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Novel Elimination Reactions Leading to Azacycloheptene Derivatives[1]

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Two isomeric 1-methyl-4-phenylazacycloheptenes have been made by two different novel elimination reactions. Reasons are given for believing these compounds to be *cis* positional isomers, and reaction mechanisms for their formation are proposed.

In the course of preparing additional compounds related to the nonaddicting analgesic ethoheptazine,[3] two novel elimination reactions were encountered in which an ethylenic bond was introduced into the azacycloheptane ring. These reactions led to the positional isomers (Fig. 1) 1-methyl-4-phenylazacycloheptene-3 (I) and 1-methyl-4-phenylazacycloheptene-4 (II). While definitive structures have not been assigned to I and II, evidence is given to show that the compounds are isomers, and that they probably have the *cis* configuration.

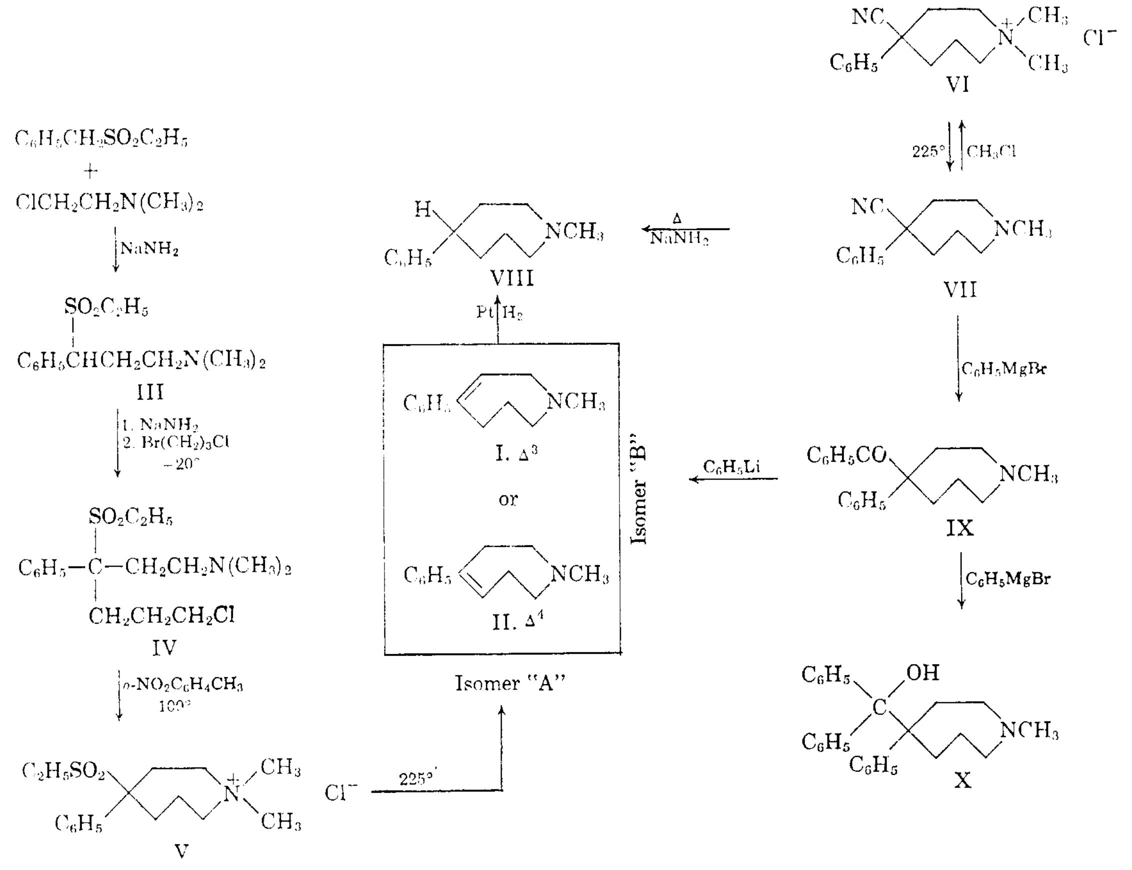

Figure 1

One of the azacycloheptene isomers, designated isomer "A", was obtained at the last step of a process intended to give a sulfone analog of ethoheptazine. It resulted from the high temperature decomposition of 1-methyl-4-phenyl-4-ethylsulfonylazacycloheptane methochloride (V). The synthesis of V is outlined in Fig. 1. Alkylation of the sodio derivative of benzyl ethyl sulfone with 2-dimethylaminoethyl chloride produced 1-phenyl-3-dimethylaminopropyl ethyl sulfone (III), which was converted to the 1,6-amino chloride (IV) by treatment of the sodio derivative of III with trimethylene chlorobromide at −20°. Compound V (m.p.

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(1) Taken in part from the Ph.D. thesis of J. Diamond, Temple University (1955).

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(3) The generic name for 1-methyl-4-phenyl-4-carbethoxyazacycloheptane, also known as Zactane^R.

248–250° dec.) was obtained in 49% yield by cyclization of IV in *o*-nitrotoluene at 100°.

In a previous publication,[4] we reported that 1 - methyl - 4 - phenyl - 4 - cyanoazacycloheptane methochloride (VI) readily lost methyl chloride at 225° in trimethylnonanol forming the corresponding tertiary amine (VII); the addition of methyl chloride to VII produced VI again (Fig. 1). When the sulfone methochloride (V) was treated similarly at 225° in trimethylnonanol, a sulfur-free tertiary amine (I or II, isomer "A") was obtained of composition $C_{13}H_{17}N$. In order to confirm the fact that V had undergone additional decomposition