analyzed by GLC, the peak area ratios of product to standard being converted to molar ratios by detector-response calibration charts constructed by using authentic materials. The qualitative analysis of several reaction mixtures indicated the absence of 1,9-octalin, the *trans*-1-decalols, and the *trans*-1-decalyl acetates. The product distribution was essentially independent of the concentration of the amine within the limits 0.030–0.17 M for amine and 0.15 to 1.15 M for nitrite; the same molar ratio of nitrite to amine was always used. All experiments were run in duplicate.

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Registry No. 1, 936-35-6; 2, 23017-71-2; *trans,cis*-2-decalol, 2529-06-8; *trans,trans*-2-decalol, 5779-35-1; *trans,cis*-2-decalyl acetate, 66964-88-3; *trans,trans*-2-decalyl acetate, 66964-89-4; *trans*-2-decalone, 16021-08-2; *trans,cis*-2-decalol-2-*d*, 73688-54-7; *trans,cis*-2-decalyl nitrite, 73688-55-8; *trans,trans*-2-decalyl nitrite, 73688-56-9; nitrous acid, 7782-77-6.

Deamination of Axial and Equatorial *trans*-2-Decalylamines by the *N*-Nitrosoamide Method in Various Solvents. Remarkable Stereochemistry and Efficiency of Capture of a Cationic Intermediate by Acetonitrile[1]

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Product distributions have been determined for thermal decomposition of the axial ethyl *N*-(*trans,trans*-2-decalyl)-*N*-nitrosocarbamate (**3**) and the equatorial epimer (**4**) in cyclohexane, acetic acid, acetonitrile, and sulfolane. In cyclohexane, the axial substrate gives mainly elimination and the substitution product is predominantly the ester of retained configuration; the equatorial epimer gives almost equal quantities of elimination and substitution product, the latter consisting of 1.7 times more retained than inverted ester. In the other three solvents, the retention–inversion ratios for the two substrates are nearly interchanged due to an increase in the ratio of equatorial to axial product which occurs in these more hydroxylic or polar solvents. It is believed that the preference for equatorial product formation in these solvents is due to (1) unpairing of an inverted ion pair or its precursor with attack of carboxylic acid or acetonitrile on the relatively free carbocation mainly to give the more stable equatorial substitution product and (2) in the case of the axial isomer, increased rearrangement to give largely equatorial 2-decalyl product. The results in acetic acid and acetonitrile are rather similar except that acetonitrile is more effective at scavenging the cationic intermediate (via a nitrilium ion which is converted to an imide), and there is evidence for a significant degree of cation capture from the frontside, probably by a solvent molecule which is closely associated with the diazo function. The decrease in olefin yield which occurs in the equatorial but not in the axial case in proceeding from cyclohexane or sulfolane to acetic acid or acetonitrile is believed to be due to decreased removal of α- and cis β-protons by the counterion due to the decreased basicity of the latter and/or its greater distance from these protons in the ion pair intermediate; previous work indicates that in the axial case this decrease in olefin production is compensated for by the removal of a trans β-proton by these somewhat basic solvents.

Our approach to the investigation of the mechanistic details of deaminations by nitrous acid diazotization and related methods[3] has been the study of the product distributions upon deamination of the conformationally homogeneous trans-fused 2-decalylamines in systematically varied solvent systems[4] or of regiospecifically and stereospecifically α- and β-deuterated derivatives in invariant solvents.[5,6]

We were particularly interested in the well-known generalizations about the differences in product array between axial and equatorial amines. Early generalizations[9] held that axial amines give nearly all elimination and the small yield of substitution product is nearly all inverted while equatorial amines give nearly all substitution product of retained configuration. More recently, it has been held that the substitution product in the case of the axial amine is approximately equally inverted and retained.[10,11] This contrasts sharply with the solvolysis of cyclohexyl sulfonate esters, both axial and equatorial epimers of which give a large yield of olefin and a small yield of largely inverted substitution product.[12] In contrast to such generalizations, it is shown in the preceding paper[4a] that upon nitrous acid deamination in nonhydroxylic solvents containing small amounts of acetic acid, axial and equatorial amines actually behave in a remarkably similar manner with regard to the distribution of substitution products; they give 59–65% of an approximately equimolar mixture of retained alcohols and acetates and 35–41% of inverted product which is very predominantly acetate. As the acetic acid concentration

(1) Taken in part from the Ph.D. thesis of J. Solash, University of Pittsburgh, 1972.

(2) Andrew Mellon Predoctoral Fellow.

(3) For leading general references to deamination in nonaromatic systems, see the preceding paper.[4a]

(4) (a) T. Cohen, A. D. Botelho, and E. J. Jankowski, *J. Org. Chem.*, preceding paper in this issue; (b) T. Cohen and E. Jankowski, *J. Am. Chem. Soc.*, **86**, 4217 (1964).

(5) (a) T. Cohen and A. R. Daniewski, *J. Am. Chem. Soc.*, **91**, 533 (1969); (b) T. Cohen, A. R. Daniewski, G. M. Deeb, and C. K. Shaw, *ibid.*, **94**, 1786 (1972).

(6) The *trans*-decalyl system was chosen in preference to the 4-*tert*-butylcyclohexyl system[7] largely because of the ease and certainty of labeling in specific fashion at one of the two β-positions.[5] An additional consideration was that meaningful comparison of the results in the related steroid system would be possible.

(7) The 4-*tert*-butylcyclohexyl system has been studied by others. See ref 8 of this paper and ref 8b, e, and f of the preceding paper.[4a]

(8) H. Maskill and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2*, 1462 (1976).

(9) J. A. Mills, *J. Chem. Soc.*, 260 (1953); A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956); see also A. K. Bose, *Experientia*, **9**, 256 (1953).

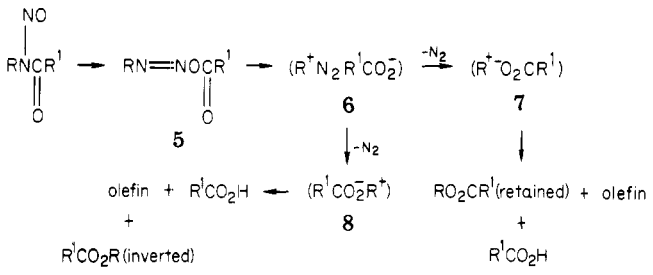
(10) See footnotes 7 and 8 of the preceding paper.[4a]

(11) F. W. Bachelor and E. H. White, *Can. J. Chem.*, **50**, 364 (1972); E. H. White and F. W. Bachelor, *Tetrahedron Lett.*, 77 (1965).

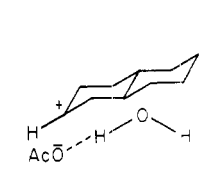
(12) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. J. Whiting, *J. Chem. Soc. B*, 355 (1968), and references cited therein.

