AMINONITRILE REARRANGEMENT AND THE CLEAVAGE OF 1,1-DIALKYL-Δ^2-TETRAHYDROPYRIDAZINIUM SALTS

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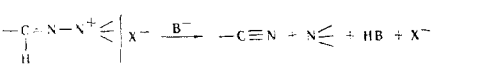
1,1-Dimethyl- and 1-ethyl-1-methyl-Δ^2-tetrahydropyridazinium iodides undergo an aminonitrile rearrangement under the action of alkali with the formation of γ-dialkylaminobutyronitriles.

The aminonitrile rearrangement has been used as a method of showing the structure of the oxidation product of 3-methylhexahydropyridazine which is 6-methyl-Δ^2-tetrahydropyridazine.

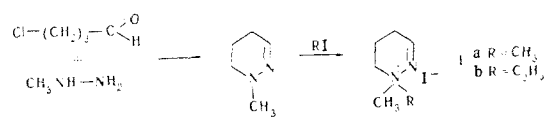
Under the action of NaOH, 3-methyl-substituted Δ^2-tetrahydropyridazinium salts, for which the aminonitrile rearrangement is excluded split off the substituent from the nitrogen atom and undergo far-reaching decomposition.

While the behavior in the presence of bases of aldehydehydrazonium derivatives and of 1,1-dialkyl-Δ^2-pyrazolinium salts has been the object of systematic studies [1] and it has been shown that all the substances investigated without exception undergo cleavage at the N—N^+ bond (aminonitrile rearrangement):

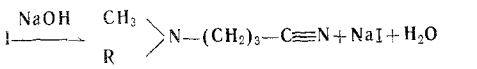


up to the present time not a single example of such a reaction has been described for compounds in which the fragment —CH=N—N^+< is included in the pyridazine ring (1,1-dialkyl-Δ^2-tetrahydropyridazinium salts). A study of just these substances should answer the question of the limits of applicability of the aminonitrile rearrangement which, as has been postulated previously [2], is a general property of substances containing the —CH=N—N^+< grouping.

With this aim, we have for the first time synthesized 1,1-dialkyl-Δ^2-tetrahydropyridazinium salts by the action of alkyl iodides on the previously unknown 1-methyl-Δ^2-hydropyridazine, which was obtained by the condensation of methylhydrazine with γ-chlorobutyraldehyde:



and we have then subjected them to the action of alkali. In the presence of 20% aqueous NaOH solution, even at room temperature both salts are converted in high yields (65%) into the corresponding γ-dialkylaminobutyronitriles:

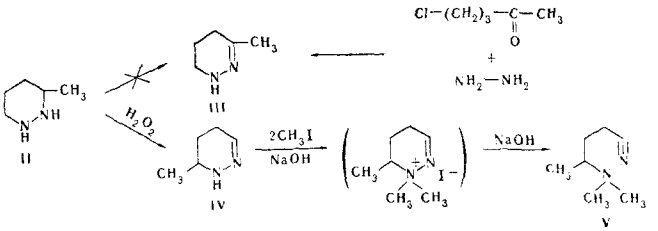


The structure of the latter was confirmed by means of derivatives, analyses, and IR spectra (intense absorption of the C≡N group at 2248 cm^{-1}) and by comparing their constants with literature data.

Thus, it has been shown that the aminonitrile rearrangement also extends to derivatives of Δ^2-tetrahydropyridazine and, in sum, it may be concluded that this reaction is a general property of aldehydehydrazonium derivatives regardless of whether the —CH=N—H^+< link is part of an open chain or is included in a five- or six-membered heterocycle.

It is interesting that for the six-membered derivative the rearrangement takes place with the same ease as for the five-membered rings [3] (room temperature), i.e., under somewhat milder conditions than for compounds with an open chain (boiling in water with alkali [4–6] or in ethanol with sodium ethoxide [4]).

