(0.05 mole) of styrene oxide, 8.0 g. (0.1 mole) of pyridine and 10.3 g. (0.05 mole) of pyridine hydriodide was heated on the steam-bath. Within two minutes, the pyridine hydriodide had dissolved and a vigorous reaction began. After the reaction subsided, the mixture was heated ten minutes more, cooled, layered with ether and rubbed with an applicator stick until the entire mass crystallized. The crude mixture of products weighed 13.2 g.

The solid material was leached three times with 75-cc. portions of boiling acetone and the 4.0 g. left was dissolved in 20 cc. of water containing a little alcohol. On cooling, 0.7 g. (4.2%) of a substance melting at 244–252° separated. After recrystallization from water, pure 1-(2-phenyl-2-hydroxyethyl)-pyridinium iodide (IIIa), melting at 252–255°, was obtained.

On cooling the acetone extracts from above, there separated out a compact crystalline product, 8.7 g. (52%),[13] m. p. 125–129°. Recrystallization from acetone gave pure 1-(1-phenyl-2-hydroxyethyl)-pyridinium iodide (IVa), m. p. 128–129°.

(b) **Pyridinium Perchlorate and *p*-Toluenesulfonate.**—As in the previous procedure, high melting acetone-insoluble salts were obtained. However, no crystalline material separated from the acetone extracts, even after concentration. Subsequently, each oil was treated with sodium iodide in acetone. At this point, the pyridinium perchlorate reaction started to deposit crystals. On long cooling of the acetone solution, followed by filtration, a 56% yield of IVa, melting at 128–129° was obtained. The sodium iodide treated acetone solution of the *p*-toluenesulfonate reaction immediately gave a precipitate of sodium *p*-toluenesulfonate. The mixture was heated and filtered. After long cooling, there separated from the filtrate a 52% yield of IVa, melting at 128–129°.

The Oxidation of IIIc to 1-Phenacylpyridinium Perchlorate.—According to the directions of Krohnke,[4] 0.15 g. of 1-(2-phenyl-2-hydroxyethyl)-pyridinium perchlorate (IIIc) in 1 cc. of water was heated under reflux for six hours with 0.5 cc. of 6 *N* sulfuric acid and 0.075 g. of sodium dichromate. On cooling, there separated out long yellow needles, which were filtered off and washed with ice-water. The yellow crystals weighing 0.1 g. (93%), were recrystallized from acetone-water, using norite, yielding white crystals melting at 189°. This material gave no depression in a mixed melting point with an authentic sample of 1-phenacylpyridinium perchlorate prepared in this Laboratory.[5]

Reactions Involving 1-Phenyl-2-bromoethanol.—By heating 1-phenyl-2-bromoethanol[14] with pyridine, on a steam-bath for twenty-four hours, and then washing the product with ether, an essentially quantitative yield of crude 2-phenyl-2-hydroxyethylpyridinium bromide was obtained. An aqueous solution of the bromide on treatment with 48% hydriodic acid gave the corresponding iodide (IIIa); yield 90%; m. p. 252–255°[15] after crystallization from alcohol-water. In a similar manner the following salts were prepared by action of the corresponding bases on 2-phenyl-2-bromoethanol; 1-(2-phenyl-2-hydroxyethyl)-3-picolinium iodide, m. p. 175–177°[15] crystallized from alcohol-water; and 2-(2-phenyl-2-hydroxyethyl)-isoquinolinium iodide, m. p. 173–176° crystallized from alcohol.

No compounds of type IV were observed in any of these reactions.

Reactions Involving 2-Phenyl-2-iodoethanol.—2-Phenyl-2-iodoethanol[6] was heated with pyridine, on a steam-bath for thirteen hours. The resulting reaction mixture was washed with dry ether and the crude crystalline product was recrystallized from acetone; yield, 82%, of 1-(1-phenyl-2-hydroxyethyl)-pyridinium iodide (IVa), m. p. 128–129°[15]; in a similar manner the reaction of 2-phenyl-2-iodoethanol with β-picoline and isoquinoline gave 83% of 1-(1-phenyl-2-hydroxyethyl)-3-picolinium iodide, m. p. 131–132°, and 86% of 2-(1-phenyl-2-hydroxyethyl)-isoquinolinium iodide, m. p. 146–147°.

Summary

1. The reaction of styrene oxide with pyridine hydriodide gives a mixture of salts consisting of 1-phenyl-2-hydroxyethylpyridinium iodide and 2-phenyl-2-hydroxyethylpyridinium iodide.

2. The generality of this reaction was established by allowing styrene oxide to react with a variety of strong acid salts of pyridine and by allowing it to react with salts of a number of pyridine-type bases.

(13) By reworking all mother liquors including that from which the high melting compound separated, the total yield of IVa, the low melting compound, was 75%.

(14) Read and Reid, *J. Chem. Soc.*, 1487 (1928).

(15) No depression in mixed melting point with the corresponding salt prepared from styrene oxide.

