Synthesis and crystal structure of 17-deaza-17-methyl thionium isomorphinan (isosulforphanol) perchlorate, an isostere of the opiate isolevorphanol

BERNARD BELLEAU, UGO GULINI,[1] AND BARBARA GOUR-SALIN

Department of Chemistry, McGill University, Montreal (Que.), Canada H3A 2K6

AND

F. R. AHMED

Division of Biological Sciences, National Research Council, Ottawa, Ont., Canada K1A 0R6

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No morphinan analog carrying a heteroatom other than nitrogen at position 17 has yet been synthesized. The synthesis of the position 17 sulfur analog of the perchlorate salt of ($\pm$)-isolevorphanol is described. The strategy adopted is based on the classical Grewe synthesis of morphinans and, under narrowly defined conditions, the title compound isosulforphanol (**3a**) and an intermediate by-product **13** resulting from an unusual non-bridged head ring closure of **11a** were obtained. The X-ray structures of both **3a** and **13** were determined. Crystals of **13** ($C_{17}H_{22}OS$) are monoclinic, space group $P2_1/a$, $a = 17.080(2)$, $b = 9.372(1)$, $c = 9.327(1)$ Å, $\beta = 108.67(1)$, $V = 1414.4$ Å^3, $Z = 4$. Final $R = 0.034$ for 2545 reflections. The crystals of **3a** ($C_{17}H_{23}OS^+ \cdot ClO_4^-$) are orthorhombic, space group $Pna2_1$, $a = 10.934(1)$, $b = 9.219(1)$, $c = 17.131(2)$ Å, $V = 1726.8$ Å^3, $Z = 4$. Final $R = 0.053$ for 1018 reflections. The $C_{17}H_{23}OS^+$ molecule has been identified by this X-ray analysis as S-methyl isosulforphanol (Fig. 2). The structure of **13** is shown in Fig. 1. The stereochemical outcome of the Grewe-like synthesis is thus established as proceeding in a reversed manner when sulfur replaces the nitrogen in the final cyclization step. Preliminary pharmacological studies showed that **3a** is a potent agonist in the central nervous system but a potent antagonist on the guinea-pig ileum.


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Jusqu'à maintenant, aucun analogue de la morphinane portant un hétéroatome autre que l'azote en position 17 n'a été synthétisé. On décrit la synthèse d'un analogue portant un atome de soufre en position 17; il s'agit du perchlorate du ($\pm$)-isolévorphanol. La stratégie adoptée se base sur la synthèse classique des morphinanes développée par Grewe et, utilisant des conditions étroitement définies, on a obtenu le composé isosulforphanol (**3a**) mentionné dans le titre ainsi qu'un sous-produit intermédiaire (**13**) provenant d'une cyclisation inhabituelle du composé **11a** à une position différente de la tête de pont. Faisant appel à la diffraction des rayons-X. On a déterminé les structures des deux composés **3a** et **13**. Les cristaux du composé **13** ($C_{17}H_{22}OS$) sont monocliniques et appartiennent au groupe d'espace $P2_1/a$ avec $a = 17,080(2)$, $b = 9,372(1)$, $c = 9,327(1)$ Å, $\beta = 108,67(1)$, $V = 1414,4$ Å^3, $Z = 4$. On a obtenu une valeur de R de 0,034 pour 2545 réflexions. Les cristaux du composé **3a** ($C_{17}H_{23}OS^+ \cdot ClO_4^-$) sont orthorhombiques et appartiennent au groupe d'espace $Pna2_1$ avec $a = 10,934(1)$, $b = 9,219(1)$, $c = 17,131(2)$ Å, $V = 1726,8$ Å^3 et $Z = 4$. On a obtenu une valeur finale de R de 0,053 pour 1018 réflexions. L'analyse par rayons-X de la molécule de $C_{17}H_{23}OS^+$ a permis de l'identifier comme étant le S-méthyl isosulforphanol (fig. 2). La figure 1 illustre la structure du composé **13**. On a ainsi établi que le résultat stéréochimique de la synthèse de Grewe est inversé lorsqu'on remplace l'azote par le soufre dans l'étape finale de cyclisation. Des études pharmacologiques préliminaires indiquent que le composé **3a** est un agoniste potentiel dans le système nerveux central mais un antagoniste potentiel dans l'iléum du cochon d'inde.

[Traduit par le journal]

Introduction

A decade ago we reported the surprising observation that structurally induced pyramidal inversion about the basic nitrogen of the potent narcotic analgesic levorphanol (**1**) suppressed its in vivo activity (1). The idea that the nitrogen lone-pair directionality in levorphanol (**1**) and analogous narcotic analgesics is a stereoselective determinant of productive interaction with the morphine receptor was put forward, and the most obvious implication of this stereoelectronic parameter centers on the ability of the N lone pair to act as a proton acceptor and (or) donor at physiological pH (1), the rest of the molecule serving as a selective carrier of this pivotal atom (2). Although the quality of the receptor response can sometimes be modulated by geometrical inversion to the isomeric planar stereochemistry as in **2**, the available evidence based on studies with several analogs (3) allows the firm conclusion that affinity for the receptor can be favoured equally well by the flattened main skeleton of the isomorphinans (**2**).

1   **2**
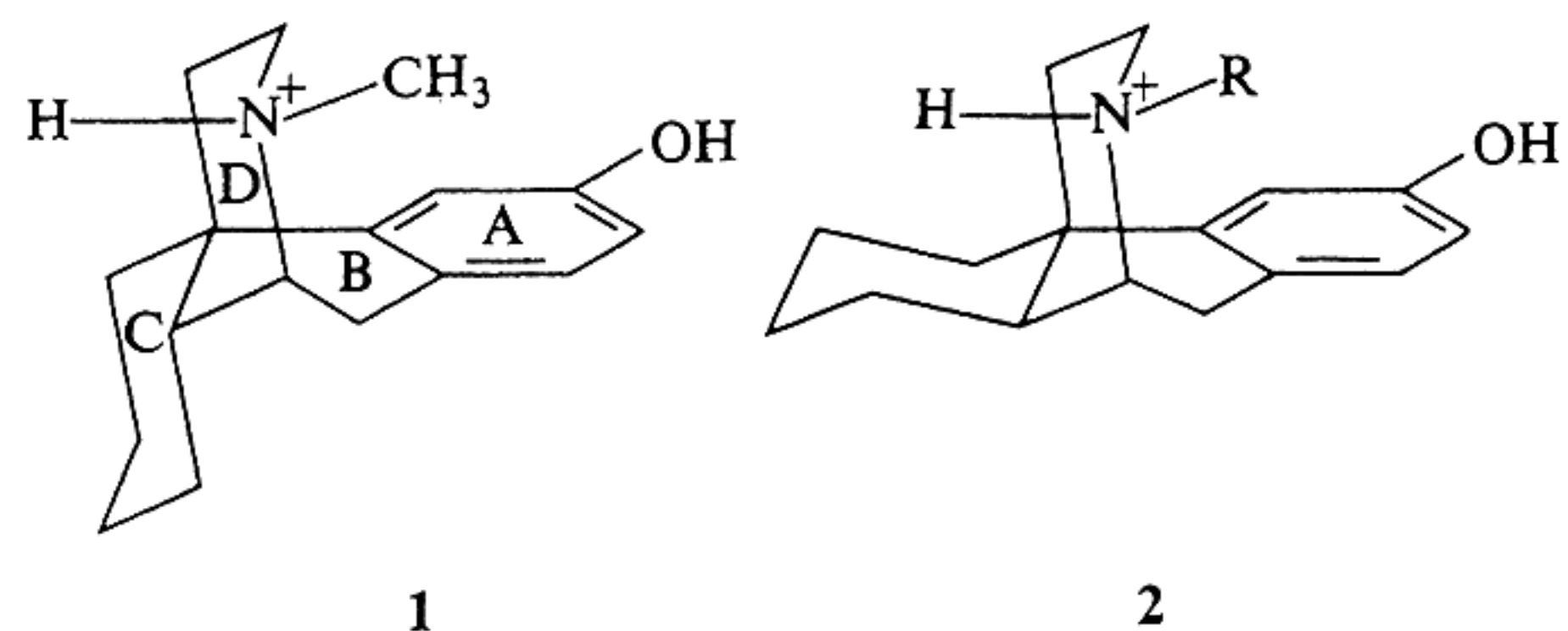
In recent years, a number of publications have appeared which purport to demonstrate that the N lone-pair directionality as we perceived it (1) would be unimportant in the receptor recognition process (4–6). However, in all these cases the morphinan analogs studied either exhibited very weak activity (5, 6) or were "so toxic that the observed activity was equivocal" (4).