We have established that the aminonitrile rearrangement can be used to elucidate the structure of isomeric tetrahydropyridazines. Thus, the product of the oxidation of 3-methylhexahydropyridazine (II) was previously ascribed [7] the formula of 3-methyl-Δ^2-tetrahydropyridazine (III).

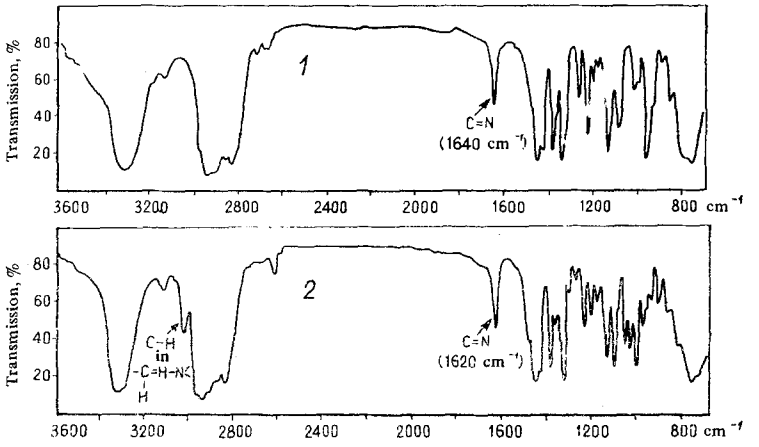


However, its constants and the melting point of the phenylthiourea derivative prepared from it differed considerably from the corresponding figures for authentic III prepared from methyl γ-chloropropyl ketone and hydrazine [8]. We have also found similar differences in the constants (see the experimental part).

In addition, by gas-liquid chromatography* we have established that the product of the oxidation of II and substance III from methyl γ-chloropropyl ketone are pure, but different, substances.

Substantial differences were also observed in the IR spectra of the substances (see figure), particularly in the 800-1400 cm^{-1} region. In the product of the oxidation of II, the frequency of the C=N bond is located at 1620 cm^{-1}, and in substance III the corresponding absorption is at 1640 cm^{-1}. It is known [9] that the

*"Tsvet" chromatograph. Glass column 120 cm long, 10% of cyanoethylated mannitol on Celite 545 (50-70 mesh), carrier gas nitrogen.



IR spectra: 1) 3-methyl-Δ^2-tetrahydropyridazine (III); 2) 6-methyl-Δ^2-tetrahydropyridazine (IV). UR-10 spectrophotometer. Layer thickness 27μ. Rate of scanning the spectrum 150 cm^{-1}/min; recording scale 12 mm/100 cm^{-1}; slit opening program no. 4.

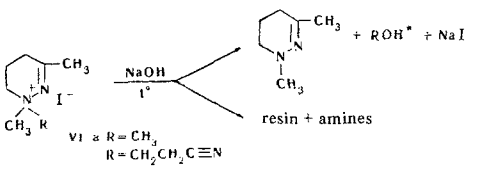
value of the C=N frequency for aldehyde hydrazones is lower (about 1610 cm^{-1}) than for ketone hydrazones (about 1640 cm^{-1}). The spectrum of the substance prepared from II also has a strong band at 3017 cm^{-1} which is not found in that of compound III and which is apparently due to the stretching vibrations of C—H in the $-C(H)=N-N<$ grouping [10]. It might be assumed that the oxidation of II forms a substance with an aldehydehydrazone structure, i.e., 6-methyl-Δ^2-tetrahydropyridazine (IV) and not its 3-methyl-substituted isomer. In this case, an aminonitrile rearrangement should be characteristic of the product of the exhaustive methylation of IV, in contrast to the quaternary salt prepared from III. In actual fact, when IV was treated with methyl iodide and alkali we isolated γ-dimethylaminovaleronitrile (V) in 12% yield* and thereby unambiguously showed the structure of the dehydrogenation product II as 6-methyl-Δ^2-tetrahydropyridazine.