with dechloromethylation, "A" was treated with methyl chloride and a new sulfur-free methochloride (m.p. 245–247° dec.) was formed. To rule out the possibility that "A" and VIII,[4] were identical, a mixed melting point of the hydrochloride (m.p. 144–146°) of VIII with the hydrochloride (m.p. 150–152°) of "A" showed that they were not identical, and the higher refractive index of "A" suggested the presence of unsaturation.

The presence of one ethylenic bond in "A" was established by catalytic hydrogenation. The hydrogenation product and its methiodide derivative were identical in all respects with VIII and its methiodide. This proved the presence of the azacycloheptene moiety in "A" since the structure of VIII had previously been established.[4]

The conjugation of the ethylenic bond with the phenyl group was shown by the ultraviolet absorption spectrum of "A," which exhibited a pronounced maximum ($\lambda_{max}^{C_2H_5OH}$ 2450 Å, e_{max} 10,500) resembling that of styrene ($\lambda_{max}^{C_2H_5OH}$ 2480 Å, e_{max} 13,500). This limited the location of the ethylenic bond to positions 3, 4 or 4, 5 permitting a choice of either I or II for "A."

Another azacycloheptene isomer, designated isomer "B," was encountered while investigating the reaction of 1-methyl-4-phenyl-4-benzoylazacycloheptane (IX) with phenyllithium. The preparation of IX from VII (Fig. 1) has already been reported.[4]

Although phenylmagnesium bromide with IX gave the normal diphenylcarbinol derivative (X), IX reacted abnormally with phenyllithium resulting in the loss of a carbon fragment and the formation of a tertiary amine (I or II, isomer "B") of composition $C_{13}H_{17}N$. The hydrochloride of "B" (m.p. 189–190°) was not identical with the hydrochloride of "A" nor the hydrochloride of VIII. The refractive index of "B" indicated the presence of unsaturation.

Isomer "B" rapidly absorbed one mole of hydrogen, establishing the presence of an ethylenic bond, and the reduction product was identified as VIII. The ultraviolet absorption spectrum of "B" exhibited a pronounced maximum ($\lambda_{max}^{C_2H_5OH}$ 2450 Å. e_{max} 12,400) resembling that of "A" and of styrene. It was apparent that the ethylenic bond of "B" was also in conjugation with the phenyl group and must necessarily be at position 3,4 or 4,5. We therefore conclude that "A" and "B" are positional isomers represented by structures I and II. We have not prepared a sufficient quantity of either of the isomers to use a chemical method of distinguishing between structures I and II.

