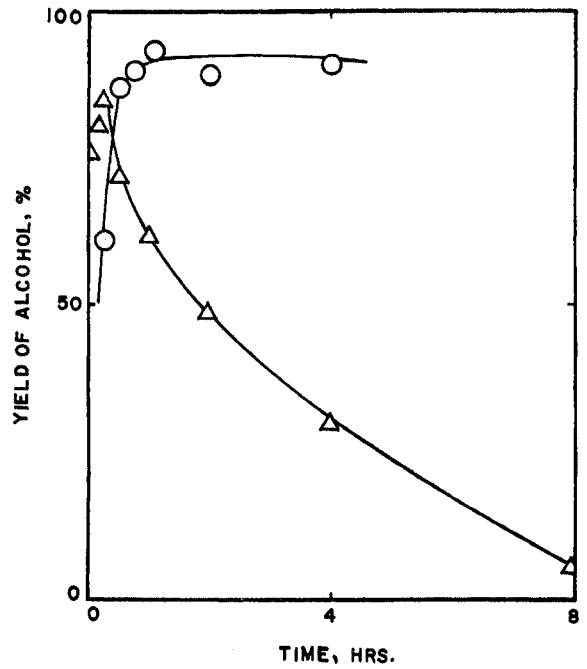


Figure 3.—Comparison of the oxymercuration of 2,3-dimethyl-2-butene at room temperature, Δ, and at 0°, O.

stituted (*e.g.*, tetramethylethylene) olefins are best run at 0° to minimize side reactions.

Experimental Section

Materials.—All olefins used were commercially available and were used as obtained unless glpc or index of refraction data indicated inpurities.

Mercuric acetate (Mallinckrodt Chemical Works), mercuric nitrate and mercuric oxide (J. T. Baker Chemical Co.), trifluoro acetic acid (3M Co.), sodium borohydride (Metal Hydrides, Inc.), and tetrahydrofuran (Fischer Scientific Co.) were used without further purification. Mercuric trifluoroacetate was prepared by a variation[6] of the method of Shearer and Wright.[25]

Oxymercuration Procedure.—The general procedure and various modifications have been discussed in appropriate places in the text.

Analysis.—The alcohol products were identified by comparison of gas chromatographic retention times with those of authentic samples of the alcohols. In several cases the products were isolated and compared with the known alcohols. Quantitative determinations were made by adding a suitable standard to the reaction mixture after reduction by borohydride. Calculations of yields were then made on the basis of relative thermal conductivities of standard and product as determined by integration of peaks obtained from a solution of standard and authentic alcohol. Analyses were carried out on either an F & M Model 300 chromatograph or a Perkin-Elmer Model 226 chromatograph. Integrations were obtained by using either a disk chart integrator or a Keuffel and Esser Co. planimeter.

Registry No.—1-Pentene, 109-67-1; 1-hexene, 592-41-6; 1-dodecene, 112-41-4; 1-octadecene, 112-88-9; 3,3-dimethyl-1-butene, 558-37-2; styrene, 100-42-5; 2,3-dimethyl-2-butene, 563-79-1.

(25) D. A. Shearer and G. F. Wright, *Can. J. Chem.*, **33**, 1002 (1955).

Factors Affecting Base-Induced Rearrangements of α-Chloro-α,α-diphenylacetamides

S. SAREL, J. T. KLUG, AND AVIVA TAUBE

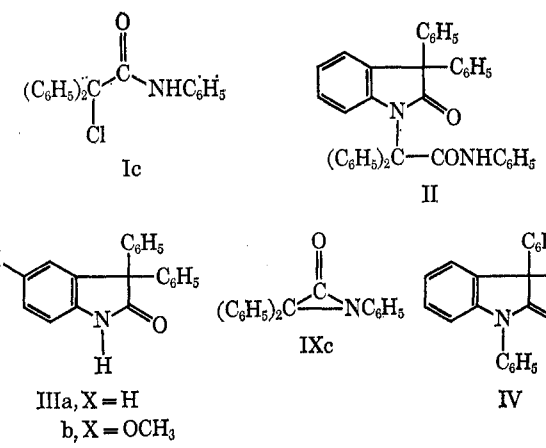
Department of Pharmaceutical Chemistry, The Hebrew University School of Pharmacy, Jerusalem, Israel

Received September 9, 1969

Effects of substituents and conditions on product distribution in reactions of N-substituted α-chloro-α,α-diphenylacetamides (Ia–Ie) with sodium amide in liquid ammonia, with liquid ammonia, and with aqueous ammonia are described. In liquid ammonia, in the presence or in the absence of sodium amide, the reaction leads to a product mixture consisting of two types of rearrangement products: (a) substituted ureas (VIIa and VIIb) and N-substituted α-amino amides (VIb–VIe), and (b) one displacement product (Va–Ve). These results are discussed in terms of a multistage process involving the intermediacy of a reactive α-lactam which undergoes two modes of ring opening. Formation of corresponding oxindoles (III) from the reactions of I in aqueous ammonia is also discussed.

Although α-chloro-α,α-diphenylacetanilide (Ic) was known since 1912,[1] a more systematic study of its chemistry has been realized only in the last decade. This development was induced by the endeavors aimed at synthesizing 1,3,3-triphenylaziridinone (α-lactam, IXc) from the reaction of Ic with strong bases.[2]

The reaction of Ic with sodium hydride in boiling benzene[3] was shown to yield a mixture of oxindole derivatives of structures II (predominant),[4] III (minor), and Ic (in minute quantities).[5] The formation of IXc as an intermediate was invoked to explain the Ic → II conversion.[4]



(1) H. Klinger and G. Nickell, *Justus Liebigs Ann. Chem.*, **390**, 365 (1912).

(2) Endeavors aimed at synthesizing IXc from the reaction of Ic with strong base were unfruitful: (a) I. Lengyel and J. C. Sheehan, *Angew. Chem., Int. Ed. Engl.*, **7**, 25 (1968); (b) J. C. Sheehan and J. H. Beeson, *J. Amer. Chem. Soc.*, **89**, 366 (1967). (c) However, H. E. Baumgarten, R. D. Clark, L. S. Endres, L. D. Hagemeier, and V. J. Elia [*Tetrahedron Lett.*, 5033 (1967)] have reported that "1-*t*-butyl-3,3-diphenylaziridinone does not appear to be appreciably less stable thermally than the monophenyl α-lactam, 1-*t*-butyl-3-phenylaziridinone [H. E. Baumgarten, *et al.*, *J. Amer. Chem. Soc.*, **85**, 3303 (1963)], although it is *much more reactive chemically.*"

(3) S. Sarel and H. Leader, *ibid.*, **82**, 4752 (1960).

(4) S. Sarel, J. T. Klug, E. Breuer, and F. D'Angeli, *Tetrahedron Lett.*, 1553 (1964).

