SYNTHESIS OF 11-AMINODRIM-7-ENE FROM DRIMENOL

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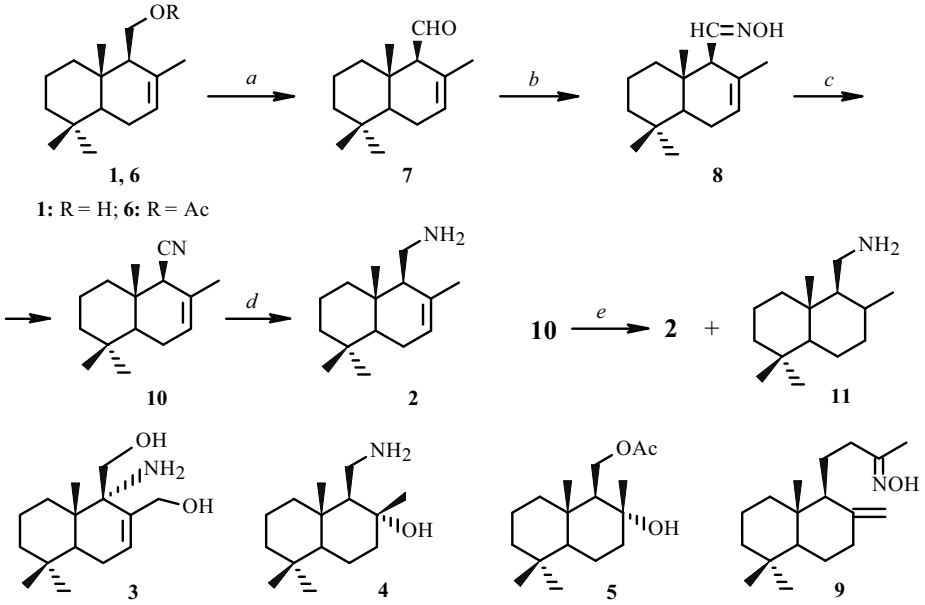
11-Aminodrim-7-ene was synthesized from drimenol in four steps. Drimenol was oxidized into drimenal and its oxime was dehydrated by p-*tosylchloride or acetic anhydride in pyridine to form 9-cyano-11-nordrim-7-ene, reduction of which by $LiAlH_4$ in the presence of anhydrous $AlCl_3$ produced 11-aminodrim-7-ene. The reaction of 9-cyano-11-nordrim-7-ene, $NaBH_4$, and $CoCl_2 \cdot 6H_2O$ produced a mixture of drimenylamine and 7,8-dihydrodrimenylamine in a 2:1 ratio.*

Key words: synthesis, drimenol, drimenylamine, 9-cyano-11-nordrim-7-ene.

Many drimane sesquiterpenoids, including their prototype drimenol (**1**), exhibit various biological activities [1, 2]. Therefore, it seemed interesting to synthesize 11-aminodrim-7-ene (**2**), an analog of drimenol with an amino group, in order to study its biological activity. It should be noted that few *N*-containing drimane derivatives are currently known. Urones et al. [3] synthesized dihydroxyamine **3** and several of its derivatives; Barrero et al. [4], hydroxyamine **4** and several of its derivatives with amino and hydroxy groups.



a. P_2O_5, DMSO, 20°C, 95%; *b*. $NH_2OH \cdot HCl$, EtOH, Py, 95%; *c*. A. Ac_2O, Py, 64%, B. *p*-TsCl, Py, 90%; *d*. $LiAlH_4$, $AlCl_3$, Et_2O, 50%; *e*. $NaBH_4$, $CoCl_2 \cdot 6H_2O$, MeOH, 20°C, 91%

Scheme 1

Herein we describe the synthesis of 11-aminodrim-7-ene (**2**) from drimenol (**1**) (Scheme 1), which we have synthesized earlier [5] from drimandiol 11-monoacetate (**5**) by treatment with ethanolic H_2SO_4 (53% yield). Later we developed a twostep synthesis of drimenol (**1**) from hydroxyacetate **5** consisting of selective elimination of the C_8-hydroxy group during brief reaction with methanesulfonic acid trimethylsilyl ether ($MeSO_3SiMe_3$) in CH_3CN at 18-20°C to form drimenylacetate (**6**,