DISCUSSION

The possibility that "A" and "B" were geometric isomers rather than positional isomers was considered. *Cis-trans* isomerism, however, was ruled out for three reasons: (1) The improbability of the existence of a *trans*-azacycloheptene ring may be deduced from the stereochemistry of the cycloalkenes. *trans*-Cyclohexene does not exist[5] and *trans*-cycloheptene has never been isolated.[6] The more strained *trans*-isomer, first encountered with cyclooctene,[7] becomes possible only with sufficiently large ring structures, when the repulsion between neighboring atoms is diminished. (2) The azacycloheptene isomers "A" and "B" did not exhibit differences in chemical or physical properties expected of *cis-trans* ring isomers. (3) For those systems where geometric isomerism exists, the ultraviolet absorption maximum and extinction coefficient for the more stable isomer differs from that of the labile form by $\Delta\lambda_{max} = 50\text{–}150$ Å and $\Delta\ e_{max} = 5000\text{–}11{,}000$; the more stable isomer has the larger values.[8] In the case of the azacycloheptene isomers "A" and "B," their ultraviolet absorption spectra are very similar, $\Delta\lambda_{max} = 0$ and $\Delta\ e_{max} = 1900$, indicating that the two compounds are thermodynamically similar, and probably of the *cis*-azacycloheptene configuration.

The thermal decomposition of sulfone V led to an olefin (isomer "A") apparently as a result of the loss of ethylsulfinic acid as well as methyl chloride. This represents an unusual reaction as sulfones are generally very stable toward pyrolysis.[9] However, examples of the cleavage of sulfones to sulfinic acid salts and olefins are known when strong alkali is employed at elevated temperature. Unlike the latter reactions, which are believed to occur by an E_2 mechanism,[10] the thermal decomposition of V occurred in the absence of strong alkali, and appears to resemble the Cope reaction.[11]

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[4] J. Diamond, W. F. Bruce, and F. T. Tyson, *J. Org. Chem.*, **22**, 399 (1957).

[5] G. W. Wheland, *Advanced Organic Chemistry*, 2nd ed., Wiley, New York, 1949, p. 376.

[6] K. Ziegler, *et al.*, *Ann.*, **589**, 138 (1954).

[7] L. E. Craig, *Chem. Rev.*, **49**, 1942 (1951).

[8] H. Gilman, ed., *Organic Chemistry*, Wiley, New York, Vol. 3, 1953, p. 168.

[9] *Organic Chemistry*, Vol. 1, 1948, pp. 873, 877–8.

[10] C. M. Suter, *Organic Chemistry of Sulfur*, Wiley, New York, 1944, pp. 683–684.

[11] M. S. Newman, ed., *Steric Effects in Organic Chemistry*, Wiley, New York, 1956, pp. 310–312.

In this reaction, *t*-amine oxides are cleaved thermally to dialkylhydroxylamines and olefins. Accordingly we propose the following mechanism (Fig. 2) for the thermal decomposition of sulfone V: the abstraction of a β-hydrogen by the nucleophilic sulfone-oxygen, the shifting of an electron pair, and the cleavage of the carbon-sulfur bond.

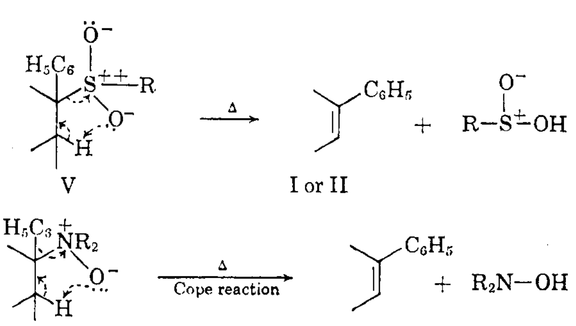

Figure 2

The abnormal formation of an olefin (isomer "B") by the reaction of IX with phenyllithium apparently involves a cleavage of the carbonyl compound by the base. We believe the reaction proceeds through the *O*-lithium salt (Xa) of the diphenylcarbinol intermediate (X), and is an example of a hydride displacement reaction (Fig. 3). The presence of three bulky phenyl groups in close proximity produces steric crowding in Xa, which is relieved by the elimination of benzophenone resulting from a shifting of electron pairs, and the displacement of a hydride ion. There is less crowding between the phenyl groups in benzophenone than in Xa. A secondary reaction follows between benzophenone and the hydride ion, which results in the formation of benzhydrol.