0022-3263/80/1945-2847$01.00/0

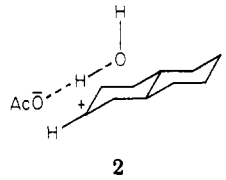
Scheme I



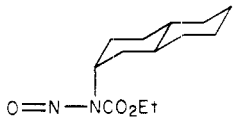
increases, there is little change in the distribution of substitution products from the axial amine, but those from the equatorial amine contain less inverted and more retained acetate.[4a] By the time the solvent is pure acetic acid, the recent generalizations with regard to substitution product become true; in solutions rich in water, the earlier generalization becomes largely valid. This behavior was attributed to the formation in the rather nonhydroxylic solvent of specifically solvated ion pairs[13] (1 from the axial amine and 2 from the equatorial amine) which can collapse



1



2



3

to retained alcohol and acetate or undergo intramolecular inversion to two new ion pairs which collapse mainly to inverted acetate. It is believed that as the acetic acid concentration increases the inverted ion pair (or its precursor) from the equatorial amine, and possibly that from the axial amine as well, tends to become unpaired and the resulting symmetrically solvated cations yield mainly equatorial solvolysis product.[4a]

Another important finding[4] is that nitrous acid destroys much of the olefin and alcohol products, although the latter can be regenerated by nitrogen ebullition. The loss of olefin prompted us[5] to supplement our work on the stereochemistry of the elimination reaction using nitrous acid deamination with another utilizing the *N*-nitrosoamide method of deamination[14] which does not have this disadvantage.

The mechanism of *N*-nitrosoamide decompositions, as elucidated by the elegant studies of White,[13,16] is abbreviated in Scheme I. The nitrogen-separated ion pairs **6** (probably an array of related structures[16a]) can, by expulsion of nitrogen, form either a retained ion pair (**7**), which yields retained ester and elimination products, or an ion pair (**8**) in which the cation, because of a molecular rotation, has become stereochemically inverted with respect to the counterion (intramolecular inversion[13]) and which results in inverted ester and elimination product. If there is present in the solvent a carboxylic acid (R^2CO_2H) which is acidic enough to protonate the "internal" counterion, $R^1CO_2^-$, then the conjugate base of the "external" acid can replace the internal ion (frontside exchange) and this can lead to solvolysis product of retained configuration.

$$RN_2O_2CR^1 + R^2CO_2H \rightarrow R^1CO_2H + (R^+\ {}^-O_2CR^2) \rightarrow RO_2CR^2$$

Our study[5] revealed that the axial *N*-nitrosocarbamate **3** formed olefin predominantly by loss of a cis proton while the equatorial epimer (**4**) gave a great deal of olefin (now calculated to be 38% of the olefin produced[15]) by an α-elimination mechanism[5b] and about 84% of the remainder via cis β-elimination; it is believed that it is largely the counterion, in this case ethyl carbonate, formed upon rearrangement of **3** and **4**,[13,14] which removes the β-protons. It was also found[5b] that with both **3** and **4** substitution of a cis 3-proton by a deuteron caused a decrease in the yield of 2-octalin, an increase in that of retained ester (in this case ethyl decalyl carbonate), and an unchanged yield of inverted ester; the interpretation was that the anion of the retained ion pair has a choice of removing a cis proton or forming a retained but not an inverted ester, which arises instead from a separate, noncompetitive, intramolecular inversion. The results also implied an interesting phenomenon, namely, that intramolecularly inverted ion pairs (or their precursors) behaved differently (giving far less elimination) than retained ion pairs derived from the opposite epimer.

We now present further results of decomposition of the epimeric *N*-nitrosoamides **3** and **4**; the product distributions are compared for decomposition in cyclohexane, acetic acid, acetonitrile, and tetramethylene sulfone (sulfolane). In view of the close similarity of the results of deaminations by nitrous acid diazotization and *N*-nitrosoamide decompositions,[13,17] this work was intended to test the conclusions registered in the preceding paper[4a] and, in general, to throw more light on the role of solvent in these deaminations.

One curious finding in the nitrous acid deamination work is that although collapse of ion pairs **1** and **2** gives mixtures of alcohols and acetates, in approximately equal quantities, the corresponding inverted ion pairs yield predominantly external substitution product (acetate) and very little "internal" product (alcohol). If the acetic acid were to protonate or hydrogen bond with a diazotic ester (**5**), then it seems likely that a specifically solvated ion pair (**9** or **10**) analogous to **1** and **2** would be formed. Would

$$RN{=}\underset{5}{NOCOR^1} + R^2CO_2H \rightarrow$$

$$R^+\ R^1CO_2H\cdots{}^-O_2CR^2 \text{ or } R^+\ R^2CO_2H\cdots{}^-O_2CR^1$$

9 **10**

this behave like **1** and **2** in that the ratio of internal to external nucleophilic attack in the inverted product differs greatly from that in the retained product?

(13) E. H. White and D. J. Woodcock in "Chemistry of the Amino Group", S. Patai, Ed., Wiley, New York, 1968, p 441.

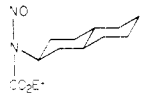
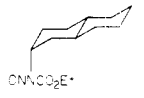
(14) For reviews of the *N*-nitrosoamide method of deamination see ref 13 and the following: R. A. Moss, *Acc. Chem. Res.*, **7**, 421 (1974); T. J. Lobl, *J. Chem. Educ.*, **49**, 730 (1972).

(15) This number is calculated from the change in the distribution of products when the α-proton of **4** is replaced by a deuteron, assuming no secondary isotope effect; that is to say that the ratio of β-elimination to axial and equatorial substitution would be identical in the unlabeled and α-deuterio cases.

(16) (a) E. H. White and K. W. Field, *J. Am. Chem. Soc.*, **97**, 2148 (1975); (b) W. J. Le Noble, E. H. White, and P. M. Dzadzic, *ibid.*, **98**, 4020 (1976).

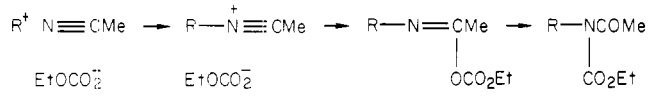
(17) R. Huisgen and C. Rüchardt, *Justus Liebigs Ann. Chem.*, **601**, 1, 21 (1956).

Table I. Decomposition of Ethyl *N*-Nitroso-*N*-(*trans*-2-decalyl)carbamates in Cyclohexane, Acetic Acid, Acetonitrile, and Sulfolane[a]

substrate	solvent[c]	product distribution, %[b] olefin	axial carbonate	axial acetate or imide[d]	equatorial carbonate	equatorial acetate or imide[d]
 4	A	46	20 (37)		34 (63)	
	B	14	5.0 (6)	5.5 (6)	37 (43)	38 (45)
	C	13	5.5 (6)	5.0 (6)	23 (27)	53 (61)
	D	43	5.8 (10)		51 (90)	
 3	A	78	19 (85)		3.4 (15)	
	B	78	8.2 (38)	5.1 (23)	3.2 (15)	5.3 (24)
	C	70	6.0 (20)	12 (39)	2.6 (9)	10 (33)
	D	85	9.9 (65)		5.4 (35)	

[a] The heating bath was held at 85 °C. [b] Percent of total product. The numbers in parentheses are percentages of substitution product for ease of comparison with results in ref 4a. [c] A = cyclohexane, B = acetic acid, C = acetonitrile, D = sulfolane. [d] Acetate ester for experiments in acetic acid; imides **11**, for experiments in acetonitrile.