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70% yield) and subsequent saponification of ester **6** by methanolic KOH into **1** (86% yield). The total yield of **1** from hydroxyester **5** was 60% in this instance. Drimenol (**1**) was oxidized into drimenal (**7**) by P_2O_5 and dimethylsulfoxide as before [7] (95% yield).

Drimenal oxime (**8**) was prepared by reaction of drimenal (**7**) with hydroxylamine hydrochloride in ethanol:pyridine. According to TLC, it was a mixture of the *Z*- and *E*-isomers. The oxime of 14,15-bisnorlabd-8-(17)-en-13-one (**9**) was used as an example [8] to show that the isomer with the higher R_f had the *E*-configuration. Furthermore, the *E*-configuration of **9** is energetically more favorable and, therefore, the predominant isomer in the mixture should most probably be the *E*-isomer. The isomer with the higher R_f value predominated in the drimenal oxime (**8**) obtained by us. Its content isolated after recrystallization from hexane was 80% of the mixture, i.e., the ratio of *Z*- and *E*-isomers in the mixture was approximately 1:4.

Next we investigated the production of drimenylamine **2** via reduction of drimenal oxime (**8**) by various methods. Prolonged refluxing of drimenal oxime with $LiAlH_4$ in ether, THF, or glyme [9] gave amine **2** in yields of 20-30%. Its yield could not be increased by refluxing oxime **8** with $LiAlH_4$ in ether in the presence of anhydrous $AlCl_3$ [10] or treatment with $NaBH_4$ in CH_3OH in the presence of MoO_3 [11]. Oxime **8** did not in general react upon heating to 60-70°C in DMF with $NaBH_4$ and NaI or upon prolonged stirring in CH_3OH with $NaBH_4$ adsorbed on Amberlite A_{26}. Refluxing oxime **8** with Na in propanol [12] produced a complicated mixture of products that did not contain amine **2**.

Because **2** could not be synthesized in satisfactory yield by reduction of drimenal oxime (**8**), we decided to convert **8** into the corresponding nitrile **10** and then reduce it to amine **2**.

We tried several methods that according to the literature would convert oximes into nitriles in order to synthesize **10**. In particular, **8** was reacted with the following reagents: a) Ac_2O in Py [13]; b) Ph_3P in CH_3CN:CCl_4 [14]; c) SeO_2 in $CHCl_3$ [15]; d) $AlCl_3 \cdot 6H_2O$ and KI in CH_3CN [16]; e) *p*-TsOH and freshly calcined $MgSO_4$ in $CH_3C_6H_5$; and f) *p*-TsCl in Py. Positive results were obtained only for methods a), b), and f), the yields of **10** for which were 64, 40, and 90%, respectively.

We also tried direct synthesis of **10** from **7** by refluxing in anhydrous toluene with $NH_2OH \cdot HCl$, anhydrous $MgSO_4$, and *p*-TsOH or with $NH_2OH \cdot HCl$ in Py:$CH_3C_6H_5$ in analogy with the literature [17, 18]. However, we obtained under these conditions **8** in quantitative yield. Earlier several aldehydes were converted to nitriles by treating them with NH_4Cl in dry Py in the presence of freshly prepared Cu powder under an O_2 atmosphere. However, when we performed this reaction with **7**, it produced a multi-component product mixture that did not contain **10**. As a result, we found that the acceptable methods for synthesizing **10** were reactions of **8** with *p*-TsCl or Ac_2O in Py.