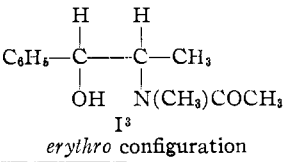
EVANSTON, ILLINOIS RECEIVED MAY 26, 1949

[CONTRIBUTION FROM THE CHEMICAL BRANCH, DIVISION OF MEDICINE, FOOD AND DRUG ADMINISTRATION, FEDERAL SECURITY AGENCY]

Mechanism and Stereochemical Course of Acyl Migrations in Derivatives of Ephedrine and ψ-Ephedrine

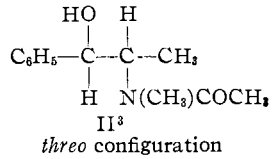
BY LLEWELLYN H. WELSH

It has been reported[1] that treatment of N-acetyl-(−)-ephedrine, I, with hot 5% hydrochloric acid quantitatively yielded a mixture of (−)-ephedrine and its diastereomer, (+)-ψ-ephedrine, in the ratio of 38:62,[2] and that inversion took place at the number one carbon atom during an N → O shift of the acetyl group prior to hydrolysis of the ester salt so formed. Under the same conditions N-acetyl-(+)-ψ-ephedrine, II, gave a product in which complete retention of configuration was evident.



I[3]

erythro configuration



II[3]

threo configuration

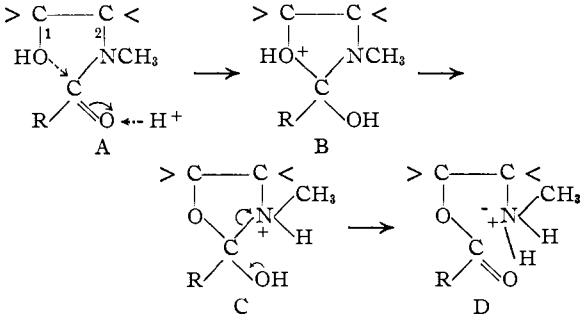
(1) Welsh, THIS JOURNAL, **69**, 128 (1947).

(2) When this reaction is carried out under temperature conditions more closely controlled than those formerly employed, a ratio of 33:67 results

(3) The projection formulas are based on the work of Leithe, *Ber.*, **65**, 660 (1932), and of Freudenberg, *et al.*, THIS JOURNAL, **54**, 234 (1932); *Ann.*, **510**, 223 (1934). Jarowski and Hartung, *J. Org. Chem.*, **8**, 565 (1943), have misinterpreted the publication of Leithe, and are in error when they state that the relative configuration of the methylamino-bearing carbon atom is unsettled.

Stereochemical results similar to these were obtained when the corresponding dry crystalline N-acetyl hydrochlorides[4] were heated at 110°. This similarity of results makes it apparent that hydrolytic cleavage of the amide linkage is not responsible for uninverted material in the product from reactions conducted in aqueous media. It was also reported that the N → O rearrangement of N-acetylephedrine in 90% acetone occurred with predominant retention of configuration.

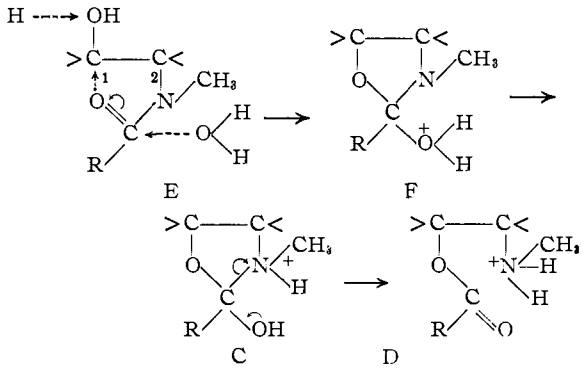
It would seem that two mechanisms are involved in the rearrangements, one leading to inversion, the other to retention of configuration.[5] A mechanism for retention is shown below.[6] Such



Retention (*R*) mechanism

a process would lead to retention of configuration since no bond of the asymmetric center is involved.[7] It is analogous to one used to represent the acid-catalyzed hydrolysis of carboxylic esters.[8] In the rearrangement, the alcoholic hydroxyl, rather than a water molecule, acts as an electron donor to the carbonyl carbon.

A suitable mechanism for inversion, given below, assumes that complete inversion at carbon one would occur as a result of a back-side approach of carbonyl oxygen while a proton attacks the hydroxyl oxygen.[9a,b]



Inversion (*I*) mechanism

TABLE I

N-AROYL DERIVATIVES OF 1-PHENYL-2-METHYLAMINO-1-PROPANOLS, $C_6H_5CHOHCH(CH_3)N(CH_3)COC_6H_4X$

X	M. p., °C. (cor.)	$[\alpha]^{20}D$ [a]	Empirical formula	Nitrogen, % Calcd.	Found [b]
		(−)-Ephedrine series			
H	110–110.5	−54.8 [c]	$C_{17}H_{19}NO_2$		[d]
o-F	127.5	−50.6	$C_{17}H_{18}FNO_2$	4.88	4.83
o-Cl	152–152.5	−30.9	$C_{17}H_{18}ClNO_2$	4.61	4.59
o-Br	159.5–160	−21.0	$C_{17}H_{18}BrNO_2$	4.02	4.00
o-CH_3	155–155.5	−39.9	$C_{18}H_{21}NO_2$	4.94	4.91
o-OCH_3	191.5–193	−66.4	$C_{18}H_{21}NO_3$	4.68	4.56
o-NO_2	117–118	−16.5	$C_{17}H_{18}N_2O_4$	8.91	8.80
		(+)-ψ-Ephedrine series			
H	137–137.5	+135.2	$C_{17}H_{19}NO_2$	5.20	5.18
o-F	134.5	+115.6	$C_{17}H_{18}FNO_2$	4.88	4.86
o-Cl	162.5–163	+102.7	$C_{17}H_{18}ClNO_2$	4.61	4.56
o-Br	153.5	+ 90.0	$C_{17}H_{18}BrNO_2$	4.02	3.99
o-CH_3	162.5–163	+121.0	$C_{18}H_{21}NO_2$	4.94	4.92
o-OCH_3	155–156	+116.2	$C_{18}H_{21}NO_3$	4.68	4.65
o-NO_2	208–208.5	+135.5 [e]	$C_{17}H_{18}N_2O_4$	8.91	8.85

