218. Synthesis of Aristoteline-Type Alkaloids

Part II[1])

The Structure of Neohobartine, a Side Product of the Hobartine-Aristoteline Transformation

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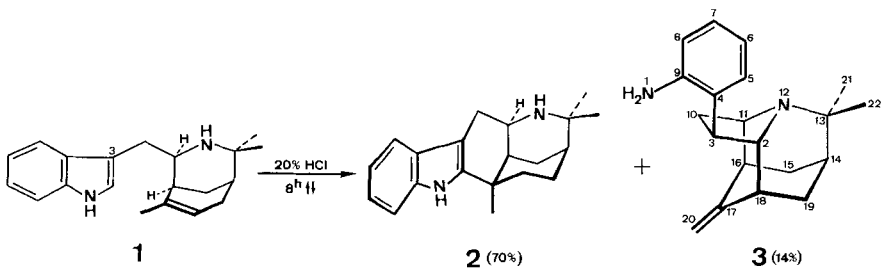
Summary

The structure of neohobartine (**3**), a side product of the acid-catalyzed conversion of (−)-hobartine (**1**) into (+)-aristoteline (**2**), has been elucidated by spectroscopic methods. Possible mechanistic pathways leading to its 1-azaadamantane skeleton are discussed.

Recently the acid-catalyzed transformation of synthetic (−)-hobartine (**1**) into (+)-aristoteline (**2**) *(Scheme 1)* has been employed to corroborate the absolute configuration of the former [1]. The same reaction had been used before by *Lévy et al.* [2] and by *Stevens & Kenney* [3] in the last step of their syntheses of (±)-aristoteline. Whereas neither of the two groups mentioned the formation of a by-product in this reaction, we noticed the appearance of a minor unpolar component [1].

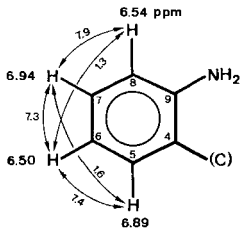
In this communication, data are presented which suggest structure **3** for this side product, for which the trivial name neohobartine is proposed.

Scheme 1

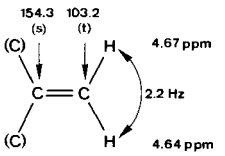


[1]) [1] should be considered as part 1 of this series.

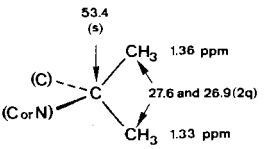
Following the treatment of synthetic (–)-hobartine (**1**) with 20% HCl, neohobartine (**3**) was isolated in 14% yield from the resulting mixture by column chromatography as an optically active crystalline material. The mass spectrum of **3** shows a strong M^+ at m/z 294 (rel. int. = 100%) indicating a molecular formula of $C_{20}H_{26}N_2$; thus **3** is isomeric with **1** and **2**. The UV absorption spectrum [λ_{max} 292 (3.88), 244 (sh, 3.86) in EtOH] (which undergoes a strong hypochromic shift upon addition of acid) is clearly not consistent with the presence of an indole chromophore but rather is characteristic for aniline derivatives [4]. This proposal was substantiated by an examination of the low-field part of the ^{1}H-NMR spectrum (300 MHz) of **3** which revealed the presence of 4 adjacent aromatic protons having chemical shifts and coupling constants in the expected range for *o*-alkyl-aniline derivatives (unit **A**) [5]. That **3** contains indeed a primary aromatic NH_2-group was confirmed through the formation of a red azo dye by coupling the corresponding diazonium salt with *β*-naphtol [6].



A



B

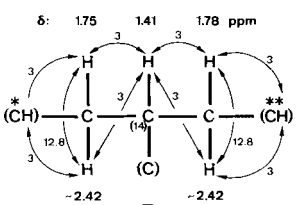


C

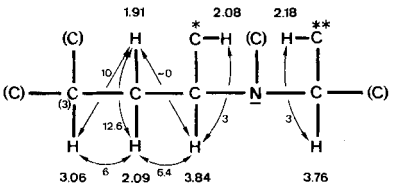
From the ^{13}C-NMR spectrum it could be seen that the remaining 14 C-atoms of **3** are spread among 2 CH_3-groups (27.6 and 26.9 ppm), 4 CH_2-units (103.2, 34.8 and 2 × 33.8 ppm), 6 CH-groups (62.9, 59.7, 48.5, 42.9, 42.2 and 32.5 ppm) and 2 fully substituted C-atoms (154.3 and 53.4 ppm). The two most deshielded signals (103.2 (*t*) and 154.3 (*s*)) suggest the presence of a methylidene group (unit **B**) which is readily identified in the ^{1}H-NMR spectrum as an *AB*-system located at 4.67 and 4.64 ppm (^2J = 2.2 Hz).

Since the 2 CH_3-groups appear as *singlets* in the ^{1}H-NMR spectrum (1.33 and 1.36 ppm) they must be attached to the remaining quaternary C-atom (fragment **C**).