The desired product, 11-aminodrim-7-ene (**2**), was obtained in 50% yield by refluxing **10** with $LiAlH_4$ in Et_2O in the presence of anhydrous $AlCl_3$ [20]. The structure of **2** was confirmed by IR, PMR, ^{13}C NMR, and mass spectra. The molecular peak in the mass spectrum was missing but a peak for $[M + H]^+$ had 100% intensity. It fragmented with loss of NH_3 to form an ion-radical with *m*/*z* 205 and with loss of CH_2NH_3 to form an ion with *m*/*z* 191. Further fragmentation led to a set of ions typical of mass spectra of bicyclic decalin systems that occur in drimane sesquiterpenoids and labdane diterpenoids [21].

Reduction of **10** by $NaBH_4$ and $CoCl_2 \cdot 6H_2O$ in CH_3OH produced a mixture of **2** and 7,8-dihydro-11-aminodrimane (**11**), which occurred as a mixture of water-soluble hydrochlorides. Its IR spectrum contained maxima at 3400, 1950, 1580, and 1490 cm^{-1} that were characteristic of hydrochlorides of primary amines. The PMR spectrum of the mixture indicated that it contained the hydrochlorides of **2** and **11** in a 2:1 ratio.

Thus, we synthesized **2** and its mixture with **11** that are interesting as compounds with potential biological activity. We struggled with definite difficulties for the seemingly simple transformation from **1** to **2**.

EXPERIMENTAL

Melting points were determined on a Boetius heating stage. IR spectra were recorded on a Specord 75 spectrophotometer. PMR and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Bruker Advance DRX-400 spectrometer (400.13 and 100.62 MHz, respectively). Chemical shifts are given on the δ scale in ppm relative to the resonance of $CHCl_3$ as an internal standard (resonances at δ 7.24 and 77.00 ppm, respectively). Resonances in ^{13}C NMR spectra were assigned using the DEPT technique and were compared with spectra of known related compounds [22, 23]. Mass spectra were recorded in Finnigan MAT 8230 (EI, 70 eV), Waters ZAB-HSQ (FAB), and Bruker-Daltronics FT-ICR (ESI) spectrometers.

The course of reactions was monitored by TLC on Silufol plates with detection by I_2 vapor. Column chromatography used silica gel L 100/400. Ether extracts were dried over anhydrous $MgSO_4$.

Preparation of 8. A solution of **7** (0.47 g, 2.13 mmol) in EtOH (2.5 mL) and Py (2.5 mL) was treated with $NH_2OH \cdot HCl$ (0.164 g, 2.36 mmol), stirred, left at 24°C for 24 h, poured into water (50 mL), and extracted with Et_2O (3 × 50 mL). The extract was washed with HCl (5%, 5 × 15 mL), $NaHCO_3$ solution (2 × 15 mL), and water (2 × 15 mL), and dried. The Et_2O was distilled in vacuo to afford **8** (0.47 g, 95%), which was crystallized by adding hexane. According to TLC, elemental analysis, and spectral data, the product was a mixture of the *Z*- and *E*-isomers of oxime **8**.

TLC: Silufol, benzene:ether (3:1), R_f 0.57 and 0.68. $C_{15}H_{25}NO$.

Recrystallization of the product from hexane produced the *E*-isomer of **8** (0.38 g, 80%), R_f 0.68, mp 95-96°C.

IR spectrum (CCl_4, ν, cm^{-1}): 840, 1690 (>C=C<H), 930 (N–O), 1620 (C=N), 3220 (br.), 3590 (=N–OH). PMR spectrum (δ, ppm, J/Hz): 0.87 (s, 3H, CH_3-15), 0.91 (s, 6H, CH_3-13, CH_3-14), 1.56 (s, 3H, CH_3-12), 2.64 (d, 1H, J = 8.8, H-9), 5.58 (m, 1H, H-7), 7.31 (d, 1H, J = 9.6, H-11), 8.69 (1H, br.s, =NOH).

^{13}C NMR spectrum (δ, ppm): 15.79 (C-15), 19.16 (C-2), 22.64 (C-13), 22.83 (C-12), 24.33 (C-6), 33.72 (C-4), 33.89 (C-14), 36.83 (C-10), 40.92 (C-1), 42.89 (C-3), 50.08 (C-5), 56.48 (C-9), 124.43 (C-7), 131.20 (C-8), 154.22 (C-11).