In an effort to clarify further the stereoelectronic role on activity of the N lone pair of morphinan related compounds, we undertook the synthesis of the sulfonium analogs **3a** and **3b** which, for convenience, shall be referred to as S-methyl isosulforphanol and S-methyl sulforphanol respectively. In the

3a   3b
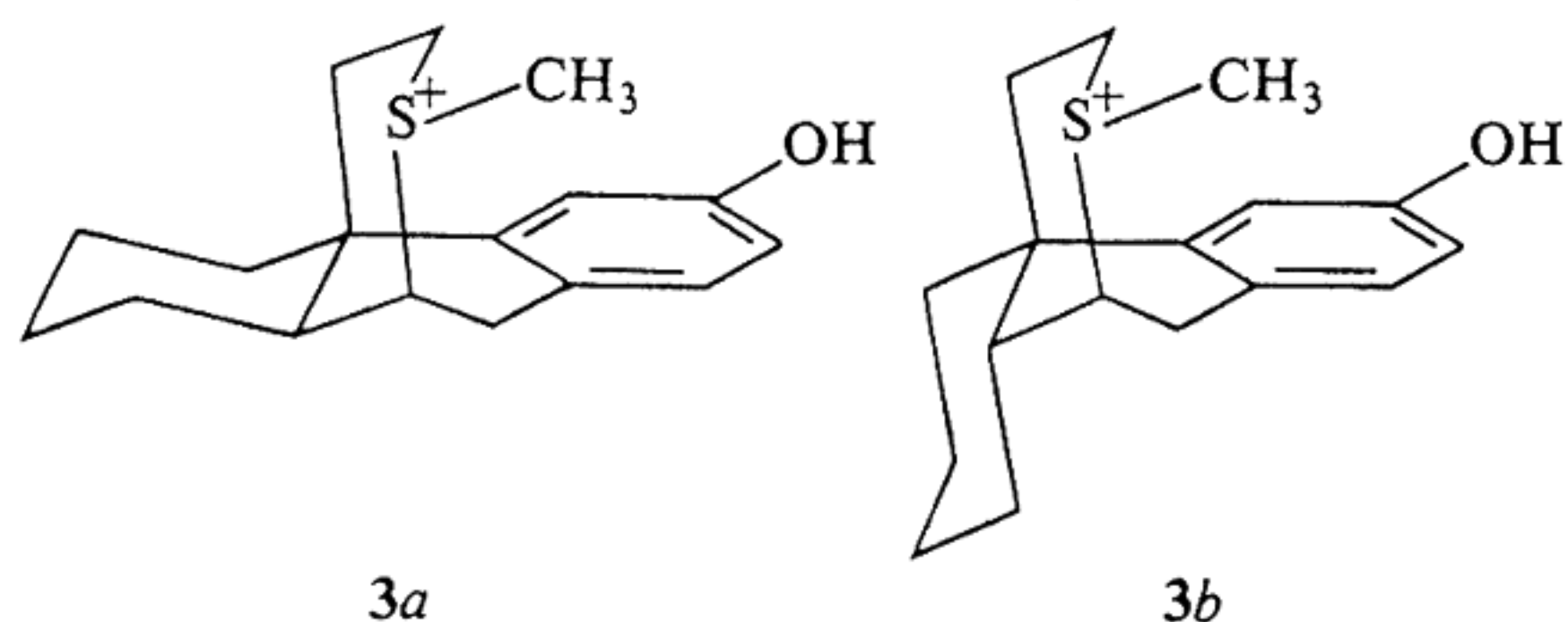
stereoelectronic and physico-chemical sense, sulfonium ions are, for the purpose of electrostatic pairing, close relatives of protonated tertiary amines and not of quaternary nitrogen compounds. Therefore, we hoped that pharmacological studies with the sulfonium analogs 3a and 3b would help in the clarification of the separate roles of ion pairing and of hydrogen bond complex formation at the counter-acceptor site level of the morphine receptor.

The purpose of this report is to describe a synthetic route leading exclusively to stereochemistry 3a. A non-morphinan-like side product of structure 13 was also obtained. A following paper will describe an alternate methodology allowing the generation of both 3a and 3b.

The commercial Grewe synthesis (7) of levorphanol (8–10) (1) provides a conceptual basis for the construction of the ring system of 3. However, the scheme as applied to levorphanol (1) has not been previously tested with a relevant sulphur analog and special experimental methodologies had to be introduced for the successful production of the sulphur-containing ring system.

Results and discussion

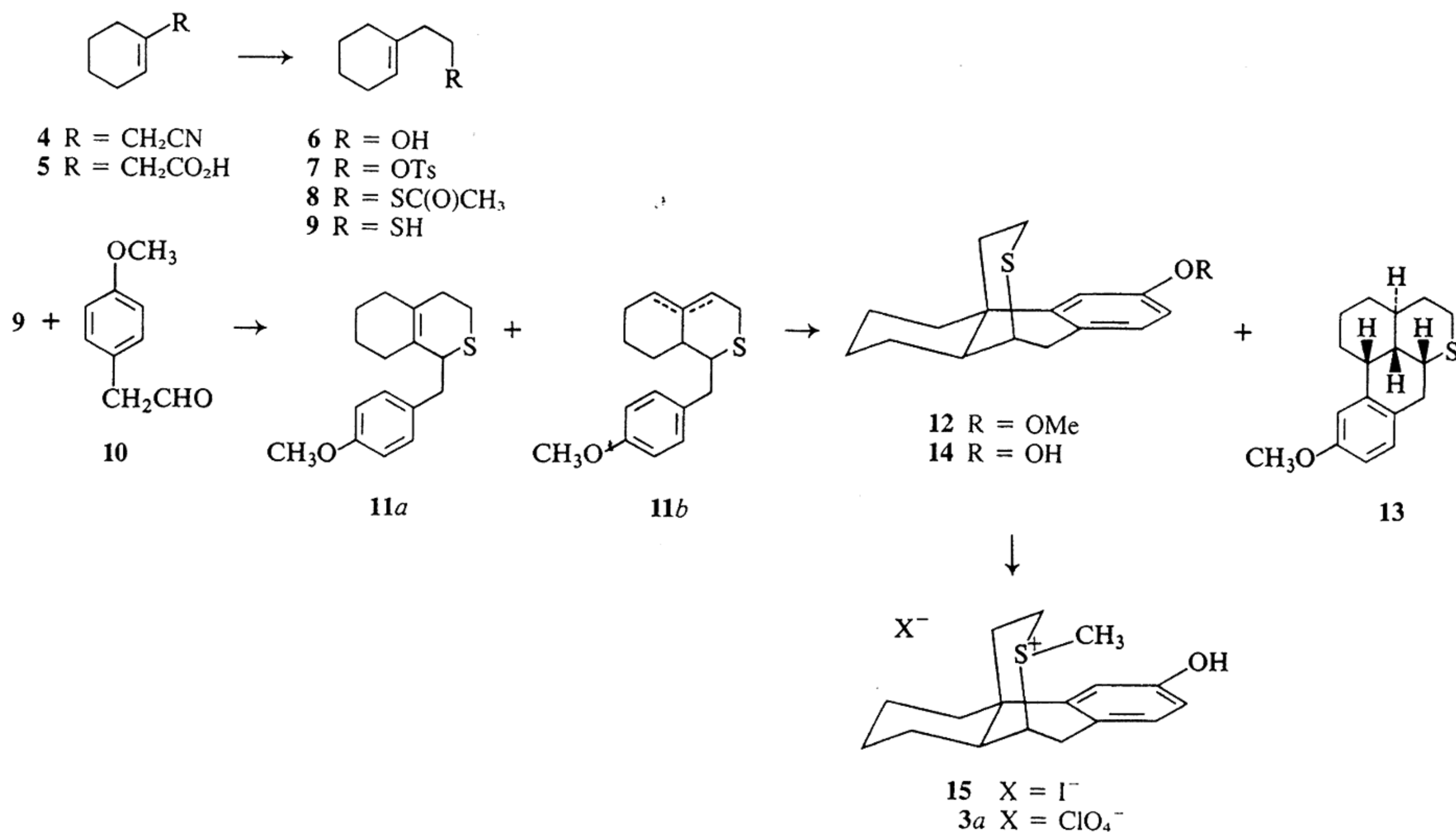The synthesis of S-methyl isosulforphanol (3a) was carried out as summarized in Scheme 1.

