Sodium Borohydride Reduction of Cross-Conjugated 1-Pyrrolines. The Reinvestigation of the Formation of a 1-Azabicyclo[3.2.0]heptane[1]

A. I. MEYERS AND H. SINGH

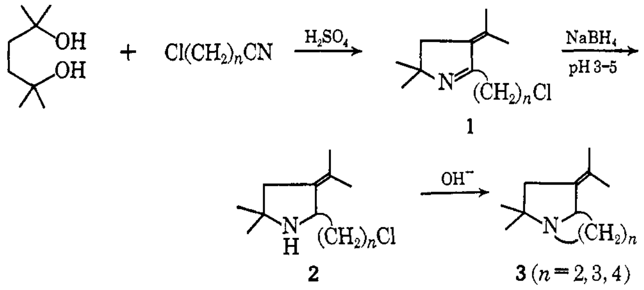
Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122

Received January 29, 1968

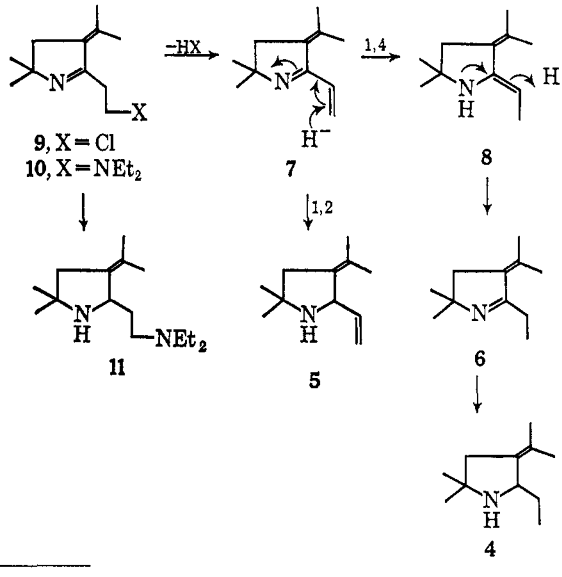
The cyclization of 2-(2-chloroethyl)-3-isopropylidene-5,5-dimethyl-1-pyrroline (**1**) has been reexamined and found to give, in addition to the previously reported 1-azabicyclo[3.2.0]heptane system (**3**, $n = 2$), two other products, 3-isopropylidene-5,5-dimethyl-2-vinylpyrrolidine (**5**) and 2-ethyl-3-isopropylidene-5,5-dimethylpyrrolidine (**4**). The latter two products were formed from the intermediate 2-vinyl-1-pyrroline derivative (**7**) by 1,2 and 1,4 addition of sodium borohydride. A study to determine the effect of varying conditions on the reduction of **7** was made and in all cases the 3-isopropylidene group was unaffected whereas 1,4 addition was the predominant path taken. Spin-decoupling experiments were performed on the 1-pyrrolines and long-range coupling between the isopropylidene methyl protons and the ring protons was observed.

