageous for the preparation from benzaldehyde through N,N'-benzylidenebisamines.



The previously known method in conversion of benzaldehyde to N,N'-benzylidenebisamine was improved in yield by using a dehydrating agent, boron trioxide, and the succeeding course, which had been unknown, to N-α-amidobenzylamine was performed by two ways such as one method using hydrogen chloride in the solution, and the other with fusion.

Abundant data concerning the formation of N,N'-arylmethylenebisamines from aromatic aldehydes and secondary amines have been reported. According to these methods, the reaction is carried out by heating the mixture with or without solvent and yields of the product are not sufficiently high (30—80%), varying with papers. An adaptation of boron trioxide as a dehydrating agent in the reactions with benzaldehyde was found to be very effective for rising the yields. A variety of examples of this reaction were provided as shown in Table I. In general, reaction was carried out under uniform condition in which a benzene solution of the secondary amines was added to a suspension of boron trioxide in a benzene solution of aldehyde at 45° and followed by heating for two hours. Indication in Table I are results of these successful experiments. The five bisamines were obtained throughout in above 85% of yield, which had not been otherwise easily accessible. Among these, N,N'-benzylidene-

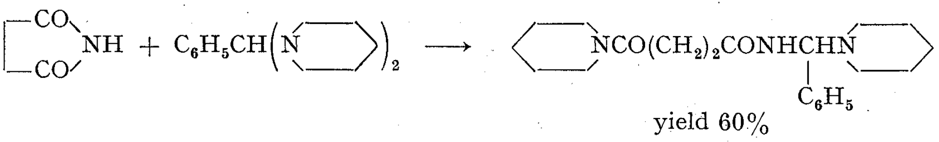
---

1) Part XXII: M. Sekiya and Y. Terao, *Yakugaku Zasshi*, **88**, 1085 (1968).
2) Location: *Oshika, Shizuoka.*
3) E. Macovski and C. Bachmeyer, *Chem. Ber.*, **77**, 495 (1944).
4) M. Sekiya and K. Ito, *Chem. Pham. Bull.* (Tokyo), **11**, 888 (1963).
5) H. Shechter, S. S. Rawalay and M. Tubis, *J. Am. Chem. Soc.*, **86**, 1701 (1964).
6) H. Shechter and S. S. Rawalay, *J. Am. Chem. Soc.*, **86**, 1706 (1964).

bispyrrolidine and N,N'-benzylidenebis(N-methylbenzylamine) have not been known previously. On the contrary, the following secondary amines did hardly react with the aldehyde under the abovementioned standard conditions, resulting in almost complete recovery of the starting materials; diethylamine, diisopropylamine, di-*n*-butylamine, *n*-butylmethylamine, 2-methylpiperidine, dibenzylamine and cyclohexylmethylamine. Of course, conceivable products from these amines have not been described in the literature. The above failures appear suggestive of steric effect, presumably owing to increase of steric requirement over some extent.

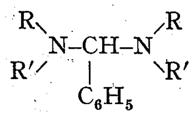
We then performed the syntheses of several N-α-amidobenzyl compounds from the five bisamines obtained by the above method. A method (Method A) is that to a dioxane solution of bisamine and amide in 1.5:1 molar proportion, dry hydrogen chloride in dioxane (one molar equiv. of HCl) was added under refluxing. By this method the four bisamines, N,N'-benzylidene–bis(dimethylamine), -bispiperidine, -bismorpholine, and -bis(methylbenzylamine), reacted smoothly with amides such as formamide, acetamide, phenylacetamide and benzamide, which were selected as representatives. This method, however, failed in the examination only with N,N'-benzylidenebispyrrolidine. Accordingly, for preparation of this compound an alternative method (Method B) was developed, in which a mixture of the bisamine and amide in 2:1 molar proportion was fused on heating at 85—90°. Table II indicates the results of the experiments of Method A and B. As can be seen, fair yields of N-α-amidobenzyl compounds were gained throughout by both the methods and the thirteen compounds in Table II have not been known previously.

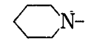
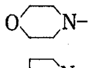
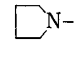
In addition an experiment with succinimide was examined by the fusing method. However, in this case the reaction resulted in rupture of succinimide ring giving γ-oxo-N-(α-piperidinobenzyl)-1-piperidinobutyramide.