The nitrile group of 1-cyclohexen-1-yl acetonitrile (4) (11)

was hydrolyzed with aqueous sodium hydroxide to yield the known acid (5) in 85% yield. Lithium aluminum hydride reduction of the acid functionality led cleanly to the alcohol (6) which was treated with p-toluenesulfonyl chloride to yield 7 in 72% yield. The latter tosylate was reacted with potassium thioacetate in dry THF to give 2-(cyclohexen-1-yl)ethanethiol acetate (8) in 85% yield after purification by distillation. The thiol acetate functionality of 8 was cleaved with sodium methoxide in methanol at room temperature to yield the free thiol 9, which was reacted with p-methoxyacetaldehyde (10) (12) in a mixture of trifluoroacetic acid and acetic acid at room temperature to yield a mixture of double bond isomers of intermediate 11 in 37% yield. These experimental conditions appeared critical and are unlike those employed in the nitrogen series. Reaction of the latter with anhydrous hydrogen fluoride at −78°C, followed by chromatographic purification of the crude product, afforded a 34% yield of 3-methoxy-17-deaza-17-thiaisomorphinan (12) and a 5% yield of the isomeric ring structure (13). It is worth noting that, in our hands, the success of this reaction was critically dependent on the use of hydrogen fluoride as solvent and catalyst. Boron tribromide treatment of 12 at −78°C led to 3-hydroxy-17-deaza-17-thiaisomorphinan (14), which was converted to the methyl iodide salt (15) in 88% yield by reaction with methyl iodide in acetonitrile at room temperature. Anion exchange processing yielded (±)S-methyl isosulforphanol perchlorate (3a) whose nmr spectrum in chloroform indicated that only one geometrical isomer was present. The assigned structure 3a and that of the by-product 13 were elucidated by X-ray diffraction analysis.

Crystal structure analysis

(a) Data measurement (Tables 1–4)

Crystal data for $C_{17}H_{22}OS$ (13) and the S-methyl isosulforphanol perchlorate, $C_{17}H_{23}OS^+ \cdot ClO_4^-$ (3a), are presented in Table 1. The X-ray measurements were carried out on a Nonius

4 R = CH₂CN
5 R = CH₂CO₂H

6 R = OH
7 R = OTs
8 R = SC(O)CH₃
9 R = SH

12 R = OMe
14 R = OH

15 X = I⁻
3a X = ClO₄⁻

SCHEME 1

TABLE 1. Crystal data

Parameter	13	3a
Formula	$C_{17}H_{22}OS$	$C_{17}H_{23}OS^+ \cdot ClO_4^-$
M_r	274.4	374.9
System	Monoclinic	Orthorhombic
Space group	$P2_1/a$	$Pna2_1$
a (Å)	17.080(2)	10.934(1)
b	9.372(1)	9.219(1)
c	9.327(1)	17.131(2)
β (°)	108.67(1)	—
V (Å^3)	1414.4	1726.8
Z	4	4
$F(000)$	592	792
D_X (g cm^{-3})	1.288	1.442
Crystal dimensions (mm)	$0.60 \times 0.60 \times 0.10$	$0.03 \times 0.07 \times 0.57$
ω-scan range (°)	$1.10 + 0.14 \tan\theta$	$0.80 + 0.14 \tan\theta$
ω-speed (° min^{-1})	0.65–3.35	0.46–1.68
No. of unique reflections	2915	1522
Threshold limit	$2.0\sigma(I)$	$1.5\sigma(I)$
No. of obs. reflections	2545	1018
$R = \Sigma\|F_o\| - \|F_c\|/\Sigma\|F_o\|$	0.034	0.053
$R_w = [\Sigma w(\Delta F)^2/\Sigma w\|F_o\|^2]^{1/2}$	0.042	0.071
$s = [\Sigma w(\Delta F)^2/(m - n)]^{1/2}$	0.43	1.37
Max. (shift/esd)	0.39	0.48
Mean (shift/esd)	0.09	0.10

TABLE 2. Fractional atomic coordinates ($\times 10^4$; $\times 10^5$ for S) and equivalent temperature factors (Å^2) for $C_{17}H_{22}OS$ **13**. Estimated standard deviations are in parentheses

Atom	x	y	z	B(eq)
C(1)	4071(1)	5899(2)	−27(2)	3.2
C(2)	4407(1)	6142(2)	1497(2)	3.3
C(3)	3944(1)	5845(2)	2440(2)	3.0
C(4)	3150(1)	5299(2)	1842(1)	2.9
C(5)	1344(1)	4807(2)	501(2)	3.6
C(6)	1110(1)	6380(2)	333(2)	4.2
C(7)	727(1)	6779(2)	−1322(2)	4.1
C(8)	1281(1)	6399(2)	−2267(2)	3.2
C(9)	2118(1)	4391(2)	−2933(2)	3.3
C(10)	2947(1)	5152(2)	−2354(2)	3.6
C(11)	3273(1)	5354(2)	−660(2)	2.9
C(12)	2804(1)	5053(1)	282(1)	2.6
C(13)	1938(1)	4418(1)	−375(2)	2.9
C(14)	1536(1)	4820(2)	−2056(2)	2.9
C(15)	838(1)	6754(2)	−3932(2)	4.3
C(16)	1344(1)	6480(2)	−4976(2)	4.9
S(17)	16500(3)	46275(5)	−49683(4)	4.3
O(18)	4327(1)	6141(1)	3934(1)	4.3
C(19)	3906(1)	5827(2)	4981(2)	4.0

TABLE 3. Fractional atomic coordinates ($\times 10^4$) and equivalent temperature factors (Å^2) for $C_{17}H_{23}OS^+ \cdot ClO_4^-$ **3a**. Estimated standard deviations are in parentheses