(5) J. C. Sheehan and S. W. Frankenfeld, *J. Amer. Chem. Soc.*, **83**, 4792 (1961).

TABLE I
REACTIONS OF α-CHLORO-α,α-DIPHENYLACETAMIDES (Ia–Ie) WITH SODIUM AMIDE

$$I \xrightarrow{NaNH_2\text{–}NH_3} V + VI + VII$$

Substrate	R in I	Product distribution, % V	VI	VII
Ia	H	20	...	70
Ib	C_6H_{11}	4	≤1	88
Ic	C_6H_5	18	19	49
Id	p-$C_6H_4OCH_3$	43	19	28
Ie	p-$C_6H_4SO_2N(CH_3)_2$	57	28	5

was achieved by fractional crystallization and/or by column chromatography.

Distribution of products resulting from the reactions of Ia–Ie with sodium amide in liquid ammonia are given in Table I. Table II summarizes the results obtained in the reactions of Ia–Ic with liquid ammonia under various conditions. The results obtained from the reactions of Ia–Ie in aqueous ammonia are assembled in Table III. Tables IV–VIII summarize the melting points, ir spectra, and analysis of products appearing in Tables I–III.

TABLE II
REACTION OF α-CHLORO-α,α-DIPHENYLACETAMIDES WITH AMMONIA UNDER VARIOUS CONDITIONS

$(C_6H_5)_2CCONHR$ | Cl I	NH_3	Temp, °C	$NaNH_2$	$(C_6H_5)_2$-CCONHR | OH V	$(C_6H_5)_2$-CCONHR | NH_2 VI	$(C_6H_5)_2$-CCONH$_2$ | NHR VI	$(C_6H_5)_2$-CHNCONH$_2$ | R VII
R = H	Liquid	−33	+	...	20	...	70
R = H	Liquid	Room	−	...	20	...	79
R = H	Aqueous	Room	−	20	75	...	...
R = C_6H_5	Liquid	−33	+	...	19	18	49
R = C_6H_5	Liquid	Room	−	...	32	29	39
R = C_6H_5	Aqueous	Room	−	35	25	...	...
R = C_6H_{11}	Liquid	−33	+	...	4	1	88
R = C_6H_{11}	Liquid	Room	−	...	72	4	16
R = C_6H_{11}	Aqueous	Room	−	28	60	...	...

Of particular interest is the reaction of Ic with sodium amide in liquid ammonia, which was shown to provide a mixture of three isomeric products, two of which (VIc and VIIc) must arise from rearrangement reactions, whereas the third one (Vc) seemingly constitutes a displacement product.[6]

The present study was aimed at clarifying the base-induced rearrangement of α-halo amides into the corresponding α-amino amides (VI) and urea derivatives (VII), and factors influencing the extent of these reactions. The substrates (Ia–Ie) were prepared by allowing α-chloro-α,α-diphenylacetylchloride to react with a slight excess of the appropriate amine at low temperature.

The α-chloro amides listed above were exposed to the action of (a) sodium amide in liquid ammonia at −33°, (b) liquid ammonia at 25° (autoclave), and (c) concentrated aqueous ammonia at room temperatures.

The products from the reactions in sodium amide and in liquid ammonia invariably comprised the respective displacement product V and the two rearrangement products VI and VII. Separation of V, VI, and VII

$$(C_6H_5)_2C(Cl)\text{—}CONHR \longrightarrow (C_6H_5)_2C(NH_2)\text{—}CONHR + (C_6H_5)_2C(NHR)\text{—}CONH_2 + (C_6H_5)_2CH\text{—}N(R)\text{—}CONH_2$$

I V VI VII

a, R = H
b, R = C_6H_{11}
c, R = C_6H_5
d, R = p-$C_6H_4OCH_3$
e, R = p-$C_4H_4SO_2N(CH_3)_2$

(6) S. Sarel, F. D'Angeli, J. T. Klug, and A. Taube, *Israel J. Chem.*, **2**, 167 (1964).

TABLE III
REACTIONS OF α-CHLORO-α,α-DIPHENYLACETAMIDES (Ia–Ie) WITH AQUEOUS AMMONIA

$$I \xrightarrow{NH_4OH} V + XX + \text{oxindole (III)}$$

Substrate	Product distribution, % V	XX	Oxindole
Ia	75	20	...
Ib	60	28	...
Ic	25	35	10 (IIIa)
Id	25	17	52 (IIIb)
Ie	29	63	...

Structural assignments were based on ir, nmr, and mass spectral determinations, and in some cases also by comparison with specimens obtained from independent syntheses.

The 1700–1500-cm^{-1} region in the ir spectra was proved to be of analytical interest. From the location of the amide I and amide II absorption bands in the spectra,[7] it was possible to characterize the type of the amide (V or VI). Thus, secondary amide V shows very strong absorption at 1530 cm^{-1}, owing to the bending vibration of the N–H (amide II band), whereas similar absorption for the primary amide VI occurs at 1600 cm^{-1}.

Mass spectra were shown to be an extremely valuable and reliable tool in the deduction of the structures of the isomeric α-amino amides. In analogy to esters of α-amino acids,[8] we found that in all α-amino amides the most abundant fragments are ions resulting from α cleavage, as depicted below.

$$(C_6H_5)_2C(NR_3R_4)\text{—}CONR_1R_2 \longrightarrow [(C_6H_5)_2C{=}NR_3R_4]^+ + R_1R_2$$

m/e 180

(7) L. J. Bellamy, "Infrared Spectra of Complex Molecules," Methuen, London, 1958.

(8) K. Biemann, J. Seibl, and F. Gapp, *J. Amer. Chem. Soc.*, **83**, 3795 (1961).

TABLE IV

PHYSICAL AND ANALYTICAL DATA OF α-CHLORO-α,α-DIPHENYLACETAMIDES

$(C_6H_5)_2CCONHR$
|
Cl

I

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}					
			C	H	N	C	H	N						
Ia	H	115	68.28	4.92	5.71	68.21	4.91	5.66	3450		1680	1670	1590	
Ib	C_6H_{11}	89–90	73.27	6.76	4.27	73.54	6.91	4.33	3450		1667			1530
Ic	C_6H_5	88–89	79.20	5.61	4.62	78.94	5.45	4.39	3370	3340	1675			1530
Id	p-$C_6H_4OCH_3$	103–105	71.69	5.12	3.98	71.41	5.05	4.12	3440	3290	1690	1615		1530
Ie	p-$C_6H_4SO_2N(CH_3)_2$	155–156	61.61	4.89	6.53	61.91	5.07	6.72				1660	1580	1530

