

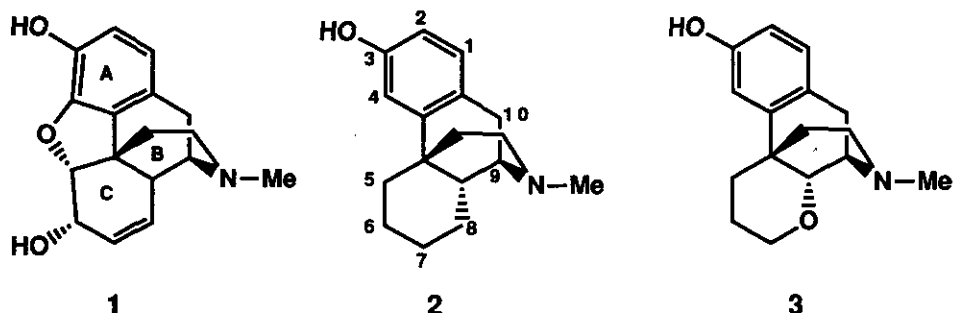
ANOMALOUS CYCLIZATION IN AN ATTEMPTED SYNTHESIS OF THE '7-THIOMORPHINAN', SYSTEM[#]

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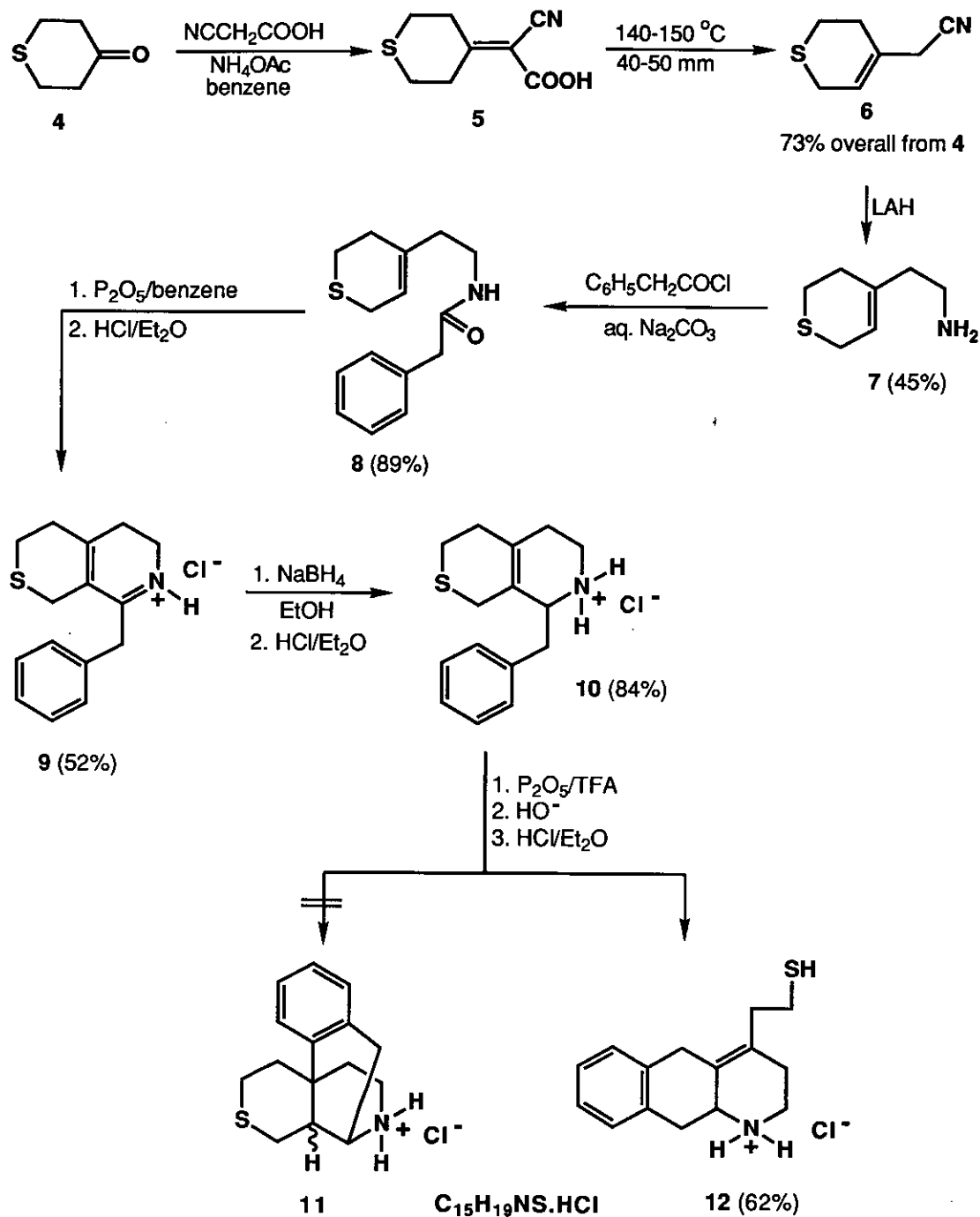
Abstract - The acid catalyzed cyclization of 8-benzyl-3,4,5,6,7,8-hexahydro-1*H*-thiopyrano[3,4-*c*]pyridine hydrochloride (**10**) did not furnish the expected the '7-thiomorphinan' (**11**) but 4-(2-mercaptoethyl)-1,2,3,5,10,10a-hexahydrobenzo-[*g*]quinoline (**12**) instead. The synthesis of **10** 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 coworkers³ 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-thio-morphinan' (**11**), a prototype of a new condensed heterocyclic ring system⁴ and would now like to report on an unexpected reaction encountered in that attempt.



