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THE NITROSOAMIDE AND NITROUS ACID DEAMINATIONS OF THE ALICYCLIC PRIMARY AMINES, α AND β 3-AMINOCHOLESTANE[1]

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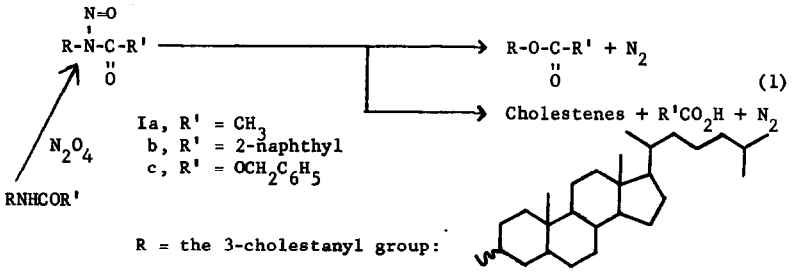
It is apparent that the course of deamination of alicyclic amines depends on the conformation of the amino groups;[2-5] the early reports,[2] based largely on still earlier deamination results,[3] claimed that equatorial amines yielded alcohols with complete retention of configuration and that axial amines yielded alcohols with predominant inversion. Shoppee,[4] somewhat later, claimed that in steroids, both equatorial and axial amines yielded alcohols with complete retention of configuration. Recently, Hückel has shown that among substituted cyclohexylamines, both families (with equatorial and axial amino groups respectively) yield alcohols with concurrent inversion and retention of configuration.[5] We now report that the early conclusions must be modified and that in line with Hückel's latest work,[5] the deamination of steroidal amines, as exemplified by α and β 3-aminocholestane, also proceeds with concurrent retention and inversion of configuration. In addition, we report on the first application of the nitrosoamide reaction to the deamination of alicyclic amines and show that in the nitrosoamide reaction and possibly in the nitrous acid deamination, a part of the inverted product must be formed by an intramolecular process.

We have examined principally the nitrosoamide decomposition of the 3-aminocholestanes using nitrosoacetamides (Ia), 2-naphthamides (Ib), and carbobenzyloxyamides (Ic). The overall reaction is represented by Eq. 1.



The general mechanism of this reaction has been discussed elsewhere.[6,1b]

The aminocholestanes were prepared by published procedures,[7] purified as the acetyl derivatives, and obtained free by prolonged hydrolysis with acetic and hydrochloric acid mixtures. The β-nitrosoamides (Ia,b) and the α and β-nitrosocarbamates (Ic) were prepared by reaction of the parent amides with nitrogen tetroxide in methylene chloride at -20°C[6,8] followed by isolation. The α-nitrosoamides were very unstable, presumably the result of steric crowding of the axial nitrosoamido group, and these compounds were prepared by a low temperature method.[1b] The crude reaction mixtures were chromatographed on alumina to separate them into cholestene, ester and alcohol fractions and these were analyzed individually. The acetates and carbonates were analyzed by comparing their infrared spectra with standards. The naphthoates were converted to the alcohols *via* lithium aluminum hydride reduction and the alcohols analyzed according to the method of Vail and Wheeler.[9]

The experimental results (Table I) show that predominant retention of configuration occurs in all the cases. In each run, however, one notes considerable inversion of configuration. Since inversion of configuration *via* a displacement reaction can be brought about by the acid liberated in the elimination reaction[10] (eq. 1), reagents were added in several runs to insure that only the intramolecular reaction would be observed. In two nitrosoacetamide runs, an excess of diazomethane was used to scavenge the

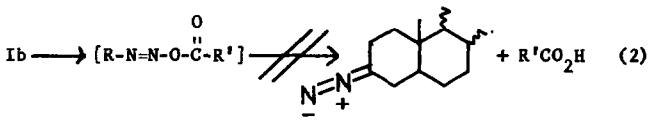
TABLE I

Decomposition of the Nitrosoamides of α and β 3-Aminocholestane

Compd.	Config.	Solvent[a] + Molar Equiv. of Addend	% Olefins[b]	% Esters[b]	Composition of Esters 3α	3β
Ib	α	Ether[c]	69	14	52	48
Ic	α	Hexane	84	16	83	17
Ic	α	Ether + 125 CH_2N_2	89	8	76	24
Ia	β	Cyclohexane + 42 CH_2N_2	45	44	35	65
Ia	β	$CHCl_3$	31	66	15	85
Ic	β	Heptane[d]	42	46	29	71
Ib	β	CH_2Cl_2 + 165 CH_3CO_2D	25	62[e]	18	82

a. All runs at room temperature unless otherwise noted. b. Corrected for a small amount of recovered amide. c. At -20°C. d. At 99°C. e. In addition, there was obtained 10% acetates, % comp.: 25% 3α, 75% 3β.

acetic acid, and in a nitrosonaphthamide run, an excess of O-deuterioacetic acid was added to swamp out the naphthoic acid liberated. In all cases, considerable inversion of configuration was still observed. In the deuterioacetic acid run, furthermore, little or no deuterium was incorporated in either the cholestanyl naphthoates or acetates isolated,[11] indicating that diazoalkanes were not involved as reaction intermediates (Eq. 2).[12]



(2)

We conclude that the acetates in the diazomethane runs and the naphthoate ester in the deuterioacetic acid run were formed in intramolecular reactions, and that the inversion of configuration observed is an "intramolecular inversion".[6] This is the second example of this phenomenon, although the deaminations of sec-butylamine[10] and 2-phenyl-2-butylamine[1b] may represent other cases. Our interpretation of the intramolecular inversion is given elsewhere.[6] The low yield of acetates in the deuterioacetic acid run indi-

cates the relative unimportance of the solvolytic pathway under our reaction conditions, especially since a part of the acetate ester is formed by "frontside exchange".[10]

The results of the nitrous acid deamination of α and β 3-aminocholestane are given in Table II.