TABLE V

PHYSICAL AND ANALYTICAL DATA OF α-HYDROXY-α,α-DIPHENYLACETAMIDES

$(C_6H_5)_2CCONHR$
|
OH

XX

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}					
			C	H	N	C	H	N						
XXa	H	154–155	73.99	5.77	6.11	73.98	5.66	6.10	3450	3400	1680	1590	1550	
XXb	C_6H_{11}	151–152	77.64	7.49	4.53	77.73	7.51	4.58	3320		1667	1665		1530
XXc	C_6H_5	177–178	79.20	5.61	4.62	78.94	5.45	4.39	3370	3340	1675			1530
XXd	p-$C_6H_4OCH_3$	183–184	75.65	5.74	4.20	76.02	5.93	4.71	3370	3340	1710	1590		1530
XXe	p-$C_6H_4SO_2N(CH_3)_2$	198–199	64.38	5.40	6.83	64.38	5.65	7.28	3420	3340	1700			1530

TABLE VI

PHYSICAL AND ANALYTICAL DATA OF α-AMINO-α,α-DIPHENYLACETAMIDES

$(C_6H_5)_2CCONHR$
|
NH_2

V

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}				
			C	H	N	C	H	N					
Va	H	150–151	74.31	6.24	12.38	74.40	6.16	12.30	3400	3390	1675	1660	
Vb	C_6H_{11}	122–123	77.88	7.84	9.08	77.54	8.06	9.48	3340		1665	1640	1520
Vc	C_6H_5	145–146	79.44	6.00	9.27	80.47	6.27	9.34	3370		1650	1600	1530
Vd	p-$C_6H_4OCH_3$	188	75.88	6.07	8.43	75.57	6.08	8.55	3400		1680	1600	1525
Ve	p-$C_6H_4SO_2N(CH_3)_2$	193–194	64.53	5.66	10.26	64.49	5.69	10.67	3400		1690	1620	1520

TABLE VII

PHYSICAL AND ANALYTICAL DATA OF α-AMINO-α,α-DIPHENYLACETAMIDES

$(C_6H_5)_2CCONH_2$
|
NHR

VI

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}				
			C	H	N	C	H	N					
VIb	C_6H_{11}	158–160	77.88	7.84	9.08	77.39	7.80	9.33	3470	3360	1680	1660	1600
VIc	C_6H_5	183–184	79.44	6.00	9.27	80.56	6.24	8.77	3480	3360	1680		1600
VId	p-$C_6H_4OCH_3$	213–214	75.88	6.07	8.43	76.32	6.56	8.70	3410	3320	1670	1640	
VIe	p-$C_6H_4SO_2N(CH_3)_2$	227–228	64.53	6.66	10.26	64.24	6.10	10.58	3420	3325	1690	1620	

TABLE VIII

PHYSICAL AND ANALYTICAL DATA OF SOME SUBSTITUTED UREAS

$(C_6H_5)_2CHNCONH_2$
|
R

VII

Compd	R	Mp, °C	Calcd, %			Found, %			Ir (KBr), cm^{-1}					
			C	H	N	C	H	N						
VIIa	H	145–146	74.31	6.24	12.38	74.42	6.20	12.42	3448	3268		1678	1613	1563
VIIb	C_6H_{11}	167–168	77.88	7.84	9.08	77.62	8.00	9.30	3450	3320		1655	1590	1580
VIIc	C_6H_5	170–171	79.44	6.00	9.27	79.64	5.85	9.31	3460	3320	3140	1670	1610	1590
VIId	p-$C_6H_4OCH_3$	177–178	75.88	6.07	8.43	76.15	6.10	8.90	3460	3320		1670	1640	
VIIe	p-$C_6H_4SO_2N(CH_3)_2$	216–217	64.53	5.66	10.26	64.61	5.85	10.27	3420	3320	3160	1670	1605	1590

Thus, by determining the *m/e* value of M − (CONR$_1$R$_2$), one can infer the nature of the substituents on the α nitrogen. Abundances of the most significant ions of the amino amides and the urea derivatives have been reported.[9]

We observed that N-aryl-α-amino amides of structures $(C_6H_5)_2C(NHAr)CONH_2$ and $(C_6H_5)_2C(NH_2)$-CONHAr lend themselves to facile acid hydrolysis[10] to the corresponding α-hydroxy amides (XX). This was advantageously utilized for characterization purposes throughout.[11] Whereas the hydrolysis of the more basic α-amino anilides V could be effected smoothly in aqueous media, the hydrolysis of the α-anilino amides VI is best achieved in 85% alcoholic solution.

$$\underset{\text{Vc–Ve}}{(C_6H_5)_2CCONHAr}\ (NH_2) \xrightarrow[H_2O,\ HCl]{\text{fast}} \underset{\text{XXc–XXe}}{(C_6H_5)_2CCONHAr}\ (OH) + NH_3$$

$$\text{Ia} + ArNH_2 \longrightarrow \underset{\text{VIc–VIe}}{(C_6H_5)_2CCONH_2}\ (NHAr) \xrightarrow[EtOH,\ HCl]{\text{slow}} \underset{\text{XXa}}{(C_6H_5)_2CCONH_2}\ (OH) + ArNH_2$$

In addition, the α-N-arylamides VIc–VIe were independently synthesized by treating α-chloro-α,α-diphenylacetamide (Ia) with respective aromatic amine.[5]

Structural assignments of substituted ureas VII were derived from their pyrolysis into cyanuric acid and the corresponding N-benzhydrylamine derivative[12] (VII → XXI), which were also obtained by way of alkaline hydrolysis of VII (VII → IX).

$$\underset{\text{XXI}}{(C_6H_5)_2CHNHR} \xleftarrow{\text{pyrolysis}} \text{VII} \longrightarrow \underset{\text{XXI}}{(C_6H_5)_2CHNHR}$$

These amines (XXI) were characterized by comparison with specimens produced independently from the reaction of benzhydrylbromide with the appropriate amine.

We noticed that substituted benzhydryl ureas of structure VII lend themselves easily and selectively to acid hydrolysis, engendering benzhydrol and the respective monosubstituted urea XXII. We took advantage of this reaction for further characterization of the urea derivatives VII.

$$\text{VII} \xrightarrow[H_2O]{H^+} (C_6H_5)_2CHOH + \underset{\text{XXII}}{RNHCONH_2}$$

From Table I it can be seen that the effect of substitution on the amido nitrogen in the substrates is reflected most significantly by the product distribution. Thus the percentage of the corresponding urea derivatives decreases in the order VIIb > VIIa > VIIc > VIId ≫ VIIe. On the other hand, formation of the unrearranged α-amino amide increases in the same order, *viz.*, Vb < Va ∼ Vc < Vd < Ve. The effect of substitution on the formation of the rearranged α-amino amide VI is not so dramatic in the case of the aryl series VIc–VId as in the case with VIb, which is formed in less than 1% yield. This suggests that in the sodium amide catalyzed reactions the I → VI rearrangements are much less sensitive to polar effects of substitution than the I → VII rearrangements. The displacement reaction I → V, likewise, is highly susceptible to polar characteristics of the substituent on nitrogen in I.