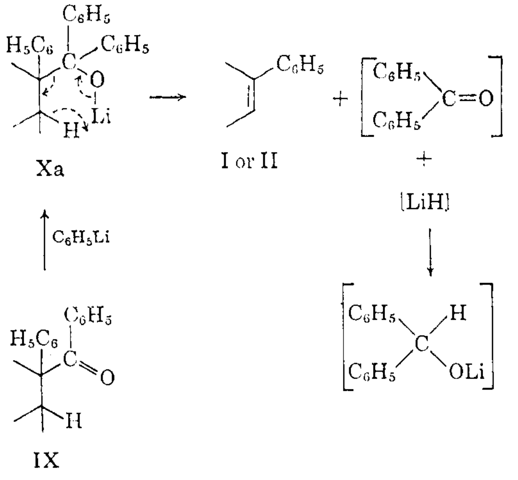

Figure 3

We believe that the difference in behavior between IX with phenyllithium and with phenylmagnesium bromide is a result of the difference in ionic character between the lithium and bromomagnesium salts of X. The ionic character of the *O*-Li bond is greater than that of the *O*-MgBr bond, allowing an oxygen electron pair of the *O*-lithium salt to participate more readily in the series of electron shifts shown in Fig. 3.

The cleavage of X by phenyllithium somewhat resembles the cleavage reaction of β-halo ketones by Grignard reagents (Fig. 4) for which a chelated intermediate is postulated.[12]

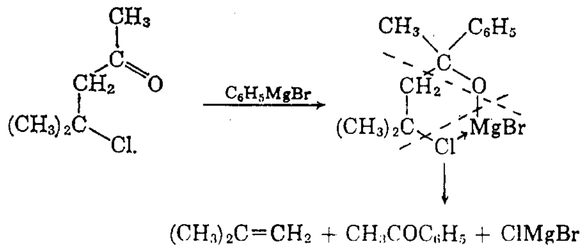

Figure 4

EXPERIMENTAL[13]

1-Phenyl-3-dimethylaminopropyl ethyl sulfone (III). Sodamide (1.1 moles, 42.9 g.) was added portionwise, under a nitrogen atmosphere, to 1.1 moles (203 g.) of benzyl ethyl sulfone[14] in 300 ml. of toluene at 35–40°, while stirring.

Two hours after the addition was completed, 2-dimethylamino-1-chloroethane (prepared from 1.1 moles, 159 g., of the hydrochloride) in 200 ml. of toluene was added dropwise at 30–35°. Two hours after the addition was completed, the cooled mixture was washed with water, and extracted with aqueous hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide solution, and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and distilled. Compound III was obtained as a yellow viscous syrup, b.p. 155–8° (0.3 mm.), n_D^{27} 1.5250; yield 146.3 g. (52.2%).

Anal. Calcd. for $C_{13}H_{21}NO_2S$: C, 61.10; N, 8.28; N, 5.48; S, 12.54. Found: C, 61.20; H, 8.23; N, 5.14; S, 12.52.

The *methiodide*, m.p. 245–247°, was formed in ether.

Anal. Calcd. for $C_{14}H_{24}INO_2S$: C, 42.30; H, 6.80; N, 3.52; S, 8.06; I, 31.9. Found: C, 42.09; N, 6.89; N, 3.48; S. 8.18; I, 32.0.

