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Angel Guzmán-Pérez [a] & Luis Angel Maldonado [a]
[a] División de Estudios de Posgrado, Facultad de Química, UNAM, 04510, México D.F., México
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A NEW TOTAL SYNTHESIS OF WITHASOMNINE

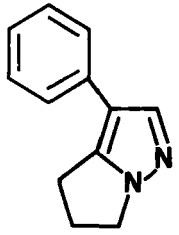
Angel Guzmán-Pérez and Luis Angel Maldonado*

División de Estudios de Posgrado, Facultad de Química,

UNAM, 04510 México D.F., México.

ABSTRACT : The pyrazole alkaloid withasomnine 1, has been synthesized by construction of the 1,2-diazabicyclo [3.3.0] octa-2,4-diene system in a single step.

The rather simple but unusual alkaloid withasomnine 1 has been synthesized in a variety of ingenious ways[1]



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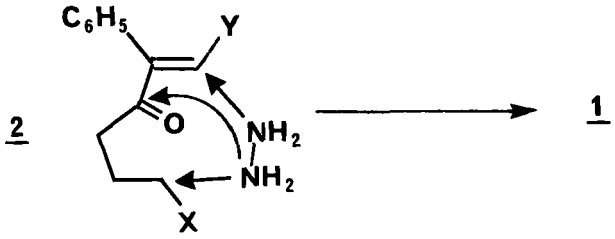
In considering new approaches to this interesting compound we were attracted by the possibility that the bicyclic system of withasomnine could be constructed in a single step by combining the

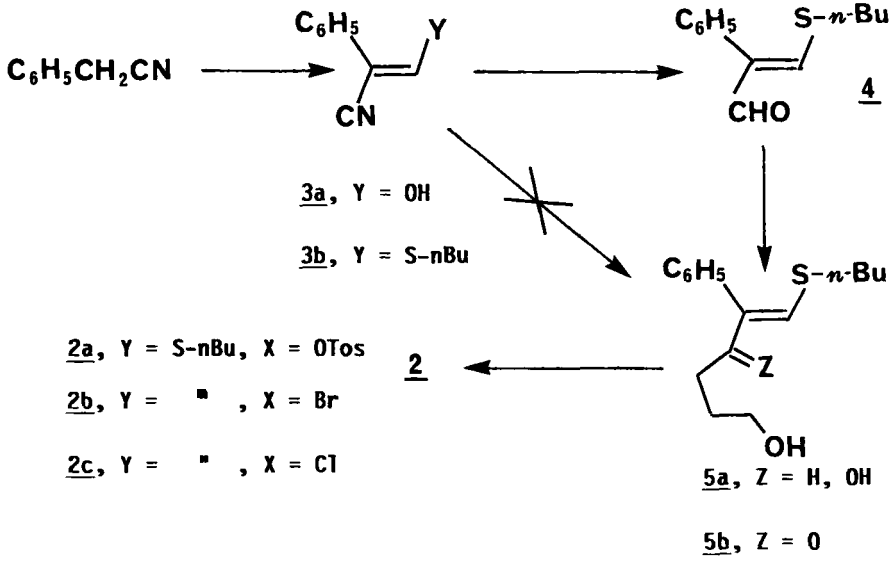
* To whom correspondence should be addressed.

well known reactions[2] of : 1) 1,3-dicarbonyl compounds (or related β-heterosubstituted enones) with hydrazine to give pyrazoles and 2) the (intramolecular) N-alkylation of azole heterocycles :



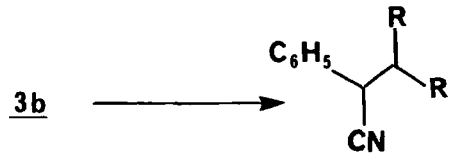
In this paper we wish to present the experimental realization of this approach.