Preparation of 10. A. A solution of **8** (0.46 g, 1.95 mmol) in Py (3.8 mL) and Ac_2O (1.9 mL, 2.06 g, 20.14 mmol) was heated at 112-116°C for 2 h, cooled in an ice bath, treated with pieces of ice and dropwise with H_2SO_4 (10%, 15 mL), and extracted with Et_2O (4 × 20 mL). The extract was washed with $NaHCO_3$ solution (3 × 10 mL) and water (3 × 10 mL), and dried. The Et_2O was distilled. The crystallized solid (0.40 g) was recrystallized from pentane to afford a product (0.27 g, 64%) with mp 87-88°C that was identical to **10** according to spectral data.

TLC: Silufol, benzene:hexane, 1:1, R_f 0.62. $C_{15}H_{23}N$.

IR spectrum (min. oil, ν, cm^{-1}): 827, 1671 (>C=C<H), 2228 (CN). PMR spectrum (δ, ppm): 0.87 (s, 3H, CH_3-13), 0.90 (s, 3H, CH_3-14), 1.05 (s, 3H, CH_3-15), 1.82 (s, 3H, CH_3-12), 3.02 (s, 1H, H-9), 5.58 (m, 1H, H-7).

^{13}C NMR spectrum (δ, ppm): 15.83 (C-15), 19.13 (C-2), 22.11 (C-13), 22.68 (C-12), 23.98 (C-6), 33.44 (C-14), 33.63 (C-4), 36.53 (C-10), 40.63 (C-1), 42.77 (C-3), 48.95 (C-5), 50.66 (C-9), 119.93 (C-11), 125.43 (C-7), 125.65 (C-8).

Mass spectrum (*m*/*z*, I_{rel}, %): 240 (68) $[M + Na]^+$, 218 (45) $[M + H]^+$, 213 (100) $[M + Na - HCN]^+$, 191 (42) $[M + H - HCN]^+$.

B. A solution of **8** (0.47 g, 1.99 mmol) and *p*-TsCl (0.61 g, 3.20 mmol) in Py (5 mL) was refluxed for 1 h, cooled in an ice bath, treated dropwise with HCl (40 mL, 5%), and extracted with Et_2O (3 × 50 mL). The extract was washed with $NaHCO_3$ solution (2 × 15 mL) and water (2 × 15 mL), and dried. The Et_2O was distilled. The solid (0.47 g) was chromatographed over a column of silica gel (9.4 g, 1:20) with elution by hexane:ether (49:1) to afford crystalline **10** (0.39 g, 90%), mp 85-86°C.

Preparation of 2. A solution of $LiAlH_4$ (100 mg, 2.64 mmol) in anhydrous Et_2O (2.5 mL) was treated with a solution of anhydrous $AlCl_3$ (0.32 g, 2.40 mmol) in anhydrous Et_2O (5 mL), stirred for 5 min, treated with a solution of **10** (80 mg, 0.368 mmol) in anhydrous Et_2O (1 mL), refluxed and stirred for 2 h, cooled in an ice bath, and treated with several pieces of ice and dropwise with H_2SO_4 (10%, 5 mL) until acidic. The Et_2O layer was removed. The aqueous layer was extracted with Et_2O (2 × 10 mL), neutralized with NH_4OH solution (24%, 5 mL), and extracted with ether (5 × 10 mL). The extract was washed with water (3 × 5 mL) and dried. The Et_2O was distilled to afford a product (57 mg) that gave a positive reaction for NH_2 with Dragendorff's solution and with aqueous ninhydrin (1%). This product was chromatographed over a column of silica gel (1.7 g, 1:30) with elution by $CHCl_3$:CH_3OH (9:1) to afford **2** (41 mg, 50%).

TLC: Alufol, $CHCl_3$:*i*-PrOH, 9:1, R_f 0.49.