First-order interpretation of the remaining signals in the ^{1}H-NMR spectrum of **3**, assisted by homonuclear decoupling experiments, revealed the presence of a quasi symmetrical sub-unit **D**.



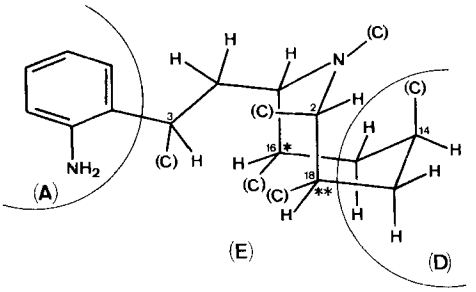
D



E

The shape of the C,H-network surrounding the alipathic N-atom was deduced from the ^{1}H-NMR data as shown in partial structure **E**.

A summation of the elements present in the 5 sub-units **A**–**E** (excluding the groups in parentheses) shows that all atoms of the molecular formula $C_{20}H_{26}N_2$ are accounted for. Further evaluation of the ^{1}H-NMR spectrum of **3** led to the conclusion that the asterisked CH-groups of partial structure **E**, which appear as unstructured *multiplets* at 2.18 and 2.08 ppm are identical with the corresponding asterisked CH-groups of **D**[2]). The pronounced deshielding of *H*–C(3) (3.06 ppm, fragment **E**) indicates that it is in a benzylic position. Thus sub-unit **A** is most likely linked to C(3) of partial structure **E**. The structural relationships deduced so far can be summarized as follows:



F

A comparison of **F** with the structure of the starting material **1** *(Scheme 1)* suggests that the gem. dimethyl group **C** should be placed between C(14) and the aliphatic N-atom and that the methylidene unit **B** (most likely derived from the olefinic CH_3-group of **1**) represents the missing link between C(16) and C(18). The only possibility to complete the resulting 1-azaadamantane partial structure is to connect C(3) with C(2). This operation leads to the constitutional formula **3** with undefined configuration at C(3). The fact that there is no significant coupling ($^3J \leq 0.5$ Hz) between *H*–C(2) and *H*–C(3) points to a dihedral angle of *ca.* 90° between these two H-atoms[3]). Inspection of *Dreiding* models shows that an orthogonal relationship between *H*–C(2) and *H*–C(3) results if the *o*-aniline substituent of **3** occupies the *exo*-position at C(3) as shown in *Scheme 1*.

The formation of a compound of structure **3** upon acid treatment of hobartine (**1**) can be rationalized by assuming that C(3) of the starting material is protonated to yield the indolenine cation **I**[4]) *(Scheme 2)*, which is attacked by either of the two internal

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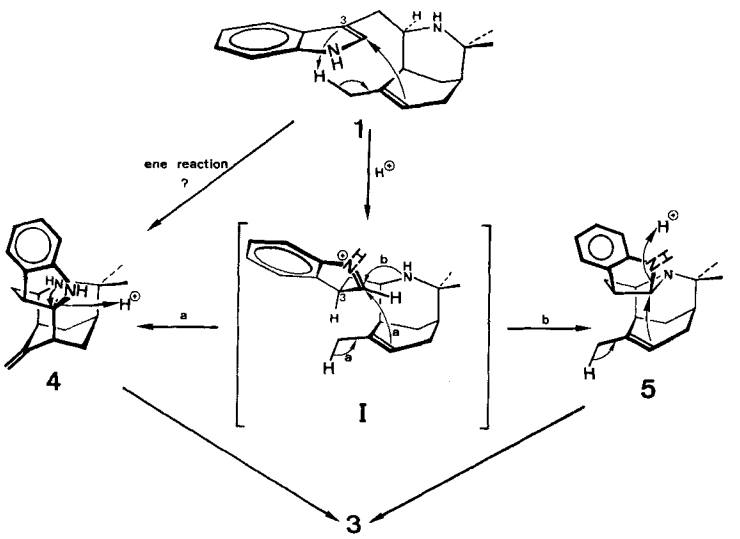
[2]) Decoupling experiments furnished only ambiguous information as to whether CH* of **D** corresponds to CH* or CH** of **E** or *vice versa*. However, since **D** has a local plane of symmetry through the central atom C(14) this uncertainty has no deleterious effect on the logics employed to deduce the structure of **3**.

[3]) The symmetrically disposed fragment H_{endo}–C(10)/*H*–C(11) also shows a vanishing coupling constant (*cf.* **E**), whereas $^3J(H_{exo}$–C(10)/*H*–C(11)) amounts to 6.4 Hz.

[4]) There is ample precendence showing that the protonation of indole ($pK_a \approx -3$) and its derivatives occurs predominantly, if not exclusively at C(3), *cf.* [7] and ref. therein.

Scheme 2



nucleophilic sites ($\Delta^{17,18}$ or N(12)) to produce the intermediate dihydroindole derivatives **4**[5]) and/or **5**.

A subsequent intramolecular nucleophilic displacement of the protonated amino group at C(2) in the intermediates **4** or **5** would then lead to **3**[6]). To date, no experiments which could discriminate between these different mechanistic possibilities have been carried out.