In addition to this, it was of interest to study the cleavage of 3-substituted tetrahydropyridazinium salts, the structure of which excludes the aminonitrile rearrangement. We synthesized two such salts (VIa) and (VIb) by the action of methyl iodide on 1,3-dimethyl-Δ^2-tetrahydropyridazine (VII), which was obtained from methyl hydrazine and methyl γ-chloropropyl ketone, and on 1-β-cyanoethyl-3-methyl-Δ^2-tetrahydropyridazine (VIII), which was prepared by cyanoethylating III.

It was found that on being heated with alkali, VIa and VIb underwent cleavage but their transformation differed from the cleavage of their five-membered analogs which, as has been shown [16], open the pyrazoline ring at the C—N^+ bond with the formation of α,β-conjugated N,N-dialkylhydrazones.

In our case, the behavior of the salts is probably due to the impossibility of the formation by the opening of the tetrahydropyridazine ring of a product stabilized by conjugation. Consequently, for VI the splitting off of the substituent (R) from the nitrogen atom with the formation of VII is more likely, particularly where R contains a mobile β-hydrogen atom. In actual fact, the cleavage of VIb takes place under milder conditions and VII is formed in higher yield.

However, because of the low strength of the N—N^+ and C—N^+ bonds, in addition to this there is far-reaching decomposition with resinification and the liberation of volatile bases, which becomes the main direction of the reaction for VIa:



*For VIb the corresponding olefin and water.

EXPERIMENTAL

1,1-Dimethyl-Δ^2-tetrahydropyridazinium iodide (Ia) and its rearrangement. The condensation of γ-chlorobutyraldehyde [11] with methylhydrazine gave a 10% yield of 1-methyl-Δ^2-tetrahydropyridazine, bp 49° C (11 mm); d_4^{20} 0.9265; n_D^{20} 1.4720. Found, %: C 61.39, 61.13; H 10.11, 10.10; N* 28.37; 28.35%; MR_D 29.67. Calculated for $C_5H_{10}N_2$, %: C 61.19; H 10.27; N 28.55%; MR_D 29.54. The IR

*The low yield is probably due to the fact that in the two-stage alkylation process taking place in an alkaline medium the excess of alkali causes the aminonitrile rearrangement and the V so formed undergoes the further action of methyl iodide.

*Combustion over copper oxide did not give satisfactory results. Acceptable figures were obtained on combustion by the method of Mikhailova and Khromov-Borisov [17]. Substances VII and VIII were subjected to combustion in the same way.

spectrum had the bands of the bonds C=N (1620 cm^{-1}) [9] and C—H in the —C=N—N< grouping (about 3000 cm^{-1}) [10].

A solution of 4.5 g (0.045 mole) of 1-methyl-Δ^2-tetrahydropyridazine in 50 ml of benzene was treated with 5 ml of methyl iodide. After a day, the light yellow precipitate that had deposited was filtered off with suction and dried in a vacuum desiccator. The yield of Ia was 11 g (98%). Mp 135° C (from ethanol). Found, %: N 11.60, 11.58. Calculated for $C_6H_{13}N_2I$, %: N 11.63.

A solution of 10.4 g (0.043 mole) of Ia in 25 ml of water was treated with 50 ml of 20% NaOH. With appreciable evolution of heat, an upper mobile layer separated out, and after the mixture had been saturated with solid caustic soda this was separated off, dried with alkali, and distilled in vacuum.

This gave 3.1 g (65%) of **γ-dimethylaminobutyronitrile** with bp 60° C (9 mm); d_4^{20} 0.87045; n_D^{20} 1.4280. Found, %: MR_D 33.17. Calculated for $C_6H_{12}N_2$: MR_D 33.27. The IR spectrum had strong bands at 2248 cm^{-1} (C≡N group) and 2780 cm^{-1} (dimethylamino group) [12]. **Picrate**: mp 118–120°C (from ethanol).

