ANOMALOUS CYCLIZATION IN AN ATTEMPTED SYNTHESIS OF THE '7-THIOMORPHINAN', SYSTEM#

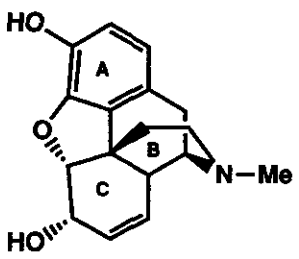
Parthasarathi Rajagopalan*[a] and Joseph C. Calabrese[b]

a. CNS Diseases Research, The Du Pont Merck Pharmaceutical Company, Wilmington, DE 19880-0353, U.S.A.

b. Central Research and Development Department, E.I. Du Pont de Nemours and Company, Wilmington, DE 19880-0228, U.S.A.

Abstract - The acid catalyzed cyclization of 8-benzyl-3,4,5,6,7,8-hexahydro-1*H*-thiopyrano[3,4-*c*]pyridine hydrochloride (**10**) did not furnish the expected the '7-thiomorphinan' (**11**) but 4-(2-mercaptoethyl)-1,2,3,5,10,10a-hexahydrobenzo-[*g*]quinoline (**12**) instead. The synthesis of **10** and the mechanism of formation of **12** are described.

Since the time it was firmly established, the structure of morphine (**1**), has been dissected and modified in every conceivable way with a view to generate simpler compounds with equal or enhanced analgesic activity and/or reduced undesirable side effects.[1] Such effort has met with considerable success and one of the earliest such analgesics to be developed is the morphinan (**2**),[2] which is in clinical use under the generic name levorphanol. However, very few attempts have been made to introduce a hetero atom in ring C of the morphine skeleton to evaluate the effect of such a modification on the analgesic activity and side effect profile. Monkovic and coworkers[3] have described the synthesis of, and the analgesic/antagonist activity in, a series of '8-oxamorphinans' of the type (**3**). When that publication appeared, we were engaged in the synthesis of the '7-thiomorphinan' (**11**), a prototype of a new condensed heterocyclic ring system[4] and would now like to report on an unexpected reaction encountered in that attempt.



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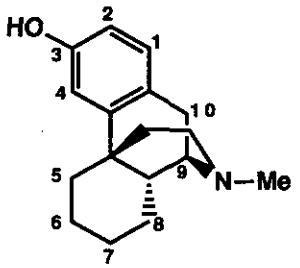

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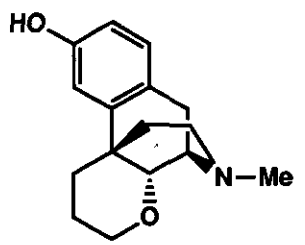