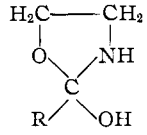
[a] Rotations are in U.S.P. chloroform, c = 3 (unless otherwise noted), l = 2. [b] Semi-micro Kjeldahl. [c] c = 4. [d] Chen, in a review in *J. Am. Pharm. Assoc.*, **15**, 625 (1926), has reported that this compound, m. p. 113°, has been prepared by Nagai. It does not appear to be indexed in the Western literature. [e] c = 0.9.

In view of the stereochemical results afforded by rearrangements of the acetylated diastereomers, one must ascribe to the ψ-ephedrine derivatives certain characteristics, inherent in the space relationships in the parent aminoalcohol, which enormously favor rearrangement with retention of configuration, while the relationships in the derivatives of ephedrine must permit rearrangement with either retention or inversion the proportion of which can be influenced relatively easily by variations in experimental conditions.

(4) In these substances the proton is probably linked to the amide oxygen: see Wheland, "The Theory of Resonance," John Wiley & Sons, Inc., New York, N. Y., 1944, p. 181.

(5) At the "Meeting in Miniature" of the Philadelphia Section of the American Chemical Society, January 23, 1948, a paper entitled "Electronic Interpretation of the *p*H-Dependent Acyl Migration in 2-Aminoethanol Systems" was presented by Dr. A. Gero to whom this writer is indebted for a copy of the manuscript. The mechanism proposed for the N → O shift in that paper will not account for rearrangement with inversion of configuration. In some respects it resembles the *R* mechanism presently proposed.

(6) Phillips and Baltzly, THIS JOURNAL, **69**, 200 (1947), have postulated the formation of a hydroxyoxazolidine, corresponding to the cyclic structures in the mechanism presented here.



(7) Retention of configuration may occur in many cases as the result of an even number of inversions as has been explained by Winstein and co-workers in a series of papers which have appeared in THIS JOURNAL since 1942 under the general title of "The Role of Neighboring Groups in Replacement Reactions." It is evident that such an explanation is not applicable to these rearrangements.

(8) Watson, "Modern Theories of Organic Chemistry," second ed., Oxford University Press, London, 1941, p. 130.

(9) (a) Frush and Isbell, *Bur. Standards J. Research*, **27**, 413 (1941), have presented a similar mechanism in explaining the formation of orthoesters, with inversion, from acetohalogen sugars in the Koenigs-Knorr reaction. (b) Fodor, Bruckner, Kiss and Óhegyi, *J. Org. Chem.*, **14**, 337 (1949), in explaining the appearance of O-benzoyl-ψ-ephedrine hydrochloride in some of their experiments on the action of ethanolic hydrogen chloride on racemic N-benzoylephedrine, have assumed that inversion results from the action of the acid on asymmetric center 1 whereby the hydroxyamide of the ψ-ephedrine configuration is formed prior to acyl migration. Such an interpretation cannot be applied to the migrations effected in this Laboratory, since the configuration of ephedrine is almost literally unaffected by the experimental conditions which effect rearrangement and inversion in its N-acyl derivatives[1]; the inversion seems clearly to be the result of a displacement reaction in which a neighboring group, in this case acylamino, participates. See Winstein, *et al.*,[7] also McCasland, Clark and Carter, THIS JOURNAL **71**, 637 (1949).

TABLE II

DATA RELATING TO REARRANGEMENTS OF COMPOUNDS OF TABLE I IN BOILING 5% HYDROCHLORIC ACID

X[a]	Total inversion, %	Time for rearr., minutes	Sample, mg.	% Hydrol.	Wt., mg.	Hydroxyamide fraction M. p., °C.	Hydroxyamide fraction $[\alpha]^{20}D$[b]	% Invers.	Total recovery, %[c]
				Ephedrine series					
H	77.2	5	651.3	3.3	629.9	.....	+ 93.6[d]	78.1	..
o-F	94.4	20	691.7	4.3	662.0	128.5–133	+106.3	94.4	98.5
o-OCH_3	94.9	60	700.0	24.6	528.0	149.5–156	+106.8	94.9	98.3
o-NO_2	97.0	35	740.4	0.9	733.4	207–207.5	+130.9[e]	97.0	99.1
o-Cl	99.3	60	732.8	4.0	703.5	162–162.5	+102.1	99.6	99.6
o-CH_3	99.9	30	681.0	1.7	669.2	162–163.5	+120.9	99.9	99.0
o-Br	98.7	90	837.7	3.6	809.2	152.5–153.5	+ 88.8	98.9	98.7
				ψ-Ephedrine series					
H	0.0	3	649.9	1.3	641.3	.....	+135.3	0.0	99.6
o-F	0.3	20	691.7	2.9	671.6	.....	+115.1	0.3	98.9
o-OCH_3	0.3	15	700.5	11.8	617.8	.....	+115.8	0.2	98.6
o-NO_2	Slight	Incomplete	...	..	...	.....	.....	..	..
o-Cl	2.6	660	730.5	23.7	557.2	160.5–162	+100.5	1.6	98.7
o-CH_3	2.4	420	682.7	10.5	611.3	.....	+118.2	1.7	99.0
o-Br	2.8	>720	841.0	12.9	732.8	151.5–153	+ 87.8	2.0	98.9