Literature data: bp 187° C (761 mm); d_4^{20} 0.870; n_D^{20} 1.4276 [13]; mp of the picrate 120° C [14].

1-Ethyl-1-methyl-Δ^2-tetrahydropyridazinium iodide (Ib) and its rearrangement. When 1.05 g (0.011 mole) of 1-methyl-Δ^2-tetrahydropyridazine and 3 ml of ethyl iodide in 25 ml of benzene were allowed to stand for a week at room temperature, 2.4 g (98%) of Ib was obtained in the form of a viscous yellow oil. It was treated in a similar manner to Ia, and distillation yielded 0.8 g (65%) of **γ-ethylmethylaminobutyronitrile** with bp 92° C (22 mm), d_4^{20} 0.8668; n_D^{20} 1.4330. Found, %: C 66.70, 66.80; H 11.50, 11.10; N 22.25, 22.29%. MR_D 37.84. Calculated for $C_7H_{14}N_2$, %: C 66.62; H 11.18; N 22.20%. MR_D 38.18. The IR spectrum had the absorption of a nitrile group (2248 cm^{-1}). **Picrate***: mp 70°C (from ethanol. Found, %: N 19.81, 19.86. Calculated for $C_7H_{14}N_2 \cdot C_6H_3(NO_2)_3OH$, %: N 19.85. Literature data: bp 95–96°C (33 mm) [15].

3-Methyl-Δ^2-tetrahydropyridazine (III). With stirring and external cooling with cold water, 174 g (1.44 mole) of methyl γ-chloropropyl ketone was added dropwise to a solution of 47 g (1.44 mole) of 99.2% hydrazine in 200 ml of methanol. The solvent was distilled off in vacuum and the residue was treated with 250 ml of 50% aqueous NaOH. The organic layer that separated out was removed and, after being dried over alkali, distilled in vacuum through a Vigreux column (12 theoretical plates). This gave 99 g (70%) of III. Bp 67° C (13 mm); d_4^{20} 0.9745; n_D^{20} 1.4933. Mp of the phenylthiourea from III—117°C. Literature data [8]: bp 78°C (30 mm); d_4^{20} 0.9714; n_D^{20} 1.4950; mp of the phenylthiourea 124°C.

3-Methylhexahydropyridazine (II). In portions, 20 g (0.44 mole) of metallic sodium was added to a mixture of 38 g (0.39 mole) of III and 200 ml of ethanol at such a rate that the alcohol boiled gently. After all the sodium had been added, the sodium ethoxide was decomposed by the addition of 70 ml of water. After the ethanol had been distilled off, the upper layer was separated off, dried with solid alkali, and distilled. This gave 28 g (74%) of II with bp 56° C (13 mm); d_4^{20} 0.9356; n_D^{20} 1.4776. Literature data [7]: bp 45–46°C (18 mm); d_4^{20} 0.9350; n_D^{20} 1.4742.

6-Methyl-Δ^2-tetrahydropyridazine (IV). With stirring, 30 ml of 30% hydrogen peroxide was added over 30 min to a solution of 20 g (0.2 mole) of II in 80 ml of water containing 0.1% of cupric chloride cooled externally with a mixture of ice and salt. The mixture was kept at room temperature for another half-hour after which it was saturated with solid caustic soda. The organic layer that separated was removed and dried over alkali and the IV (11 g, 56%) was distilled at a temperature of 67–68°C (16 mm); d_4^{20} 0.9662; n_D^{20} 1.4895. Mp of the phenylthiourea from IV—104–105°C. Literature data [7]: bp 65°C (15 mm); d_4^{20} 0.9666; n_D^{20} 1.4880; mp of the phenylthiourea 106° C.