4-Phenyl-4-ethylsulfonyl-1-methylazacycloheptane methochloride (V). While stirring a solution of 0.55 mole (140.5 g.) of III in 1 l. of toluene, under a nitrogen atmosphere, 0.66 mole (25.7 g.) of sodamide was added portionwise at 35–40°. Two hours after the addition was completed, the temperature of the mixture was lowered to −30°, and 0.60 mole (94.5 g.) of trimethylene chlorobromide in 150 ml. of toluene was added dropwise at −30° to −20°. One-half hour after the addition was completed, the mixture was allowed to warm to room temperature and stand overnight. The cooled mixture was then washed with water, and extracted with aqueous hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide solution, and extracted with ether. After drying the ether extract over anhydrous potassium carbonate, it was filtered, and the filtrate concentrated under reduced pressure. The liquid residue, containing the 1,6-aminochloride (IV), was diluted to 550 ml. with *o*-nitrotoluene, and the solution heated at 100° for 2 hr. whereupon V precipitated. The mixture was cooled, the

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[12] J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, 1956, pp. 373–374.

[13] All melting points were determined in a capillary using a stirred oil bath and are uncorrected.

[14] H. Bohm, *Ber.*, **69B**, 1610 (1936); H. Bohm and H. Fischer, *Ber.*, **75B**, 1310 (1942).

white crystalline precipitate filtered off, and washed with acetone. The yield of V, m.p. 248–250° dec., was 90 g. (49.3 %).

Anal. Calcd. for $C_{16}H_{26}ClNO_2S$: C, 57.9; H, 7.90; N, 4.22; S, 9.66; Cl, 10.68. Found: C, 58.11; H, 8.18; N. 4.00; S, 9.26; Cl, 10.72.

1-Methyl-4-phenylazacycloheptene-3 or -4 (I or II). *Isomer A*. Compound V (0.055 mole, 18.3 g.) was suspended in 100 ml. of trimethylnonanol. The mixture under a nitrogen atmosphere was heated to its reflux temperature (*ca.* 225°) with stirring. The mixture turned dark. The exit gases burned with a blue-green flame in the presence of copper, indicating methyl chloride evolution. A sulfurous odor was also observed. After 1 hr. at its reflux temperature, the mixture was cooled, and extracted with aqueous hydrochloric acid. The acid extract was washed with ether, made basic with sodium hydroxide solution, and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and distilled. Isomer A, (Compound I or II), was obtained as pale yellow liquid, b.p. 100–105° (0.3 mm.), n_D^{26} 1.5565, ultraviolet absorption maximum at $\lambda_{max}^{C_2H_5OH}$ 2450 Å, e_{max} 10,500; yield 6.8 g. (66%). The base was unstable and therefore difficult to analyze. Its structure was confirmed by hydrogenation.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.4; H, 9.13; N, 7.48; S, 0.0. Found: C, 82.30; H, 9.08; N, 6.97; S, 0.0.

The *hydrochloride*, m.p. 150–152°, was formed in acetone-methyl isobutyl ketone. A mixture with the hydrochloride of isomer B melted at 117–130°, indicating their difference.

Anal. Calcd. for $C_{13}H_{18}ClN$: C, 70.0; H, 8.13; N, 6.26; Cl, 15.85. Found: C, 69.96; H, 8.68; N, 6.31; Cl, 15.42.

The *methochloride*, m.p. 245–247°, was formed in acetone-ether. A mixture of the latter derivative with V (m.p. 248–250°) melted at 220–222°, thereby showing their difference.

Anal. Calcd. for $C_{14}H_{20}ClN$. C, 70.7; H, 8.48; N, 5.89; Cl, 14.92. Found: C, 70.49; H, 8.69; N, 5.80; Cl, 14.78.

The *methiodide*, m.p. 183–185°, was formed in acetone.

Anal. Calcd. for $C_{14}H_{20}IN$: C, 51.1; H, 6.12; N, 4.25; I, 38.52. Found: C, 51.03; H, 6.52; N, 4.10; I, 38.6.