Atom	x	y	z	B(eq)
Cl	1074(2)	376(3)	0	4.5
O(1)	2243(9)	1035(13)	−129(6)	8.2
O(2)	963(8)	−46(15)	799(5)	9.3
O(3)	959(10)	−868(10)	−470(6)	7.9
O(4)	98(14)	1288(18)	−145(10)	13.6
C(1)	2115(9)	4127(10)	1320(5)	3.3
C(2)	3194(8)	4073(10)	1742(6)	3.7
C(3)	3152(8)	4379(11)	2520(6)	3.8
C(4)	2090(8)	4710(10)	2904(5)	3.1
C(5)	−222(9)	4693(12)	3743(5)	3.6
C(6)	−1465(9)	4918(13)	4141(6)	4.4
C(7)	−2527(8)	4215(13)	3689(6)	4.2
C(8)	−2530(9)	4827(12)	2856(6)	4.2
C(9)	−1272(8)	4979(10)	1587(5)	3.3
C(10)	−145(9)	4409(10)	1174(5)	3.6
C(11)	998(9)	4430(10)	1683(5)	3.5
C(12)	979(8)	4778(9)	2487(5)	2.6
C(13)	−204(8)	5213(9)	2893(5)	2.8
C(14)	−1307(8)	4555(11)	2459(5)	3.2
C(15)	−219(8)	6905(11)	2877(6)	3.6
C(16)	−193(10)	7549(11)	2061(6)	4.1
S(17)	−1522(2)	6937(3)	1530(2)	3.7
O(18)	4271(6)	4301(8)	2911(4)	4.7
C(19)	−1264(11)	7389(12)	543(7)	5.2

CAD-4 diffractometer using Ni-filtered Cu radiation. While crystals of **13** were well formed and of good size, those of **3a** were minute and poorly formed; hence, data collection for **13** was taken to $2\theta = 150°$ while that for **3a** was limited to $2\theta = 130°$. The cell parameters were derived by a least-squares fit to the angular settings of 22 reflections with $84 < 2\theta < 148°$ for **13**, and 20 reflections with $52 < 2\theta < 88°$ for **3a**. The intensities were measured in the $\omega-2\theta$ scan mode for the ranges stated in Table 1, and extended by 25% at each side for the background measurements. Three standard reflections measured after every hour of exposure time varied within $\pm 1.3\%$ of their mean values. The net intensities were corrected for scale variations, Lorentz and polarization effects, and for ab-

sorption by Gaussian integration. The absorption corrections were in the range 1.206–2.597 for **13** and 1.109–2.467 for **3a**.

(b) Structure determination

Structure **13** was determined by the direct method of symbolic addition (13). All the non-hydrogen atoms were observed in the E map and, after partial refinement of their parameters, the H atoms were located from a difference Fourier map. Refinement of the atomic coordinates and anisotropic thermal parameters (isotropic for H) and a scale factor, constituting a total of 260 parameters, was by block-diagonal least squares, minimizing $\Sigma w(F_o - F_c)^2$ with $w = \{1 + [(\|F_o\| - 3)/25]^2\}^{-1}$ and excluding the unobserved reflections as well as four strong ones (020, 320, 400, and $\overline{2}01$) showing extinction effect.

Structure **3a** was determined by the heavy atom method, using a Patterson and three Fourier syntheses for location of the non-hydrogen atoms. The H atoms were located from a difference map at a later stage. Refinement was as described for **13**, except that the weights were calculated according to the expression $w = \{1 + [(\|F_o\| - 10)/30]^2\}^{-1}$; the z coordinate for Cl was fixed to define the origin along the z axis, and the H parameters were not refined, so that the number of refined parameters was 216. The (020) reflection which showed an extinction effect was excluded.

The scattering factor curves were from refs. 14 and 15, and all calculations were performed with the aid of the NRC program system (16) and ORTEP (17). The final atomic coordinates and equivalent isotropic thermal parameters are listed in Tables 2 and 3.[2]