γ-Dimethylaminovaleronitrile (V). Over half an hour, 21.3 g (0.15 mole) of methyl iodide in 20 ml of methanol and 6 g (0.15 mole) of caustic soda in 50 ml of CH_3OH were added simultaneously from different dropping funnels to a mixture of 14.7 g (0.15 mole) of IV and 50 ml of methanol cooled with water, and the mixture was then stirred for the same time, after which another 25 g of methyl iodide was added over an hour. The reaction mixture was left overnight. After the solvent and the unchanged methyl iodide had been distilled off in vacuum, the viscous residue was treated with 50 ml of 50% aqueous caustic soda. The organic layer that separated out was dried with alkali and distilled in vacuum. In the distillation, a considerable part of the substance resinified. In addition to a small unidentified low-boiling fraction, 2.0 g (12%) of V was isolated in the form of an oily liquid with a specific amine-like odor. Bp 85° C (16 mm); n_D^{20} 1.4430. Found, %: N 22.23, 22.51%; mol. wt. 125.9; 127.3. Calculated for $C_7H_{14}N_2$, %: N 22.20%; mol. wt. 126.2. The IR spectrum of V has bands at 2245 cm^{-1} C≡N group) and at 2780 cm^{-1} (dimethylamino group) [12]. **Picrate**: mp 101–102°C (from ethanol). Found, %: N 20.16, 19.82. Calculated for $C_7H_{14}N_2 \cdot C_6H_3(NO_2)_3OH$, %: N 19.85. **Hydrochloride.** Dry hydrogen chloride was passed through a solution of 0.5 g of V in 25 ml of ether. This gave 0.630 g (98%) of a white precipitate of the hydrochloride of V with mp 127–128°C (from a mixture of ether and ethanol). Found, %: Cl 21.72, 21.78. Calculated for $C_7H_{14}N_2 \cdot HCl$, %: Cl 21.85.

1,3-Dimethyl-Δ^2-tetrahydropyridazine (VII). With stirring, 98.4 g (1.92 mole) of methylhydrazine was added over 30 min to 231 g (1.92 mole) of methyl γ-chloropropyl ketone, using external cold-water cooling (pronounced evolution of heat!). Then the reaction mixture was diluted two-fold with water and was stirred at room temperature for another 2 hr, after which 60 g of KOH was added and the upper layer was separated off, dried with KOH, and distilled in vacuum through a Vigreux column (12 theoretical plates). The yield of VII was 93.8 g (44%). Bp 49° C (16 mm); d_4^{20} 0.9138; n_D^{20} 1.47376. Found, %: C 63.88, 64.80; H 10.75, 10.24; N 25.17, 24.74%; MR_D 34.49. Calculated for $C_6H_{12}N_2$, %: C 64.25; H 10.75; N 24.98%; MR_D 34.19. The IR spectrum had absorption at 1635 cm^{-1} (—C=N— bond) [9]. **Picrate**—light yellow prisms with mp 90–91°C (from ethanol). Found, %: N 20.76, 20.63. Calculated for $C_6H_{12}N_2 \cdot C_6H_3(NO_2)_3OH$, %: N 20.52. The **methiodide (VIa)** was obtained similarly to Ia (90%) yield. White prisms with mp 150–151°C (from ethanol by the addition of ether). Found, %: N 11.09, 11.11; I 49.15, 49.40. Calculated for $C_7H_{15}N_2I$, %: N 11.34; I 49.40.

1-(β-Cyanoethyl)-3-methyl-Δ^2-tetrahydropyridazine (VIII) was obtained similarly to the 1-(β-cyanoethyl)-Δ^2-pyrazolines [18]. A mixture of 15 g (0.15 mole) of III and 12 g (0.285 mole) of freshly-distilled acrylonitrile in 100 ml of water was heated under reflux in the boiling water bath for 2 hr 30 min. The upper layer was separated off and the lower was extracted with ether. The extract was combined with the upper layer and dried with $MgSO_4$ and after the solvent had been driven off the residue was distilled in vacuum. Yield 13 g (57.4 g). Bp 116°C (9 mm); d_4^{20} 1.0076; n_D^{20} 1.4395. Found, %: C 63.44, 63.70; H 8.80, 8.86; N 27.78, 27.98. Calculated for $C_8H_{13}N_3$, %: C 63.54; H 8.67; N 27.78. IR spectrum, ν cm^{-1}, 1650 (—C=N—) [9], 2250 (—C≡N).