[a] As one reads down the column, the ortho substituent increases in size: the dissociation constants (K_{th}) × 10^5 of the respective acids are 6.3, 54.1, 8.1, 671, 114, 12.3, 140. [b] Rotations are in U. S. P. chloroform, $c = 3$ (unless otherwise noted), $l = 2$. [c] These percentages are based on the weight of sample and the weight of the hydroxyamide fraction plus the hydroxyamide equivalent of the aminoalcohol hydrochloride fraction. [d] $c = 4$. [e] $c = 0.9$.

To obtain additional information concerning the N → O shift it was decided to investigate reactions in which migrating aroyl groups are involved. For this purpose a series of benzoyl and ortho-substituted benzoyl derivatives were prepared from the diastereomeric aminoalcohols and aroyl chlorides by the Schotten–Baumann reaction. These derivatives, along with analytical data and physical constants, are listed in Table I.

In one series of experiments, the several hydroxyamides were rearranged completely by refluxing with 5% hydrochloric acid. The aminoester salts so formed were rearranged back to hydroxyamides (a process which has not been observed to cause configurational changes[1]) by addition of alkali. Since some hydrolysis of ester salts occurs during the refluxing with acid to yield aromatic acid and parent aminoalcohol, the mixture was subjected to the separation described in the experimental part. The compositions of the hydroxyamide fractions were determined polarimetrically. The proportion of ephedrine and ψ-ephedrine in the basic fractions was determined by thermal analysis. The results of rearrangements conducted thus are summarized in Table II which also includes information on the order of size[10] of the ortho-substituents and dissociation constants[11] of the aromatic acids corresponding to the *o*-substituents.

Consideration of the results in the ephedrine series shows that the presence of an ortho-substituent on the migrating group results in a decided increase in the proportion of molecules rearranging with inversion. In addition, it is evident that among the ortho-derivatives there is no correlation between the electron displacement characteristics of the migrating groups (as measured by the K_{th} of the parent acids) and the per cent. of inversion. On the other hand, although there is a small spread (*ca.* 6%) between the maximum and minimum inversion produced, there is apparently a rough direct relationship between the size of the ortho-substituent and the extent of inversion. The effect of the ortho-substituent can be attributed to its selective steric influence on the elements of the carbonyl group[12] whereby the approach of hydroxyl oxygen to carbonyl carbon in the *R* mechanism is hindered to a much greater degree than is the approach of carbonyl oxygen to carbon one in the *I* mechanism.

From the data in Table II relating to ψ-ephedrine derivatives, one might conclude that the appearance of about 2.5% inversion in rearrangements of the CH_3, Cl and Br derivatives is a result of the proposed *I* mechanism. That the major part, if not all, of this figure is due to another type of reaction is indicated by the appearance of almost 2% inversion as a result of refluxing O-*o*-chlorobenzoyl-ψ-ephedrine hydrochloride with dilute acid for a period of time comparable to that required for rearrangement. How this inversion occurred is not obvious. It is possible that the considerably longer periods of time necessary for complete rearrangement of the CH_3, Cl and Br derivatives are due to their low solubilities or slow rates of solution in the heterogeneous system.

It is evident that the properties peculiar to the ψ-ephedrine configuration which promote rear-

(10) Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 362.

(11) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 149-152.

(12) Cohen and Schneider, THIS JOURNAL, **63**, 3382 (1941).

rangement with retention are considerably greater than the ortho-effect which tends to favor rearrangement according to an inversion mechanism.

The reaction velocity of the rearrangement of N-benzoyl-ψ-ephedrine at 30° was investigated by preparing a 95% ethanolic solution approximately 0.1 molar with respect to both hydroxyamide and hydrogen chloride, and following the progress of the reaction by measuring titrimetrically the consumption of acid after various intervals of time. By graphic means (Fig. 1) it was determined that rearrangement proceeds according to second order kinetics over the range studied (0–75%) with a velocity constant of *ca.* 8.2×10^{-1}. The velocity of

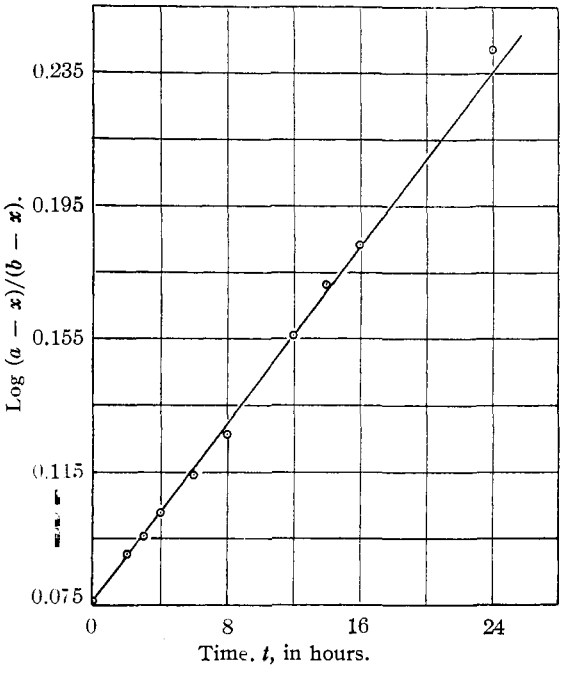


Fig. 1.—Graph showing second order reaction rate for rearrangement of N-benzoyl-(+)-ψ-ephedrine in hydrochloric acid–ethanol: *a* is initial concn. of hydrogen chloride, *b* is initial concn. of hydroxyamide, *x* is concn. of rearrangement product (all in moles per liter).