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[2] The structure factor tables, parameters for the H atoms, and anisotropic thermal parameters for the non-hydrogen atoms are available, at a nominal charge, from the depository of unpublished data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.
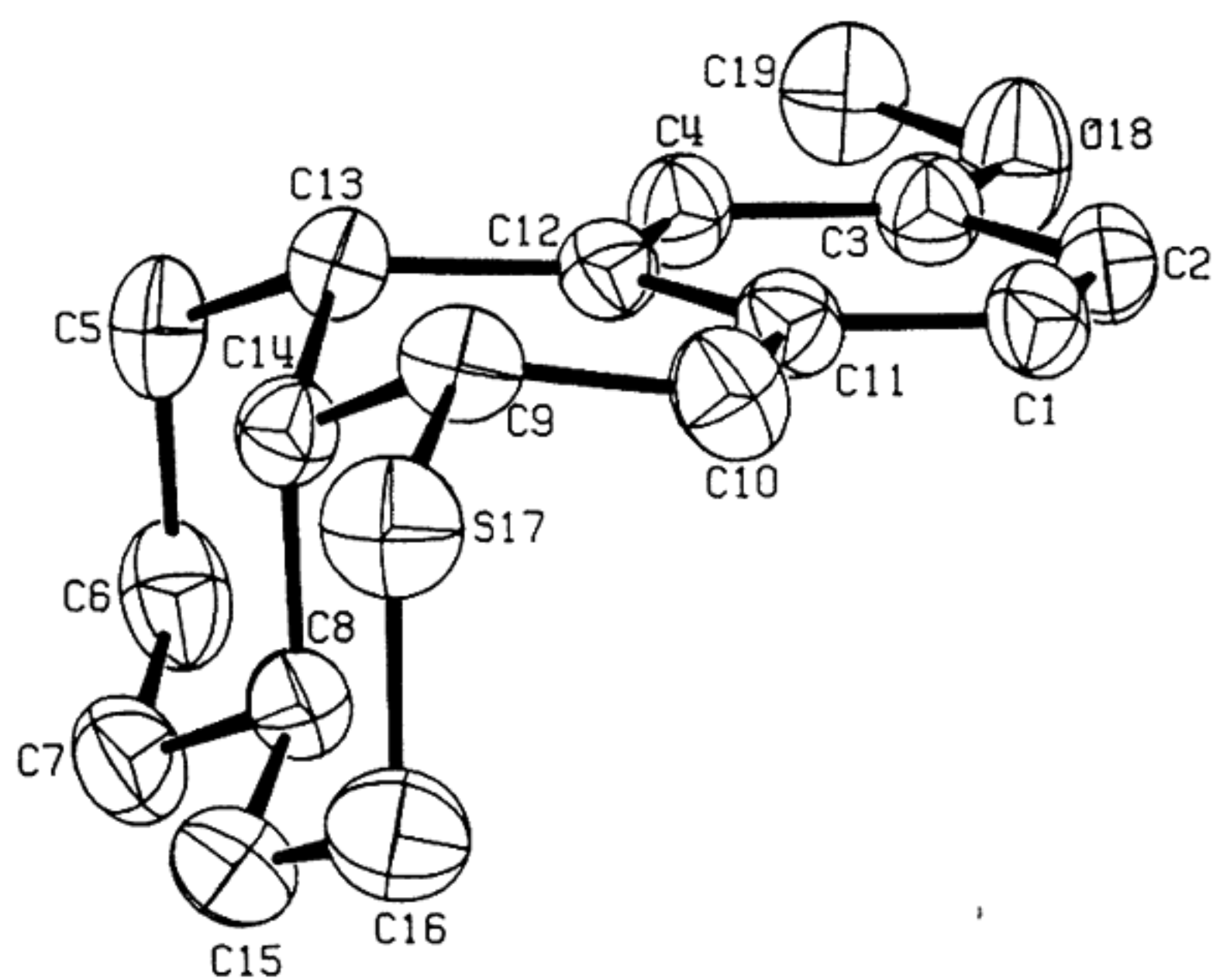
FIG. 1. A view of the molecular structure of $C_{17}H_{22}OS$ (**13**) showing the conformation and atom numbering. The thermal ellipsoids are drawn at 50% probability and the H atoms have been omitted.
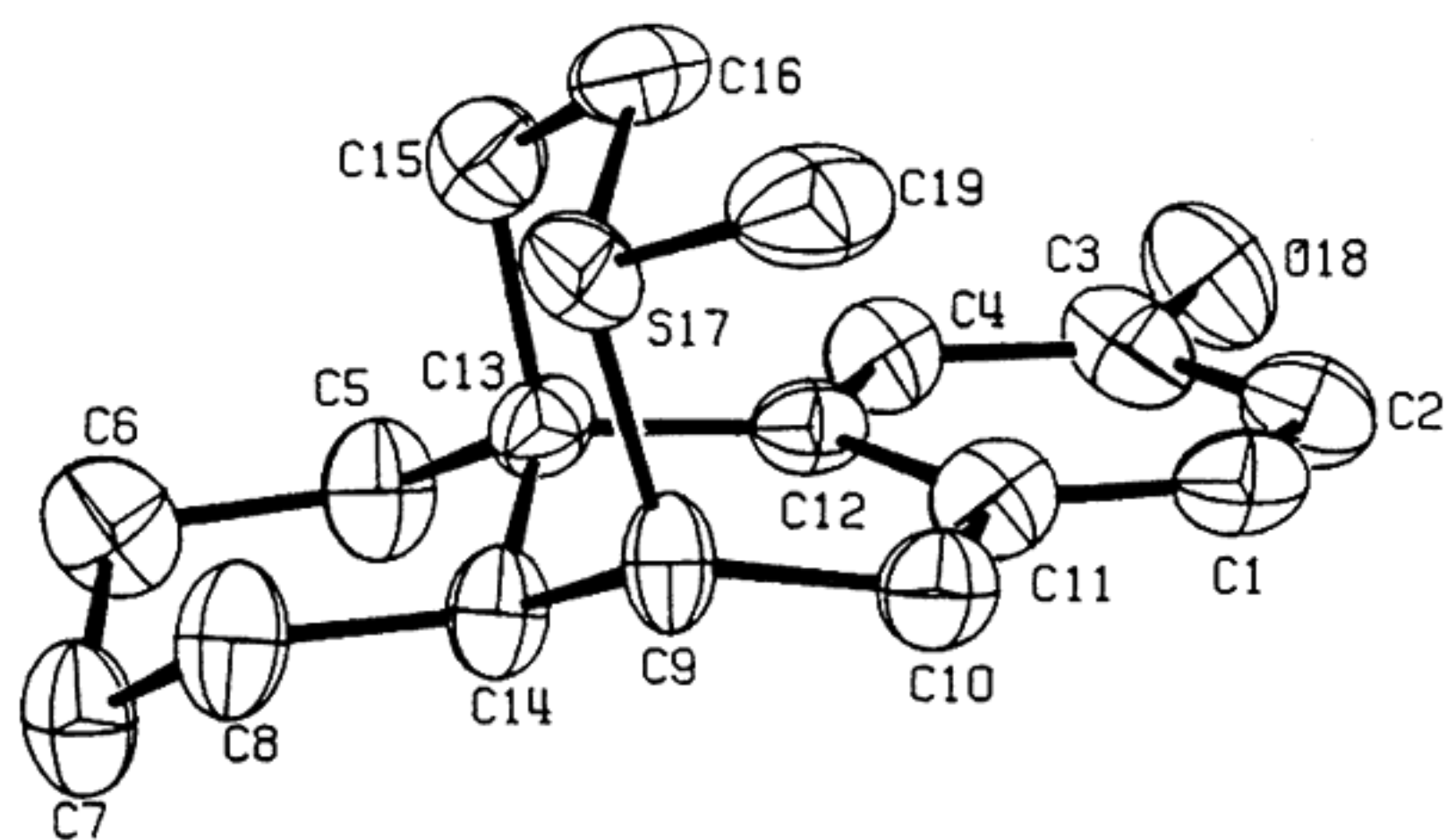

FIG. 2. A view of the molecular structure of $C_{17}H_{23}OS^+$ (**3a**) showing the conformation and atom numbering. The thermal ellipsoids are drawn at 50% probability and the H atoms have been omitted. This view is for the opposite enantiomorph of the coordinates listed in Table 3.

Structural analyses

The molecular conformations and atom numbering for compounds **13** and **3a** are presented in Figs. 1 and 2, respectively. Whereas the piperidine ring in levorphanol is fused along the C(9)—C(14) and C(13)—C(14) bonds, the $C_{17}H_{22}OS$ product shown in Fig. 1 has the corresponding ring fused at C(9)—C(14) and C(8)—C(14). Also, the methyl group which is substituted at N(17) in levorphanol is found to be substituted instead at O(18). These anomalies, however, are not present in molecule **3a** (Fig. 2), which is shown to possess the correct S-methyl isosulforphanol structure.

The bond lengths and valence angles for compounds **13** and **3a** are listed in Table 4. Equivalent bond lengths in the two molecules are comparable, with the largest difference of 0.032(11) Å in the C(3)—O(18) bond being insignificant at the 0.1% probability level. However, six pairs of equivalent valence angles show significant differences of 3.3(8)–5.2(6)° with the largest difference occurring at C(10)—C(9)—S(17) and C(14)—C(9)—S(17), probably as a result of the differences in molecular conformations. In both molecules the endocyclic angle C(9)—S(17)—C(16) is 99.0 ± 0.4°, which is considerably smaller than the normal tetrahedral angle of 109.7°.

The aromatic ring is planar; χ^2 ($= \Sigma\Delta^2/\sigma^2$) is 7.7 for molecule **13** and 11.1 for **3a**. The adjacent ring has nearly the same

conformation in both molecules with insignificant differences (within ±1.3°) in the corresponding torsion angles. The absolute values of the torsion angles in the sulfonium ring and the remaining ring are 52.5(2)–61.1(2)° and 53.4(2)–57.1(s)° for molecule **13**, compared to 58.7(7)–67.0(8)° and 50.6(10)–58.2(11)° for molecule **3a**, respectively.

While there are no short intermolecular interactions in the crystals of compound **13**, there is a short contact in **3a** of 2.789(12) Å between the hydroxyl O(18) and O(3) of the perchlorate group, indicative of a possible hydrogen bond between them.

These structural analyses establish that the substitution of a basic nitrogen by a sulfur in a Grewe-like process for morphinan synthesis unexpectedly leads to a complete reversal of the B/C ring junction stereochemistry of the product. The *trans*-geometry of the resulting sulforphan **12** can hardly be attributed to the different nature of the Friedel–Crafts catalyst (hydrogen fluoride); rather, it is likely that the longer C—S bonds (>1.8 Å) relative to the C—N bonds of morphinans serve to relieve 1,3-axial compressions between the ring D sulfur atom and the ring C hydrogens, thus reversing the thermodynamic stability of the transition states leading respectively to morphinans and sulforphans.

The unexpected formation of the polyhydro-thiabenzanthracene by-product **13** is best explained by the involvement of a double bond isomerization of **11a** followed by direct electrophilic attack of the phenyl ring. This implies the intermediacy of a secondary carbonium ion intermediate which probably accounts for the very low yield (~5%) of product.