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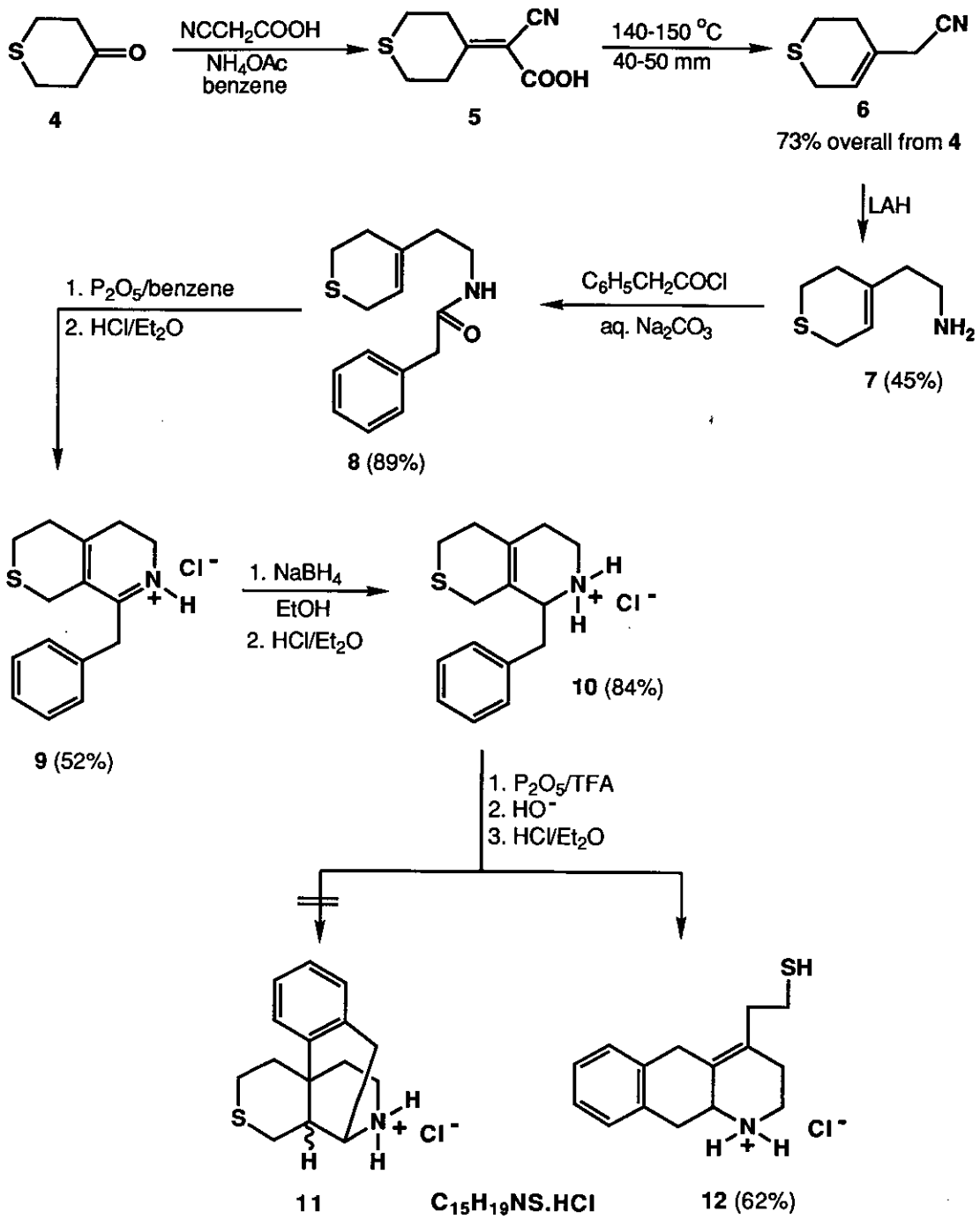
#Dedicated, with warm regards and best wishes, to Prof. Edward C. Taylor on his seventieth birthday.

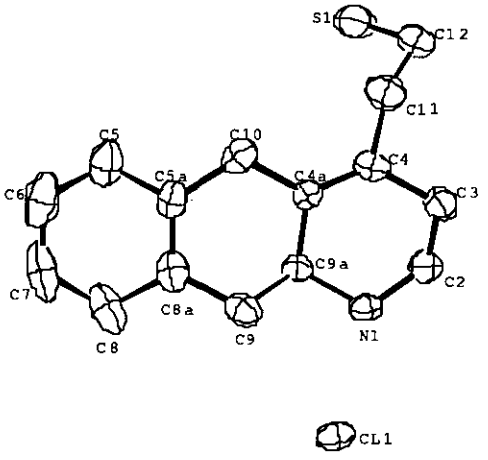
Scheme 1


NCCH2COOH
NH4OAc
benzene
140-150 °C
40-50 mm
4
5
6
73% overall from 4
LAH
7 (45%)
C6H5CH2COCl
aq. Na2CO3
1. P2O5/benzene
2. HCl/Et2O
8 (89%)
1. NaBH4
EtOH
2. HCl/Et2O
9 (52%)
10 (84%)
1. P2O5/TFA
2. HO-
3. HCl/Et2O
11
C15H19NS.HCl
12 (62%)

