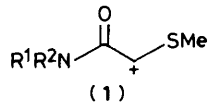
One-step Synthesis of the Erythrinane Skeleton by Acid-promoted Double Cyclization of *N*-(Cyclohex-1-enyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-α-(methylsulphinyl)acetamide and its Derivatives

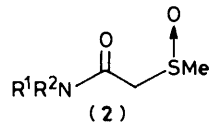
Hiroyuki Ishibashi,*, Kazumi Sato, and Masazumi Ikeda
Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan
Hiroshi Maeda, Shuji Akai, and Yasumitsu Tamura
Faculty of Pharmaceutical Sciences, Osaka University, 1—6 Yamada-oka, Suita, Osaka 565, Japan

On being heated with toluene-*p*-sulphonic acid, *N*-(cyclohex-1-enyl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]-α-(methylsulphinyl)acetamide (**8**) underwent double cyclization to give the erythrinane derivative (**11**), which was converted into the amide (**13**) by reduction with Raney nickel and into the enamide (**14**) by thermolysis of the corresponding sulphoxide. The double cyclization of the sulphoxide (**18**) gave a stereoisomeric mixture of the ether products (**19a**) and (**19b**). On treatment with Raney nickel, either (**19a**) or (**19b**) afforded a mixture of the alcohols (**20a**) and (**20b**), each of which was oxidized with chromium trioxide–pyridine to give the same ketone (**21**). The sulphoxide (**25**) also cyclized to afford two products (**26**) and (**27**), but in low yields, which were desulphurized with Raney nickel to give the erythrinones (**28**) and (**29**), respectively.

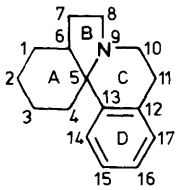
The use of thionium ions as initiators in cationic olefin cyclization has attracted a great deal of attention in recent years.[1] In a previous paper,[2] we showed that the Pummerer reaction intermediates (**1**) derived from the α-sulphinylacetamides (**2**) are useful as highly reactive initiating groups for olefin cyclization. We now describe a novel one-step synthesis of the erythrinane skeleton (**3**) by utilization of the cyclization initiated by the thionium ions (**1**).[3]



(**1**)



(**2**)



(**3**)