The sulfonium analog **3a** (isosulforphanol) was tested as the perchlorate salt for its effect on the opiate receptors of the guinea-pig ileum (GPI) longitudinal muscle, the mouse *vas deferens*, and the central nervous system (CNS) of hooded rats by the intracerebroventricular route of administration. The results, which have been recently reported in preliminary form (18), showed that analog **3a** displays marked affinity for the opiate receptor while inducing divergent effects in the GPI and the CNS respectively. The mechanistic significance of these observations is under active investigation.

Experimental

General

Melting points and distillation temperatures are uncorrected. Infrared spectra were recorded on a Perkin–Elmer model 297 spectrophotometer. Proton nuclear magnetic resonance (^1H nmr) spectra were measured using a Varian XL-200 spectrometer. Tetramethylsilane was employed as the internal standard for all compounds. Mass spectrometric measurements were recorded on Dupont 21-492B or LKB 9000 mass spectrometers.

2-(1-Cyclohexen-1-yl) acetic acid (5)

1-Cyclohexen-1-yl acetonitrile (**4**) (50 g, 0.415 mol) and sodium hydroxide (30 g, 0.075 mol) were dissolved in H_2O (300 mL) and heated at reflux for 20 h. The reaction mixture was extracted with chloroform (3 × 75 mL) to remove any unwanted side products. The remaining aqueous layer was acidified and again extracted with chloroform (3 × 75 mL). The combined extracts were dried and solvent removed *in vacuo* to yield a green oil which was distilled (bp 155–157°C/20 Torr; 1 Torr = 133.3 Pa) to give 49 g (0.35 mol, 85% yield) of a white waxy solid, mp ≈ 26°C; ir ($CHCl_3$): 2920, 1700 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.56–1.92 (m, 4H), 2.00–2.18 (m, 4H, allylic), 3.00 (s, 2H, CH_2COO), 5.71 (s, 1H, C=CH), 8.00 (br s, 1H, COOH); m/e: 111 (M^+ − COOH, base peak).

2-(1-Cyclohexen-1-yl)ethanol (6)

A solution of 2-(1-cyclohexen-1-yl) acetic acid (10 g, 0.071 mol)

TABLE 4. Bond lengths and valence angles and their estimated standard deviations in parentheses, for **13**: $C_{17}H_{22}OS$ and **3a**: $C_{17}H_{23}OS^+ \cdot ClO_4^-$

	Bond length (Å)	
Bond	**13**	**3a**
C(1)—C(2)	1.371(3)	1.385(13)
C(1)—C(11)	1.397(3)	1.399(13)
C(2)—C(3)	1.386(3)	1.363(14)
C(3)—C(4)	1.387(3)	1.369(13)
C(3)—O(18)	1.365(2)	1.397(11)
C(4)—C(12)	1.403(3)	1.411(12)
C(5)—C(6)	1.522(3)	1.535(14)
C(5)—C(13)	1.536(3)	1.533(12)
C(6)—C(7)	1.518(3)	1.539(14)
C(7)—C(8)	1.527(3)	1.534(15)
C(8)—C(14)	1.537(3)	1.521(13)
C(8)—C(15)	1.531(3)	—
C(9)—C(10)	1.521(3)	1.515(13)
C(9)—C(14)	1.530(3)	1.543(12)
C(9)—S(17)	1.821(2)	1.828(10)
C(10)—C(11)	1.510(3)	1.524(13)
C(11)—C(12)	1.394(3)	1.414(12)
C(12)—C(13)	1.529(3)	1.522(12)
C(13)—C(14)	1.543(3)	1.542(12)
C(13)—C(15)	—	1.560(12)
C(15)—C(16)	1.517(3)	1.519(14)
C(16)—S(17)	1.812(2)	1.805(11)
S(17)—C(19)	—	1.764(11)
O(18)—C(19)	1.417(2)	—
Cl—O(1)	—	1.432(10)
Cl—O(2)	—	1.428(9)
Cl—O(3)	—	1.407(10)
Cl—O(4)	—	1.381(16)

	Valence angle (deg)	
Bond	**13**	**3a**
C(2)—C(1)—C(11)	121.8(2)	121.3(8)
C(1)—C(2)—C(3)	119.3(2)	118.3(9)
C(2)—C(3)—C(4)	120.1(2)	123.0(9)
C(2)—C(3)—O(18)	115.0(2)	115.4(8)
C(4)—C(3)—O(18)	124.9(2)	121.6(8)
C(3)—C(4)—C(12)	120.8(2)	119.8(8)
C(6)—C(5)—C(13)	111.8(1)	113.0(8)
C(5)—C(6)—C(7)	110.9(1)	112.8(9)
C(6)—C(7)—C(8)	112.6(1)	108.3(8)
C(7)—C(8)—C(14)	110.7(1)	110.8(8)
C(7)—C(8)—C(15)	109.8(1)	—
C(14)—C(8)—C(15)	111.5(1)	—
C(10)—C(9)—C(14)	112.2(1)	112.6(7)
C(10)—C(9)—S(17)	111.2(1)	116.1(6)
C(14)—C(9)—S(17)	112.5(1)	107.3(6)
C(9)—C(10)—C(11)	114.9(2)	113.3(8)
C(1)—C(11)—C(10)	118.1(2)	117.3(8)
C(1)—C(11)—C(12)	119.2(2)	119.4(8)
C(10)—C(11)—C(12)	122.7(2)	123.2(8)
C(4)—C(12)—C(11)	118.9(2)	118.1(8)
C(4)—C(12)—C(13)	120.9(1)	120.8(8)
C(11)—C(12)—C(13)	120.2(1)	121.1(8)
C(5)—C(13)—C(12)	114.4(1)	111.3(7)
C(5)—C(13)—C(14)	109.1(1)	109.0(7)
C(5)—C(13)—C(15)	—	109.2(7)
C(12)—C(13)—C(14)	111.8(1)	109.9(7)
C(12)—C(13)—C(15)	—	105.3(7)
C(14)—C(13)—C(15)	—	112.1(7)

TABLE 4. (*Continued*)

	Valence angle (deg)	
Bond	**13**	**3a**
C(8)—C(14)—C(9)	112.9(1)	114.4(8)
C(8)—C(14)—C(13)	112.4(1)	113.9(8)
C(9)—C(14)—C(13)	109.0(1)	110.4(7)
C(8)—C(15)—C(16)	114.6(2)	—
C(13)—C(15)—C(16)	—	114.0(8)
C(15)—C(16)—S(17)	112.5(1)	109.1(7)
C(9)—S(17)—C(16)	98.6(1)	99.3(5)
C(9)—S(17)—C(19)	—	105.1(5)
C(16)—S(17)—C(19)	—	106.3(5)
C(3)—O(18)—C(19)	118.6(1)	—
O(1)—Cl—O(2)	—	109.8(6)
O(1)—Cl—O(3)	—	109.7(6)
O(1)—Cl—O(4)	—	113.8(8)
O(2)—Cl—O(3)	—	108.6(6)
O(2)—Cl—O(4)	—	105.8(8)
O(3)—Cl—O(4)	—	108.9(8)

in dry ether (30 mL) was added dropwise to a suspension of $LiAlH_4$ (2.8 g, 0.074 mol) in dry ether (20 mL) under N_2. After the addition had been completed the reaction mixture was allowed to stir under N_2 for an additional 1.5 h. The remaining unreacted $LiAlH_4$ was decomposed by the dropwise addition of water. The reaction mixture was slowly added to a 1 N aqueous solution of HCl (100 mL). The ether layer was removed and the remaining aqueous layer extracted with ether (3 × 75 mL). The combined organic extracts were dried and the ether removed *in vacuo*. The residue was distilled (bp 101–102°C/20 Torr) to yield 7.16 g (0.57 mol, 80% yield) of a colorless oil; ir (CHCl$_3$): 3610 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.58–1.80 (m, 4H), 1.96–2.15 (m, 4H, allylic), 2.26 (m, 2H, = —CH$_2$), 3.54 (s, 1H, OH), 3.68 (t, 2H, J = 4 Hz, CH$_2$O), 5.56 (s, 1H, C=CH); m/e: 126 (M$^+$), 108, 79 (base peak).