From the data assembled in Table II it is clear that the rearrangement of I to VI and VII is effected by ammonia alone,[13] although it requires somewhat higher temperatures than in the presence of sodium amide. Whereas in the cases of Ia and Ic, yields of the rearrangement products VI and VII compare with the sodium amide reactions, yields of VIb and VIIb from the reaction of the least acidic amide, Ib, drop dramatically if sodium amide is excluded from the reacting system.

In view of the above we deemed it of interest to investigate the behavior of Ia–Ie in concentrated aqueous ammonia at room temperature. The results are summarized in Table III. It can be seen from this table that the rearrangements of the types I → VI and I → VII were not observed. The displacement reactions, forming α-hydroxy acetamides (I → XX) and α-amino acetamides (I → V), are predominant. The XX to V ratio is greater than one, where R = aryl, and considerably smaller than one in the case where R = H or C_6H_5. The most striking difference between these two groups of substrates (with the exclusion of the electron-deficient Ie) is noted in the product composition. Compounds Ic and Id give rise to oxindole derivatives, IIIa and 5-methoxy-3,3-diphenyloxindole (IIIb), in 10 and 51.4% yields, respectively.

5-Methoxy-3,3-diphenyloxindole (IIIb) was conveniently obtained, in good yield, also by thermal dehydrochlorination (250°) of Id. This is in parallel to the thermal conversion of Ic into IIIa. Klinger[1] assigned a hexaphenyldiketopiperazine structure to the product similarly obtained by heating Ic (neat) at 250°. This assignment is proved to be erroneous, and the correct structure of the product is IIIa.

It is most likely that the I → VI and I → VII rearrangements proceed *via* a common intermediate of an α-lactam structure. Possible mechanisms for the reaction are described in Charts I–III.

Mechanisms 1–3 depict the I → VI + VII rearrangement as a multistage process, involving an initial 1,3-elimination stage to form a true α-lactam, followed by nucleophilic attack on carbonyl carbon to give X, which in turn undergoes ring opening to give VI and VII. Mechanistically, they represent three different routes for the elimination step.

Mechanism 1 is an intramolecular SN2-type displacement which could also be labeled as a SNi process. The best analogy appears to be the Ramberg–Backlund reaction of α-bromo sulfone.[14]

(9) (a) E. Breuer, S. Sarel, A. Taube, and J. Sharvit, *Israel J. Chem.*, **6**, 777 (1968); (b) A. Taube, Doctoral Dissertation, The Hebrew University of Jerusalem, 1968.

(10) *Cf.* (a) R. N. Lacey, *J. Chem. Soc.*, 1933 (1960); (b) A. G. Davis and J. Kenyon, *Quart. Rev.* (London), **9**, 203 (1955).

(11) J. T. Klug, Doctoral Dissertation, The Hebrew University of Jerusalem, 1965.

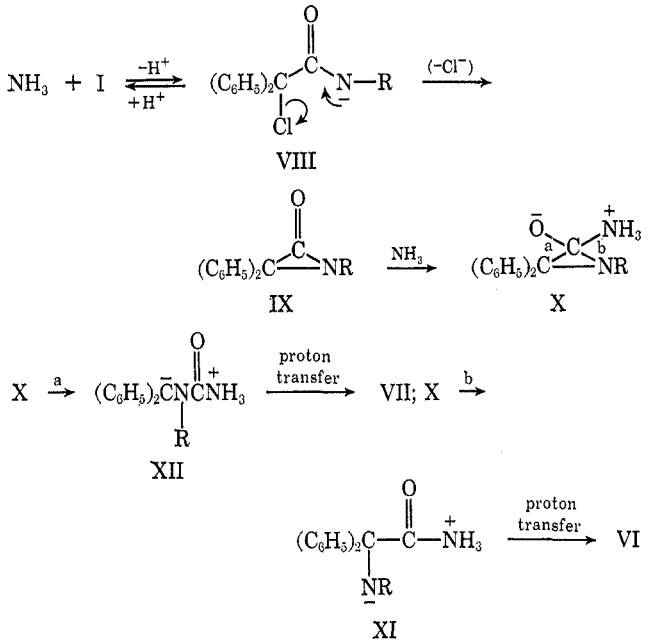
(12) (a) T. Mukaiyama, M. Tokiazawa, and H. Takei, *J. Org. Chem.*, **27**, 803 (1962); (b) T. Mukaiyama, H. Takei, and Y. Koma, *Bull. Chem. Soc. Jap.*, **36**, 95 (1963), and references cited therein.

(13) *Cf.* S. Sarel, A. Taube, and E. Breuer, *Chem. Ind.* (London), 1095 (1967). See also ref 2c.

(14) L. Ramberg and B. Backlund, *Ark. Kemi Mineral Geol.*, **13A**, No. 27 (1940). See F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968), and references cited therein.

CHART I

MECHANISM 1



solvolysis to form a carbonium ion XVIII, which gives an α-lactam species XIX. This mechanism, although it appears to be likely in displacement reactions occurring in aqueous ammonia (I → V + XX), seems unlikely in the sodium amide induced rearrangements, since it gives no role to the base.

The attachment of ammonia to α-lactam carbonyl to form a dipolar adduct X is invoked to explain substituent effects in the sodium amide catalyzed rearrangement of I into VI and VII. Two modes of ring opening are envisaged for the ammonia adduct: (a) mode a, which pursues the route X → XII → VII; and (b) mode b, which follows the X → XI → VI route. The inductive effects of the substituents on nitrogen are expected to increase yields of urea derivatives in the order VIIb > VIIa > VIIc > VIId > VIIe (mode a), and likewise to decrease yields of VI (mode b), which was found to be the case.

It is not possible to estimate the yield of VIa from the reaction of Ia, since VIa is identical with Va, which results from a displacement reaction. From another study described in a following paper,[17] it is inferred that Va originates mainly from the Ia → X → XI → Va route.