Experimental

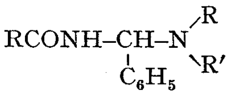
N,N'-Benzylidenebisamines General Procedure——The bisamines listed in Table I were obtained by the following general procedure. To a solution of 10.6 g (0.1 mole) of benzaldehyde in 60 ml of benzene 11.6 g

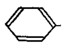
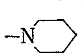
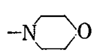
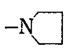
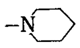
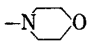
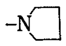
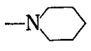
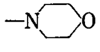
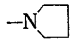
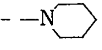
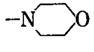
TABLE I. N,N'-Benzylidenebisamines 
$\begin{matrix}R\\R'\end{matrix}>N-\underset{\displaystyle C_6H_5}{CH}-N<\begin{matrix}R\\R'\end{matrix}$

$\begin{matrix}R\\R'\end{matrix}>N-$	Yield (%)	mp or bp (°C)	Appearance (recrystn. solvent)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
$\begin{matrix}CH_3\\CH_3\end{matrix}>N-$	85	71—72/5 mmHg (lit.a), 57—60/0.9 mmHg)	colorless liquid	$C_{11}H_{18}N_2$	74.11	10.18	15.71	73.76	9.84	15.64
$\begin{matrix}CH_3\\C_6H_5CH_2\end{matrix}>N-$	94	45	needles (petr. ether)	$C_{23}H_{26}N_2$	83.59	7.93	8.48	83.52	7.89	8.37
	93	81—81.5 (lit.b), 80.5—81)	needles (iso-Pr_2O)							
	93	105.5—106 (lit.b), 105.5—106)	needles (iso-Pr_2O)							
	95	41	needles (petr. ether)	$C_{15}H_{22}N_2$	78.21	9.63	12.16	77.91	9.40	12.10

a) S.V. Lieberman, *J. Am. Chem. Soc.*, **77**, 1114 (1965)
b) A. T. Stewart, Jr. and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 1098 (1955)

Table II. N-α-Amidobenzyl Derivatives


$$RCONH\text{-}\underset{C_6H_5}{\underset{|}{CH}}\text{-}N\begin{smallmatrix}\diagup R\\ \diagdown R'\end{smallmatrix}$$

RCONH-	$-N\begin{smallmatrix}\diagup R\\ \diagdown R'\end{smallmatrix}$	Method	Yield (%)	mp (°C)	Appearance (recrystn. solv.)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	ν_{max}^{KBr} (cm^{-1}) -CONH-		
CONH-	$-N\begin{smallmatrix}\diagup CH_3\\ \diagdown CH_3\end{smallmatrix}$	A	97	107—108	needles (benzene)	$C_{16}H_{18}ON_2$	75.56	7.13	11.02	75.83	7.25	11.10	3304	1630	1525
	$-N\begin{smallmatrix}\diagup CH_3\\ \diagdown CH_2C_6H_5\end{smallmatrix}$	A	80	112—113	needles (iso-PrOH)	$C_{22}H_{22}ON_2$	79.97	6.71	8.48	80.13	6.75	8.75	3347	1639	1526
		A	91	144 (lit.[a], 148—149)	needles (benzene)	$C_{19}H_{22}ON_2$	77.52	7.53	9.52	77.52	7.27	9.67	3316	1630	1525
		A	80	166—167	needles (EtOH)	$C_{18}H_{20}O_2N_2$	72.95	6.80	9.45	73.03	6.90	9.40	3293	1638	1521
		B	76	110—111	needles (benzene)	$C_{18}H_{20}ON_2$	77.11	7.19	9.99	77.72	7.24	9.59	3319	1636	1531
CH_2CONH-	$-N\begin{smallmatrix}\diagup CH_3\\ \diagdown CH_3\end{smallmatrix}$	A	97	90—91.5	needles (EtOH–petr. ether)	$C_{17}H_{20}ON_2$	76.08	7.51	10.44	76.33	7.36	10.45	3300	1648	1520
	$-N\begin{smallmatrix}\diagup CH_3\\ \diagdown CH_2C_6H_5\end{smallmatrix}$	A	98	112	needles (PrOH)	$C_{23}H_{24}ON_2$	80.20	7.02	8.13	80.32	6.98	8.16	3275	1648	1536
		A	95	158.5	needles (MeOH)	$C_{20}H_{24}ON_2$	77.88	7.84	9.08	77.99	7.57	9.07	3298	1645	1520
		A	92	145	needles (EtOH)	$C_{19}H_{22}O_2N_2$	73.52	7.14	9.03	73.08	7.20	8.90	3294	1648	1525
		B	86	111—112	needles (benzene)	$C_{19}H_{22}ON_2$	77.52	7.53	9.52	77.76	7.49	9.36	3280	1636	1544
CH_3CONH-	$-N\begin{smallmatrix}\diagup CH_3\\ \diagdown CH_3\end{smallmatrix}$	A	93	144—145	needles (benzene)	$C_{11}H_{16}ON_2$	68.72	8.39	14.57	69.22	8.38	14.45	3260	1645	1530
	$-N\begin{smallmatrix}\diagup CH_3\\ \diagdown CH_2C_6H_5\end{smallmatrix}$	A	93	145—146 (lit.[b], 150—151)	needles (benzene)	$C_{17}H_{20}ON_2$	76.08	7.51	10.44	76.23	7.51	10.28	3254	1645	1545
		A	97	144—145 (lit.[b], 148—149)	needles (MeOH)	$C_{14}H_{20}ON_2$	72.38	8.68	12.16	72.27	8.66	12.18	3314	1645	1525
		A	86	142—143 (lit.[b], 151—152)	needles (benzene)	$C_{13}H_{18}O_2N_2$	66.64	7.74	11.96	66.72	7.81	11.93	3330	1648	1525
		B	77	111—112	needles (benzene)	$C_{13}H_{18}ON_2$	71.52	8.31	12.83	71.28	8.36	12.81	3307	1645	1528
HCONH-		A	94	109—110	needles (EtOH)	$C_{13}H_{18}ON_2$	71.52	8.31	12.83	71.48	8.20	13.02	3290	1643	1516
		A	77	141	needles (EtOH)	$C_{12}H_{16}O_2N_2$	65.43	7.32	12.72	65.68	7.29	12.64	3297	1656	1514