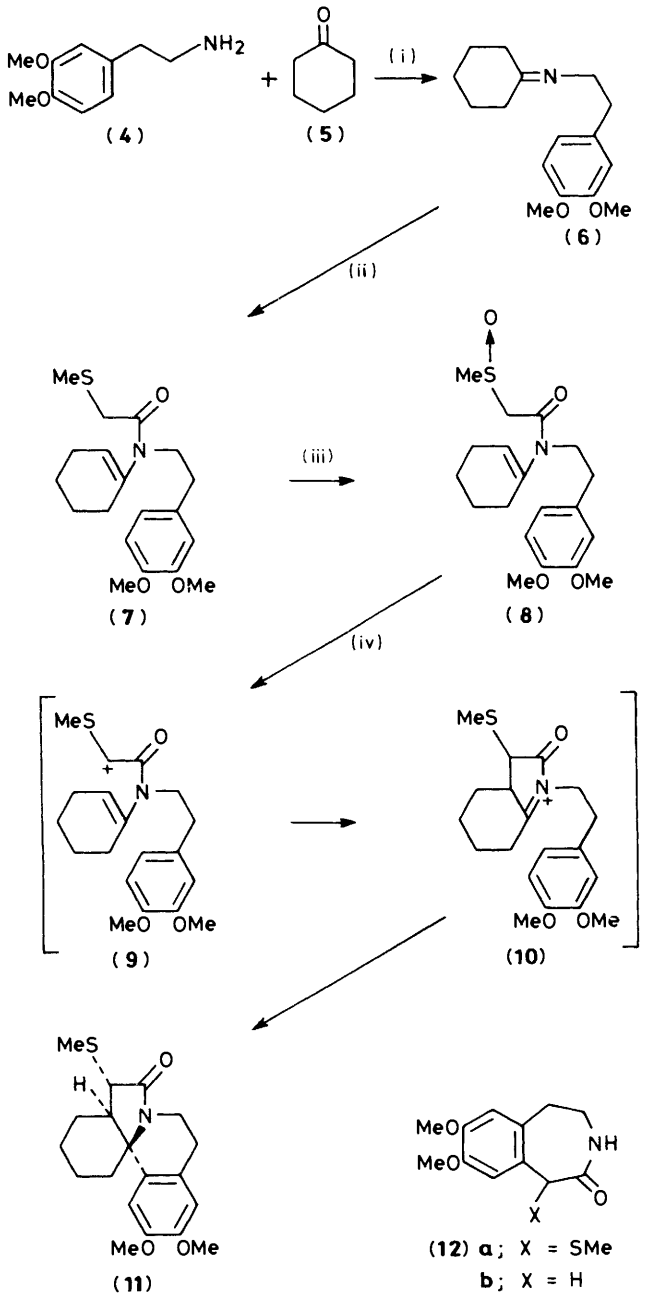
Our synthetic route to the erythrinane skeleton is illustrated in Scheme 1. The starting sulphoxide (**8**) was prepared easily from 2-(3,4-dimethoxyphenyl)ethylamine (**4**) and cyclohexanone (**5**) in three steps, *i.e.*, the imine (**6**), prepared by condensation of (**4**) and (**5**), was acylated with α-(methylthio)acetic anhydride[4] and the resulting enamide (**7**) was then oxidized with sodium metaperiodate to afford sulphoxide (**8**) in 48% overall yield. The cyclization of (**8**) was effected by treatment with 2 equiv. of anhydrous toluene-*p*-sulphonic acid in boiling ethylene dichloride to give the erythrinane derivative (**11**) in 60% yield accompanied by the formation of a small amount (8%) of the 3-benzazepine derivative (**12a**). The structure of compound (**11**) was confirmed by its desulphurization with Raney nickel to give the *cis*-erythrinanone (**13**) whose i.r., n.m.r., and mass spectral data were well in accord with those described in the literature.[5] A similar reduction of (**12a**) gave the benzazepinone (**12b**).[6]

The formation of the erythrinane (**11**) from (**8**) may involve an olefinic cyclization of the Pummerer reaction intermediate (**9**) and successive aromatic cyclization of the resultant acyliminium (**10**).[7] The formation of the benzazepine derivative (**12a**) can be explained by an intramolecular attack of the thionium ion on the aromatic ring in place of the olefin.

Compound (**11**) was transformed into some erythrinane derivatives (Scheme 2). Oxidation of (**11**) with sodium metaperiodate followed by thermolysis of the resulting sulphoxide in refluxing toluene gave the unsaturated lactam (**14**)[5b,8] in 81% yield [based on (**11**)]. This ready elimination of methanesulphenic acid allowed us to assign the stereochemistry of the methylthio group on C-7 and 6-H in (**11**) to be *cis*. Reduction of (**13**) with lithium aluminium hydride gave the erythrinane (**15**)[5b,9] in 79% yield. A similar reduction of enamide (**14**) afforded the erythrinene (**16**)[9] in 16% yield together with (**15**) (28%).