There is always some ambiguity concerning the genesis of products in which a hydroxylic solvent has displaced the nitrogen because of frontside exchange or, at least, hydrogen bonding of the solvent to the anionic component of an ion pair. The studies in acetonitrile were intended to elucidate the role of nucleophilic solvent attack uncomplicated by such effects.[18,19] Acetonitrile attacks cations to form nitrilium ions (the Ritter reaction).[20] We[21] and others[18,22] have successfully demonstrated the existence of organic cations in certain reactions by scavenging with nitriles. It is clear from previous work[21] that successful cation capture in the present case would result in the formation of an imide (**11**, R = *trans*-2-decalyl). In



11

the experiments in acetonitrile, the yields of axial and equatorial imides of this structure were determined in addition to those of the epimeric *trans*-2-decalyl ethyl carbonates.

In proceeding from cyclohexane (ϵ = 2) to acetonitrile (ϵ = 38), not only has the solvent become a cation scavenger but also the medium has become far more polar. Thus, the decompositions were also carried out in sulfolane (ϵ = 44) to control for a polarity increase.

Results and Discussion

Before discussing the results of the *N*-nitrosoamide decompositions which are displayed in Table I, we shall deal with the questions of (1) diazoalkane intermediates and (2) rearrangement. (1) The following isotope effect and labeling data with respect to decomposition of the *N*-nitrosocarbamates **3** and **4** in cyclohexane have been reported;[5b] substitution of a deuterium atom at the carbinyl carbon atom of the equatorial isomer (**4**) caused a significant decrease in olefin yield and only a minor change in the ratio of axial to equatorial ethyl decalyl carbonate esters; furthermore, whereas the olefins had lost substantial deuterium, the esters had lost none. A likely explanation of these results is that the counterion removes an α-proton from some species to produce a diazoalkane which loses nitrogen with a 1,2 hydrogen shift to give olefin at a far greater rate than it reacts with ethyl hydrogen carbonate to give ester.[23] Thus, in cyclohexane, the distribution of substitution products is independent of the degree of α-elimination; in the more polar solvents, any contribution from a diazoalkane mechanism would be diminished.[24] Replacement of the 2-proton with deuterium in the axial isomer (**3**) has no significant effect on the olefin yield, only a very small percentage of the olefin product has lost deuterium, and the ester products have lost none; thus, the intermediacy of diazoalkanes is even less important in the axial case. (2) While rearrangement via hydride transfer from the 1-position is, in principle, detectable in the 2-decalyl system by determination of 1-decalyl substitution products and of 1,9-octalin, rearrangement from the 3-position is not detectable because it results in the 2-decalyl cation. From the work of Maskill and Whiting[8] on decomposition of nitrosoamides of *N*-nitroso-*N*-*cis*- and -*trans*-4-*tert*-butylcyclohexyl amides in carboxylic acid solvents, it is clear that such rearrangement is of very minor consequence in the case of equatorial isomers and, indeed, we detected only trace quantities of unidentified products that could be the result of rearrangement. However, their work makes clear that rearrangement is a more serious problem with respect to the axial epimer; decomposition of the axial *N*-nitrosoacetamide in butyric acid gave acetates which were 31% rearranged and butyrates which were 38% rearranged. With the axial isomer **3**, we have reported[5b] that 12% of the olefin is rearranged and in more polar solvents rearrangement should be still more serious.[13,24a] Thus, we have some restrictions with regard to interpretations of the results in the axial but not in the equatorial cases. However, as will be seen, the degree of rearrangement in the axial case in acetic acid can be approximated by the results of the study by Maskill and Whiting and an interpretation in broad terms of our results in this case is possible.

(18) After this work was completed, White and Field[16a] reported that acetonitrile was quite effective as a scavenger of cations in a nonstereochemical study of the decomposition of an *N*-nitrocarbamate; 32% of the cations were scavenged.

(19) In agreement with a literature report, we found that scavenging the intermediates with aromatic compounds such as anisole was only marginally successful; L. Friedman and A. T. Jurewicz, *J. Am. Chem. Soc.*, **91**, 1808 (1969).

(20) J. J. Ritter and P. O. Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948); H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.*, **89**, 209 (1956); R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

(21) T. Cohen and G. L. Deets, *J. Am. Chem. Soc.*, **94**, 932 (1972); *ibid.*, **89**, 3939 (1967); T. Cohen and G. L. Deets, *J. Org. Chem.*, **37**, 55 (1972).

(22) M. A. Ratcliff, Jr., and J. K. Kochi, *J. Org. Chem.*, **36**, 3112 (1971); J. K. Kochi and A. Bemis, *J. Am. Chem. Soc.*, **90**, 4038 (1968).

(23) However, we can not rule out an alternative mechanism in which the counterion removes the proton from the decalyl cation *after* nitrogen loss: R. A. Olofson, S. W. Walinsky, J. P. Marino, and J. L. Jernow, *J. Am. Chem. Soc.*, **90**, 6554 (1968). This mechanism would not invalidate the argument that we are making.

(24) (a) L. Friedman in "Carbonium Ions", Vol. 2, G. A. Olah and P. R. Schleyer, Eds., Wiley-Interscience, New York, 1970, p 655; (b) J. T. Keating and P. S. Skell, *ibid.*, p 573.

Decomposition of 3 and 4 in various solvents provided the products shown in Table I in overall yields exceeding 93%. No unreacted carbamates were found among the decomposition products.

The product distribution for decomposition of 3 and 4 in cyclohexane does not correspond at all to the generalizations for nitrous acid deamination. Although the axial isomer (3) does indeed produce mainly olefin, almost one-half of the product from the equatorial isomer is also olefin. The deviation from the generalizations with regard to the stereochemistry of the substitution products is far greater, the axial epimer giving overwhelmingly retained ester (ratio of retention/inversion = 5.7) and the equatorial epimer giving mainly retained but a very significant quantity of the inverted, less stable, axial ester (ratio = 1.7). Our product distributions for 3 and 4 are very close to those reported by Bachelor and White for *N*-nitrosoamide decompositions of the epimeric 3-cholestanylamines in hydrocarbon solvents.[11]

It is highly unlikely that rearrangement is responsible for the high retention/inversion ratio found for the ester from the axial substrate since rearranged internal ester from an axial *N*-nitrosoacetamide decomposition in butyric acid is overwhelmingly equatorial.[8] Most of the inverted ester is undoubtedly formed in the process of intramolecular inversion.[11,13] The importance of this process is presumably a function of the juxtaposition of the two ions and the nitrogen molecule in intermediate ion pairs of retained configuration. A reasonable explanation for the greater extent of intramolecular inversion in the equatorial case is that the ethyl carbonate counterion, just after fragmentation of the diazotic ester (5), should be positioned closer to the plane of the carbocation than in the axial case. This assumes a flattening of the two carbon atoms adjacent to the sp^2 carbon atom as one finds in the case of cyclohexanone.[25] Thus, less rotation of the cation is required in the equatorial than in the axial case to bring the backside of the cation within easy attacking range of the counterion.

