

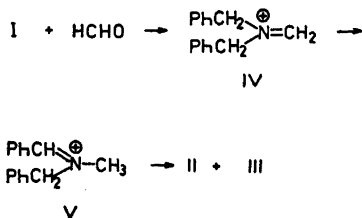
The Interpretation of an Abnormal Reaction Path Occurring during the Methylation of Certain Secondary Norbornanemethylamines with Formaldehyde in Acetic Acid

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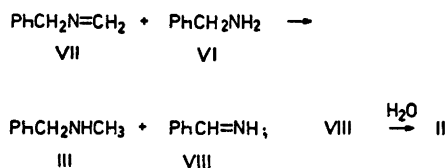
The carbon-nitrogen bond cleavage which occurs as a side reaction during the methylation of certain norbornanemethylamines with formaldehyde in acetic acid was investigated by employing deuterated and undeuterated reactants and by interpreting the NMR and mass spectra of the reaction products. It was shown that the pathway of the side reaction involves an intramolecular 1,3-hydride shift.

In the methylation of primary and secondary amines with formaldehyde, known as the Eschweiler-Clarke procedure,¹ the yields are best when the reaction is carried out in formic acid, although the reaction also proceeds in acetic acid.² In some cases carbonyl compounds²⁻⁹ and secondary amines² are found among the by-products. Clarke *et al.*² suggest for the formation of the by-products benzaldehyde (II) and *N*-methylbenzylamine (III) by the methylation of dibenzylamine (I) a mechanism which proceeds *via* subsequent intermediate cations IV and V and the hydrolysis of V to the compounds II and III. These intermediate steps would include an intramolecular hydrogen shift (Scheme 1). On the other hand, Pine and



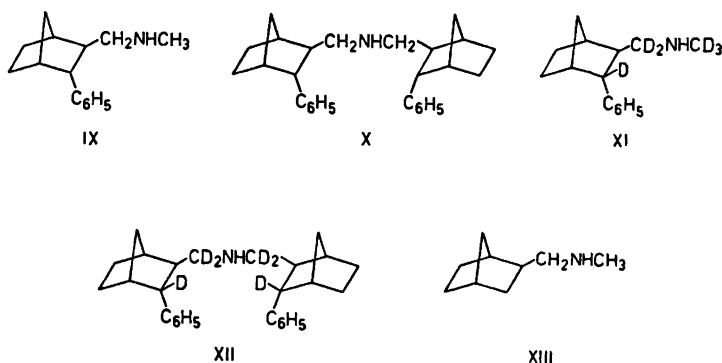
Scheme 1.

Sanchez¹⁰ suggest that the reaction leading to aldehyde II during the methylation of benzylamine (VI) with formaldehyde in formic acid involves an intermolecular hydrogen shift between the Schiff base VII (from VI and formaldehyde) and VI. The hydrolysis of the subsequent benzylidene amine (VIII) leads to aldehyde II (Scheme 2).



Scheme 2.

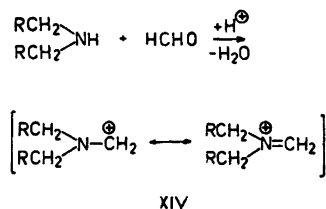
When studying the reaction of 2-norbornene with formaldehyde and secondary amines in acetic acid, it has been observed that the primary reaction products, secondary norbornanemethylamines, whose formation involves a 1,5-hydride shift, are methylated during the course of the reaction to the corresponding tertiary amines, and that these methylations include a side reaction which leads to carbonyl compounds and secondary amines.¹¹ Furthermore, when comparing the reaction products obtained from the reaction of 2-phenyl-2-norbornene, formaldehyde, and dimethylamine with those obtained from the corresponding reaction of 2-norbornene, the conclusion has been drawn that the formation of the main components found in the product mixture of the reaction follows a similar mechanism.¹² It



has not been investigated, however, if in the side reaction of the methylation the transfer of a hydrogen atom from the carbon atom adjacent to nitrogen is an intramolecular or an intermolecular process. To clarify this question, in the present study secondary amines IX and X (from 2-phenyl-2-norbornene, formaldehyde, and dimethylamine¹²), deuterated amines XI and XII (from 2-phenyl-2-norbornene, perdeuterioformaldehyde, and hexadeuteriodimethylamine), and secondary amine XIII (from 2-norbornene, formaldehyde, and dimethylamine¹¹) were allowed to react with formaldehyde and perdeuterioformaldehyde in acetic acid, and the products were analysed by mass and NMR spectra.