All of the naturally occurring *Erythrina* alkaloids have structures functionalized on the A ring. In order to test the applicability of this method to the synthesis of such functionalized erythrinanes, we tried to synthesize the 2-oxoerythrinane derivative (**21**) which has been converted into erysotrine (**23**).[10] The requisite sulphoxide (**18**) was prepared in 69% overall yield from (**4**) and 4-benzyloxycyclohexanone[11] by using the same procedure as described for the preparation of (**8**). Treatment of (**18**) with toluene-*p*-sulphonic acid in refluxing benzene afforded a mixture of two stereoisomeric products, which were separated by silica gel chromatography† to give isomers (**19a**) and (**19b**) in 22 and 29% yield, respectively. Compounds (**19a**) and (**19b**) were subsequently subjected to reduction with Raney nickel to give, in both cases, a mixture of the two epimeric alcohols (**20a**)[5a] and (**20b**)[5a] (in the ratio *ca.* 2:1) in 84 and 71% combined yield, respectively. This result strongly suggests that the alcohols (**20a**) and (**20b**) epimerized to each other under the reaction conditions. In fact, when the alcohols (**20a**) and (**20b**) were individually treated with Raney nickel, the same equilibrium mixtures of (**20a**) and (**20b**) as those given by reduction of (**19a**) or (**19b**) were obtained.‡ The stereochemistry of (**20a**) and (**20b**) has already been established by Mondon *et al.*[5a] as depicted in Scheme 3. Both alcohols (**20a**) and (**20b**) were oxidized by chromium trioxide–pyridine to give the same ketone (**21**),[13] whose ethylene acetal (**22a**) has already been prepared by methylation of the corresponding 16-*O*-demethyl derivative (**22b**)[10] or by acetalization of (**21**) itself with ethylene glycol.[14] The acetal (**22a**) has already been converted into erysotrine (**23**).[10]

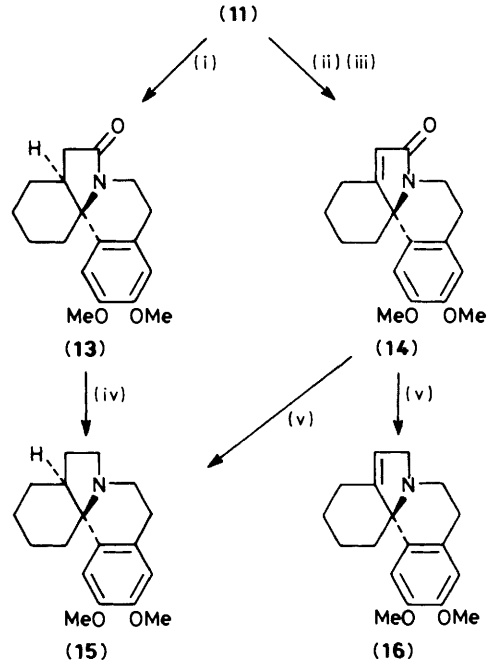
† The benzazepine derivative (**12a**) was also obtained in 11% yield.
‡ Epimerization (attended by dehydrogenation) of some substituted cyclohexanols with Raney nickel has been reported.[12]



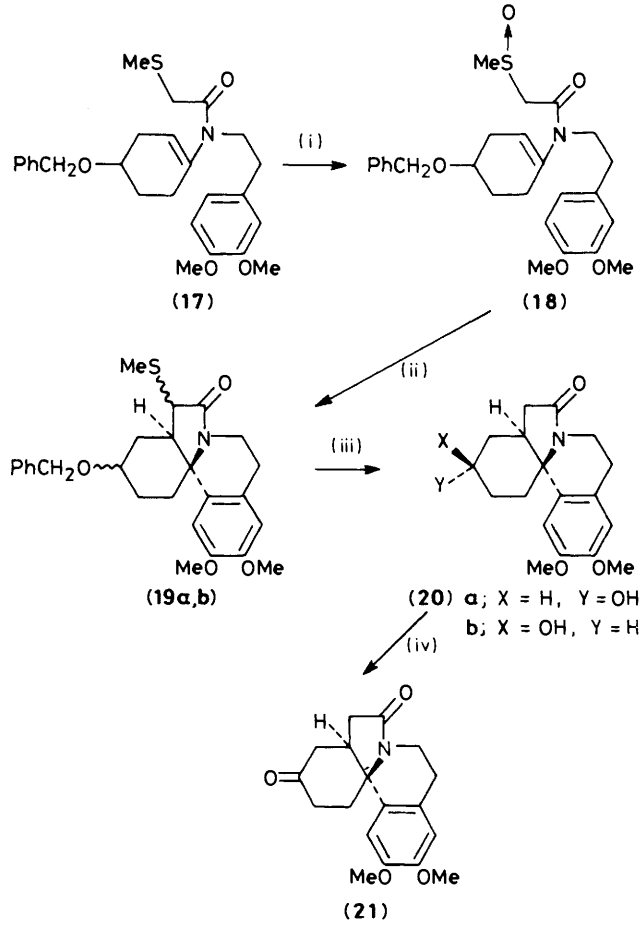
Scheme 1. *Reagents and conditions:* (i) benzene, reflux; (ii) $(MeSCH_2CO)_2O$–pyridine, benzene; (iii) $NaIO_4$, MeOH–H_2O; (iv) *p*-TsOH, $(CH_2Cl)_2$, reflux