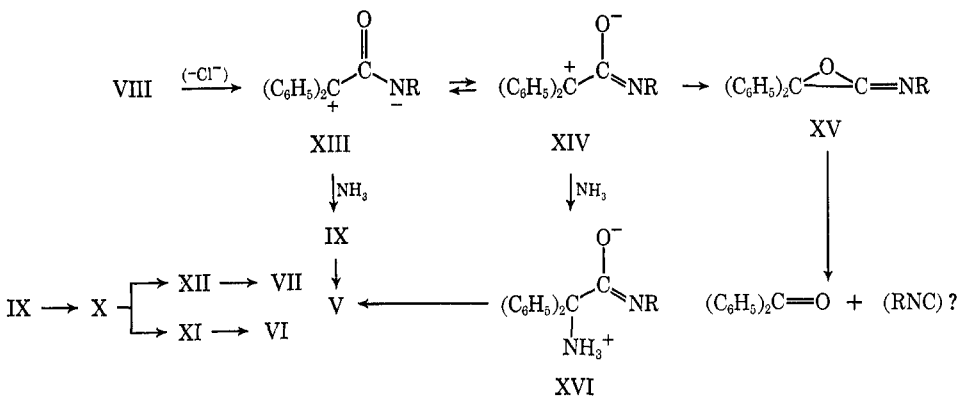
The low yield (15%) of VIIb from the reaction of Ib in the absence of sodium amide in liquid ammonia, compared with the yield (88%) from the sodium amide catalyzed reaction, is believed to be due to the low acidity of the amide group in Ib.

This amide (Ib) is the least acidic substrate, relative to Ia and Ic–Ie. It requires a stronger base for the 1,3-elimination stage (mechanisms 1–3) to form the α-lactam intermediate. As a consequence, the competing displacement reaction (Ib → Vb) *via* mechanism 4 becomes prominent.

Lack of rearrangement in the reaction of I in aqueous ammonia probably originates from the differences in basicities between liquid ammonia and aqueous ammonia. Most amides, having pK_a values of 14–34, will behave as neutral substances in aqueous ammonia but will exhibit acidic properties in liquid ammonia,[18]

CHART II

MECHANISM 2



In mechanism 2 considerable positive charge is developing at the α carbon atom as the chloride ion dissociates from the anion VIII to form dipolar ion XIII–XIV, believed to be invoked by π participation, transforming into a true α-lactam form or into the oxazirane form (XV). Formation of benzophenone in the reactions of Ia and Ib most likely arises from the fragmentation of the thermolabile XV.[2] This is in analogy to the mechanism of the Favorskii rearrangement of α-halo ketones.[15]

Mechanism 3 is a concerted 1,3 elimination giving an α-lactam intermediate. Although this possibility cannot be ruled out for our systems, no evidence in its favor could be found in the analogous Favorskii rearrangement.[15]

Mechanism 4 is based on the assumption that the role of the base is to establish an amide–imidol equilibrium,[16] and that the allylic system XVII undergoes

(15) F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *J. Amer. Chem. Soc.*, **91**, 2087 (1969), and references cited therein.

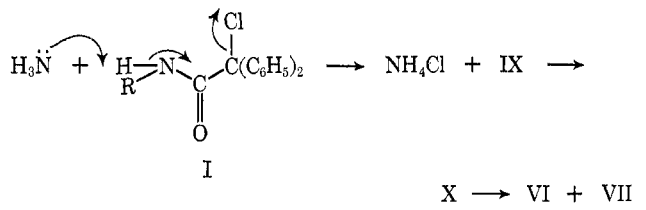
(16) The calculated value of ΔH for the amide → *imidol* change is +10 kcal/mol, compared with +18 kcal/mol obtained for the *keto* → *enol* change in ketones: G. E. K. Branch and M. Calvin," The Theory of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1945, p 288–289.

(17) S. Sarel, A. Taube, and E. Breuer, forthcoming paper.

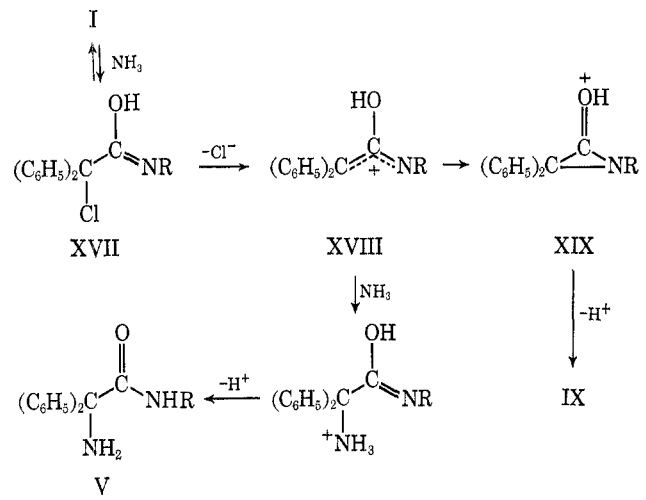
(18) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, New York, N. Y., 1963. See also R. C. Paul in "New Pathways in Inorganic Chemistry," E. A. V. Ebsworth, A. G. Maddock, and A. G. Sharpe, Ed., Cambridge University Press, New York, N. Y., 1968, p 233.

CHART III

MECHANISM 3

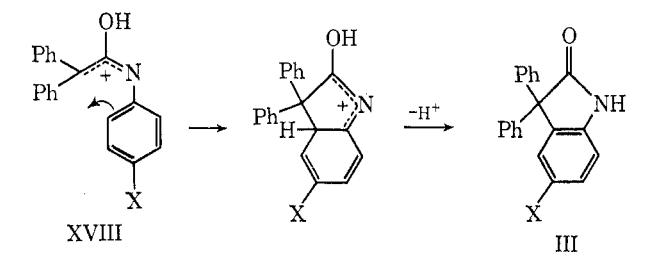


MECHANISM 4



the autoionization constant of which is *ca.* 10^{-32}. Aqueous ammonia is therefore too weak a base to play a role in 1,3-elimination reactions as formulated in mechanisms 1–3. However, mechanism 4 could be applied to explain the results summarized in Table III.

Formation of a carbonium ion of structure XVIII (mechanism 4) is invoked to explain the formation of 3,3-diphenyloxindoles (III) from the reactions of Ic and Id in aqueous ammonia. The reaction is viewed as an intramolecular cyclization process in which the electron-rich *p*-anisyl substituent contributes to the high yield (51%) of 5-methoxy-3,3-diphenyloxindole from the reaction of Id, compared with none in the case of Ie.



Experimental Section

All melting points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Column chromatography was carried out using Hopkin & Williams alkaline and neutral alumina.

N-Phenylbenzhydrylamine[19] was prepared in 63% yield from the reaction of phenylmagnesium bromide with N-phenylbenzalimine[20] in boiling toluene (18-hr reflux) and converted into its hydrochloride salt, mp 199°, by passing dry hydrogen chloride into an ethereal solution.

N-Cyclohexylbenzhydrylamine hydrochloride, mp 269–270°, was obtained in 50% yield from the addition of phenylmagnesium bromide to N-cyclohexylbenzalimine,[21] in a manner described above. The picrate melted at 185–187°.

N-(*p*-Anisyl)benzhydrylamine was prepared in 72% yield by treating benzhydryl bromide (10 mmol) with *p*-anisidine (20 mmol) in boiling benzene for 20 hr. The oily, crude product was chromatographed on an alumina column with benzene as eluent and finally isolated as its hydrochloride salt, mp 198–199° (lit.[22] mp 194°).