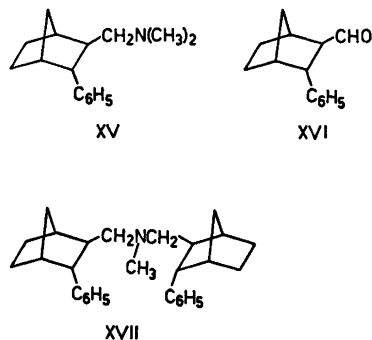
RESULTS AND DISCUSSION

It is known that the reaction of a secondary amine with formaldehyde under acidic conditions leads to carbonium-immonium ion XIV (Scheme 3). This ion is considered to function as an intermediate species not only in the Mannich reaction¹³ but also in the Leuckart-Wallach reaction, which includes the Eschweiler-Clarke methylation.¹⁴ The reduction of ion XIV leads to the methylated product, the source of the hydride ion being formic acid, which is



Scheme 3.

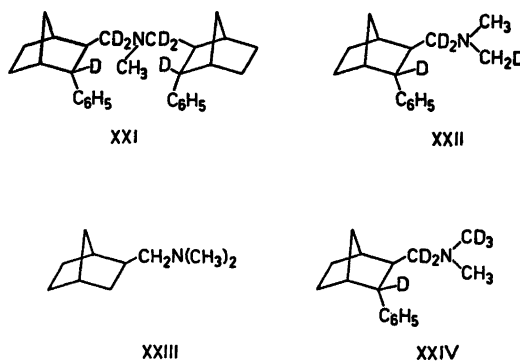
either added to the reaction mixture or is produced from formaldehyde by oxidation during the reaction. The reaction leading from ion XIV to a carbonyl compound and a secondary amine could possibly require either an isomerization suggested by Clarke *et al.*³ (Scheme 1) or an intermolecular hydride shift analogous to that in the Sommelet reaction^{3,15} as suggested by Pine and Sanchez¹⁰ (Scheme 2).



Earlier¹² the secondary amines IX and X have been methylated with formaldehyde in formic acid to the corresponding tertiary amines and the side reactions were not studied; now, the same reactions were performed in acetic acid and a more detailed characterization of the reaction products followed. After heating amine IX and formaldehyde (mol ratio 1:2) for 4 h, the reaction mixture contained tertiary amine XV, aldehyde XVI, and the starting compound IX. In the same way amine X gave, besides the normal methylation product XVII, also the cleavage products XVI and IX and the methylation product XV. These results distinctly show that during the reaction of secondary

amines IX and X with formaldehyde in acetic acid a cleavage of the carbon-nitrogen bond takes place besides methylation. Quite evidently hydrogen is released from the methylene carbon, adjacent to nitrogen, as hydride ion in the same fashion as in the Sommelet reaction of benzylamine.¹⁶

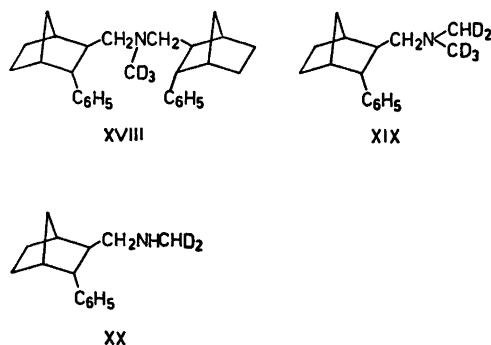
Since, according to Angyal,^{9,15} methyleneimine produced from ammonia and formaldehyde or methylenebenzylamine (VII) (a Schiff base generated from benzylamine and formaldehyde) is likely to act as a hydride acceptor in the Sommelet reaction, which occurs when heating benzylamine with hexamethylenetetramine and yields benzaldehyde, also the carbonium-immonium ions of type XIV (generated from IX or X and formaldehyde) could function as hydride acceptors. To investigate this possibility amine X hydrochloride was heated with an excess of perdeuterioformaldehyde in acetic acid for 60 h so that both X and its cleavage product, a secondary amine, would be completely methylated. Upon diluting the reaction mixture with water, the methylated amine X precipitated as hydrochloride, was filtered off and liberated from its salt with potassium carbonate. The amine was identified by NMR and mass spectra to be compound XVIII. An amine containing five deuterium atoms and an aldehyde containing no deuterium were isolated from the filtrate. These compounds were assigned the structures XIX and XVI, respectively, by the aid of NMR and mass spectra. In order to identify the precursor of XIX, amine X and perdeuterioformaldehyde (mol ratio 1:2) were heated in acetic acid for only 4 h. The secondary amine isolated from the filtrate now contained only two deuterium atoms and was assigned the