a) E. Macovski and C. Bachmeyer, *Ber.*, **77**, 495 (1944)

b) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **11**, 888 (1963) of powdered boron trioxide was added. With vigorous stirring a solution of 0.24 mole of secondary amine in 20 ml of benzene was added dropwise to the mixture, while the exothermic reaction took place immediately. At 45—50° the stirring was continued for additional 2 hr. Only in the run with dimethylamine the reaction was carried out by means of heating the whole mixture in an autoclave at 50—55°. The reaction mixture was processed by filtration and then by concentration of the filtrate under reduced pressure. Recrystallization of the residual crystalline material or distillation of the residual liquid (in the run for N,N'-benzylidenebis(dimethylamine)) gave pure N,N'-benzylidenebisamine. Physical data, analyses of the products and yields are listed in Table I.

N-α-Amidobenzylamines General Procedure——Method A: With the exception of N-α-amidobenzylpyrrolidines the N-α-amidobenzylamines were prepared by the following general procedure. To a refluxing solution of 0.045 mole of N,N'-benzylidenebisamine and 0.03 mole of amide dissolved in 35 ml of dioxane, 30 ml of dry HCl–dioxane (content of HCl: 0.03 mole) was added dropwise with stirring, while immediate precipitation of the secondary amine hydrochloride were observed. The refluxing and the stirring were continued for additional 2 hr. After removal of the hydrochloride by filtration, the filtrate was concentrated under reduced pressure. Excess of the bisamine in the residue was removed by extraction with petr. ether. Recrystallization of the undissolved crystalline residue gave pure N-α-amidobenzylamine. Yields, physical data and analyses of the products obtained by the above procedures are listed in Table II.

Method B: All the N-α-amidobenzylpyrrolidines were prepared by the following procedure. A mixture of 0.02 mole of N,N'-benzylidenebispyrrolidine and 0.01 mole of amide was heated to give a melting liquid. The heating at 85—90° with stirring was continued for 3.5 hr. Then excess of the bispyrrolidine in the mixture was removed by extraction with petr. ether. N-α-Amidobenzylpyrrolidine was obtained by recrystallization of the resulting solid residue. In Table II the date of the products obtained are listed.

γ-Oxo-N-(α-piperidinobenzyl)-1-piperidinobutyramide——A mixture of 7.8 g (0.03 mole) of N,N'-benzylidenebispiperidine and 2 g (0.02 mole) of succinimide was heated and the melting liquid was stirred at 115—120° for 3 hr. The reaction mixture was treated by the same procedures as described in Method B. Recrystallization from acetone gave needles, mp 141°. Yield 4.2 g (60%). *Anal.* Calcd. for $C_{21}H_{31}O_2N_3$: C, 70.55; H, 8.74; N, 11.76. Found: C, 70.54; H, 8.43; N, 11.57. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3316, 1644, 1629 (shoulder), 1525.

Acknowledgement The authors thank Mr. K. Narita, Mrs. H. Suzuki and Mrs. T. Hoshikawa for elemental analyses.