Anal. Calcd for $C_{20}H_{20}ClNO$: C, 73.7; H, 6.1; N, 4.3. Found: C, 73.6; N, 4.4.

N^4-(Benzhydryl)-N^1-dimethylsulfanylamide.—*p*-Aminobenzene-N,N-dimethylsulfonamide was obtained in 72% yield according to the literature,[23] mp 170–171° (prisms from ethanol).

The title compound was prepared in 63% yield by allowing a mixture of *p*-aminobenzene-N,N-dimethylsulfanylamide (9.5 mmol), benzhydryl bromide (10.5 mmol), and triethylamine (3 ml) in dry dioxane (50 ml) to stand at room temperature for 1 week. Colorless prisms were obtained from chloroform, mp 209–210°, ir (KBr) 3350 and 1580 cm^{-1}.

Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.8; H, 6.0; N, 7.7. Found: C, 69.1; H, 6.2; N, 7.7.

Cyclohexylurea, mp 205°, was prepared according to the literature.[24]

Preparation of α-Chloro-α,α-diphenylacetamides.—All N-substituted acetamides (Ia–Ie) were prepared by treating α-chloro-α,α-diphenylacetyl chloride[25] with 2 equiv of amine in dry ether.[1] Physical and analytical data are listed in Table IV.

Reaction of α-Chloro-α,α-diphenylacetamides with Sodium Amide in Liquid Ammonia.—α-Halo amides included in this study were similarly allowed to react with sodium amide in liquid ammonia. Physical and analytical data of the products obtained are given in Tables VI–VIII. The following procedure is representative.

A. Reaction of Ic with Sodium Amide in Liquid Ammonia.—To a mixture of sodium amide (0.5 g, 0.0128 mol) in dry liquid ammonia (70 ml), Ic (3.2 g, (0.01 mol) was added with stirring during 5 min. The ammonia was allowed then to evaporate and the residue was neutralized with ammonium chloride (0.5 g). The resulting mixture was treated first with cold dilute acid and then extracted with ether, leaving behind 1.47 g (49%) of VIIc, mp 170–171°. The nmr spectrum ($CDCl_3$) of VIIc exhibits a multiplet at τ 5.08 ($CONH_2$) and a multiplet centered at τ 2.85 (15 aromatic protons + benzhydrilic proton). Physical and analytical data for the corresponding compound are listed in Table VIII.

To the acidic filtrate, sodium carbonate was added and the alkaline precipitate was filtered and crystallized from ethanol, yielding 0.545 g (18.15%) of Vc, mp 145–146°. Physical and analytical data for corresponding compounds are listed in Table VI.

The ethereal extracts were concentrated and the residue was crystallized from benzene–petroleum ether, providing 0.56 g (18.5%) of VIc, mp 183–184°. Physical and analytical data for related compounds are listed in Table VII.

B. Reaction of Ib with Sodium Amide in Liquid Ammonia.—Reaction B was carried out as described above. The solid residue left after the evaporation of ammonia was crystallized from chloroform–ligroin, affording 88% VIIb, mp 167–168°. The nmr spectrum ($CDCl_3$) VIIb exhibits a singlet at τ 4.1 (one benzhydrilic proton), a multiplet at τ 5.5 ($CONH_2$), and a multiplet centered at τ 2.65 (aromatic protons).

The mother liquor was chromatographed on an alumina column (10 g) and eluted with petroleum ether. The first fraction contained benzophenone (4%), which was characterized as its 2,4-dinitrophenylhydrazone. The second fraction contained only a minute amount (less than 1%) of VIb, mp 158–160°, while the last fraction, eluted with benzene, contained Vb (4%), mp 113–114°.

(19) H. Gilman, J. E. Kirby, and C. R. Kinney, *J. Amer. Chem. Soc.*, **51**, 2252 (1929).

(20) L. A. Bigelow and H. Eatough, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1951, p 80.

(21) E. D. Bergmann and S. Pinchas, *Rec. Trav. Chim. Pays-Bas*, **71**, 161 (1952).

(22) P. Grammaticakis, *Compt. Rend.*, **210**, 716 (1940).

(23) E. L. Eliel and K. W. Nelson, *J. Org. Chem.*, **20**, 1657 (1955).

(24) O. Wallach, *Justus Liebigs Ann. Chem.*, **343**, 46 (1905).

(25) J. H. Bilman and P. H. Hidy, *J. Amer. Chem. Soc.*, **65**, 760 (1943).

Acid Hydrolysis of 1,1-Disubstituted Ureas. A. Hydrolysis of VIIc.—Compound VIIc (0.65 g, 2.15 mmol) was dissolved in a 35-ml solution of hydrochloric acid (3%) in ethanol (60%). The mixture was refluxed for 4 hr and then concentrated to half of its volume. Hydrochloric acid (12%, 25 ml) was added and the resulting solution was extracted with benzene. The organic layer was evaporated and the oily residue was distilled under diminished pressure to give benzhydrol (71%), bp 102–104° (0.4 mm).

Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.60; H, 6.72.

The acidic aqueous layer was rendered alkaline and the resulting solution was concentrated. The precipitate formed was filtered, giving 0.12 g (40%) of phenylurea, mp 147°. A mixture melting point with a sample prepared according to the literature[26] was not depressed.

B. Hydrolysis of VIIb, in a manner described above, yielded cyclohexylurea, mp 201–205°, and benzhydrol (73%).

Base Hydrolysis of 1,1-Disubstituted Ureas. A. Hydrolysis of VIIc.—A solution of VIIc (1.6 mmol) in 0.07 *M* 85% ethanolic potassium hydroxide (35 ml) was refluxed for 5 hr and then processed in the usual way. Crystalline N-phenylbenzhydrylamine, mp 170–171°, was isolated. Its hydrochloride had a melting point of 199°, showing identity with an authentic specimen.

B. Hydrolysis of VIIb in the manner described yielded N-cyclohexylbenzhydrylamine, which was characterized as its hydrochloride, mp 269–270°, and its picrate, mp 186–187°.

Pyrolysis of 1,1-Disubstituted Ureas. A. Pyrolysis of VIIc.—Compound VIIc (0.6 g, 2 mmol) was heated to 250° for 10 min. The resulting melt was cooled and then extracted with acetone (20 ml). The insoluble solid was crystallized from water, yielding 0.065 g (75.5%) of cyanuric acid.

Anal. Calcd for $C_3H_3N_3O_3$: C, 27.91; H, 2.34; N, 32.56. Found: C, 28.08; H, 2.99; N, 32.64.

The acetone extract was evaporated, and N-phenylbenzhydrylamine (XXI) was isolated as the hydrochloric salt, mp 199°. A mixture melting point with a sample prepared as described was not depressed.