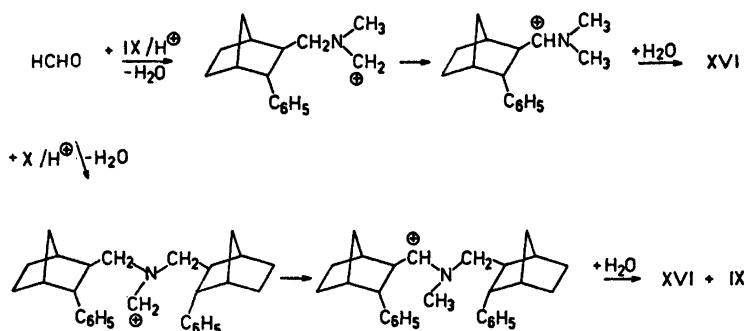


structure XX. When the deuterated secondary amine XII (corresponding to X) was heated with an excess of formaldehyde in acetic acid for 60 h, the methylation product was, as expected, amine XXI and the methylated cleavage product was amine XXII.

The formation of XVIII from X and correspondingly XXI from XII indicates that the hydrogens of the methyl group in the actual methylation product originate from formaldehyde or its oxidation product, formic acid. The formation of amine XIX from X and perdeuterioformaldehyde, occurring by cleavage yielding XX and by subsequent methylation of XX with perdeuterioformaldehyde, and the corresponding formation of amine XXII from XII and formaldehyde are in accordance with the assumption that cations such as XIV function as acceptors of the hydride and the deuteride during the cleavage of the carbon-nitrogen bonds. In order to find out if the hydride transfer takes place intermolecularly, a mixture of amines XI and XIII was heated with formaldehyde in acetic acid. Amine XXIII, which is the methylation product of XIII, did not, according to the mass spectrum, contain any deuterium whereas compound XXIV is the methylation product of XI. This crossover experiment shows that the intermolecular hydrogen transfer from the carbon, adjacent to nitrogen, to the carbonium-immonium ion in the other molecule is out of question.

An intramolecular 1,3-hydride shift followed by a hydrolysis according to Scheme 4 seems to be the best explanation for the cleavage of the carbon-nitrogen bond which occurs as a side reaction during the methylation of secondary amines IX and X with formaldehyde in





Scheme 4.

acetic acid. This mechanism is analogous to that presented by Clarke *et al.*² who used the pathway in Scheme 1 to explain the side reaction taking place in the methylation of dibenzylamine with formaldehyde in formic acid.

EXPERIMENTAL

Preparation of the reactants. *N*-Methyl-*exo*-2-norbornanemethylamine (XIII), *N*-methyl-*endo*-3-phenyl-*exo*-2-norbornanemethylamine (IX), and 1,1'-bis(*endo*-3-phenyl-*exo*-2-norbornyl)dimethylamine (X) were prepared as described earlier.^{11,12} To prepare the deuterated secondary amines XI and XII, 15.95 g (0.094 mol) of 2-phenyl-2-norbornene, 0.205 g of perdeuterioparaformaldehyde (equivalent to 0.064 mol of perdeuterioformaldehyde), and 10 g (0.114 mol) of hexadeuteriodimethylammonium chloride were allowed to react in acetic acid (30 ml) at 85–105 °C for 15 min. Addition of water and ether to the reaction mixture precipitated 1,1'-bis(*endo*-3-phenyl-*exo*-2-norbornyl-3*d*)di-(methyl-*d*₄)amine (XII) as hydrochloride, which was then liberated from its salt by potassium carbonate in a hot water-ethanol mixture. C₂₈H₂₈D₈N (391.62). Mass spectrum: M⁺ *m/e* 391. NMR spectrum (in C₆D₆): δ 7.21 (10 H, a singlet, the phenyl protons), 2.33–2.00 (4 H, the bridgehead protons), 1.80 (2 H, the endoprotons at C-2), and 1.65–0.87 ppm (12 H, the other norbornanering protons). *N*-Methyl-*d*₃-*endo*-3-phenyl-*exo*-2-norbornane-3*d*-methyl-*d*₂-amine (XI) was isolated from aqueous acetic acid and purified by the Hinsberg method. C₁₈H₁₅D₅N (221.38). Mass spectrum: M⁺ *m/e* 221 (9 %) and the base peak at *m/e* 49 (100 %) belonging to the fragment CD₂NH⁺ = CD₂. NMR spectrum (in C₆H₆): δ 7.21 (5 H, a singlet, the phenyl protons), 2.37–2.02 (2 H, the bridgehead protons), 1.78 (1 H, the endoprotons at C-2), and 1.70–1.00 ppm (6 H, the other norbornanering protons).