In 1961, the formation of 1-azabicycloalkanes (**3**) was reported[2] to occur *via* the sequential process shown in Scheme I. The bicyclic bases were obtained in good yields without isolation of any of the intermediates, **1** and **2**. In connection with another study, the 1-azabicyclo[3.2.0]heptane, **3** ($n = 2$), was required and upon examination of an 8-year-old sample by gas chromatography it was found to consist of a three-component mixture. In order to determine whether the bicyclic base had deteriorated in storage or whether the previously reported compound was indeed a mixture, the synthesis was repeated in exactly the same manner. Although the infrared spectrum and elemental analysis of "pure" **3** ($n = 2$) were in accord with the previously reported results, the gas chromatogram revealed three distinct peaks in the ratio 2.5:1:2.4. The nmr spectrum of the mixture confirmed the complexity of "pure" **3** ($n = 2$) and exhibited signals in the vinyl region (4.6–6.1 ppm) as well as signals which disappeared upon the addition of heavy water. The mixture was separated by collection from the gas chromatograph effluent and each fraction examined by nmr. The first fraction, which represented 42.4% of the mixture, possessed a well-defined triplet at 0.89 ppm (3 H, $J = 7$ Hz), a quartet partially hidden at 1.2–1.6 ppm (2 H, $J = 7$ Hz), a broad signal centered at 3.78 ppm (1 H), two sharp singlets at 1.03 (3 H) and 1.35 ppm (3 H), a broad intense peak at 1.67 ppm (6 H), an AB quartet centered at 1.95 and 2.27 ppm (2 H, $J = 14$ Hz), and a broadened peak at 1.75 ppm (1 H) which was exchangeable with deuterium oxide. The infrared spectrum possessed a broad band at 2.95 μ as the only distinctive feature. These data suggested that the initial component of the mixture was the 2-ethylpyrrolidine derivative, **4**. The second fraction collected, representing 16.9% of the mixture, possessed an exchangeable proton signal ($\sim$1.3 ppm), the characteristic terminal vinyl signals at 4.6–6.1 ppm (3 H), a doublet at 4.25 ppm (1 H, $J = 8$ Hz), a broad singlet at 1.65 ppm (6 H), two sharp singlets at 1.08 (3 H) and 1.26 ppm (3 H), and a diffuse AB quartet centered at 2.27 ppm. The infrared spectrum exhibited absorption at 2.95 and 6.08 μ. These data were consistent with the 2-vinylpyrrolidine, **5**. The third and final component representing 40.7% of the mixture did not exhibit any change in its nmr spectrum upon the addition of heavy water. The spectrum contained two sharp singlets at 0.92 (3 H) and 1.12 ppm (3 H), a broad triplet and a diffuse triplet (indicating long-range coupling) at 1.56 (3 H) and 1.69 ppm (3 H), respectively, an AB quartet at 2.30 and 2.65 (2 H, $J = 10$ Hz), a multiplet centered at 3.30 ppm (2 H), and a diffuse doublet at 4.35 (1 H). The infrared spectrum possessed no absorption in the 3-μ region. This component was considered to be the 1-azabicyclo[3.2.0]heptane, **3** ($n = 2$), originally reported.[2] To confirm the structures assigned to **4** and **5**, their synthesis was accomplished using 2,5-dimethyl-2,5-hexanediol and propionitrile and acrylonitrile, respectively,[3] to obtain the 1-pyrrolines, **6** and **7** (Scheme II). The former was reduced in 94%

SCHEME I



SCHEME II



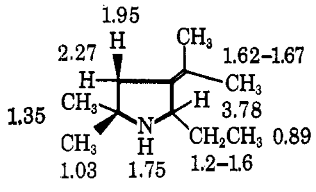
---

(1) This study was supported by the National Institutes of Health (NIGMS-06248-08) and the U. S. Army Research and Development Command (DA-49-193-MD-2991). This is Contribution No. 328 to the Army Research Program on Malaria.

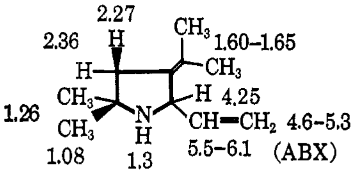
(2) A. I. Meyers and W. Y. Libano, *J. Org. Chem.*, **26**, 4399 (1961).

(3) A. I. Meyers and J. J. Ritter, *ibid.*, **23**, 1918 (1958).