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

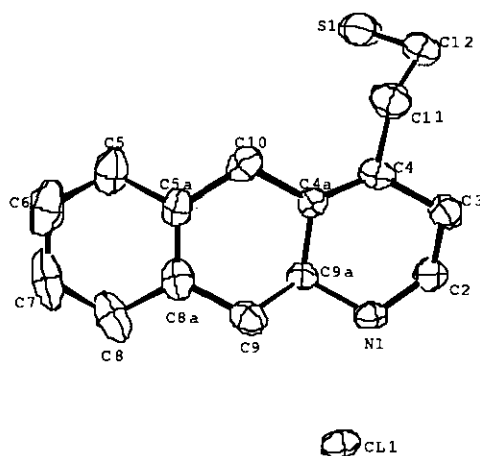
Scheme 1



The method we adopted for the synthesis of the '7-thiomorphinan' (**11**) which closely followed the Grewe route² 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°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 C₁₅H₁₉NS.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**.

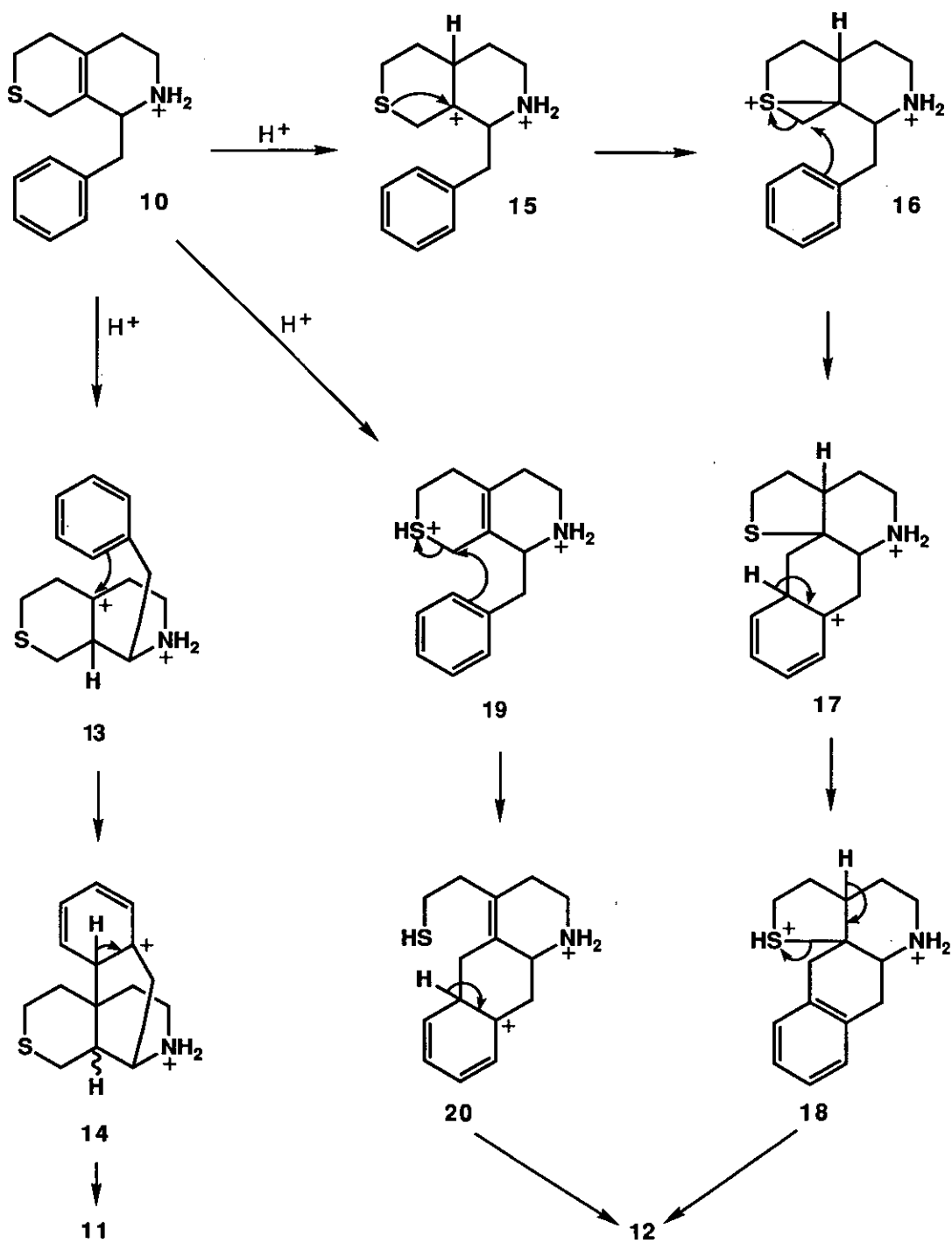
Two different mechanisms, outlined in Scheme 2, can be invoked to rationalize the formation of **12**. One involves the protonation at either terminus of the double bond of **10** (**13** and **15**, respectively) followed by either electrophilic aromatic substitution leading, *via* **14**, to the expected 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, $\sim 0.27 \times 0.09 \times 0.35$ mm, orthorhombic, Pccn (No. 56), $a = 14.571(1)$, $b = 27.218(2)$, $c = 7.360(1)$ Å, from 25 reflections, $-T = -70^\circ C$, $V = 2918.9 \text{ Å}^3$, $Z = 8$, $FW = 281.85$, $D_c = 1.283 \text{ g/cc}$, $\mu(\text{Mo}) = 3.81 \text{ cm}^{-1}$.

Data Collection and Treatment: Enraf-Nonius CAD4 diffractometer, MoK α radiation, 3825 data collected, $1.5^\circ \leq 2\theta \leq 55.0^\circ$, maximum $h, k, l = 9 \ 18 \ 35$, data octants = + + +, ω scan method, scan width = 1.20 – $1.90^\circ \omega$, scan speed = 1.70 – $5.00^\circ/\text{min.}$, typical half-height peak width = $0.14^\circ \omega$, 2 standards collected 28 times, 2% fluctuation, 7.0% variation in azimuthal scan, no absorption correction, 1321 unique reflections with $I \geq 3.0\sigma(I)$, (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 $C-H = .95 \text{ Å}$. The sulfhydryde 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 $[s^2(I) + 0.000912]^{-1/2}$, refined anisotropic: all non-hydrogen atoms, isotropic: H, fixed atoms: H, 175 parameters, data/parameter ratio = 7.55, final $R = 0.054$, $R_w = 0.053$, error of fit = 1.58, max $\Delta/\sigma = 0.01$, largest residual density = 0.40 e/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*-naphtho[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 Warrenner, Department of Chemistry, Australian National University, Canberra, Australia, for suggesting this mechanism.

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