The required acyclic substrates to test the key reaction, compounds 2, were conveniently prepared as shown in the scheme :



Scheme

Formylation of phenylacetonitrile with HCO_2Et and NaH in Et_2O (catalytic EtOH) gave the known[3] 3-hydroxy-2-phenyl acrylonitrile 3a, mp 161-162° in 92 % yield. Thioether formation to 3b was then accomplished with n-BuSH in toluene (catalytic TosOH, azeotropic removal of H_2O). Since thioketal 6a[4] was an unavoidable contaminant in this reaction, the crude reaction product of the thioetherification reaction was submitted to a DBU treatment under vacuum (to remove the n-BuSH). This afforded compound 3b in consistent yields of 80-85 % ; compound 3b[5] : oil, bp 140-150°/1.7 ; ir (film) : 2230 (CN), 1610 (C=C) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 0.90 (t, J = 6 Hz, $\underline{CH_3}CH_2$), 2.80 and 2.90 (superimposed t, J = 7 Hz, $S\underline{CH_2}CH_2$ of each geometrical isomer), 7.20-7.60 (complex signal, 1 vinyl H, 5 aromatic H).



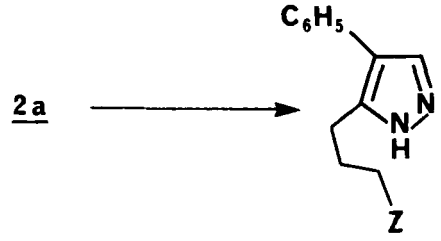
6a, R = S-nBu

6b, R = $CH_2CH_2CH_2OH$

The ease with which compound 3b adds nucleophiles in a conjugate sense was also observed when we attempted the direct conversion 3b ⟶ 5b by reaction with the functionalized Grignard reagent 7, $ClMgOCH_2CH_2CH_2MgCl$[6]. The only product obtained (50 % yield) was the double adduct 6b : oil; ir (film) : 3370 (OH), 2260 (CN) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 3.10 (broad signal, 2 OH, exchanges with D_2O), 3.30-3.60 (complex signal, 2 $CH_2\underline{CH_2}OH$), 3.90 (d, J = 6 Hz, $CH\text{-}\underline{CH}(CN)C_6H_5$) and 7.30 (s, 5 aromatic H).

Therefore, nitrile 3b was first converted in 80 % yield into the unsaturated aldehyde 4 (DIBAL, 0°, toluene; then 5 % aqueous H_2SO_4)[7] which gave quantitatively, the acid sensitive allylic alcohol 5a[8] when treated with an excess of 7 (4 equivalents). Allylic alcohol 5a : oil; ir (film) : 3370 (OH), 1600 (C=C) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 0.85 (t, J = 6 Hz, $\underline{CH_3}CH_2$), 2.50 (broad signal, 2 OH, exchanges with D_2O), 2.60 (t, J = 7 Hz, $S\underline{CH_2}CH_2$), 3.50 (distorted t, J = 6 Hz, $CH_2\underline{CH_2}OH$), 4.30 (t, J = 6 Hz, $CH_2\underline{CH}(OH)C{=}CH$), 6.15 (s, CH=C), 7.15 (s, 5 aromatic H). Finally, MnO_2 oxidation of 5a in CH_2Cl_2 (rt, 50 h) gave the hydroxyenone 5b in 78 % yield : oil; ir (film) 3420 (OH), 1660 (enone C=O), 1605 (C=C) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 0.90 (t, J = 6 Hz, $\underline{CH_3}CH_2$), 2.20 (broad signal, OH, exchanges with D_2O), 2.50 (t, J = 6 Hz, $CH_2\underline{CH_2}C{=}O$), 2.70 (t, J = 7 Hz, $S\underline{CH_2}CH_2$), 3.50 (t, J = 6 Hz, $CH_2\underline{CH_2}OH$), 7.10-7.50 (m, 5 aromatic H), 7.80 (s, CH=C).