rearrangement of benzoylephedrine was followed in a similar manner. Although no attempt was made to carry out the rearrangement under controlled temperature conditions (room temperature *ca.* 30–35°) the data are suitable for a rough comparison with those afforded by the ψ-isomer at 30°. Figure 2 graphically illustrates the great difference in speeds of rearrangement of the diastereomers.[13] It was determined that rearrangement proceeds under these conditions with predominant retention of configuration (8–23% inversion).

(13) It is noted that Bruckner, Fodor, Kiss and Kovács, *J. Chem. Soc.*, 885 (1948), report that in the diastereomeric derivatives prepared by them the N → O migration of the acyl group is instantaneous in the nor-ψ-ephedrine compound and does not occur at all in the norephedrine derivative under the same conditions.

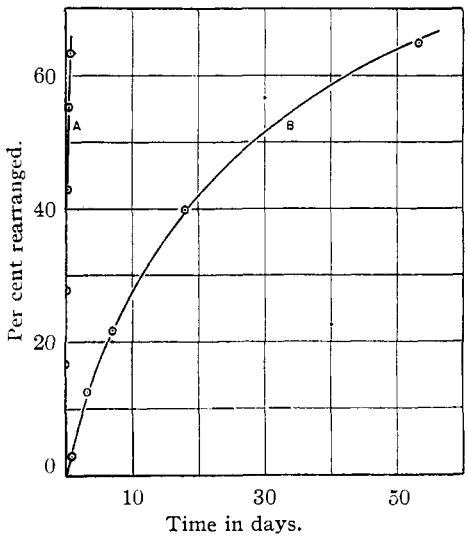


Fig. 2.—Comparison of rearrangement rates of diastereomers in 0.115 *N* ethanolic hydrochloric acid: A, benzoyl-ψ-ephedrine at 30°; B, benzoylephedrine at *ca.* 32°.

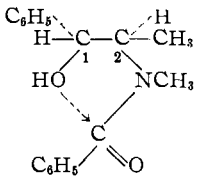
It is not a simple matter to explain the great[14] difference in the velocities of rearrangement of the diastereomers according to a retention mechanism. One would naturally expect the diastereomer having the more basic amide group to show the more rapid reaction rate; if, as has been reported,[15] ψ-ephedrine has about twice the base strength of ephedrine, and this ratio is retained in the amides, then benzoyl-ψ-ephedrine should rearrange at a greater rate than does its diastereomer.

This consideration is believed to be of secondary importance. The major factor responsible for the great difference in rates is attributed to differences in the spatial arrangements of the groups in the diastereomers.[16] Projection formula III, corresponding to structure A of the *R* mechanism, depicts a molecule of benzoyl-ψ-ephedrine at the instant the hydroxyl oxygen and carbonyl carbon atoms are closest to each other prior to actual migration. Formula IV illustrates the same situation in the diastereomer. The two embryonic ring systems are in the plane of the paper and the substituents on carbons 1 and 2 and not in the ring are above this plane where connected to solid lines and below the plane where joined to broken lines. It may be seen that a *trans* relationship exists in

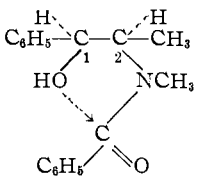
(14) The ratio is of the order of 70:1 if one compares the time required for 50% rearrangement.

(15) Abildgaard and Baggesgaard-Rasmussen, *Dansk. Tids. Farm.*, **4**, 30 (1930).

(16) Fodor, *et al.*,[9b] have assumed that for an N → O rearrangement to occur the hydroxyl and methylamido groups must have a *cis* relationship, and that as a result of restricted rotation about the bond between carbons 1 and 2 such a relationship exists in compounds having the ψ-ephedrine configuration, whereas a *trans* relationship of these two groups exists in substances having the configuration of ephedrine. Their conception of restricted rotation obviously is not related to observations on molecular models which correspond to the projection formulas of Leithe and of Freudenberg, *et al.*[3] See also Fodor and Kiss, *Nature*, **163**, 287 (1949).



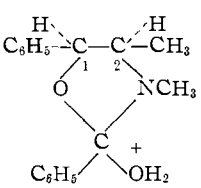
III



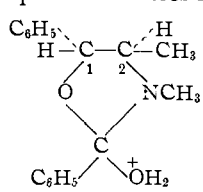
IV

the ψ-ephedrine derivative and a *cis* relationship in the diastereomer. Since a *trans* configuration should be the more equable arrangement of groups under these conditions the ψ-ephedrine configuration might be expected to augment the efforts of the hydroxyl oxygen to approach the carbon atom of the protonated amide group and thus facilitate rearrangement with retention, whereas in the ephedrine series the opposite situation would exist.