TABLE II

The Nitrous Acid Deamination of the α and β 3-Aminocholestanes

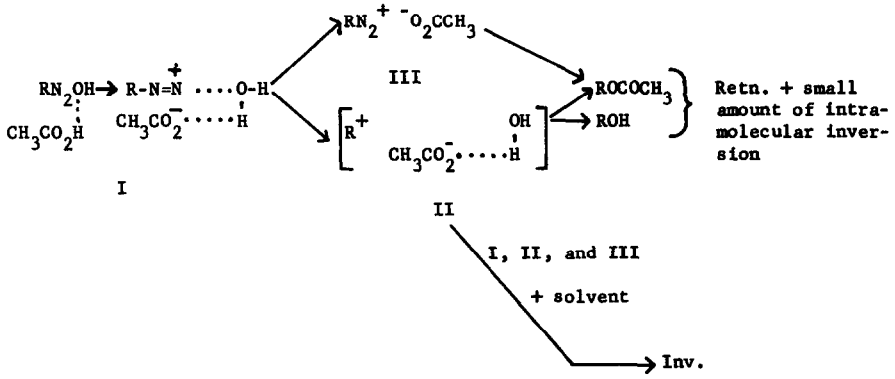
Configuration	Solvent	% Olefins	% Esters	% Comp. Esters α	% Comp. Esters β	% Alcohol	% Comp. Alcohols α	% Comp. Alcohols β
α	Acetic Acid	38	15	40	60	9	89	11
β	Acetic Acid	5	53	34	66	41	10	90
α[a]	Acetic Acid:H_2O, 1:1	45	19	--	--	13	61	39
β[a]	Acetic Acid:H O :Dioxane, 2:2:1	25	29	39	61	43	35	65

a. Yields corrected for recovered amine.

In all the runs, both inversion and retention of configuration occurred in the formation of both the alcohols and the acetates. These results, especially those of the third and fourth run in which we have attempted to duplicate the reported reaction conditions of Shoppee, do not agree with Shoppee's claim[4] that steroidal amines react with complete retention of configuration. Presumably, the analytical procedures used in their work were at fault.

The source of the alcohols is of some interest. They could be products of intermolecular reactions, since water is a product of the nitrous acid deamination. Boutle and Bunton[13] have shown that the reaction of cyclohexylamine in water with O-18 labelled nitrous acid yields cyclohexanol with over 90% of the oxygen derived from the solvent. However, in our case, the predominant retention of configuration observed for both the α and β isomers, and the fact that runs in aqueous acetic acid gave essentially the same yields of alcohols (with only slightly more inversion) than

obtained in the dry acetic acid runs (Table II), suggest that at least a part of the reaction is intramolecular and that "intramolecular inversion" has occurred in the formation of the alcohol.[14] The solvolysis observed by Boutle and Bunton may not compete with intramolecular reactions so well in a solvent of lower dielectric constant (ϵ for HOAc = 6 vs 80 for H_2O). Our general reaction scheme for the nitrous acid deamination, based in part on earlier results,[1b] is given below.



The bimolecular inversion pathway accounts for the fact that the solvolysis product is usually more highly inverted than the product of the intramolecular reaction.[1b,6,10] Intermediates of type I have been invoked recently to account for the near constant ratio of alcohol to acetate in the deamination of 2-decalylamine.[15,16]

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(11) The α and β cholestanols, obtained separate and pure from the naphthoate ester, contained less than 0.002 of an atom of deuterium per molecule and the 3-cholestanyl acetates contained less than 0.024 of an atom of deuterium per molecule (in excess of natural abundance).

(12) Otherwise, the unlikely assumption must be made that the carboxylic acid migrates to the opposite side of the diazoalkane plane faster than it exchanges a proton for the deuterium in the deuterioacetic acid making up the solvent cage, and also faster than deuterioacetic acid can react on the backside.

(13) D. L. Boutle and C. A. Bunton, J. Chem. Soc., 761 (1961).

(14) The alcohol could also come from the hydrolysis of a nitrite ester[1b] without changing our conclusions appreciably.

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(16) For deamination in mixed solvents, it has been determined that the more basic component of the solvent does not compete well in solvolysis with the less basic component (H_2O vs acetic acid, eg.) (ref. 15 and W. Hückel and E. Wilip, J. Prakt. Chem., 158, 21 (1941)). A preferential attack of the more basic species on the α-hydrogens to yield olefinic products at the expense of the substitution products can account qualitatively for this difference.