With the hydroxyenone 5b in hand, a series of derivatives with good leaving groups in the end of the chain were prepared in order to test the one pot-double cyclization reaction leading to withasomnine. However, and not completely unexpected, we rapidly found that the pyrazole formation was extremely fast; the alicyclic C-N bond being formed relatively slow. In fact our first experiment with the crude, unstable tosylate 2a and 80 % aqueous hydrazine hydrate (first in EtOH, followed by addition of Et_3N, reflux) gave the known[9] hydroxypropylpyrazole 8a, mp 95-97°, in 30 % yield :



8a, Z = OH

8b, Z = OTos

8c, Z = S-nBu

8d, Z = Cl

Evidently, the low rate alicyclic ring formation allows cleavage of the O-S bond in the tosylate group of 8b by external nucleophiles before cyclization takes place.

Searching for a more convenient substrate and since the bromide 2b was also an unstable compound, the chloro derivative 2c was prepared in 63 % yield by reaction of 5b with CCl_4 and triphenylphosphine. Chloroenone 2c : oil; ir (film) : 1670 (enone C=O), 1610 (C=C), 645 (C-Cl) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 0.90 (t, J = 6 Hz, $\underline{CH_3}CH_2$), 2.05 (quintet, J = 6 Hz, $CH_2\underline{CH_2}CH_2$), 2.65 (t, J = 6 Hz, $CH_2\underline{CH_2}C{=}O$), 2.85 (t, J = 7 Hz, $S\underline{CH_2}CH_2$), 3.60 (t, J = 6 Hz, $Cl\underline{CH_2}$-CH_2), 7.30-7.70 (m, 5 aromatic H), 8.00 (s, CH=C).

Partial success was then reached when 2c was heated with 80 % hydrazine hydrate and DBU in EtOH (reflux, 12 h); a mixture of withasomnine 1 (33 %) and thioether 8c (41 %) was, however, formed :

Thioether 8c : Crystalline solid, mp 42°; ir (film) : 3150 (NH), 1600 (C=C) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 0.90 (t, J = 6 Hz, $\underline{CH_3}CH_2$), 2.00 (quintet, J = 6 Hz, $CH_2\underline{CH_2}CH_2$), 2.50 and 2.55 (2 superimposed

t, J = 6 Hz, 2 $S\underline{CH_2}CH_2$), 3.00 (t, J = 7 Hz, pyrazole-$\underline{CH_2}CH_2$), 7.35 -7.65 (m, 5 aromatic H), 7.85 (s, pyrazole C-H), 10.20 (broad s, pyrazole N-H, exchanges with D_2O).

If the above reaction is performed by slow distillation of a n-propanol solution of 2c and 80 % hydrazine hydrate to remove azeotropically the n-BuSH formed during the pyrazole ring construction, followed by addition of DBU to induce the second cyclization, a somewhat improved yield of withasomnine is obtained (44 %). No thioether 8c was detected although the pyrazole alcohol 8a was now obtained as by-product in 25 % yield[10].

The synthetic withasomnine was identified by its mp (118°, hexane) and spectroscopic properties : ir (KBr) : 1610, 760, 700 cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 2.60 (distorted quintet, J = 7 Hz, $CH_2\underline{CH_2}CH_2$), 3.05 (t, J = 7 Hz, pyrazole-$\underline{CH_2}CH_2$), 4.10 (t, J = 7 Hz, N-$\underline{CH_2}CH_2$), 7.15-7.55 (m, 5 aromatic H), 7.70 (s, pyrazole C-H); ms (70 eV; z/e (%)) : 184.9 (12 %, M^++ 1), 183.9 (100 %, M^+), 182.9 (38.5 %, M^+-1), 50.9 (62.1 %), 49.9 (41.6 %), 39.0 (94.7 %). The mp of the picrate (171-173°, water) was also in accord with the literature.

Experiments directed to suppress side reactions in the key double cyclization transformation are planned for a near future in order to improve the present overall yield of withasomnine (11.3 % from phenylacetonitrile).