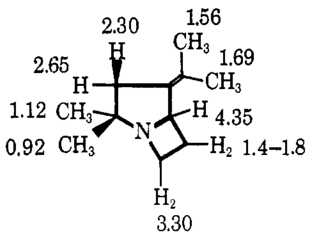
yield to the pyrrolidine derivative, **4**, utilizing aqueous sodium borohydride at pH 3–5. Comparison of this product with that isolated from the aforementioned mixture showed that they were identical in every respect. On the other hand, reduction of the 2-vinylpyrroline, **7**, under these conditions gave a 97% yield of a mixture which contained two components identical, with respect to their retention times, with **4** and **5** isolated earlier. Furthermore, both products were collected from the effluent of a gas chromatograph and exhibited nmr spectra identical with **4** and **5**. The origin of **4** (and **5**) is undoubtedly due to 1,2- and 1,4-hydride addition upon **7** resulting in **8** and **5**. The former, which is an enamine, is protonated to **6** in the acidic medium and is subsequently reduced to **4**. The successive reduction of conjugated double bonds by metal hydrides has been amply discussed in a recent review.[4] Since **7** represented an unusual cross-conjugated system, addition information regarding the factors affecting the mode of reduction were considered to be of interest. Varying conditions (time, temperature, and quantity of borohydride) were studied and the results are summarized (Table I). It can be seen that support for the above mechanism (**7** → **8** → **6** → **4**) is adequately obtained by the isolation of **6** when less than 1.0 molar equiv of sodium borohydride is employed (entry 2). The slight variation in the ratio of **4** to **5** (2–3:1) under all conditions when sufficient borohydride was used (entries 1, 4, 5, 6) is a good indication that the vinyl derivative **7** is the intermediate during the concurrent formation of the 1-azabicyclo[3.2.0]-heptane, since **4** and **5** accompanied the latter within these limits (2.5:1).



4



5



3 ($n = 2$)

The appearance of **7** as a by-product in the formation of **9** by the previously described route[2] is to be expected since β-substituted 1-pyrrolines readily eliminate hydrogen halides or amines (**10**) to form the vinyl conjugated systems. This elimination takes place merely on standing or with slight warming. It was observed that the aminoethylpyrroline, **10**, could not be distilled even under the mildest conditions and when attempts were made to determine its purity by gas chromatography only the peak characteristic of **7** was visible. However, if crude and freshly prepared **10** was reduced with sodium borohydride, it was smoothly converted into the pyrroline **11** which was completely stable during distillation. This fact is not surprising since the driving force (conjugation) for elimination has been removed. Of further interest is the fact, that in every case studied, the exocyclic double bond on the ring was completely unaffected by the borohydride reduction. It is quite probable that, even though the isopropylidene group is conjugated to the C=N link, the bulk of the methyl groups inhibit hydride attack. Steric effects upon borohydride reductions have been noted previously.[4]

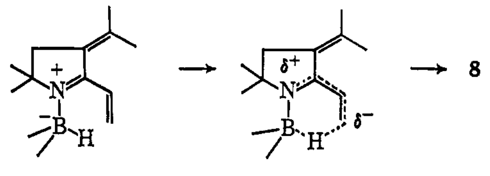
Table I

Sodium Borohydride Reduction of 3-Isopropylidine-5,5-dimethyl-2-vinyl-1-pyrroline (**7**)[a]

Entry	Moles of NaBH$_4$/ mole of **7**	T, °C	Time, hr	Total recovery, %	Compound, % **4**	**5**	**6**	**7**
1	1.0	0–5	1	97	66	34	. .	. .
2	0.5	0–5	1	95	11	29	31	29
3	1.0	(−15)–(−20)	1	85	49	33	11	6
4	2.0	0–5	1	95	67	33	. .	. .
5	1.0	0–5	3	98	65	35	. .	. .
6	2.0	0–5	3	97	70	30	. .	. .

[a] Product composition was determined using a gas chromatograph containing a 12-ft column packed with 5% KOH–Chromosorb P coated with 20% Dow Corning DC-710 at 130°. All reactions were carried out in aqueous solutions at pH 3–5 except entry 3, which was performed in the presence of added ethanol (1:1).

The predominance of 1,4 addition of borohydride in every case can be attributed to a chelation effect of the 2-vinylpyrroline with the hydride reagent giving rise to a complexed intermediate and a subsequent transition state of similar geometry. 1,2 addition would be somewhat inhibited by the presence of the 2-vinyl substituent. The nmr spectra of the 1-pyrrolines, **6** and **7**, and their reduced derivatives, **4** and **5**, deserve some comment. Examination of the 60-MHz spectrum of **7** reveals that the methyl protons of the isopropylidene group appear as diffuse triplets at δ 1.79 ($J \approx 1$ Hz) and 1.97 ppm ($J = 2$ Hz). The C-4 protons, normally expected to appear as a singlet (the *gem*-dimethyls at C-5 form a sharp six-proton singlet) resonate at δ 2.4 ppm as a broad singlet. When the latter signal is irradiated, both methyl signals are clearly decoupled to the expected singlets indicating homoallylic coupling between the protons at C-4 and the isopropylidene group.[5] Since homoallylic coupling is known to be greater in transoid than in cisoid systems, the methyl