Finally, as a model study of the synthesis of α- or β-erythroidine, the D rings of which are not aromatic, we examined the cyclization of the sulphoxide (**25**). When a solution of (**25**) in ethylene dichloride was heated in the presence of toluene-*p*-sulphonic acid, the expected products (**26**) and (**27**) were obtained in 4 and 13% yield, respectively. The structures of compounds (**26**) and (**27**) were confirmed by transforming them into the compounds (**28**)[15] and (**29**),[15] respectively, by reduction with Raney nickel.

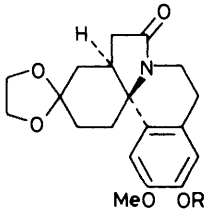
In conclusion, the present synthesis of the erythrinane skeleton is simple, and hence its synthetic applicability seems highly promising. Further investigation of the synthesis of more functionalized erythrinanes is currently under way.



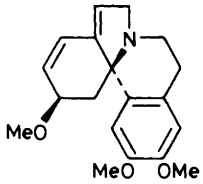
Scheme 2. *Reagents and conditions:* (i) Ra-Ni, EtOH; (ii) $NaIO_4$, MeOH–H_2O; (iii) toluene, reflux; (iv) $LiAlH_4$, THF; (v) $LiAlH_4$, Et_2O



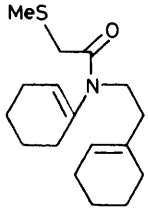
Scheme 3. *Reagents and conditions:* (i) $NaIO_4$, MeOH–H_2O; (ii) *p*-TsOH, benzene, reflux; (iii) Ra-Ni, EtOH; (iv) CrO_3–pyridine, CH_2Cl_2



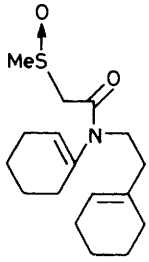
(22) a; R = Me
b; R = H



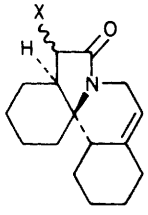
(23)



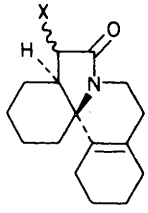
(24)



(25)



(26) X = SMe
(28) X = H



(27) X = SMe
(29) X = H

Experimental

I.r. spectra were recorded with a JASCO-IRA-1 or A-100 spectrophotometer. ^{1}H N.m.r. spectra were determined with a Hitachi R-22 (90 MHz) or JEOL JNM-PMX 60 (60 MHz) spectrometer, and δ values are quoted relative to tetramethylsilane. Mass spectra were obtained on a JEOL JMS-D-300 instrument at 70 eV and a Hitachi M-80 instrument at 20 eV. Chromatographic separation was performed either with silica gel 60 (63—200 μm) (Merck) or with activated alumina (Sumitomo).