Whereas various derivatives of 1-azaadamantane have been synthesized [11], to the best of our knowledge no compound having this skeleton has been isolated from natural sources up to now. Since (−)-hobartine (**1**) is believed to be the biogenetic precursor of (+)-aristoteline (**2**) [10], it is possible that the transformation **1**→**3** might take place in *Aristotelia* plant tissues as well, provided there is an enzyme which is capable of protonating C(3) of **1**.

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Experimental Part

General. See [12].

Acid Treatment of (−)-Hobartine (**1**). (Method: [2].) Synthetic **1** [1] (40 mg, 0.14 mmol) was dissolved in 15 ml 20% HCl and heated at reflux for 8 h. The cold mixture was put into an ice bath and treated with 30% NaOH until pH 10 was reached. Threefold extraction with $CHCl_3$, drying of the org. layers (K_2CO_3) and evaporation resulted in 40 mg of a brownish oil. Chromatography ($CHCl_3$/MeOH/conc.aq. NH_3 92:2:5, lower

[5]) The possibility that **4** may be formed *via* an intramolecular *ene* reaction (for a review see [8]) as indicated in *Scheme 2* can not be ruled out at present.

[6]) This sequence of two consecutive nucleophilic attacks at C(2) of a protonated indole derivative is reminescent of the proposed reaction mechanism for the acid-catalyzed trimerization of indole (for a review, see [9]).

phase) gave 33 mg of crude (+)-aristoteline (**2**) and 6 mg (0.02 mmol; 14%) of an oily unpolar component which was distilled (120°/0.005 Torr) to give a crystalline sample of (+)-neohobartine (**3**) (= *(+)-(1R,5S)-5-(o-aminophenyl)-2,2-dimethyl-9-methylidene-3-azatetracyclo[6.3.1.0^{3,7}.0^{4,10}]dodecane*). M.p. 80–81° (evacuated capillary). $[\alpha]_D^{25}$ = +58° (*c* = 0.38, $CHCl_3$). UV (95% EtOH): max. 292 (3.88); sh, 244 (3.86). IR (KBr): 3450*m*, 3290*w*, 3060*m*, 2940*s*, 1642*m*, 1602*m*, 1494*m*, 1457*m*, 1038*m*, 891*m*, 869*m*, 746*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.94 (*ddd*, *J* = 7.9, 7.3 and 1.6, *H*–C(7))[7]; 6.89 (*dd*, *J* = 7.4 and 1.6, *H*–C(5)); 6.54 (*dd*, *J* = 7.9 and 1.3, *H*–C(8)); 6.50 (*ddd*, *J* = 7.4, 7.3 and 1.3, *H*–C(6)); 5.6 (br. *s*, H_2N(1)); 4.67 (*d*, *J* = 2.2) and 4.64 (*d*, *J* = 2.2), (2H–C(20)); 3.84 (*dd*, *J* = 6.4 and 3, *H*–C(11)); 3.76 (*d*, *J* = 3, *H*–C(2)); 3.06 (*dd*, *J* = 10 and 6, *H*–C(3)); *ca.* 2.42 (*m*, H_S–C(15) and H_R–C(19)); 2.18 (*m*, *H*–C(18)); 2.09 (*ddd*, *J* = 12.6, 6.4 and 6, H_R–C(10)); 2.08 (*m*, *H*–C(16)); 1.91 (*dd*, *J* = 12.6 and 10, H_S–C(10)); 1.78 (*ddd*, *J* = 12.8, 3 and 3) and 1.75 (*ddd*, *J* = 12.8, 3 and 3), (H_R–C(15) and H_S–C(19)); 1.41 (*quint.*, *J* = 3, H–C(14)); 1.36 (*s*) and 1,33 (*s*), H_3C(21) and H_3C(22). ^{13}C-NMR ($CDCl_3$, 25 MHz)[7][8]): 154.3 (*s*, C(17)); 146.4 (*s*, C(9)); 131.2 (*d*, C(5)); 127.2 (*d*, C(7)); 116.1 and 115.9 (2*d*), (C(6) and C(8)); 103.2 (*t*, C(20)); 62.9 and 59.7 (2*d*), (C(2) and C(11)); 53.4 (*s*, C(13)); 48.5 (*d*, C(3)); 42.9 and 42.2 (2*d*), (C(16) and C(18)); 34.8 (*t*, C(10)); 33.8 (2*t*, C(15) and C(19)); 32.5 (*d*, C(14)); 27.6 and 26.9 (2*q*), (C(21) and C(22)). MS: 294 (100, M^+), 279 (38), 272 (2), 200 (92), 199 (28), 185 (11), 159 (23), 158 (43), 157 (8), 144 (16), 143 (18), 132 (10), 130 (36), 117 (12), 93 (21), 91 (16), 77 (12), 43 (10), 41 (16).

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[7] Biogenetic numbering [10] as shown in *Scheme 1*.

[8] The too low signal: noise ratio prevented the detection of C(4).