Reaction of *N*-methyl-*endo*-3-phenyl-*exo*-2-norbornanemethylamine (IX) with formaldehyde in acetic acid. Amine IX (0.173 g, 0.805 mmol) and

0.049 g of paraformaldehyde (equivalent to 1.63 mmol of formaldehyde) were heated in 1 ml of acetic acid in a boiling water bath for 4 h. Five ml of water and solid potassium carbonate were added to the reaction mixture until it was alkaline. The product was taken up in ether, the ether solution dried with potassium carbonate and the solvent evaporated. The residue (0.162 g) consisted of three components, which were identified by gas chromatography: *endo*-3-phenyl-*exo*-2-norbornancarbaldehyde (XVI), *N,N*-dimethyl-*endo*-3-phenyl-*exo*-2-norbornanemethylamine (XV) and amine IX in the proportion 24:29:47. Aldehyde XVI was separated from the amines by extraction and amines IX and XV were isolated by preparative gas chromatography. The structures were confirmed by NMR and IR spectra and by the reference spectra.¹²

Reaction of 1,1'-bis(*endo*-3-phenyl-*exo*-2-norbornyl)dimethylamine (X) with formaldehyde in acetic acid. A mixture of 0.15 g (0.39 mmol) of amine X and 0.021 g of paraformaldehyde (equivalent to 0.7 mmol of formaldehyde) was heated in acetic acid (1 ml) for 4 h. The treatment of the reaction mixture as described above yielded 0.145 g of crude product, which in the gas chromatogram showed peaks for aldehyde XVI, tertiary amine XV, and secondary amine IX in the proportion 60:8:32. The unreacted starting material (X) and its methylation product, 1,1'-bis(*endo*-3-phenyl-*exo*-2-norbornyl)trimethylamine (XVII) did not elute from the column. After the bis-amines X and XVII were precipitated from the solution with hydrochloric acid, compounds XVI, XV, and IX were isolated and identified as described above.

Reaction of 1,1'-bis(*endo*-3-phenyl-*exo*-2-norbornyl)dimethylamine (X) with perdeuterioformaldehyde in acetic acid. A mixture of 4.5 g (10.7 mmol) of amine X hydrochloride and 2.5 g of perdeuterioparaformaldehyde (equivalent to 73.5 mmol of perdeuterioformaldehyde) in 40 ml acetic acid was heated under reflux for 60 h. The methylated X, liberated from its hydrochloride (sparingly soluble in water and ether) with potassium carbonate (the yield of hydrochloride 0.67 g) was identified by mass

and NMR spectra as 1,1'-bis(endo-3-phenyl-exo-2-norbornyl)trimethyl-1'',1'',1''- d_3 -amine (XVIII), $C_{29}H_{33}D_3N$ (402.61). Mass spectrum: M^+ m/e 402 (1%), $M-171$ (an abstraction of the endo-3-phenyl-exo-2-norbornyl radical) at m/e 231 (4%) with the base peak at m/e 61 (100%). NMR spectrum (in C_6D_6): δ 7.21 (10 H, a singlet, the phenyl protons), 2.84–2.60 (2 H, a multiplet, the exo-protons at C-3), 2.40–1.80 (8 H, a multiplet, the *N*-methylene and bridgehead protons), and 1.65–1.00 ppm (14 H, a multiplet, the other protons).

The neutral products and the amines were isolated by extraction from aqueous acetic acid. The main neutral component, endo-3-phenyl-exo-2-norbornanecarbaldehyde (XVI) (yield 1.5 g) did not contain any deuterium according to its mass spectrum. The amine portion (yield 0.8 g) contained *N,N*-dimethyl- d_3 -endo-3-phenyl-exo-2-norbornanemethylamine (XIX) as the main component, $C_{16}H_{18}D_3N$ (234.39). Mass spectrum: M^+ m/e 234 (1%) and the base peak $CD_3N^+(CHD_2)=CH_2$ at m/e 63 (100%). NMR spectrum (in C_6D_6): δ 7.20 (5 H, a singlet, the phenyl protons), 2.71 (1 H, an approximate triplet, the exo-proton at C-3), 2.47–2.23 (2 H, a broad signal, the bridgehead protons), 2.15–1.87 (3 H, a multiplet, the protons of the *N,N*-dimethyl- d_3 -aminomethyl group), and 1.75–1.09 ppm (7 H, the other protons).