IR spectrum (film, ν, cm^{-1}): 810 (>C=C<H), 1570, 3300, 3470 (NH_2).

PMR spectrum (δ, ppm): 0.78 (s, 3H, CH_3-15), 0.85 (s, 3H, CH_3-13), 0.87 (s, 3H, CH_3-14), 1.77 (s, 3H, CH_3-12), 2.00-2.93 [m, 5H, H-9, C(11)2H and NH_2].

^{13}C NMR spectrum (δ, ppm): 15.06 (C-15), 19.44 (C-2), 22.65 (C-13), 22.76 (C-12), 24.35 (C-6), 33.63 (C-4), 33.94 (C-14), 37.14 (C-10), 39.61 (C-1), 40.22 (C-11), 42.83 (C-3), 50.61 (C-9), 58.81 (C-5), 124.51 (C-7), 133.93 (C-8).

Mass spectrum (*m*/*z*, I_{rel}, %): 222 (100) $[M + H]^+$, 205 (17) $[M + H - NH_3]^+$, 191 (15) $[M + H - CH_2NH_3]^+$, 149 (21), 135 (31), 123 (36), 119 (60), 109 (82).

11-Aminodrim-7-ene Picrate. Yellow crystalline compound, mp 182-183°C (EtOH). $C_{21}H_{30}N_4O_7 \cdot 1/2C_2H_5OH$.

Preparation of the Mixture of 11-Aminodrim-7-ene (2) and 11-Amino-7,8-dihydrodrimane (11). A solution of **10** (100 mg, 0.46 mmol) in MeOH (10 mL) was treated with $CoCl_2 \cdot 6H_2O$ (0.68 g, 2.86 mmol), stirred for 5 min, cooled in an ice bath, treated in portions over 1 h with $NaBH_4$ (0.53 g, 14 mmol), stirred for 2 h at 24°C, treated dropwise with HCl (30 mL, 3 N), stirred to dissolve Co boride, and extracted with Et_2O (3 × 10 mL). The extract was washed with water (3 × 3 mL). The

aqueous extracts were combined with the aqueous acidic layer, made basic with NH_4OH (24%, 25 mL) and extracted with Et_2O (3 × 20 mL). The extract was washed with water (2 × 5 mL) and dried. The Et_2O was distilled to afford an oily product (93 mg, 91%) that gave a positive reaction for NH_2 with Dragendorff's solution and aqueous ninhydrin (1%). Part of the product (40 mg) was dissolved in a small amount of hexane (1 mL) and treated with an excess of HCl in Et_2O. The resulting precipitate was filtered off and washed with hexane to afford crystals (43 mg, 91%), mp 210-211°C (MeOH).

IR spectrum (KBr, ν, cm^{-1}): 800 (>C=CH), 1490, 1580, 1950, 3400 (NH_3^+).

According to PMR and ^{13}C NMR spectra, the product was a mixture of **2** and **11** hydrochlorides in a 2:1 ratio.

PMR spectrum (δ, ppm, J/Hz): 0.80 (3H, s, CH_3-15), 0.84 (3H, d, J = 5.2, >CH–CH_3), 0.86 (3H, s, CH_3-13), 0.87 (3H, s, CH_3-14), 1.84 (3H, s, >C=C–CH_3), 2.94 [2H, d, J = 6.4, C(11)–H_2], 3.18 [2H, d, J = 8.4, C(11)–H_2], 5.56 [1H, br.s, C(7)–H], 8.24 and 8.31 (2 br.s, 3H each, 2 NH_3).

The ratio of **2** and **11** hydrochlorides was determined by integrating the resonances for C(11)-H_2 (2.94 and 3.18) and for NH_3 (8.24 and 8.31).