It is of considerable interest that the situation is quite the reverse when the decompositions are conducted in acetic acid; the retention/inversion ratios for total substitution product from the axial and equatorial substrates, respectively, become 1.6 and 7.1. Furthermore, in proceeding from cyclohexane to acetic acid, the olefin yield from equatorial substrate decreases sharply whereas that from axial substrate is unchanged. Thus, as found for nitrous acid deamination,[4a] the well-known and oft-quoted generalizations are quite invalid in relatively aprotic[24a] and nonpolar solvents and become valid in carboxylic acid solvents. In general, in proceeding from an aprotic solvent to the latter type of solvent, the ratio of equatorial/axial substitution product increases sharply for either substrate.

In the case of the axial substrate, the approximate contributions to this change from various sources can be ascertained by an analysis of the data of Maskill and Whiting[8] for decomposition of *N*-nitroso-*N*-4-*tert*-butylcyclohexylacetamide in butyric acid, in which case the rearranged and unrearranged substitution products could be distinguished. The unrearranged internal substitution product (acetate) is even more highly retained (retention/inversion = 12) than in our axial case in cyclohexane. However, the 20% of substitution product which is rearranged internal ester (acetate) is almost all equatorial; the 20% of substitution product which is solvent derived (butyrates) is approximately equally divided between axial and equatorial product whether one includes only unrearranged product or one combines rearranged with unrearranged butyrate esters. Thus, we can be fairly confident that in our axial case the decrease in the extent of retention in the internal product (ethyl carbonate ester) in changing from cyclohexane to acetic acid is due largely to rearrangement, which is expected to occur to a greater extent in the more polar solvent,[13,24a] and, as can be seen from Table I, the external products are equally divided between axial and equatorial esters as in the results of Maskill and Whiting.[8]

From the data in Table I, we can conclude that in the case of the equatorial substrate (4) the increase in equatorial/axial ratio in proceeding from cyclohexane to acetic acid is due to a sharp decrease in the yield of inverted internal ester (axial carbonate) combined with the production of external ester (acetate) which is very predominantly equatorial.

These results can be fully rationalized in the same way as those for the changes which occur in nitrous acid deamination in changing from relatively aprotic solvents to acetic acid. A large proportion of the process of intramolecular inversion, which occurs in the aprotic and nonpolar solvents, is not consummated in the carboxylic acid solvent; some intermediate(s) which would have given intramolecularly inverted products becomes (become) unpaired and the resulting "symmetrically solvated" cation collapses to give mainly equatorial products which reflect the solvent composition. Whereas this phenomenon is easily seen in the result of the equatorial substrate, it is partially obscured by rearrangement in the axial case. In the equatorial case, when the solvent changes from cyclohexane to acetic acid, the percentage of equatorial carbonate in the ester products decreases from 63% to 43%. According to current theory[13] this should be due largely to frontside exchange, which also yields a portion of the equatorial acetate; at the same time the percentage of axial carbonate in the ester products decreases far more dramatically, from 37% to 6%, most of the remainder ending up, it appears, as equatorial acetate. Making the same solvent change in the axial case causes a more pronounced decrease in the percentage of retained carbonate in the ester product than occurred in the equatorial case, but this decrease is due not only to frontside exchange but to rearrangement which produces equatorial products. Moreover, in the axial, unlike the equatorial, case the inverted (equatorial) carbonate remains a constant percentage of the ester product; the decrease due to ion unpairing and leading to equatorial acetate via acetolysis is compensated for by new equatorial carbonate generated by increased rearrangement in the hydroxylic solvent.

The answer to one of the questions we sought is evident in the product distribution from decomposition of the equatorial *N*-nitrosocarbamate in acetic acid. The ratio of internal (carbonate) to external (acetate) esters is essentially identical in the retained and inverted substitution products.[26] This is approximately as expected and quite different from the results in nitrous acid deamination.[4a] Thus, there is evidently something special about water in the sense that it is very inefficient in its behavior as a nucleophile during the process of intramolecular inversion; this is discussed in the preceding paper.[4a]

A result that at first glance is quite surprising is the sharp decrease in olefin yield from the equatorial substrates in proceeding from cyclohexane to acetic acid as

(25) J. B. Lambert, *J. Am. Chem. Soc.*, **89**, 1836 (1967); T. P. Forrest, *ibid.*, **97**, 2628 (1975); W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961).

(26) The nearly exact correspondence is, of course, fortuitous.

solvent and the absence of such an effect in the case of the axial isomer. However, a strong clue as to the explanation is provided by our previous discovery[5a] that whereas the β-elimination, which accompanies both decomposition of **3** and **4** in cyclohexane and nitrous acid deamination of the corresponding equatorial amine in acetic acid, is very predominantly cis in nature, that which accompanies nitrous acid deamination of the axial amine in acetic acid is 39–44% trans. Indeed, the present results would be approximately predicted by our explanation of this data.[5a] In acetic acid, as compared to cyclohexane, there is a reduced tendency for the counterion to remove the cis β-proton because hydrogen bonding with the solvent causes decreased basicity of this counterion. However, in the axial case a trans elimination becomes favorable with an axial proton being removed by the solvent either in E2 fashion[27] or, more likely, from some type of retained ion pair.[13] Applied to the present case, the extent of "internal" elimination is decreased sharply in going to acetic acid, but an intermediate derived from the axial substrate is arranged in a stereoelectronically favorable manner for solvent-induced trans elimination to occur and the latter compensates for the decrease in cis elimination by the counterion.

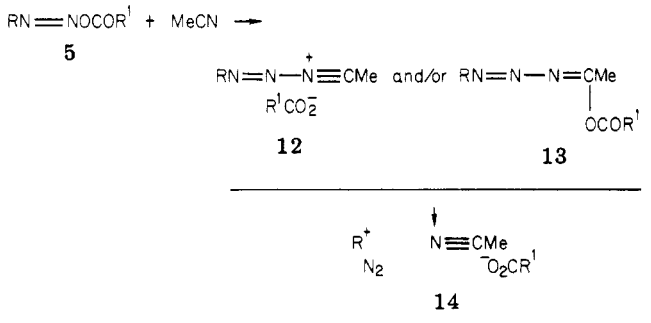
The results of the decomposition of the equatorial *N*-nitrosocarbamate (**4**) in acetonitrile indicate that this solvent is about twice as efficient at capturing the cation as is the counter anion and it is also more efficient than acetic acid. The high ratio (10) of equatorial to axial imide produced precludes substantial solvent attack upon the backside of a stereochemically retained intermediate. The source of the high yield of equatorial imide is discussed below.