In the ψ-ephedrine series, the *R* mechanism would compete with an inversion mechanism in which, by virtue of the displacement occurring at carbon 1, the hydrogen atom and phenyl group must be forced into an orientation which establishes the *cis* relationship shown in formula V which corresponds to cyclic intermediate F in the representation of the *I* mechanism. The virtual absence of inversion in the ψ-ephedrine series may



V

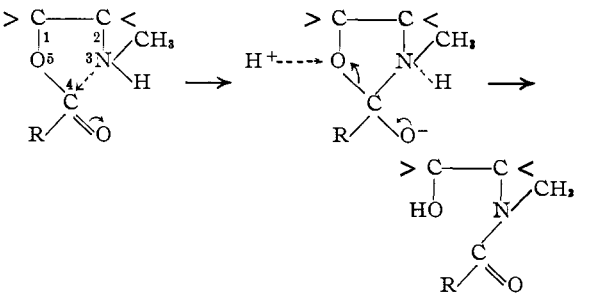


VI

be attributed to the circumstance that the energy required for this phase of the *I* mechanism is relatively high, and that the process must compete with a retention mechanism which is highly favored for reasons previously discussed.

In the ephedrine series, the inversion mechanism requires that a *trans* relationship be established in the intermediate represented by VI and corresponding to F. The displacement leading to this intermediate should be more readily achieved than that which would occur in the ψ-ephedrine series and lead to a *cis* configuration. In the ephedrine series the *I* process is competing with a retention mechanism which is not highly favored according to conclusions which have been presented. If, on this basis, it may be assumed that the two processes do not have widely differing over-all energy requirements, the observed ability of ephedrine derivatives to rearrange with either retention or inversion appears rational.

No additional study has been made in this Laboratory on the influence of various factors on the O → N shift, and no attempt will be made here to correlate the behavior of the numerous esters of aminoalcohols which have been described in the literature and which contain primary or secondary amino groups. This shift, which is not associated with inversion, could occur by the mechanism



The donation of a proton to atom 5 might take place from atom 3 of the same molecule or an adjacent rearranging molecule. In aqueous solution the donation might result from a solvent molecule. The fact that O-acetyl-ψ-ephedrine rearranges at a considerably greater speed than does its diastereomer[1] is attributed to the same factors which have been discussed in connection with the reverse migration.

Investigation of the N → O rearrangement is being continued.

Experimental

Melting points are corrected.

Sources of Aroyl Chlorides.—Benzoyl and *o*-chlorobenzoyl chlorides were obtained from Eastman Kodak Co. The five other halides were prepared from the corresponding ortho-substituted acids and thionyl chloride, and, with the exception of the nitro compound,[17] were purified by vacuum distillation.

o-Fluorobenzoic acid was prepared in 66% yield by substituting the stoichiometric amount of Eastman Kodak Co. *o*-fluorotoluene for *o*-chlorotoluene in the method of preparation of *o*-chlorobenzoic acid described by Clark and Taylor.[18] The *o*-nitrobenzoic acid[19] was Kahlbaum material, and the remainder of the acids were products of the Eastman Kodak Co.

Preparation of the Hydroxyamides.—The aminoalcohol (1.65 g., 10.0 millimoles) was dissolved in 10 cc. of chloroform and acylated by the Schotten–Baumann method with 4 cc. of 20% sodium hydroxide and a solution of 10.0–10.5 millimoles of aroyl halide in 4 cc. of chloroform. The products obtained on removing the solvent were triturated with petroleum ether and filtered off; yields of crude were practically quantitative; twice-recrystallized material averaged 82% of the theoretical. Chlorobenzoyl-ψ-ephedrine was recrystallized from ethylene dichloride. The nitrobenzoyl derivative of the same configuration was dissolved in hot pyridine and precipitated by adding propanol-2. Crude nitrobenzoylephedrine was purified best by dissolving in 10 cc. of hot trichloroethylene and adding 5 cc. of petroleum ether. The rest of the derivatives were first recrystallized by dissolving in hot 95% ethanol (10 cc. was usually used), slowly adding an equal volume of water, and finally chilling the mixture. The derivatives in this group, with the exception of methoxybenzoylephedrine, were given a second recrystallization in which benzene (10–35 cc.) and an equal volume of petroleum ether was used. Methoxybenzoylephedrine is but slightly soluble in benzene, and was therefore recrystallized a second time from ethanol–water.

Rearrangement of Hydroxyamides by Refluxing with Dilute Hydrochloric Acid (Table II).—A sample of the hydroxyamide (2.338–2.415 millimoles) was placed in a 50-cc. standard taper round-bottom flask containing a few

(17) Böetius and Römisch, *Ber.*, **68**, 1924 (1935).

(18) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 135.