The method we adopted for the synthesis of the '7-thiomorphinan' (**11**) which closely followed the Grewe route[2] to the morphinans, is outlined in Scheme 1. The commercially available tetrahydrothiopyran-4-one (**4**) was condensed with cyanoacetic acid in the presence of ammonium acetate to yield **5**, which upon thermolysis at 140-150^{0}C under vacuum (40-50 Torr) underwent decarboxylation and double bond migration to furnish the unsaturated nitrile (**6**). The amine (**7**), obtained by the lithium aluminum hydride reduction of **6**, was treated with phenylacetyl chloride in the presence of aqueous sodium bicarbonate to yield the amide (**8**), which underwent smooth Bischler-Napieralski type of cyclization with phosphorus pentoxide in boiling benzene to afford the rather unstable **9**,[5] which was isolated as the hydrochloride. Reduction of **9** hydrochloride with sodium borohydride in ethanol furnished **10**[5] which was also isolated as the hydrochloride. The critical cyclization of **10,** which was expected to provide, **11**, proved to be messy when phosphoric acid was used as in the original Grewe synthesis.[2] However, a clean reaction took place when phosphorus pentoxide in refluxing trifluoroacetic acid was used instead. The product, isolated as the hydrochloride, analyzed correctly for $C_{15}H_{19}NS.HCl$. The proton nmr spectrum of the product, while it indicated that cyclization on the benzene ring had indeed occurred, was not quite consistent with the expected structure (**11**). In order to secure its structure unequivocally, the product was subjected to single crystal X-ray analysis which revealed it to be the unexpected **12**.

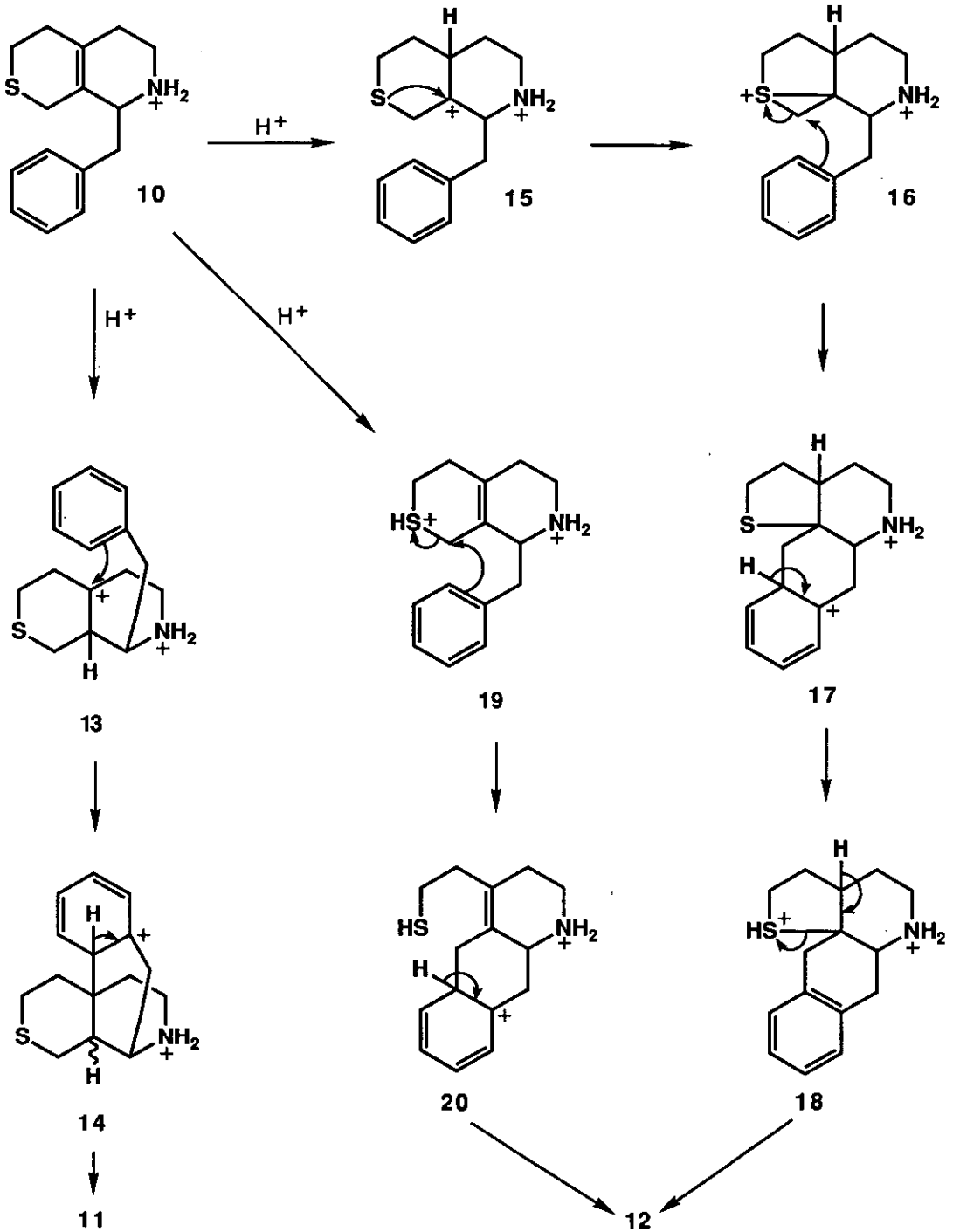
Two different mechanisms, outlined in Scheme 2, can be invoked to rationalize the formation of **12**. One involves the protonation at either terminus of the double bond of **10** (**13** and **15**, respectively) followed by either electrophilic aromatic substitution leading, *via* **14**, to the expected product (**11**), or by the attack of the proximal sulfur leading to the thieranium ion (**16**) and thence to the actually isolated product (**12**) *via* **17** and **18**. The other mechanism involves the protonation of the sulfur in preference to the double bond of **10** followed by the thiopyran ring opening by the benzene ring resulting in the formation of **12** (route **19** - **20** - **12**).[6] The absence of any **11** in the product indicates that the second mechanism is more likely.