In the case of the axial epimer (**3**), acetonitrile is also more effective at capturing the intermediate than either the internal counterion, ethyl carbonate, or acetic acid when used as solvent. Furthermore, the somewhat higher yield of axial than of equatorial imide again appears to be inconsistent with a major pathway involving attack of solvent on the backside of some intermediate. This assumes that the 39% of substitution product which is axial imide is not derived by rearrangement. This assumption appears secure in view of the finding of Maskill and Whiting[8] that only 6% of the substitution product was rearranged, axial, solvent-derived ester (less than 1% was rearranged axial internal ester).

The results of the decomposition of **3** and **4** in acetonitrile are remarkably similar to those obtained in acetic acid. In changing the solvent from cyclohexane to either acetic acid or acetonitrile, there is a sharp decrease in the yield of olefin produced from equatorial substrate; this is not due to a general increase in solvent polarity since it is not caused by the use of sulfolane as a solvent. The only difference in product distribution from equatorial substrate in acetic acid and acetonitrile is that in the latter solvent the equatorial product (which is formed in identical yield in the two solvents) is twice as rich in material (equatorial imide) formed by attack of the solvent. The only substantial difference between the results in acetic acid and acetonitrile, starting from axial substrate, is that in the latter solvent there is considerably more solvent capture.

As pointed out above, in order to explain the high ratio (~1.0) of axial to equatorial acetate produced from axial substrate in acetic acid, it is necessary to postulate either a frontside exchange or a hydrogen-bonding association of acetic acid with the internal counterion. The even higher ratio (~1.2) of axial to equatorial imide from the axial substrate in acetonitrile also appears to require some type of exchange or association process. Such a process would also explain the surprisingly greater efficiency of the weakly nucleophilic[28,29] acetonitrile than of the counterion or acetic acid at capturing the organic cation.

A reasonable possibility is that the diazotic ester **5** reacts with acetonitrile, possibly by way of a short-lived diazonium ion, to form the salt **12** and/or its covalent counterpart **13**. Fragmentation of **12** or **13** would yield



an intermediate, or an array of intermediates, represented by **14**, in which the acetonitrile may be better positioned than the ethyl carbonate anion to react with the organic cation. β-Elimination would be a less favorable process because the counterion which usually removes the β-proton is separated from the cation by the weakly basic acetonitrile molecule. Much of the α-elimination that ordinarily occurs in the case of the equatorial substrate is also suppressed for the same reason.

If the "exchange" process is efficient, then a significant proportion of the retained substitution product will be imide. In the case of axial substrate, this proportion is 67%, a figure that may be somewhat inflated by rearrangement which, as mentioned above, may provide some axial external substitution product. The proportion of imide in the retained product from equatorial substrate is 69%, but this must include not only that produced by the "frontside exchange" process but that resulting from solvent attack on unpaired cations.

The change in solvent from cyclohexane to the far more polar sulfolane causes very little change in the degree of elimination because in both solvents the counterion is positioned for effective proton removal; however, there is a revealing, sharp increase in the ratio of equatorial/axial substitution product. This increase, by a factor of 5.3, is most meaningful in the case of the equatorial substrate where rearrangement is not a serious consideration.[30] While some of this increase could be due to a diminution in the degree of intramolecular inversion caused by the high viscosity of sulfone,[16b] we believe that most of the increase in equatorial substitution product is due to attack of ethyl carbonic acid (formed in the elimination pathway) upon relatively free cations arising for the most part by unpairing of intramolecularly inverted "axial" ion pairs or their precursors; this process leads mainly to the more stable equatorial ethyl decalyl carbonate and diminishes the yield of the axial epimer. The reason for this belief is that the same high ratio of equatorial/axial substitution products occurs when acetic acid and acetonitrile are the

(27) The possibility of E2 eliminations in axial diazonium ions has been extensively discussed. For references, see ref 24 of this paper and footnote 8 of ref 5a.

(28) N. Kornblum and D. E. Hardies, *J. Am. Chem. Soc.*, **88**, 1707 (1966); C. E. Boozer and E. S. Lewis, *ibid.*, **75**, 3182 (1953); A. F. Diaz and S. Winstein, *ibid.*, **86**, 5010 (1964).

(29) The donicity (14) is less than that of ethyl acetate (17). V. Gutmann, *Electrochim. Acta*, **21**, 661 (1976).

(30) The increase (by a factor of 3) in the case of the product from axial substrate may be mostly due to an increase in rearrangement which, as discussed above, may lead to equatorial decalyl ethyl carbonate.

solvents. Both are capable of causing unpairing of ion pairs, the former largely by hydrogen bonding with the counterion and the latter by its high polarity. If the same process were to occur in the case of decomposition of the axial substrate, it would not be discernible since the intramolecularly inverted ion pair and free ions derived from it would both yield equatorial decalyl ethyl carbonate. It is likely that the more modest increase (by a factor of 3) in the ratio of equatorial/axial decalyl ethyl carbonate produced upon changing the decomposition medium of the axial substrate from cyclohexane to sulfolane is due largely to an increase in rearrangement in the more polar solvent; as mentioned above, rearranged intramolecular substitution product from the axial substrate is expected to be mainly equatorial.

Conclusions

As a result of this study and those reported in the preceding papers,[4,5] the generalizations concerning the products of deamination in cyclohexyl systems can be extended to a broader range of solvents. In nonpolar solvents, axial amines give mainly elimination and the substitution product is predominantly of retained configuration; equatorial amines yield about one-half elimination product and the one-half substitution product is modestly richer in retained rather than in inverted product. In proceeding to acetic acid or polar aprotic solvents, the retention/inversion ratios from axial and equatorial substrates become approximately interchanged due mainly to a sharp increase in the ratio of equatorial to axial substitution product in these solvents. This increased latter ratio is believed to be due to two factors: (1) an unpairing of some intermediate which was destined to form inverted internal ester and attack of hydroxylic solvent, mainly from the equatorial side, on the relatively free cation and (2) in the case of axial substrate, increased rearrangement in the more polar solvents. Surprisingly, acetonitrile is more efficient than either counterion or solvent acetic acid at capturing the intermediate, and the high degree of retention of configuration in the imides resulting from this capture leads to the hypothesis that acetonitrile is intimately associated with the diazo group before carbon–nitrogen bond rupture occurs. This phenomenon poses a situation in which any solvent which is capable of reacting with the organic cation will also be capable of reacting with the diazotic ester (or the diazonium carboxylate ion pair) and therefore may yield products similar to those from an internal counterion. It is thus problematical that a solvent can be found that will provide products derived from simple solvolysis of some intermediate.

The sharp decrease in olefin production upon changing the medium for decomposition of the equatorial substrate from cyclohexane or sulfolane to acetic acid or acetonitrile may be due to a decreased ability of the counterion to remove α- or β-protons because of hydrogen bonding, in the case of acetic acid, or of greater separation of ions, in the case of acetonitrile. The apparent insensitivity to solvent of the degree of elimination from the axial substrate may be due, in the more basic solvents, to increased solvent-induced trans elimination which compensates for the decreased cis elimination executed by the counterion.