^{13}C NMR spectrum of the predominant **2** hydrochloride in the mixture (δ, ppm): 14.13 (C-15), 18.58 (C-2), 21.86 (C-13), 22.33 (C-12), 23.55 (C-6), 32.93 (C-4), 33.10 (C-14), 36.40 (C-10), 37.92 (C-11), 39.19 (C-1), 41.76 (C-3), 49.28 (C-5), 53.30 (C-9), 125.64 (C-7), 130.21 (C-8).

^{13}C NMR spectrum of **11** hydrochloride (δ, ppm): 15.58 (C-15), 16.69 (C-12), 17.20 (C-6), 18.23 (C-2), 21.53 (C-13), 28.19 (C-8), 33.25 (C-4), 33.37 (C-14), 33.88 (C-7), 37.67 (C-10), 37.79 (C-11), 39.51 (C-1), 41.62 (C-3), 51.27 (C-5), 55.79 (C-9).

REFERENCES

1. B. J. M. Jansen and A. de Groot, *Nat. Prod. Rep.*, **21**, 449 (2004).
2. A. F. Barrero, E. A. Manzaneda, J. Altarejos, S. Salido, J. M. Ramos, M. S. J. Simmonds, and W. M. Blaney, *Tetrahedron*, **51**, 7435 (1995).
3. J. G. Urones, D. Diez, P. M. Gomez, I. S. Marcos, P. Basabe, and R. F. Moro, *Nat. Prod. Lett.*, **11**, 145 (1998).
4. A. F. Barrero, E. J. Alverez-Manzaneda, R. Chahboun, and C. Gonzalez Diaz, *Synlett*, No. 11, 1561 (2000).
5. K. I. Kuchkova, A. N. Arycu, I. P. Dragalin, and P. F. Vlad, *Izv. Akad. Nauk, Ser. Khim.*, No. 12, 2745 (2004); [Engl transl., *Russ. Chem. Bull.*, **53**, 2862 (2004).
6. K. I. Kuchkova, A. N. Arycu, A. N. Barba, and P. F. Vlad, *Chem. Nat. Comp.*, **43**, 412 (2007).
7. K. I. Kuchkova, A. N. Arycu, I. P. Dragalin, and P. F. Vlad, *Khim. Prir. Soedin.*, 152 (2005).
8. P. K. Grant, J. Siva Prasad, and D. D. Rowan, *Aust. J. Chem.*, **36**, 1197 (1983).
9. P. S. Liu, *J. Org. Chem.*, **52**, 4717 (1987).
10. R. F. Nystrom, *J. Am. Chem. Soc.*, **77**, 2544 (1955).
11. J. Ipaktschi, *Chem. Ber.*, **117**, 856 (1984).
12. R. Rausser, L. Weber, E. B. Hershberg, and E. P. Oliveto, *J. Org. Chem.*, **31**, 1342 (1966).
13. G. Hilgetag and A. Martin, eds., *Weygand-Hilgetag Preparative Organic Chemistry*, Wiley-Interscience, Chichester, Engl., 1979.
14. J. N. Kim, K. H. Chung, and E. K. Ryu, *Synth. Commun.*, **20**, 2785 (1990).
15. G. Sosnovsky and J. K. Krogh, *Synthesis*, No. 9, 703 (1978).
16. M. Boruah and D. Konwar, *J. Org. Chem.*, **67**, 7138 (2002).
17. I. Ganboa and C. Palomo, *Synth. Commun.*, **13**, 219 (1983).
18. A. Saednya, *Synthesis*, No. 3, 190 (1982).
19. P. Capdevielle, A. Lavingne, and M. Maumy, *Synthesis*, No. 6, 451 (1989).
20. T. Frejd and T. Klingstedt, *Synthesis*, No. 1, 40 (1987).
21. C. R. Enzell and R. Ryhage, *Arkiv Kemi*, **23**, 367 (1965).
22. B. L. Buckwalter, I. R. Burfitt, A. A. Nagel, E. Wenkert, and F. Naf, *Helv. Chim. Acta*, **58**, 1657 (1975).
23. A. F. Barrero and J. Altarejos, *Magn. Res. Chem.*, **31**, 299 (1993).