Single Crystal X-Ray Structure Analysis of **12**



ORTEP drawing of 12

Scheme 2



Crystal Data: $C_{15}H_{20}NSCl$, from EtOH/MeOH/ether, colorless plate, ~0.27 x 0.09 x 0.35mm, orthorhombic, Pccn (No. 56), a = 14.571(1), b = 27.218(2), c = 7.360(1) Å, from 25 reflections, -T = -70°C, V = 2918.9Å^3, Z = 8, FW = 281.85, Dc = 1.283g/cc, μ(Mo) = 3.81cm^{-1}.

Data Collection and Treatment: Enraf-Nonius CAD4 diffractometer, MoKa radiation, 3825 data collected, $1.5° \leq 2q \leq 55.0°$, maximum h, k, l = 9 18 35, data octants = + + +, w scan method, scan width = 1.20-1.90° w, scan speed = 1.70-5.00°/min., typical half-height peak width = 0.14° w, 2 standards collected 28 times, 2% fluctuation, 7.0% variation in azimuthal scan, no absorption correction, 1321 unique reflections with $1 \geq 3.0s(1)$, (collected CAB).

Solution and Refinement: Structure solved by direct methods (MULTAN). [The asymmetric unit consists of one ion pair in a general position. Hydrogen atoms were idealized with C-H = .95Å. The sulfhydride orientation was determined from a difference map.], refinement by full-matrix least squares on F, scattering factors from Int. Tables for X-ray Crystallography, Vol IV, including anomalous terms for Cl,S, weights proportional to $[s^2(I)+0.00091^2]^{-1/2}$, refined anisotropic: all non-hydrogen atoms, isotropic: H, fixed atoms: H, 175 parameters, data/parameter ratio = 7.55, final R = 0.054, Rw = 0.053, error of fit = 1.58, max Δ/s = 0.01, largest residual density = 0.40e/Å^3, near C8a.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. For an exhaustive review on the subject *cf.* 'Opioid Analgesics', by Alan F. Casy and Robert T. Parfitt, Plenum Press, New York, NY, 1986.

2. R. Grewe, Naturwiss., 1946, **33**, 333; Angew. Chem., 1947, **A59**, 198; R. Grewe and A. Mondon, Chem. Ber., 1948, **81**, 279.

3. Y. Lambert, J-P. Daris, I. Monkovic, and A.W. Pircio, J. Med. Chem., 1978, **21**, 423.

4. Trivial name for 1,2,4a,5-tetrahydro-6*H*-5,10b-iminoethano-4*H*-naptho[2,1-*c*]thiopyran.

5. **9** and **10** belong to the new condensed heterocyclic ring system, namely, 1-*H*-thiopyrano-[3,4-*c*]pyridine.

6. We thank Dr. Ronald Warrener, Department of Chemistry, Australian National University, Canberra, Australia, for suggesting this mechanism.

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