We have reported[31] that the axial *trans*,*trans*-2-decalyl bromide undergoes silver ion assisted solvolysis in acetonitrile with a high degree of substitution and essentially complete retention of configuration to produce *N*-(*trans*,*trans*-2-decalyl)acetamide. A key feature of our explanation[31] of this phenomenon is that an acetonitrile ligand of the silver ion transfers from the latter to the frontside of the carbocation as the silver ion removes the bromide ion from the alkyl halide.[32] An interesting analogy can be drawn between that reaction and the solvolysis of the ethyl *N*-(*trans*-2-decalyl)-*N*-nitrosocarbamates (**3** and **4**) in the same solvent. Nearly all of the substitution product in the silver-induced reaction and a substantial fraction of it in the *N*-nitrosocarbamate solvolysis is postulated to arise via an intermediate in which the weakly nucleophilic acetonitrile molecule is able to scavange a carbocation because of its close proximity to the latter as it is produced. Such proximity is achieved by close association of an acetonitrile molecule with the neutral leaving group AgBr in the halide solvolysis and the diazo function in the *N*-nitrosocarbamate decomposition.

Experimental Section

General. Infrared spectra were recorded on a Beckman Model IR-8 spectrometer and were calibrated against polystyrene film. Proton magnetic resonance spectra were recorded on Varian Models A-60, T-60, and A-60D spectrometers. Mass spectra were recorded on an LKB-9000 combined gas chromatograph–mass spectrometer and an ionizing voltage of 70 eV was employed. High-resolution mass spectra were recorded on an AEI MS-9 mass spectrometer.

Gas–liquid chromatographic (GLC) analyses were performed with a Varian Aerograph Model 1860-3 gas chromatograph. The recorder was equipped with a Disc Instruments, Inc., Model 204 disc integrator. The flame-ionization detector was employed. Gas chromatographic quantitative analyses were performed by calibrating the detector responses for given weights of authentic samples of product against a given weight of standard.[35] Detector responses of epimers in some instances were assumed identical. A calibration curve was thus constructed of three or four points for each product. Each analysis was repeated at least two or three times and the average values of at least two experiments are reported in Table I.

Melting points were determined on a Thomas-Kofler micro hot stage and are corrected. Boiling points are uncorrected.

Ethyl *N*-(*trans*,*cis*-2-Decalyl)carbamate. *trans*,*cis*-2-Aminodecalin was prepared by reduction of the oxime[36] of *trans*-2-decalone with sodium in alcohol according to Hückel's procedure.[37] A solution of 30 g (0.28 mol) of ethyl chloroformate in 20 mL of pentane was added dropwise over a period of 3 h to a three-neck, 250-mL flask which contained a mechanically stirred mixture of 31 g (0.20 mol) of the amine, 40 mL of water, 40 mL of pentane, and 8 g of sodium hydroxide and which was maintained at 0 °C. The layers were separated in a funnel, and the aqueous layer was washed twice with ether. The combined organic phase was washed with water, dried, and concentrated to yield the title compound in yields typically ranging from 80 to 85% after recrystallization from pentane: mp 89.0–90.0 °C; IR (CCl_4) 3484, 3367, 3012, 2941, 2882, 1704 cm^{-1}; ^1H NMR (CCl_4) δ 0.80–2.25 (m, 19 H, decalyl ring protons, except carbinyl proton, and methyl triplet), 1.22 (t, J = 7 Hz, CH_3), 3.60 (m, 1 H, NCH), 4.05 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.21 (m, 1 H, NH); mass spectrum, m/e 225 (5%, P), 196 (10%, P – ethyl), 153 (10%, P – $CO_2C_2H_4$), 136

(31) T. Cohen and J. Solash, *Tetrahedron Lett.*, 2513 (1973).

(32) Recently, these results have been explained[33] on the basis of preferred axial nucleophilic attack on a decalyl cation. A weakness of this concept is that acetolysis of *cis*-2-cyclohexyl chloride in the presence of silver hexafluoroantimonate yields three times as much inverted as retained acetate,[34] although it could be argued that acetic acid is more nucleophilic than acetonitrile (this is somewhat doubtful according to the results in the prsent paper) and that nucleophilic participation is more important with chloride, which is a poorer leaving group than bromide.

(33) J. Klein, *Tetrahedron*, **30**, 3349 (1974).

(34) P. Beak, J. T. Adams, and J. A. Barron, *J. Am. Chem. Soc.*, **96**, 2494 (1974).

(35) L. S. Ettre and A. Zlatkis, Eds., "The Practice of Gas Chromatography", Interscience, New York, 1967, pp 401–403.

(36) E. Müller and U. Heuschkel, *Chem. Ber.*, **92**, 71 (1959).

(37) W. Hückel, *Justus Liebigs Ann. Chem.*, **533**, 1 (1938).

(30%, octalin$^+$), 93 (12%), 88 (15%, $NHCO_2Et^+$), 61 (100%, $NH_2CO_2H^+$).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.52; H, 10.39; N, 6.13.

Ethyl *N*-(*trans,trans*-2-Decalyl)carbamate. *trans,trans*-2-Aminodecalin was prepared by a modification of the method of Pinkus, Pinkus, and Cohen.[38] The yield of pure amine was substantially improved by performing the ammonolysis of *trans,cis*-2-decalyl tosylate for 90 h instead of for 22.5 h. The carbamate was prepared as above: mp 62.2–63.0 °C; IR (CCl_4) 3472, 2933, 2865, 1712, 1497, 1447, 1372, 1330, 1212, 1099 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.60–2.15 (m, 19 H, decalyl ring protons, except carbinyl proton, and methyl triplet), 1.21 (t, J = 7 Hz, CH_2CH_3), 3.60–4.22 (m, 3 H, methylene quartet overlapping a br m for carbinyl H), 4.02 (q, J = 7 Hz, CH_2CH_3), 4.85 (m, 1 H, NH); mass spectrum, m/e 225 (15%, P), 196 (20%, P – ethyl), 153 (15%, P – $CO_2C_2H_4$), 136 (100%, octalin$^+$), 89 (90%, $NHCO_2C_2H_5^+$), 61 (50%, $NH_2CO_2H^+$).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.45; H, 10.37; N, 6.12.

***trans*-2-Decalols.** A solution of 400 g of a mixture of four isomeric decahydro-2-naphthols (from Koch-Light Chemical Co., England) in 500 mL of pentane was cooled for several hours in a freezer. The precipitate was recrystallized twice from pentane to give 109 g of *trans,cis*-2-decalol, mp 75.0–76.0 °C (lit. mp 72.1–74.8 °C,[39] 75 °C[40]). Chromatography on silicic acid of the mother liquor from the first crystallization, using methylene chloride containing 3% ethanol, provided a first fraction of *trans,trans*-2-decalol, which, after recrystallization from pentane, had mp 53.5–55.0 °C (lit.[40] mp 53 °C).