N-(*Cyclohex-1-enyl*)-N-[2-(3,4-*dimethoxyphenyl*)*ethyl*]-α-(*methylthio*)*acetamide* (**7**).—A solution of 2-(3,4-dimethoxyphenyl)ethylamine (**4**) (2.96 g, 16.3 mmol) and cyclohexanone (**5**) (1.60 g, 16.3 mmol) in benzene (200 ml) was heated under reflux, in a flask equipped with a Dean–Stark water separator, for 2 h. To the resultant solution containing *N*-cyclohexylidene-2-(3,4-dimethoxyphenyl)ethylamine (**6**) was added a solution of α-(methylthio)acetic anhydride[4] (6.38 g, 33 mmol) in benzene (50 ml) and pyridine (2.78 g, 33 mmol) at 0 °C and the mixture was stirred at room temperature overnight. The reaction mixture was washed successively with dil. HCl, 10% aqueous Na_2CO_3, and brine, and then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel [diethyl ether–benzene (3:7)] to give the *acetamide* (**7**) (3.27 g, 57%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 349.1719. $C_{19}H_{27}NO_3S$ requires *M*, 349.1712); $\nu_{max.}$ ($CHCl_3$) 1 630 cm^{-1}; δ($CDCl_3$) 1.4—2.3 (8 H, m), 2.21 (3 H, s), 2.65—2.90 (2 H, m), 3.22 (2 H, s), 3.45—3.70 (2 H, m), 3.83 (3 H, s), 3.86 (3 H, s), 5.58 (1 H, m), and 6.73 (3 H, br s).

N-(*Cyclohex-1-enyl*)-N-[2-(3,4-*dimethoxyphenyl*)*ethyl*]-α-(*methylsulphinyl*)*acetamide* (**8**).—A solution of sodium metaperiodate (2.50 g, 11.7 mmol) in water (40 ml) was added dropwise to an ice-cooled solution of compound (**7**) (3.96 g, 11.3 mmol) in methanol (40 ml) and the mixture was stirred at room temperature overnight. The precipitated inorganic material was removed by filtration, the filtrate was extracted with $CHCl_3$, and the extract was dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (acetone) to give *compound* (**8**) (3.50 g, 84%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 365.1654. $C_{19}H_{27}NO_4S$ requires *M*, 365.1659); $\nu_{max.}$($CHCl_3$) 1 630 cm^{-1} δ($CDCl_3$) 1.4—2.3 (8 H, m), 2.65—2.90 (2 H, m), 2.76 (3 H, s), 3.5—4.1 (4 H, m), 3.85 (3 H, s), 3.87 (3 H, s), 5.55—5.70 (1 H, m), and 6.72 (3 H, br s).

15,16-*Dimethoxy*-7α-*methylthio*-cis-*erythrinan*-8-*one* (**11**) *and* 2,3,4,5-*Tetrahydro*-7,8-*dimethoxy*-1-*methylthio*-3-*benzazepin*-2(1H)-*one* (**12a**).—A solution of the sulphoxide (**8**) (232 mg, 0.64 mmol) in ethylene dichloride (10 ml) containing toluene-*p*-sulphonic acid (220 mg, 1.28 mmol) was heated under reflux for 10 min. The reaction mixture was poured into water (10 ml) and the organic layer was separated. The aqueous layer was further extracted with $CHCl_3$ and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate). The first eluate gave the *erythrinane* (**11**) (132 mg, 60%), m.p. 169.5—170.5 °C (from $CHCl_3$–ethyl acetate) (Found: C, 65.4; H, 7.2; N, 3.8. $C_{19}H_{25}NO_3S$ requires C, 65.7; H, 7.25; N, 4.0%); $\nu_{max.}$($CHCl_3$) 1 670 cm^{-1}; δ($CDCl_3$) 1.40—2.45 (7 H, m), 2.12 (3 H, s), 2.7—3.0 (3 H, m), 3.05—3.35 (2 H, m), 3.38 (1 H, d, *J* 10 Hz), 3.87 (3 H, s), 3.91 (3 H, s), 3.95—4.25 (1 H, m), 6.62 (1 H, s), and 6.93 (1 H, s); *m/z* 347 (M^+, 23%), 301 (26), 300 (100), 290 (40), 258 (12), and 244 (16). The second eluate gave the *benzazepinone* (**12a**) (14 mg, 8%), m.p. 125—127 °C [from ethyl acetate–diethyl ether (1:1)] (Found: C, 58.55; H, 6.4; N, 5.15. $C_{13}H_{17}NO_3S$ requires C, 58.4; H, 6.4; N, 5.2%); $\nu_{max.}$($CHCl_3$) 3 410 and 1 655 cm^{-1}; δ($CDCl_3$) 2.33 (3 H, s), 2.95—3.50 (3 H, m), 3.85 (3 H, s), 3.87 (3 H, s), 4.05—4.45 (1 H, m), 4.53 (1 H, d, *J* 2 Hz), 6.54 (1 H, s), 6.69 (1 H, s), and 7.00—7.25 (1 H, br).