B. Pyrolysis of VIIb was carried out in the manner described above. From the pyrolysis of 1 g of VIIb, 0.13 g (95%) of cyanuric acid and 0.8 g (94.5%) of N-cyclohexylbenzhydrylamine (XXIb) were isolated. The latter was characterized as its hydrochloride and its picrate derivatives.

C. Pyrolysis of VIId.—From the pyrolysis of 0.5 g of VIId, cyanuric acid and 0.31 g of N-(*p*-anisyl)-benzhydrylamine were isolated. The latter was characterized as its hydrochloride, mp 198–199°.

D. Pyrolysis of VIIe.—The pyrolysis of VIIe similarly provided crystals (from chloroform) of N^1-dimethyl-N^4-benzhydrylsulfanylamide, mp 208–209°, identical in all respects with an authentic sample.

Hydrolysis of VIc into α-Hydroxy-α,α-diphenylacetamide (XXa).—Compound VIc (0.53 g, 1.75 mmol) was dissolved in a solution of hydrochloric acid (6%) in ethanol. The resulting mixture was refluxed for 2 hr, the solvents were evaporated, and the residue was extracted with chloroform. The dried chloroform extract was evaporated and the oily residue was crystallized from benzene–petroleum ether. α-Hydroxy-α,α-diphenylacetamide (XXa), 0.2 g (50%), was obtained, mp 152–154° (lit.[27] mp 154–155°). A mixture melting point with authentic sample prepared by the hydrolysis of Ia was not depressed.

Hydrolysis of VId and VIe.—The hydrolyses of VId and VIe were similarly carried out to give α-hydroxy-α,α-diphenylacetamide (XXa), mp 152–154°.

Acid Hydrolysis of V. A. Acid Hydrolysis of Vc into α-Hydroxy-α,α-diphenylacetanilide (XXc).—Compound Vc (0.3 g, 1 mmol) was dissolved in dilute hydrochloric acid (15 ml) and the solution was refluxed for 10 min. The precipitate formed was filtered, dried, and crystallized from benzene–petroleum ether, giving α-hydroxy-α,α-diphenyl acetanilide (XXc), mp 177–178°. A mixture melting point with a sample prepared by the hydrolysis of Ic was not depressed.

B. Hydrolysis of Vd and Ve.—In a similar manner, Vd and Ve were quantitatively hydrolyzed into the respective α-hydroxy derivatives XXd and XXe. Physical and analytical data are given in Table V.

Reaction of Ic with Liquid Ammonia at −33°.—To a 100-ml, three-necked flask equipped with a condenser suited for acetone–Dry Ice and a calcium chloride drying tube was introduced dry liquid ammonia (60 ml). Powdered Ic (3.21 g, 0.01 mol) was added in one portion and the reaction mixture was stirred for 10 hr. The ammonia was then allowed to evaporate and the residue was extracted with benzene. The benzene solution was washed with three 15-ml portions of water, dried over magnesium sulfate, concentrated, and chromatographed on alumina column (100 g). On elution with benzene, unchanged starting material was obtained in 8.5% yield, followed by XXc (91%), mp 177–178°. A mixture melting point with an authentic sample prepared by the hydrolysis of Ic was not depressed.

Reactions of α-Chloro-α,α-diphenylacetamides with Liquid Ammonia at Room Temperature.—Reactions of I with liquid ammonia at room temperature were carried out in an autoclave. The following procedure is representative. A mixture of Ic (3.21 g, 0.01 mol) in liquid ammonia (50 ml) contained in a sealed tube was vigorously agitated for 48 hr. Ammonia was then allowed to evaporate and the residue was extracted with benzene and chromatographed on an alumina column (100 g). Elution with 1:1 benzene–petroleum ether gave Vc, mp 142–145°. A mixture melting point with a sample obtained from the reaction of the same substrate with sodium amide was not depressed.

Further elution with benzene gave VIc (28%), mp 181–182°. A mixture melting point with product obtained from the sodium amide reaction was not depressed. The third fraction eluted by chloroform afforded VIIc, mp 170–171°, in 32.2% yield.

Reaction of α-Chloro-α,α-diphenylacetamides with Aqueous Ammonia.—A mixture of I (0.01 mol) in concentrated aqueous ammonia 20–23%, (50 ml) was magnetically stirred during 1 week at room temperature. The solid which was deposited was filtered, treated with dilute hydrochloric acid, and washed with water. The dried solid was then crystallized from benzene–petroleum ether and identified as the respective α-hydroxy-α,α-diphenylacetamide derivative. The acidic filtrate was rendered alkaline, and from it the corresponding α-amino-α,α-diphenylacetamide derivative was isolated by filtration or by extraction with benzene.

Reaction of Ic with Aqueous Ammonia.—Fractional crystallization of the solid obtained from the reaction of Ic with aqueous ammonia gave the following products: (a) α-hydroxy-α,α-diphenylacetanilide (XXc, 35%), mp 176–179°; (b) 3,3-diphenyloxindole (IIIa, 10%), mp 228–229° (lit.[5] mp 227–228°), ir (KBr) 3330, 1725, and 1680 cm^{-1}.

From the filtrate, α-amino-α,α-diphenylacetanilide (VIc, 25%), mp 145–146°, was isolated.

Thermal Conversion of Ic into 3,3-Diphenyloxindole (IIIa).—The reaction was carried out according to Klinger and Nickell.[1] Compound Ic (1 g) was heated gradually to 230° during 1 hr. Evolution of hydrogen chloride began at 150° and ceased at the end of the experiment. The cooled melt was crystallized from benzene, yielding colorless prisms (85%), of mp 226–228° (lit.[1] mp 225–226°). A mixture melting point with an authentic specimen of 3,3-diphenyloxindole (IIIa) was not depressed. Its ir spectrum was superimposable upon that of authentic IIIa.

The assigned hexaphenyldiketopiperazine structure[1] for this product was not substantiated by molecular weight determination.

Preparation of 3,3-Diphenyl-5-methoxyoxindole (IIIb).—Compound Id (0.5 g, 1.42 mmol) was heated to 250° for 5 min. Evolution of hydrogen chloride was observed. The melt was then cooled, benzene (10 ml) was added, and the resulting mixture was warmed on a water bath. The formed precipitate was filtered and crystallized from ethanol or acetone. 3,3-Diphenyl-5-methoxyoxindole, mp 259–260°, was obtained in a yield of 0.28 g (62.5%), ir (KBr) 3400, 3240, 1710, and 1670 cm^{-1}. The infrared spectrum was superimposable upon that of the product obtained from the reaction of the same substrate with aqueous ammonia.

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.98; H, 5.63; N, 4.60.

Registry No.—N-Phenylbenzhydrylamine hydrochloride, 2101-21-5; N-cyclohexylbenzhydrylamine

(26) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co. Ltd., London, 1961, p 644.