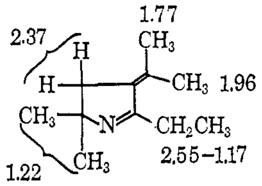


---

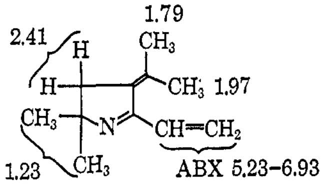
[4] R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.*, **6**, 45 (1966).

[5] N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 110.

group at 1.79 ppm is assigned *cis* to the C-4 protons and the methyl group at 1.97 ppm assigned *trans*. Similar spectral properties were observed for the 2-ethyl pyrroline, **6**, on the basis of decoupling experiments. The spectrum of **5**, on the other hand, showed no long-range coupling between the isopropylidine group and the C-4 protons. Irradiation of the AB quartet at 2.22 and 1.36 ppm failed to alter the two overlapping singlets at 1.60–1.65 ppm. Similar lack of long-range coupling was also observed in **4**. It is, therefore, concluded that the long-range coupling observed in **6** and **7** is due to the rigidity of the ring which contains four sp^2 centers (not including the 2-substituents) and is absent in **4** and **5** owing to the increased flexibility of the five-membered ring. Since coupling depends upon [cos^2 θ (CH$_2$C=C)][cos^2 θ (CH$_3$C=C)] relationship of the dihedral angles of the homoallylic protons involved,[6] the rigidity of **6** and **7** allows the C-4 protons and the methyl protons to assume a 90° orientation with respect to the C=C. When the C=N is reduced, the ring, with its added flexibility, may assume several successive conformations resulting in the destruction of the dihedral angles necessary to produce long-range coupling.



6



7

Experimental Section[7]

The nmr spectra were taken on a Varian A-60 spectrometer using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. Spin decoupling was performed on a Varian V-6058 instrument. Infrared spectra were taken on a Perkin-Elmer 257 grating spectrophotometer. The gas chromatography experiments were performed on a F & M 500 gas chromatograph equipped with a disk integrator. The accuracy of the determinations were ±2%.

3-Isopropylidene-5,5-dimethyl-1-azabicyclo[3.2.0]heptane (3, n = 2).—The previously reported[2] synthesis was repeated and the pure azabicycloheptane derivative obtained by gas chromatographic separation as described earlier: bp 110° (40 mm); n^{25}D 1.4785.

Anal. Calcd for C$_{11}$H$_{19}$N: C, 80.00; H, 11.51; N, 8.48. Found: C, 79.98; H, 11.21; N, 8.49.

2-Ethyl-3-isopropylidene-5,5-dimethyl-1-pyrroline (6) and 3-isopropylidene-5,5-dimethyl-2-vinyl-1-pyrroline (7) were prepared as described in a previous report.

2-Ethyl-3-isopropylidene-5,5-dimethylpyrrolidine (4).—A solution of **6** (16.5 g, 0.1 mol) in 1.2 *M* sulfuric acid (15 ml) was cooled to 0° with stirring and the pH adjusted to 3–4 by the addition of 6 *M* sodium hydroxide. The reduction and isolation was carried out in exactly the same manner as the typical procedure for the reduction of **7** (below). There was obtained 15.8 g (94.5%) of the reduced product, **4**, bp 39–40° (1 mm). The spectral properties have been discussed in the text.

Anal. Calcd for C$_{11}$H$_{21}$N: C, 79.15; H, 12.57; N, 8.38. Found: C, 79.09; H, 12.36; N, 8.29.