2,3,4,5-*Tetrahydro*-7,8-*dimethoxy*-3-*benzazepin*-2(1H)-*one* (**12b**).—Compound (**12a**) (82 mg, 0.31 mmol) was heated under reflux in ethanol (5 ml) containing Raney nickel W-2 (1 g) for 1 h. The Raney nickel was removed by filtration and the solvent was evaporated off, and then the residue was chromatographed on silica gel (acetone) to give the desulphurized product (**12b**) (57 mg, 84%), m.p. 197.5—198.0 °C (from ethanol) (lit.,[6] 191.5—193.5 °C) (Found: C, 65.0; H, 6.9; N, 6.5. Calc. for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3%); $\nu_{max.}$($CHCl_3$) 3 410 and 1 660 cm^{-1}; δ($CDCl_3$) 2.99 (2 H, t, *J* 6 Hz), 3.50 (2 H, t, *J* 6 Hz), 3.75 (2 H, s), 3.82 (6 H, s), 6.54 (1 H, s), 6.58 (1 H, s), and 6.95 (1 H, br).

15,16-*Dimethoxy*-cis-*erythrinan*-8-*one* (**13**).—By the same procedure as described for the preparation of (**12b**), compound (**11**) (300 mg, 0.87 mmol) was reduced with Raney nickel (2 g) to give the erythrinanone (**13**)[5] (257 mg, 99%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 301.1673. Calc. for $C_{18}H_{23}NO_3$: *M*, 301.1676); $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1}; δ($CDCl_3$) 1.45—3.40 (14 H, m), 3.86 (3 H, s), 3.89 (3 H, s), 4.0—4.3 (1 H, m), 6.58 (1 H, s), and 6.87 (1 H, s); *m/z* 301 (M^+, 28%), 272 (3), 259 (18), 258 (100), 246 (2), 245 (13), 244 (14), 217 (3), 216 (4), 214 (3), 202 (1), and 200 (2).

15,16-*Dimethoxyerythrin*-6-*en*-8-*one* (6,7-*Didehydro*-15,16-*dimethoxyerythrinan*-8-*one*) (**14**).—A solution of sodium metaperiodate (113 mg, 0.53 mmol) in water (4 ml) was added dropwise to a stirred solution of compound (**11**) (150 mg, 0.43

mmol) in methanol (5 ml) at 60 °C and the mixture was stirred at the same temperature for 2 h. The mixture was extracted with $CHCl_3$ and the solvent was evaporated off. The resulting crude sulphoxide was dissolved in toluene (10 ml) and then the mixture was heated under reflux for 10 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel [acetone–$CHCl_3$ (1:5)] to give the enone (**14**)[5b,8] [104 mg, 81% based on (**11**)] as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 299.1517. Calc. for $C_{18}H_{21}NO_3$: M, 299.1519); $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1}; δ($CDCl_3$) 1.2—4.3 (12 H, m), 3.86 (3H, s), 3.89 (3 H, s), 5.90 (1 H, s), 6.73 (1 H, s), and 7.08 (1 H, s); *m/z* 299 (M^+, 100%), 298 (21), 284 (11), 271 (27), 270 (56), 258 (16), 257 (16), 256 (10), and 240 (11).