α-(1-Methyl-4-phenylazacylcloheptyl-4)-diphenylcarbinol (X). A solution of phenylmagnesium bromide was prepared, under a nitrogen atmosphere, from 0.070 g.-atom (1.7 g.) of magnesium turnings and 0.075 mole (11.9 g.) of bromobenzene in 100 ml. of anhydrous ether. To this solution, 0.050 mole (14.7 g.) of compound IX[4] in 200 ml. of toluene was added, during 0.5 hr., at 30° while stirring. By distilling off the ether, the temperature of the mixture was raised to 90°, and maintained at this temperature for 2.5 hr. The cooled mixture was extracted with aqueous hydrochloric acid, the acid extract washed with ether, made basic with ammonium hydroxide, and extracted with ether. After drying the ether extract over anhydrous potassium carbonate, it was filtered, and concentrated. The residue crystallized on standing. Compound X, m.p. 144–145°, was obtained by trituration of the residue with petroleum ether, and filtration; yield 5.4 g. (29.1%).

Anal. Calcd. for $C_{26}H_{29}NO$: C, 84.10; H, 7.87; N, 3.77. Found: C, 83.66; H, 7.92; N, 3.74.

The *hydrochloride*, m.p. 223–224°, was formed in acetone-ether.

Anal. Calcd. for $C_{26}H_{30}ClNO$: N, 3.43. Found: N, 3.24.

1-Methyl-4-phenylazacycloheptane-3 or -4 (I *or* II). *Isomer B*. A solution of phenyllithium was prepared, under a nitrogen atmosphere, from 0.24 g.-atom (1.7 g.) of lithium shot and 0.12 mole (18.7 g.) of bromobenzene in 100 ml. of ether. To this solution, 0.09 mole (26.4 g.) of compound IX[4] in 100 ml. of toluene was added during 0.5 hr. while stirring. The temperature of the mixture was raised to 90°, and maintained for 3 hr. The cooled mixture was extracted with aqueous hydrochloric acid, the acid extract made basic with sodium hydroxide solution, and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and distilled. Compound I or II, isomer B, was obtained as a yellow liquid, b.p. 95–105° (0.25 mm.), n_D^{25} 1.5605; ultraviolet absorption maximum at $\lambda_{max}^{C_2H_5OH}$ 2450 Å, e_{max} 12,400; yield 12.4 g. (73.8%). The base was unstable and therefore difficult to analyze. Its structure was confirmed by hydrogenation and preparation of the hydrochloride.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.4; H, 9.13; N, 7.48. Found: C, 82.6; H, 9.32; N, 6.94.

The *hydrochloride*, m.p. 189–90°, was formed in ether and recrystallized from acetone-methanol.

Anal. Calcd. for $C_{13}H_{18}ClN$: C, 70.0; H, 8.13; N, 6.26; Cl, 15.85. Found: C, 69.13, 69.30; H, 8.26; N, 6.26; Cl, 15.80.

Catalytic hydrogenation of 1-methyl-4-phenylazacycloheptene-3 or -4. Isomer A. (a) A mixture of 0.0025 mole (0.47 g.) of isomer A (or its hydrochloride) and 0.00025 mole (0.05 g.) of platinum oxide in 15 ml. of methanol was shaken with hydrogen at 25° near atmospheric pressure. Almost the theoretical amount of hydrogen (87 ml.) was absorbed within 10 min., and no further absorption was observed. The catalyst was filtered off, and the filtrate concentrated. The residue was diluted with acetone-ether, and methyl iodide added.

The *methiodide*, m.p. 147–148°, of the hydrogenation product of A, admixed with the methiodide of VIII, obtained by the decyanation of VII,[4] melted at 146–147°, proving their identity.

Isomer B. (b) A mixture of 0.0025 mole (0.47 g.) of isomer B (or its hydrochloride) and 0.00025 mole (0.05 g.) of platinum oxide in 15 ml. of methanol was shaken with hydrogen at 25° near atmospheric pressure. The theoretical amount of hydrogen (87 ml.) was absorbed within 5 min., and then no further absorption was observed. The catalyst was filtered off, and the methanol distilled from the filtrate under reduced pressure. After diluting the residue with acetone-ether, methyl iodide was added.

The *methiodide*, m.p. 147–149°, of the hydrogenation product of B, admixed with the methiodide of VIII, obtained by the decyanation of VII,[4] melted at 146–148°, proving their identity.

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