Amine X hydrochloride (3.66 g, 9.51 mmol) and 0.65 g of perdeuterioparaformaldehyde (equivalent to 19.1 mmol of perdeuterioformaldehyde) were allowed to react in acetic acid (30 ml) for 4 h as described above. After precipitating the unreacted starting material X and the methylated amine as a hydrochloride, a secondary amine was recovered from the diluted aqueous acetic acid solution (yield 10 mg, 5% of amine XIX as impurity). The amine was identified by mass spectroscopy as *N*-methyl- d_3 -endo-3-phenyl-exo-2-norbornanemethylamine (XX), $C_{15}H_{15}D_3N$ (217.35). Mass spectrum: M^+ m/e 217 (2%) and the base peak $CHD_2-NH^+=CH_2$ at m/e 46 (100%).

Reaction of 1,1'-bis(endo-3-phenyl-exo-2-norbornyl-3d)di(methyl- d_3)amine (XII) with formaldehyde in acetic acid. Amine XII hydrochloride (0.42 g, 1 mmol) and paraformaldehyde (0.15 g, equivalent to 5 mmol of formaldehyde) were heated in 7 ml of acetic acid for 60 h. The reaction mixture was treated as described above yielding the methylated XII, 1,1'-bis(endo-3-phenyl-exo-2-norbornyl-3d)trimethyl-1,1',1'- d_3 -amine (XXI), $C_{29}H_{31}D_3N$ (405.64). Mass spectrum: M^+ m/e 405 (1%), $M-172$ (an abstraction of endo-3-phenyl-exo-2-norbornyl-3d) m/e 233 (7%) and the base peak at m/e 63 (100%). NMR spectrum (in C_6D_6): δ 7.23 (10 H, a singlet, the phenyl protons), 2.37–1.80 (9 H, the bridgehead protons, the C-2 endo-protons and the *N*-methyl protons at 2.09 as a singlet), and 1.70–0.83 ppm (12 H, the other protons). In the gas chromatogram the retention time of the main neutral component, which was isolated

from aqueous acetic acid solution, is the same as that of endo-3-phenyl-exo-2-norbornanecarbaldehyde (XVI). The main amine component was identified by mass and NMR spectra as *N,N*-dimethyl- d_3 -endo-3-phenyl-exo-2-norbornane-3d-methyl- d_3 -amine (XXII), $C_{16}H_{18}D_4N$ (233.38). Mass spectrum: M^+ m/e 233 (3%) and the base peak $CH_3(CH_2D)N^+=CD_2$ at m/e 61 (100%). NMR spectrum (in C_6D_6): δ 7.22 (5 H, a singlet, the phenyl protons), 2.33 (2 H, a multiplet, the bridgehead protons), 2.08 (5 H, a singlet, the protons of *N,N*-dimethyl- d_3 group), 1.89 (1 H, the endo-proton at C-2), and 1.55–1.07 ppm (6 H, the other protons).

Treatment of a mixture of N-methyl-exo-2-norbornanemethylamine (XIII) and N-methyl- d_3 -endo-3-phenyl-exo-2-norbornane-3d-methyl- d_3 -amine (XI) with formaldehyde in acetic acid. A mixture of 0.13 g (0.9 mmol) of amine XIII, 0.205 g (0.95 mmol) of amine XI, and 0.16 g of paraformaldehyde (equivalent to 5.09 mmol of formaldehyde) was heated in 1.6 ml of acetic acid for 9 h. The neutral products and the amines were separated by extraction. *N,N*-Dimethyl-exo-2-norbornanemethylamine (XXIII), the methylation product of amine XIII, distilled at 70 °C/10 Torr in a bulb tube oven and contained no deuterium according to the mass spectrum. The mass spectrum was the same as that of XXIII formed from XIII and formaldehyde.¹¹ The methylation product of amine XI distilled in a bulb tube oven at 120 °C/0.2 Torr and was identified by its mass spectrum as *N,N*-dimethyl-1,1,1- d_3 -endo-3-phenyl-exo-2-norbornane-3d-methyl- d_3 -amine (XXIV), $C_{16}H_{17}D_6N$ (235.40). Mass spectrum: M^+ m/e 235 and the base peak $CH_3(CD_3)N^+=CD_2$ at m/e 63 (100%).

Apparatus. The apparatus employed is the same as used in the previous investigation.¹²

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