(19) Kindly supplied by Mr. Theodore Perrine of the National Institute of Health.

small pieces of carborundum and 5 cc. of water. The mixture was heated under reflux until it gently boiled, then through the condenser 5 cc. of 10% hydrochloric acid (13.7 millimoles) was added from a pipet at such a speed that boiling was not interrupted.[20] The mixture was refluxed until all insoluble matter had disappeared. The time required varied with the hydroxyamide; those which required only a few minutes to form a homogeneous system were refluxed an additional five minutes to ensure complete reaction, whereas the more refractory compounds were refluxed from ten to twenty minutes after solution was complete. Occasionally the ester hydrochlorides crystallized out when rearrangement mixtures were allowed to stand overnight. The condenser and its tip were rinsed with a small amount of water, as was the neck of the flask, and the reaction mixture plus rinsings was made alkaline by adding 3.5 cc. of 20% sodium hydroxide. The heavy oil which precipitated was induced to solidify, and the solid masses were reduced to a coarse powder. The alkaline mixture was allowed to stand at least one hour to ensure that the O → N shift was complete, and was then quantitatively transferred to a separatory funnel by the use of water and U. S. P. chloroform. The system was acidified by the addition of 1.5 cc. of sulfuric acid (50% by weight) and immediately shaken. The separated chloroform layer was washed by shaking with 3 cc. of water in a second separator, and aromatic acid was extracted from the solvent by a subsequent shake-out with 10 cc. of 5% sodium hydroxide in a third funnel. The extract was then filtered through a pledget of cotton wool into a beaker, and the aqueous phases in the three funnels were extracted with an additional five 15- to 20-cc. portions of chloroform which were passed through the train of separators. The combined, filtered chloroform extracts were concentrated to a small volume, transferred to a tared 50-cc. beaker, and evaporated to dryness on the steam-bath in a current of air. Addition of a small quantity of ether to the hydroxyamide residue facilitated the crystallization of any amorphous areas present, and, after removal of this solvent, the vessel was heated one-half hour at 110°, cooled in a desiccator, and weighed. The difference between the weights of sample and recovered hydroxyamide represented the amount of material hydrolyzed. The melting point and specific rotation of the residue were determined.

The aminoalcohol fraction was isolated as the hydrochloride from the aqueous phases in the first and second funnels by a method described elsewhere.[21] After purification by treatment with small amounts of ethylene dichloride–ether, the melting range of the mixture of salts was determined, and the composition was estimated by referring to a temperature–composition diagram. As may be seen in Table II, it was necessary to apply but a slight correction to the inversion found in the hydroxyamide fraction in order to obtain the value for total inversion.

It was not practicable to completely rearrange N-*o*-nitrobenzoyl-ψ-ephedrine under conditions similar to those used on the other compounds probably because of its solubility characteristics. A 370-mg. (1.18 millimoles) sample was refluxed for six hours with about 20 cc. of 5% hydrochloric acid. The unrearranged material was filtered off, and the filtrate was worked up as in the other rearrangements. A hydroxyamide fraction of 43 mg., corresponding to 12% of the sample, was obtained. The melting point (204–205.5°) indicated the presence of a small amount of inverted material.

Originally it was planned to evaluate the stereochemical results of these rearrangements by the procedure used on the acetyl compounds,[1] *i. e.*, after completion of the N → O shift, to effect complete acid hydrolysis of the products by continued refluxing, and determine the composition of the aminoalcohol mixture so obtained. Acid hydrolysis of the mixture of benzoyl ester salts was found to proceed very slowly, however. It was practicable to convert the mixed benzoyl ester salts to hydroxyamides, quantitatively hydrolyze the latter in a 10% solution of sodium hydroxide in 50% ethanol, extract out the mixed aminoalcohols, and ascertain the proportion of inverted material in the mixture of hydrochlorides ultimately obtained. The total inversion figure corresponding to benzoylephedrine in Table II was thus determined; the mixture of hydrochlorides of ephedrine and ψ-ephedrine amounted to 99.1%. Efforts to use alkaline hydrolysis on the *o*-chlorobenzoyl derivatives showed that the substances are resistant to cleavage under these conditions, and no attempts were made to apply the procedure to other ortho-compounds.

Kinetics of Rearrangement of N-Benzoyl-ψ-ephedrine (Fig. 1).—In a 100-cc. volumetric flask was placed 2.598 g. (0.00965 mole) of N-benzoyl-(+)-ψ-ephedrine and 47 cc. of 95% ethanol. After the solid had dissolved, the flask was placed in a constant temperature bath maintained at 29.9 ± 0.2°. After equilibration, 50 cc. of a solution of concentrated hydrochloric acid in 95% ethanol (0.2301 *N* at 30° with respect to hydrogen chloride) was quickly transferred to the flask from another vessel in the bath by means of a pipet; timing of the reaction was started at the beginning of the addition. The mixture was brought up to volume by adding the necessary small amount of ethanol, and was made homogeneous by thorough agitation. As the reaction progressed, 10-cc. aliquots of the solution were pipetted out and transferred to a beaker containing 100 cc. of water which was agitated by a motor-driven stirrer. The time of beginning of addition of the aliquot to the water was taken as the end of a given reaction period. The unconsumed acid in the aqueous dilution was determined by adding standardized 0.1 *N* sodium hydroxide, dropwise and with vigorous stirring, to a methyl red end-point. From these data the concentration of rearrangement product, x, present after each reaction period was calculated. From the figures so obtained for x, and the initial concentration of acid (a, 0.1151 *M*) and of hydroxyamide (b, 0.0965 *M*), the values of the various expressions, $\log a - x/b - x$, were obtained and plotted against the appropriate reaction periods, t (Fig. 1). The best straight line based on the plot corresponded to the equation, $\log (a - x)/(b - x) = 0.006593\ t + 0.0766$, and an average reaction velocity constant of 8.16×10^{-1}. The volume of 0.1 *N* acid theoretically consumed after each reaction period was calculated by use of the equation and may be compared with the experimentally determined consumption in the following sequence in which the first figure is the reaction period in hours and the parenthetical figure is the calculated consumption of acid in cc.: 2, 1.62 (1.55); 3, 2.13 (2.16); 4, 2.68 (2.70); 6, 3.49 (3.58); 8, 4.14 (4.29); 12, 5.34 (5.34); 14, 5.81 (5.74); 16, 6.11 (6.08); 24, 7.16 (7.06). All of the deviations, with the possible exception of that corresponding to the eight-hour period (0.15 cc.), are considered to be within the experimental error of the titrations. The sum of the deviations in the nine determinations equals −0.02 cc.