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3. Ghosh, B.N., J. Chem. Soc., 1916, 109, 105.

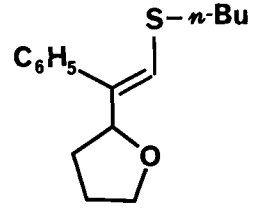
4. A pure sample of thioketal 6a was isolated by preparative tlc (hexane 95-AcOEt 5, 3 elutions). Oil; ir (film) : 2240 (CN) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 0.85 (t, J = 6 Hz, 2 $\underline{CH_3}CH_2$), 2.50 (t, J = 7 Hz, 2 $S\underline{CH_2}CH_2$), 3.90 (d, J = 6 Hz, $(-S)_2\underline{CH}$-$\underline{CH}(CN)C_6H_5$), 4.20 (d, J = 6 Hz, $(-S)_2\underline{CH}$-CH(CN)C_6H_5), 7.40 (s, 5 aromatic H).

5. Although irrelevant for the purposes of the synthesis, compound 3b was the only intermediate which apparently was obtained as a mixture of geometric isomers, as evidenced by the two partially superimposed triplets at δ 2.80 and 2.90 in the pmr spectrum ($S\underline{CH_2}CH_2$ for each isomer). For the same reason, the structures of the other intermediates even though geometrically pures were not assigned and thus the structures drawn in this paper does not necessarily represent the correct geometrical isomer.

6. Cahiez, G., Alexakis, A. and Normant, J.F., Tetrahedron Lett., 1978, 3013.

7. Aldehyde 4 : oil; ir (film) : 2740 and 1685 (unsaturated CH=O), 1615 (C=C) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 0.90 (t, J = 6 Hz, $\underline{CH_3}$-CH_2), 2.80 (t, J = 7 Hz, $S\underline{CH_2}CH_2$), 7.30 (s, 5 aromatic H), 7.40 (s, CH=C), 9.30 (s, CH=O).

8. Traces of acid easily cyclizes 5a into the tetrahydrofuran 10 :



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oil; ir (film) : 1610 (C=C), 1100 (C-O) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 0.85 (t, J = 6 Hz, $\underline{CH_3}CH_2$), 2.60 (t, J = 7 Hz, $S\underline{CH_2}CH_2$), 3.80 (complex signal, $O\underline{CH_2}CH_2$), 4.60 (t, J = 6 Hz, CH=C-$\underline{CH}(OR)CH_2$), 6.25 (s, CH=C), 7.25 (s, 5 aromatic H).

9. See reference 1a. Ir (KBr) : 3200-2850 (OH and NH), 1600 (C=C) cm^{-1}; pmr ($CDCl_3$, 90 MHz) δ 1.85 (quintet, J = 6 Hz, $CH_2\underline{CH_2}CH_2$), 2.90 (t, J = 6 Hz, pyrazole-$\underline{CH_2}CH_2$), 3.65 (t, J = 6 Hz, $HO\underline{CH_2}$-CH_2), 5.75 (broad s, OH and NH, exchanges with D_2O), 7.20-7.40 (m, 5 aromatic H), 7.60 (s, pyrazole C-H). As expected, cyclization of the derived crude tosylate 8b with NaH gave withasomnine in 33 % yield, along with recovered 8a (30 % yield).

10. From our point of view the formation of 8a under this reaction conditions is remarkable, as far as the hydrolysis of an unactivated primary chloro derivative requires somewhat harsh conditions. Perhaps, ring opening of the alicyclic ring in withasomnine by HO^- (pyrazolyl anion as leaving group) explains this unusual chloride "hydrolysis". A similar explanation can also be advanced for the conversion 2c ⟶ 8c (see text), although the direct displacement of an intermediate chloropropylpyrazole 8d by the highly nucleophilic n-butyl mercaptide anion seems equally plausible. Anyway, it is also surprising that no ether formation (by solvent participation) had been isolated from these reactions in alcoholic solvents.

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