(27) H. Klinger and O. Standke, *Chem. Ber.*, **22**, 1214 (1889).

hydrochloride, 844-41-7; N-cyclohexylbenzhydrylamine picrate, 989-12-8; *p*-aminobenzene-N-N-dimethylsulfonamide, 1709-59-7; N-(benzhydryl)-N′-dimethylsulfanylamide, 23511-18-4; cyclohexylurea, 698-90-8; N-(*p*-anisyl)benzhydrylamine hydrochloride, 23511-20-8; 3,3-diphenyl-5-methoxyoxindole, 20367-84-4; Ia, 722-96-3; Ib, 797-73-9; Ic, 741-36-6; Id, 23522-81-8; Ie, 23522-82-9; Va, 15427-81-3; Vb, 23522-84-1; Vc, 741-37-7; Vd, 23522-86-3; Ve, 23522-87-4; VIb, 15779-18-7; VIc, 741-38-8; VId, 23522-90-9; VIe, 23522-91-0; VIIa, 724-18-5; VIIb, 741-68-4; VIIc, 741-69-5; VIId, 23568-88-9; VIIe, 23568-89-0; XXa, 4746-87-6; XXb, 17003-65-5; XXc, 5554-37-0; XXd, 20594-45-0; XXe, 23568-86-7.

The Mechanism of Tetralone Formation from the Acid-Catalyzed Reaction of 2-(N,N-Dimethylamino)-1,4-diphenyl-1,4-butanediol

STEPHEN A. FINE

Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

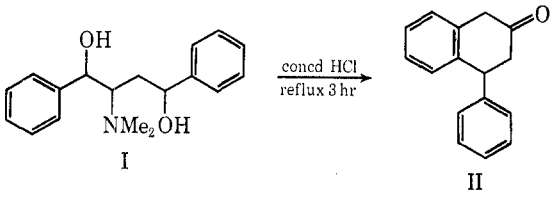
ROBERT L. STERN[1]

Department of Chemistry, Oakland University, Rochester, Michigan 48063

Received April 28, 1969

The mechanism of formation of 4-phenyl-2-tetralone from the reaction of 2-(N,N-dimethylamino)-1,4-diphenyl-1,4-butanediol with acid was investigated. A number of potential reaction intermediates were synthesized. These included 1,4-diphenyl-3-buten-2-one, 1,4-diphenyl-3-butene-1,2-diol, and 1,4-diphenyl-1,2,4-butanetriol. The first two of these compounds failed to give 4-phenyl-2-tetralone on treatment with hydrochloric acid. The triol did furnish 4-phenyl-2-tetralone in acid, but it was indirectly shown that the triol was not an intermediate in the reaction. A cyclic amino alcohol, 2-(N,N-dimethylamino)-4-phenyl-1-tetralol, afforded 4-phenyl-2-tetralone in high yield upon treatment with acid. Results of kinetic studies were consistent with intermediacy of the cyclic amino alcohol. Experimental data suggests a mechanism in which the cyclic amino alcohol undergoes dehydration to an enamine with subsequent hydrolysis to 4-phenyl-2-tetralone.

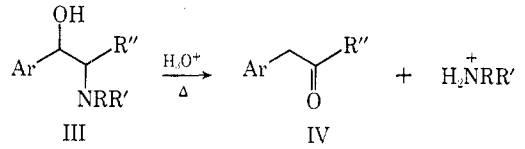
In a previous communication[2] we reported the acid-catalyzed conversion of 2-(N,N-dimethylamino)-1,4-diphenyl-1,4-butanediol (I) into 4-phenyl-2-tetralone (II). We now wish to report the results of



I II

experiments aimed at elucidating the mechanism of tetralone formation.

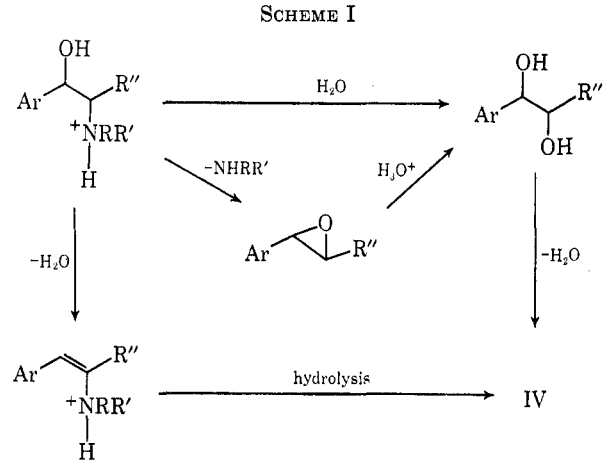
α-Aryl-β-amino alcohols are known to undergo cleavage to β-keto compounds upon treatment with strong mineral acids.[3-6] In these reactions R and R′



III IV

may be either hydrogen or alkyl, while R″ may be hydrogen, alkyl, or aryl. Because of their pharmaceutical activity, many amino alcohols related to III have been prepared; however, there are few studies dealing with the acid-catalyzed cleavage of these compounds. Among the mechanisms[3-5,7] which have been suggested to account for the cleavage, two proposals merit attention. These are outlined in Scheme I. One proposal involves conversion of the amino

SCHEME I



alcohol into a glycol, either *via* displacement of amine by neighboring hydroxyl and hydrolytic cleavage of the resulting epoxide or *via* direct displacement of amine by water.[3,4] The intermediate glycols are known to undergo acid-catalyzed dehydration to β-aryl ketones or aldehydes. In the cleavage of ephedrine derivatives with concentrated phosphoric acid the intermediate glycols were, indeed, isolated, but the mechanism of glycol formation has not been convincingly resolved.[8]

(1) To whom inquiries should be addressed.

(2) (a) S. A. Fine and R. L. Stern, *J. Org. Chem.*, **32**, 4132 (1967). (b) In ref 2a 4-phenyl-2-tetralone was synthesized independently *via* intramolecular Friedel–Crafts reaction of 1,4-diphenyl-3-buten-2-one. An unexpected by-product, not reported previously in this synthesis, was 2-naphthol, isolated by extracting the crude product with sodium hydroxide followed by acidification.

(3) F. Kröhnke and A. Schulze, *Chem. Ber.*, **75**, 1154 (1942).

(4) H. Auterhoff and H. J. Roth, *Arch. Pharm.* (Weinheim), **289**, 470 (1956).

(5) P. T. Sou, *Bull. Fac. Sci. Univ. Franco-Chinoise*, **5**, 1 (1935); *Chem. Abstr.*, **30**, 4463 (1936).

(6) In ref 5 enamines were isolated when β-amino alcohols were treated with PCl_5.

(7) J. H. Fellman, *Nature*, **182**, 311 (1958).