Reduction of 3-Isopropylidene-5,5-dimethyl-2-vinyl-1-pyrroline (7). Typical Procedure (Entry 1, Table I).—A solution of **7** (8.15 g, 0.05 mol) in 20 ml of 1.5 *M* sulfuric acid was cooled to 0° in an open beaker. The electrodes of a pH meter (Beckman Zeromatic) were inserted and 6 *M* sodium hydroxide added to render the solution pH 3–4. A solution of sodium borohydride (1.9 g, 0.05 mol) in 10 ml of water containing 1 drop of 35% sodium hydroxide was added dropwise with magnetic stirring to the above maintaining the temperature between 0 and 5° and the pH 3–5 by the periodic addition of 4 *M* sulfuric acid. The addition of the reducing solution required 15 min (as in all cases in Table I) and then the mixture was stirred for 1 hr at 0° and pH 3–5. The mixture was then made strongly alkaline with 35% sodium hydroxide maintaining the temperature of the beaker contents below 15° during the neutralization. The alkaline solution was extracted with ether; the latter solution was dried (Na$_2$SO$_4$), concentrated, and distilled giving 8.0 g (97%) of a mixture of **4** and **5**, bp 110–117° (40 mm). A sample was removed and introduced into the gas chromatograph giving the data tabulated.

2-(2-Diethylaminoethyl)-3-isopropylidene-5,5-dimethyl-1-pyrroline (10).—To a cold (0°), stirred solution of 3-diethylaminopropionitrile (25.3 g) in 200 g of concentrated sulfuric acid was added, in portions through a powder funnel, 2,5-dimethyl-2,5-hexanediol (29.2 g) over a 30-min period. The mixture was stirred at 0–5° for 2 hr and poured onto 400 g of chipped ice. The aqueous mixture was extracted with chloroform until the latter extracts were colorless and then made alkaline with 35% sodium hydroxide. Care was taken to maintain the temperature of the solution below 25° during the neutralization. The oil which had separated was extracted with ether, dried (K$_2$CO$_3$), and concentrated to give 25.7 g of crude **10**. Thin layer chromatography (dioxane) indicated that the product was only slightly contaminated with a minor component. Attempted distillation at 70° (0.1 mm) resulted in considerable elimination of the amine moiety giving a mixture of **10** and the vinyl pyrroline **7**.

The crude product (**10**) had ir bands (neat) at 6.09 (C=C), 6.28 μ (C=N); nmr (CDCl$_3$), δ 2.75 (s, 4, >NCH$_2$CH$_2$N<), 2.62 (q, 4, -CH$_2$CH$_3$), 2.40 (m, 2, C,4), 2.00 (t, 3, J = 2 Hz, =CCH$_3$), 2.81 (t, 3, J = 0.5 Hz, =CCH$_3$), 0.9–1.4 [s, t, 12, (CH$_3$)$_2$, -CH$_2$CH$_3$)$_2$].

The product was used without further attempts at purification for the subsequent experiment.

2-(2-Diethylaminoethyl)-3-isopropylidene-5,5-dimethylpyrrolidine (11).—A solution of **10** (11.8 g, 0.05 mol) in 50 ml of 4 *M* sulfuric acid was cooled to 0–5° in a beaker and fitted with electrodes from a pH meter. The pH was adjusted to 3-5 by the dropwise addition of 6 *M* sodium hydroxide. Sodium borohydride (1.9 g, 0.05 mol) dissolved in 15 ml of water containing 1 drop of the aforementioned pH and temperature. After stirring for 1.5 hr, the solution was rendered alkaline (pH 9–10) and extracted repeatedly with ether. The extracts were dried (K$_2$CO$_3$), concentrated, and distilled to give 5.8 g (50%) of **11**: bp 66–70° (0.1 mm); ir (neat), 2.96 (NH); nmr (neat), δ 3.86 (m, 1, H-2).

Anal. Calcd for C$_{15}$H$_{30}$N$_2$: C, 75.67; H, 12.60; N, 11.76. Found: C, 75.30; H, 12.88; N, 11.44.

Registry No.—Sodium borohydride, 1303-74-8; **3** (n = 2), 16336-07-5; **4**, 16336-08-6; **7**, 16336-09-7; **10**, 16336-10-0; **11**, 16336-11-1.

---

[6] M. Karplus, *J. Chem. Phys.*, **33**, 1842 (1960).

[7] Analyses performed by Galbraith Laboratories, Knoxville, Tenn.