(20) These are the reaction conditions referred to in footnote (2).

(21) Welsh, *J. Assoc. Official Agric. Chem.*, **30**, 467 (1947); **31**, 528 (1948).

Velocity of Rearrangement of N-Benzoylephedrine.—The progress of the rearrangement of N-benzoyl-(−)-ephedrine was experimentally followed as described above except as regards control of temperature. Facilities were not available for maintaining a regulated temperature over extended periods of time, and the reaction was allowed to proceed at the prevailing temperature of summer heat (within the approximate range of 30–35° and an average of *ca.* 32°). The consumption of acid was calculated in terms of percentage of rearrangement and the results are plotted against time in curve B, Fig. 2. Progress of the rearrangement of N-benzoyl-(+)-ψ-ephedrine is similarly plotted in curve A, Fig. 2.

A 10-cc. aliquot, representing a reaction period of fifty-three and one-third days, was used to determine the stereochemical course of rearrangement of the ephedrine derivative. Titration showed that 168 mg. (64.8%) had rearranged. The titrated solution was taken to dryness at room temperature and dried in a desiccator. The bulk of the residue was transferred to a test-tube, and the remainder was removed by the use of water and a rubber policeman. The rinsings, totaling about 15 cc., were added to the dry material, and the mixture was allowed to stand, with frequent stirring, for one-half hour. It was then filtered, and the undissolved hydroxyamide was washed with an additional 7–8 cc. of water. This fraction of unrearranged material weighed 66 mg., or 25.4% of the sample. The filtrate and washings were acidified with a few drops of hydrochloric acid, and the dissolved unrearranged hydroxyamide was extracted with small portions of ethylene dichloride. The residue of unrearranged benzoylephedrine obtained from the filtered extracts weighed 32.1 mg. (12.3% of the sample). The acidic solution containing aminoester salts was basified with 20% sodium hydroxide (to bring about the O → N shift), allowed to stand one hour, acidified with 50% sulfuric acid, and extracted with chloroform. Each extract was washed with alkali before filtering. The residue of hydroxyamides, representing material which had originally undergone the N → O shift, weighed 143.4 mg., equivalent to 55.2% of the sample or 85.2% of the weight calculated from the titration. It showed $[\alpha]^{20}D$ −31.1° (U. S. P. chloroform, c = 1.2, l = 2) which corresponds to a mixture of diastereomers containing 9.3% of the ψ-ephedrine derivative. The difference between the rearranged material isolated and that calculated from the titration is 24.9 mg., and represents substance lost in one way or another during the various operations. If it represents uninverted hydroxyamide, the minimum inversion produced corresponds to 8% of the rearranged material. If it represents inverted material, the maximum inversion produced is 23%.

O-*o*-Chlorobenzoyl-(+)-ψ-ephedrine Hydrochloride.—This substance was prepared by refluxing *o*-chlorobenzoyl-(−)-ephedrine with 5% hydrochloric acid. The crude product from the chilled reaction mixture was recrystallized from ethyl acetate; the yield of rectangular plates was 83%. The substance is a monohydrate: m. p. (hot stage) 80–85° followed by resolidification and remelting at 131–132°; $[\alpha]^{20}D$ +57.1° (water, c = 3, l = 2).

Anal. Calcd. for $C_{17}H_{18}ClNO_2 \cdot HCl \cdot H_2O$: Cl (ionic), 9.90. Found: Cl (ionic), 9.79.

On undergoing the O → N shift the salt quantitatively yielded the related hydroxyamide, m. p. 162–163°.

A sample was refluxed for six hours with 4.5% hydrochloric acid. Processing the mixture gave a hydroxyamide fraction of 76.9% of the sample weight; $[\alpha]^{20}D$ +101.0° (U. S. P. chloroform, c = 3, l = 2) corresponding to 1.3% inversion in the fraction. The fraction of aminoalcohol hydrochlorides, m. p. 178–182°, was equivalent to 21.3% of the sample; $[\alpha]^{20}D$ + 57.8° (water, c = 0.9, l = 2) representing 4.1% inversion in the fraction. The maximum inversion effected by the hot acid on the ester salt therefore totaled 1.9%.

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Summary

1. Reaction mechanisms have been proposed to account for the inversion and retention of configuration observed during acyl migrations between nitrogen and oxygen in derivatives of ephedrine and ψ-ephedrine.

2. A series of benzoyl and *o*-substituted benzoyl derivatives of these aminoalcohols has been prepared and subjected to the N → O rearrangement under different conditions. The stereochemical results of the rearrangements have been discussed in terms of the properties of the migrating radicals and the proposed mechanisms.

3. The consistent retention of configuration observed in rearrangements in the ψ-ephedrine series and the ability of ephedrine derivatives to rearrange with either retention or inversion have been interpreted in the light of the different space relationships existing in the diastereomers and on the basis of the proposed mechanisms.

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