***trans,cis*-2-Decalyl Acetate.** To an ice cold stirred solution of 5.0 g of *trans,cis*-2-decalol in 20 mL of pyridine and 20 mL of pentane was slowly added 3.6 mL of freshly distilled acetyl chloride in 10 mL of pentane, and the mixture was then allowed to stir for 2 h at ambient temperature. The solution was decanted from the precipitate of pyridine hydrochloride and washed with water, dilute hydrochloric acid, and water. The dried (magnesium sulfate) organic layer was concentrated to afford a yellow green oil. Distillation [bp 72–74 °C (0.7 torr) (lit.[37] bp 124 °C (15 torr)] provided a clear colorless oil in 80% yield: IR (film) 2941, 2862, 1733, 1451, 1370; ^{1}H NMR (CCl_4) δ 0.65–2.28 (m, 19 H, decalyl protons, except carbinyl proton, and methyl singlet), 1.96 (s, 3 H, CH_3), 4.05–4.92 (m, 1 H, width at half-height = 25 Hz, HCO).

***trans,trans*-2-Decalyl Acetate.** *trans,trans*-2-Decalol was acetylated as above. The ester had bp 59.0–59.5 °C (0.4 torr) [lit.[37] bp 124 °C (15 torr)]: IR (film) 2933, 2865, 1736, 1447, 1368; ^{1}H NMR (CCl_4) δ 0.60–2.03 (m, 19 H, decalyl protons, except carbinyl proton, and methyl singlet), 1.95 (s, 3 H, CH_3), 5.00 (m, 1 H, width at half-height = 7 Hz, HCO).

***trans*-1-Octalin and *trans*-2-Octalin.** A mixture of these octalins was obtained by heating at reflux for 5 min a solution of 30.8 g (0.100 mol) of *trans,cis*-2-decalyl tosylate[38] in 50 mL of ethylene glycol monoethyl ether containing 2.3 g (0.10 mol) of dissolved sodium. The cooled solution was poured into 200 mL of water and extracted with hexane. The extract was distilled at 60 °C (0.2 torr) to give 8.17 g (0.061 mol, 61% yield) of the mixed octalins.[41]

Ethyl *trans,cis*-2-Decalyl Carbonate. A solution of 1.7 g (16 mmol) of ethyl chloroformate in 20 mL of anhydrous ether was added with stirring to an ice-cold solution of 2.0 g (13 mmol) of *trans,cis*-2-decalol in 20 mL of anhydrous pyridine and the mixture was heated to reflux at which it was maintained for 2 h. The cooled mixture was diluted with water and extracted with ether. The ether layer was dried and concentrated to afford 3 mL of white oil. Distillation at 80–82 °C (0.04 torr) provided 2.1 g (71% yield) of a clear, colorless oil: IR (film) 2941, 2865, 1739, 1449, 1370 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.53–3.20 (m, 19 H, decalyl protons, except carbinyl proton, and methyl triplet), 1.27 (t, J = 7 Hz, CH_2CH_3), 3.90–4.80 (m, 3 H, methylene q superimposed on br m whose width at half-height = 26 Hz, HCN), 4.25 (q, J = 7 Hz, CH_2CH_3); mass spectrum, m/e 153 (10%, P – carbethoxy), 136 (100%, octalin$^+$), 121 (12%), 91 (10%, $C_2H_5OCO_2H_2^+$).

Ethyl *N*-Acetyl-*N*-(*trans,cis*-2-decalyl)carbamate. An essentially quantitative yield as a slightly yellow oil (GLC impurities less than 0.5%) was obtained by treatment of ethyl *N*-(*trans,cis*-2-decalyl)carbamate with acetyl chloride in acetic anhydride containing a small quantity of concentrated sulfuric acid:[42] IR (film) 2941, 2857, 1733, 1689, 1449, 1408, 1370, 1242, 1212 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.60–2.30 (m, 19 H, decalyl protons, except carbinyl proton, and methyl triplet), 1.35 (t, J = 7 Hz, CH_2CH_3), 2.32 (s, 3 H, $COCH_3$), 4.05–4.65 (m, 3 H, carbinyl H and q for CH_2 of ethyl), 4.22 (q, J = 7 Hz, CH_2CH_3); mass spectrum, m/e 267 (1%, P), 224 (5%, P – CH_3CO), 194 (15%, R – $CO_2C_2H_5$), 132 [100%, $NH_2(CO_2C_2H_5)(COCH_3)^+$], 43 (50%, $COCH_3^+$); high-resolution mol wt 267.1848, calcd for $C_{15}H_{25}NO_3$ 267.1834.

Ethyl *N*-Acetyl-*N*-(*trans,trans*-2-decalyl)carbamate. Using the same procedure on the epimeric carbamate only led to acetylation of about 10% of the starting material as judged by GLC. The acetylated material, as expected, had a slightly shorter retention time than the equatorial epimer. A combined gas chromatograph–mass spectrum showed m/e 267 (1%, P), 224 (45%, P – CH_3CO), 152 (8%, P – CO_2Et – CH_2CO), 136 (98%, octalin$^+$), 121 (20%), 107 (15%), 95 (60%), 67 (50%), 43 (100%, CH_3CO^+). The product of decomposition of the *N*-nitrosocarbamates in acetonitrile with a slightly shorter retention time than that of the equatorial imide had an identical mass spectrum with that of this material.

Deamination Procedure. The amides were nitrosated with dry N_2O_4 according to the procedure of White[43] except that the temperature used was –10 to –20 °C. After 0.5 h, the solution was concentrated under vacuum at –20 to 0 °C to yield the *N*-nitrosoamide, as a liquid in the case of the axial epimer (**3**) and a solid, mp 51.0–51.5 °C (unchanged after recrystallization from pentane), in the case of the equatorial epimer (**4**). Usually the crude *N*-nitrosocarbamate was decomposed immediately, but in some cases **4** was recrystallized before use; the product distributions were the same but the overall yields were improved from ~93% to ~97% upon using recrystallized *N*-nitrosocarbamate.

The decomposition was performed by heating a flask with a reflux condenser containing about 100 mg of the *N*-nitrosocarbamate in 5 mL of the appropriate solvent under a positive pressure of nitrogen with a fluidized sand bath maintained at 85 °C. The acetic acid was dried before use by heating with 12% of its weight of acetic anhydride at 80–83 °C for 12 h. The Fisher Certified acetonitrile was heated at reflux over calcium hydride over night and then distilled on to 4-Å molecular sieves. Sulfolane was kindly supplied in pure form (less than 10^{-3} M in water) by Professor J. F. Coetzee. Pyrolysis was allowed to proceed until the initial greenish solution turned colorless or lightly yellow; this was 20 min for the unstable axial epimer (**3**) and 7 h for the equatorial compound (**4**). A weighed quantity of benzophenone was added to the cooled reaction mixture, as an internal standard, and the products were analyzed by gas chromatography. The identities of the products were determined by comparison of the retention times with those of authentic samples and by observing peak-height enhancement upon coinjection with the authentic specimen on three different chromatographic columns. In some cases combined gas chromatography–mass spectrometry was used.

The octalins and *trans,cis*-2-decalyl carbonate were shown to be stable to the decomposition conditions in acetic acid and in acetonitrile and to the workup conditions. The equatorial imide was shown to be stable to the decomposition conditions in acetonitrile containing a little ethanol. The mixture of octalins was shown to be stable to a refluxing cyclohexane solution of ethyl *N*-nitroso-*N*-cyclohexylcarbamate, prepared in the same way as the equatorial *N*-nitrosocarbamate **4**.