2-(1-Cyclohexen-1-yl)ethanol tosylate (7)

2-(1-Cyclohexen-1-yl)ethanol (**6**) (9.0 g, 0.071 mol) was dissolved in dry pyridine (50 mL) and cooled to 0°C. A solution of *p*-toluenesulfonyl chloride (15 g, 0.079 mol) in dry pyridine (75 mL) was added at 0°C and the reaction mixture was sitrred at 0°C for 2 h. After a further 24 h at 0°C the solution was poured into a solution of ice-water (300 g) and extracted with methylene chloride (3 × 75 mL). The combined organic extracts were washed with cold 10% aqueous HCl (6 × 50 mL) to remove any pyridine. The organic layer was dried and the solvent removed *in vacuo*. Low temperature recrystallization yielded 14.2 g (0.051 mol, 72.3% yield) of a white solid; mp ≈ 23°C; ir (CHCl$_3$): 2940, 1600, 1360, 1170, 970, 930 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.4–1.5 (m, 4H), 1.53–1.9 (m, 4H, allylic), 2.2–2.3 (m, 2H, = —CH$_2$), 2.41 (s, 3H, ArCH$_3$), 4.05 (t, 2H, J = 2 Hz, CH$_2$O), 5.37 (br s, 1H, =CH), 7.33, 7.75 (ABq, 4H, J = 4 Hz, ArH); m/e: 280 (M$^+$), 200, 155, 109 (base peak).

2-(1-Cyclohexen-1-yl)ethanethiol acetate (8)

2-(1-Cyclohexen-1-yl)ethanol tosylate (**7**) (16 g, 0.057 mol) was dissolved in dry THF (150 mL) and a solution of potassium thioacetate (25 g, 0.23 mol) in dry THF (200 mL) was added. The reaction mixture was heated at reflux for 2 h and the THF was removed *in vacuo*. The residue was dissolved in H$_2$O (100 mL) and extracted with methylene chloride (3 × 75 mL). The combined organic extracts were dried and the solvent removed *in vacuo*. The yellow oil was purified by distillation (bp 113°C/5 Torr) to yield 8.97 g (0.049 mol, 85.5% yield) of a pale yellow oil; ir (neat): 1690, 1435, 1350, 1120, 950, 620 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.4–1.64 (m, 4H), 1.94–1.98 (m, 4H, allylic), 2.12–2.20 (m, 2H, = —CH$_2$), 2.28 (s, 3H, C(O)CH$_3$), 2.91 (t, 2H, J = 4 Hz, CH$_2$S), 5.44 (s, 1H, =CH); m/e: 184 (M$^+$), 108

(base peak). *Anal*. calcd. for $C_{10}H_{16}OS$: C 65.17, H 8.75; found: C 65.39, H 8.75.

2-(1-Cyclohexen-1-yl)ethanethiol (9)

Methanol (50 mL) was degassed by passing N_2 through the solution. Sodium (1.44 g, 0.063 mol) was added and the solution stirred until all the sodium had dissolved. A solution of 2-(1-cyclohexen-1-yl)-ethanethiol acetate (4.4 g, 0.024 mol) in dry THF (10 mL) was added and the reaction mixture was stirred under N_2 for 4 h. The solution was diluted with saturated aqueous NaCl (100 mL) and the pH adjusted to 4 with 10% aqueous citric acid. The aqueous layer was extracted with ether (4 × 75 mL). The combined organic extracts were dried and the solvent removed *in vacuo*. The residue was distilled (bp 116°C/45 Torr) to give 0.065 g (0.0455 mol, 72.3% yield) of a colorless oil; ir (neat): 2900, 1440, 720 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.34–1.39 (m, 1H, SH), 1.51–1.65 (m, 4H, CH$_2$CH$_2$), 2.53–2.59 (m, 2H, CH$_2$S), 5.46 (br s, 1H, C=CH); *m/e*: 142 (M$^+$, base peak), 126, 108. *Anal*. calcd. for $C_8H_{14}S$: C 67.54, H 9.91; found: C 67.32, H 9.80.

p-Methoxyacetaldehyde (10) (ref. 12)[3]

4-Allylanisole (5 mL) was added to a vigorously stirred solution of aqueous H_2O_2 (30%, 37 mL, 1.2 mol) and aqueous formic acid (90%, 160 mL, 4.2 mol) and the reaction mixture was heated to 40°C. The temperature was maintained between 40 and 45°C by heating or cooling as necessary while a further 35 mL of 4-allylanisole (0.26 mol) was added dropwise. The reaction mixture was stirred overnight at room temperature and evaporated to dryness *in vacuo*. To the remaining red residue was added aqueous NaOH (37%, 45 mL), at 45°C, and H_2O (65 mL). The solution was heated to 50°C for 1 h. After cooling, concentrated HCl (33 mL) was added and the aqueous layer extracted with CHCl$_3$ (3 × 75 mL). The combined organic extracts were dried, filtered, and the solvent removed *in vacuo*. The residue was purified by distillation (bp 150–152°C/25 Torr) through an air-cooled condenser to afford 29.8 g (0.16 mol, 63% yield) of 1,2-dihydroxy-3-(4-methoxyphenyl)propane; ir (CHCl$_3$): 3400, 2930, 1610, 1505 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 2.6 (d, 2H, $J = 4$ Hz, CH$_2$Ar), 3.4 (m, 1H, CHO), 3.5–3.8 (m, 2H, CH$_2$O), 3.7 (s, 3H, OCH$_3$), 4.1 (br s, 1H, OH), 6.78 (d, 2H, $J = 4$ Hz, ArH), 7.1 (d, 2H, $J = 4$ Hz, ArH); *m/e*: 182 (M$^+$), 148, 121 (base peak).

1,2-Dihydroxy-3-(4-methoxyphenyl)propane (22.3 g, 0.12 mol) was dissolved in dry benzene (1250 mL). One-tenth of the solvent (125 mL) was distilled off under N_2 and, after cooling, one equivalent of lead tetraacetate (55.4 g, 0.12 mol) was added and the mixture stirred at room temperature overnight. The suspension was poured onto H_2O (1000 mL) and the lead oxides removed by filtration through Celite. The aqueous layer was separated, the organic layer washed with H_2O (2 × 500 mL), saturated NaHCO$_3$ (1 × 500 mL), and then dried, filtered, and concentrated *in vacuo*. The residue was distilled (bp 76–77°C/0.25 Torr) to yield 8.3 g (0.06 mol, 45% yield) of p-methoxyacetaldehyde as a yellow liquid; ir (neat): 1720, 1670, 1580, 1510 cm^{-1}; ^{1}H nmr (CD$_2$Cl$_2$) δ: 3.48 (br s, 2H, CH$_2$O), 3.7 (s, 3H, OCH$_3$), 6.8–7.1 (m, 4H, ArH), 9.6 (br s, HCO); *m/e*: 150 (M$^+$), 121 (base peak).