The methiodide **(VIb)** was synthesized in the same way as the other quaternary salts. Viscous yellow oil (90% yield).

Cleavage of the methiodides VIa and VIb. A mixture of the alkiodides (0.2 mole) and a 150% excess of powdered NaOH was heated in the oil bath in a Würtz flask with a thermometer immersed in the mixture, a descending condenser, and a receiver containing solid NaOH to the outlet of which were attached in series two Tishchenko bottles containing 100 ml of 18% HCl and a Tishchenko bottle containing bromine water. The decomposition of VIa took place at 150–280°C and that of VIb at 80–100 C. The volatile bases were absorbed by the hydrochloric acid. The bromine water was not decolorized in either of the experiments. The distillate collected in the receiver was dried with alkali and distilled. The light fractions were absorbed in 18% HCl and distillation of the residue yielded pure VII. The constants, IR spectra, and mp of the picrate of the latter

*According to Corse et al. [15], mp 155–156° C. We consider these figures to be erroneous, since repeated recrystallization did not raise the melting point of the derivative.

were accurately identical with the authentic figures. The yield of VII from VIa was 30% and from VIb 70%. The salts of the volatile bases absorbed by the HCl were evaporated and dried to constant weight and were then extracted with hot chloroform. The unextracted part, NH_4Cl, was filtered off on a Büchner funnel and, after drying, weighed. The extract, treated similarly, was recrystallized from ethanol and the equivalent of the salt was determined by titration (with an alcoholic solution of NaOH to phenolphthalein). The equivalents found were close to the calculated figures. VIa gave 60% of NH_3 and 60% of dimethylamine, and VIb gave 25% of NH_3.

REFERENCES

1. Yu. A. Naumov and I. I. Grandberg, Usp. khim., 35, 21, 1966.

2. B. V. Ioffe and K. N. Zelenin, Abstracts of Papers at a Conference on Five-Membered Nitrogen-Containing Heterocycles [in Russian], Rostov on Don, 1962.

3. B. V. Ioffe and K. N. Zelenin, ZhOKh, 33, 3231, 1963.

4. R. F. Smith and L. E. Walker, J. Org. Chem., 27, 4372, 1962.

5. B. V. Ioffe, Z. I. Sergeeva, and K. M. Dervinskaite, ZhOKh, 33, 2794, 1963.

6. I. I. Grandberg, ZhOKh, 34, 569, 1964.

7. Yu. S. Shabarov, M. G. Kuz'min, and R. Ya. Levina, ZhOKh, 30, 2473, 1960.

8. A. N. Kost, I. I. Grandberg, A. P. Terent'ev, and S. N. Milovanova, ZhOKh, 29, 93, 1959.

9. R. W. Wiley, S. C. Slaymaker, and H. Kraus, J. Org. Chem., 22, 204, 1957.

10. B. V. Ioffe and K. N. Zelenin, ZhOKh, 33, 3594, 1963.

11. R. B. Loftfield, J. Am. Chem. Soc., 73, 1365, 1951.

12. K. D. Hill and C. D. Meakins, J. Chem. Soc., 760, 1958.

13. W. Keil, Z. Physiol. Chem., 171, 246, 1927.

14. F. Petit, Bull. Soc. Chem. Belg., 5, 12, 775, 1926.

15. J. Corse, J. T. Bryant, and H. A. Shonle, J. Am. Chem. Soc., 68, 1905, 1946.

16. B. V. Ioffe and K. N. Zelenin, DAN, 154, 864, 1964.

17. T. A. Mikhailova and N. V. Khromov-Borisov, ZhAKh, 20, 359, 1965.

18. S. I. Suminov and A. N. Kost, Izv. VSh, 6, no. 4, 601, 1963.

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