Acknowledgment. This work was supported in part by Grants AM 06419 from the National Institutes of Health and GU-3184 from the National Science Founda-

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(40) W. Hückel, *Justus Liebigs Ann. Chem.*, **411**, 1 (1925).
(41) J. W. Powell and M. C. Whiting, *Tetrahedron*, **12**, 168, 278 (1961).
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tion. We thank Dr. C. K. Shaw for providing some of the compounds needed for this study, Professor Emil White for helpful suggestions, and the Chemistry Department of the University of North Carolina at Chapel Hill for its hospitality to T.C. while he was on leave there during the writing of much of this paper.

Registry No. 3, 23015-31-8; **4**, 23018-02-2; *trans,cis*-2-aminodecalin, 23017-71-2; ethyl chloroformate, 541-41-3; *trans,trans*-2-aminodecalin, 936-35-6; *trans,cis*-2-decalol, 2529-06-8; *trans,trans*-2-decalol, 5779-35-1; *trans,cis*-2-decalyl acetate, 66964-88-3; *trans,trans*-2-decalyl acetate, 66964-89-4; *trans*-1-octalin, 2001-49-2; *trans*-2-octalin, 2001-50-5; ethyl *trans,cis*-2-decalylcarbonate, 73688-49-0; ethyl *N*-acetyl-*N*-(*trans,cis*-2-decalyl)carbamate, 73688-50-3; ethyl *N*-(*trans,cis*-2-decalyl)carbamate, 73688-51-4; ethyl *N*-acetyl-*N*-(*trans,trans*-2-decalyl)carbamate, 73688-52-5; ethyl *N*-(*trans,trans*-2-decalyl)carbamate, 73688-53-6.

The Hantzsch 1,4-Dihydropyridine Synthesis as a Route to Bridged Pyridine and Dihydropyridine Crown Ethers[1]

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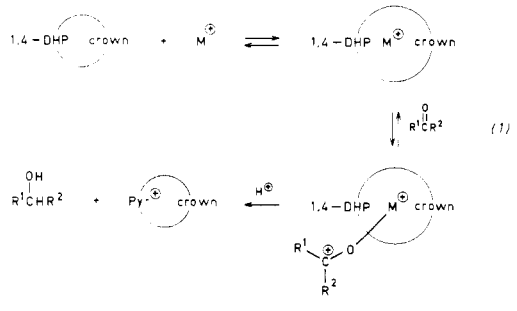
Mono-, di-, tri-, and tetraethylene glycols were transesterified with ethyl acetoacetate to give the bis(acetoacetate esters) **1a–d**. On treatment of **1c,d** with formaldehyde and excess $(NH_4)_2CO_3$ in H_2O a crude mixture of 1,4-dihydropyridines was obtained from which, after dehydrogenation to the pyridine form, the 3,5-bridged 2,6-dimethylpyridines **2c,d** were isolated along with dimers **7c,d**. Similar reaction of **1a** gave only dimer **7a**. The bridged pyridine **2d** was methylated to give pyridinium salt **3d**, which was reduced with $Na_2S_2O_4$ to give 1,4-dihydropyridine **4d**. Stable sodium salts of **4d** and **6d** were isolated. Bridged pyridines **10a–c** substituted with, respectively, methyl, phenyl, and 2-furyl at the γ position of the pyridine ring have also been prepared, using **1d**, $(NH_4)_2CO_3$, and acetaldehyde, benzaldehyde, and 2-furfuraldehyde and Hantzsch condensation followed by dehydrogenation and chromatographic separation. Protection of the 1,3-dicarbonyl system of ethyl 4-bromo-3-oxobutanoate as its Na chelate followed by nucleophilic substitution with the bisalkoxides from tetra-, penta-, and hexaethylene glycols gave 4-substituted bis(acetoacetate esters) **16a–c**. These on Hantzsch condensation yielded in low yield 2,6-bridged Hantzsch 1,4-dihydropyridines (**17a–c**). Treatment of **17a,b** with alkali metal hydrides gave insoluble materials thought to be the internally solvated alkali metal salts of the (vinylogous) amide nitrogen of the 1,4-dihydropyridine.

Introduction

Metal ions catalyze the reductions by 1,4-dihydropyridines (1,4-DHP) of many carbonyl compounds.[4] This is true both in enzymic reactions and in the reactions of simpler 1,4-DHP's. We are interested in the design of synthetic 1,4-DHP-containing systems wherein the efficiency of this catalytic aspect is high. One appealing approach to such an objective is to incorporate the 1,4-DHP into a poly(ethylene glycol) chain having sufficient "crown ether" character to complex a metal ion. If the position of the metal ion relative to the 1,4-DHP can be arranged properly, one can imagine the operation of the reaction sequence shown in eq 1.[5] The 1,4-DHP on (formal) loss of hydride is converted to a pyridine (Pyr) if the nitrogen atom bears a hydrogen and to a pyridinium salt (Pyr^+) if the nitrogen atom is alkylated.



We have reported on the success of this strategy.[1,6] For reasons of design that will be discussed in subsequent publications, the (dihydro)pyridine has been incorporated as an integral section of the macrocyclic system[7] rather than as an appendage to an already formed crown ether.[8] We describe here the results of our initial attempts to secure such systems using an approach based on a modified Hantzsch dihydropyridine synthesis.[9]

Results and Discussion

The best known version of the Hantzsch condensation is the reaction of an acetoacetate derivative with a carbonyl compound, usually but not always an aldehyde, and ammonia (eq 2). Considerable variation in structure can be

(1) Previous publication in this series: van Bergen, T. J.; Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1979**, *44*, 4953. Also de Vries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 2759.
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(3) Undergraduate exchange student from Hope College, Holland, MI.
(4) For a compilation of references on this subject, see ref 1.
(5) Prior to our efforts in this direction, the synthesis of dihydropyridines or pyridinium salts bridged with poly(methylene) chains has been described: (a) Overman, L. E. *J. Org. Chem.* **1972**, *37*, 4214. (b) Dittmer, D. C.; Blidner, B. B. *Ibid.* **1973**, *38*, 1973. For a recent review of reductions by 1,4-DHP's, see: Kill, R. J.; Widdowson, D. A. *Bioorg. Chem.* *4*, 239–275.
(6) van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 3882.
(7) See, for example: Behr, J. P.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1978**, 143.
(8) Many pyridine-containing macrocycles incorporating poly(ethylene glycol), poly(methylene), or other chains have been prepared. A review complete through 1976 is given: Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513. For recent examples and citations of very recent literature see also: Newkome, G. R.; Kawato, T. *J. Org. Chem.* **1979**, *44*, 2693. Newkome, G. R.; Kawato, T.; Nayak, A. *Ibid.* **1979**, *44*, 2697. Heimann, U.; Vögtle, F. *Angew. Chem.* **1978**, *90*, 211.
(9) Review: Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.

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