1-(p-Methoxybenzyl)-3,4,5,6,7,8-hexahydro-1H-isobenzothiapyran (11a)

2-(Cyclohexen-1-yl)ethanethiol (9) (3.5 g, 0.025 mol)[†] was dissolved in acetic acid (6 mL) and the solution added dropwise to a stirred solution of the preceding p-methoxyphenylacetaldehyde (9.2 g, 0.061 mol) in trifluoroacetic acid (12 mL) and acetic acid (6 mL) under argon at room temperature. The reaction mixture was stirred for 20 h and then poured onto ice-water (50 mL) and the mixture neutralized with saturated sodium bicarbonate solution. The aqueous layer was extracted with ether (3 × 75 mL), the combined extracts dried, and the solvent removed *in vacuo* to yield a yellow oil which was purified by flash chromatography (8 in. × 1 in. silica gel 60 (230–400 mesh)) using petroleum ether/ethyl acetate 50:1 (v/v) as the eluent to give 1.2 g (4.69 mmol) of 11a and 0.6 g (2.34 mmol) of 11b (28.1%

[3] Experimental details previously unreported in this reference.

yield overall); ir (11a) (neat): 2920, 1610, 1510, 1240, 750 cm^{-1}; ^{1}H nmr (11a) (CDCl$_3$) δ: 1.0–3.0 (complex m, 15H), 3.75 (s, 3H, OCH$_3$), 6.8 (d, 2H, $J = 4$ Hz, ArH), 7.1 (d, 2H, $J = 4$ Hz, ArH); *m/e* (11a): 274 (M$^+$), 153, 83 (base peak). *Anal*. calcd. for $C_{17}H_{22}OS$: C 74.40, H 8.08; found: C 74.36, H 8.01. Infrared (11b) (neat): 2920, 1610, 1510, 1240, 750 cm^{-1}; ^{1}H nmr (11b) (CDCl$_3$) δ: 1.0–3.0 (complex m, 14H), 3.75 (s, 3H, OCH$_3$), 5.6 (br s, 1H, =CH), 6.8 (d, 2H, $J = 8.6$ Hz, ArH), 7.1 (d, 2H, $J = 8.55$ Hz, ArH); *m/e* (11b): 274 (M$^+$), 83 (base peak).

3-Methoxy-17-deaza-17-isothioamorphinan (12)

The isomers of 11 (1.8 g, 7.03 mmol) were dissolved in anhydrous HF at −78°C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 24 h. The HF was evaporated and the remaining residue dissolved in ether. The ethereal solution was washed several times with water, dried, and the solvent removed *in vacuo*. The red-colored residue was purified by flash chromatography (8 in. × 1 in. silica gel 60 (230–400 mesh)) using petroleum ether/ethyl acetate 50:1 (v/v) to give 0.61 g (2.2 mmol), 34% yield of 12 (mp 73–74°C) and 0.1 g (0.36 mmol), 5.1% yield of 13; mp 134–135°C; ir (12) (KBr disc): 1610, 1570, 1490, 1420, 1280, 1040, 800, 590 cm^{-1}; ^{1}H nmr (12) (CDCl$_3$) δ: 1.2–2.8 (complex m, 14H), 3.24 (d, 1H, $J = 8$ Hz, CHAr), 3.8 (s, 3H, OCH$_3$), 6.7–7.0 (m, 4H, ArH); *m/e* (12): 274 (M$^+$), 213 (base peak). *Anal*. calcd. for $C_{17}H_{22}OS$: C 74.40, H 8.08; found: C 74.61, H 8.17. Infrared (13) (KBr disc): 2930, 1610, 1500, 1260, 1230, 1040, 800 cm^{-1}; ^{1}H nmr (13) (CDCl$_3$) δ: 0.8–3.2 (complex m, 16H), 3.7 (s, 3H, OCH$_3$), 6.8–7.2 (m, 3H, ArH); *m/e* (13): 274 (M$^+$, base peak). The X-ray of this compound is shown in Fig. 1.

3-Hydroxy-17-deaza-17-isothiamorphinan (14)

3-Methoxy-17-deaza-17-isothiamorphinan (12) (0.59 g, 2.14 mmol) was dissolved in dry methylene chloride (20 mL) at −78°C under argon. A solution of BBr$_3$ (0.342 mL in 3 mL CH$_2$Cl$_2$) was added at −78°C and the reaction allowed to warm to room temperature. After 17 h the solution was poured onto H_2O (50 mL) and the organic layer collected. The aqueous layer was extracted with methylene chloride (3 × 50 mL) and the combined organic extracts were dried and the solvent removed *in vacuo*. The residue was purified by flash chromatography (1 in. × 4 in. silica gel 60 (230–400 mesh)) using chloroform as the eluent to yield 0.47 g (1.82 mmol, 85.6% yield) of white crystals; mp 177–178°C; ir (KBr disc): 3290, 2910, 1620, 1580, 1500, 1285 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.1–2.8 (m, 14H), 3.25 (d, 1H, $J = 8$ Hz, $J = 3$ Hz, CHAr), 4.6 (s, 1H, OH), 6.6–7.1 (m, 3H, ArH); *m/e*: 260 (M$^+$), 57 (base peak). *Anal*. calcd. for $C_{16}H_{20}OS$: C 73.80, H 7.74; found: C 73.98, H 7.70.

3-Hydroxy-17-deaza-17-isothiamorphinan-17-methyl onium iodide (15)

3-Hydroxy-17-deaza-17-isothiamorphinan (0.155 g, 0.596 mmol) was dissolved in CH$_3$CN (1.5 mL) containing methyl iodide (4 mL). The reaction mixture was allowed to stand for 20 h and dry ether was added to maximum precipitation of white crystals of the iodide salt. These were collected, washed with dry ether, and dried *in vacuo* to yield 0.210 g (5.22 × 10^{-1} mmol, 88% yield) of white crystals; ir (KBr disc): 3260, 2930, 1615, 1490, 1290 cm^{-1}; ^{1}H nmr (CDCl$_3$/CF$_3$COOH) δ: 1.0–4.0 (m, 16H), 2.95 (s, 3H, SCH$_3$), 6.7–7.2 (m, 3H, ArH); *m/e*: 260 (M$^+$ − CH$_3$I), 142 (CH$_3$I, base peak). *Anal*. calcd. for $C_{17}H_{23}IOS$: C 50.75, H 5.76; found: C 50.61, H 5.57.

S-Methyl isosulforphanol perchlorate (3a)

A methanol solution of the preceding salt (15) (0.210 g, 0.52 mmol) was passed through an anion exchange column in the perchlorate form (prepared as described below) to yield a methanol solution of S-methyl isosulforphanol perchlorate. Removal of the solvent yielded 0.154 g (0.412 mmol, 79% yield) of white crystals. The product was recrystallized from CH$_3$CN/hexane to give 0.132 g (0.352 mmol, 67.5% yield) of long white needles. Nuclear magnetic resonance analysis indicated only one type of methyl group was present; ir (KBr disc): 3350, 1610, 1100 (ClO$_4^-$), 620 (ClO$_4^-$) cm^{-1}; ^{1}H nmr (CD$_3$CN

δ: 1.1–4.0 (m, 16H), 2.9 (s, 3H, SCH₃), 6.7–7.1 (m, 3H, ArH); m/e: 260 (M⁺ − MeClO₄), 28 (base peak). The X-ray structure of the compound is shown in Fig. 2.

The anion exchange column was prepared using analytical grade resin AG1-X8 from B10-RAD (100–200 mesh) in the chloride form. The resin was washed with aqueous NaOH (1 N) and then to neutrality with distilled water, followed by washing with dilute aqueous perchloric acid (5%). The resin was again washed to neutrality with distilled water and then methanol. It was packed into a small column (1/2 in. × 2 in.), a methanol solution of **15** applied to the top of the column, and the product eluted under a low pressure of nitrogen.

Acknowledgements

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