15,16-*Dimethoxy*-cis-*erythrinane* (**15**).—A solution of the amide (**13**) (120 mg, 0.40 mmol) in anhydrous tetrahydrofuran (THF) (1 ml) was added dropwise to an ice-cooled suspension of lithium aluminium hydride (70 mg, 1.84 mmol) in anhydrous THF (5 ml) and the mixture was heated under reflux for 4 h. Water was added to the reaction mixture and the precipitated inorganic material was removed by filtration, and then the filtrate was dried over KOH. The solvent was evaporated off and the residue was chromatographed on alumina [diethyl ether–light petroleum (b.p. 60—80 °C) (1:1)] to give the amine (**15**) (90 mg, 79%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 287.1879. Calc. for $C_{18}H_{25}NO_2$: M, 287.1884); $\nu_{max.}$(film) 1 610, 1 505, 1 465—1 440, 1 400, 1 355, 1 255, 1 245, 1 215, 1 120, 1 100, 1 015, 1 005, 990, 850, 780, and 765 cm^{-1}; δ($CDCl_3$) 1.1—2.5 (13 H, m), 2.65—3.35 (4 H, m), 3.81 (3 H, s), 3.85 (3 H, s), 6.45 (1 H, s), and 6.65 (1 H, s); *m/z* 287 (M^+, 24%), 258 (3), 245 (18), 244 (100), 231 (11), 230 (19), and 214 (3). These spectral (i.r., n.m.r., and mass) date are well in accord with those reported.[5b] Its picrate had m.p. 181—183 °C (from ethanol) (lit.,[9] 182—183 °C).

15,16-*Dimethoxyerythrin*-6-*ene* (6,7-*Didehydro*-15,16-*dimethoxyerythrinane*) (**16**).—A solution of the amide (**14**) (99 mg, 0.33 mmol) in anhydrous diethyl ether (5 ml) was added to an ice-cooled suspension of lithium aluminium hydride (19 mg, 0.5 mmol) in anhydrous diethyl ether (5 ml) and the mixture was heated under reflux for 10 h. After the usual work-up, the crude products were separated by chromatography on alumina [diethyl ether–ethyl acetate (4:1)]. The first eluate gave the amine (**15**) (26 mg, 28%), which was identical with that obtained by reduction of (**13**) as described above. The second eluate gave the amine (**16**) (15 mg, 16%) as an oil, pure by t.l.c. and n.m.r. spectroscopy, δ($CDCl_3$) 1.1—3.7 (14 H, m), 3.87 (6 H, br s), 5.54 (1 H, m), 6.64 (1 H, s), and 7.03 (1 H, s); *m/z* 285 (M^+, 100%), 284 (64), 270 (14), 257 (14), 256 (52), 255 (2), 243 (25), 242 (61), 229 (2), and 226 (11). Its picrate had m.p. 182—184 °C (from ethanol) (lit.,[9] 181 °C) (Found: C, 56.0; H, 5.05; N, 11.1. Calc. for $C_{24}H_{26}N_4O_9$: C, 56.0; H, 5.1; N, 10.9%).

N-(4-*Benzyloxycyclohex*-1-*enyl*)-N-[2-(3,4-*dimethoxyphenyl*)*ethyl*]-α-(*methylthio*)*acetamide* (**17**).—By the same procedure as described for the preparation of (**7**), compound (**17**) was obtained from 2-(3,4-dimethoxyphenyl)ethylamine (2.72 g, 15.1 mmol), 4-benzyloxycyclohexanone[11] (3.08 g, 15.1 mmol), and α-(methylthio)acetic anhydride (5.87 g, 30.2 mmol) in 78% yield (5.36 g) as an *oil* (Found: C, 68.5; H, 7.3; N, 3.3. $C_{26}H_{33}NO_4S$ requires C, 68.5; H, 7.3; N, 3.1%); $\nu_{max.}$($CHCl_3$) 1 635 cm^{-1}; δ($CDCl_3$) 1.7—2.5 (6 H, m), 2.18 (3 H, s), 2.6—3.2 (2 H, m), 3.21 (2 H, s), 3.4—3.9 (3 H, m), 3.81 (6 H, s), 4.53 (2 H, s), 5.3—5.6 (1 H, m), 6.69 (3 H, s), and 7.26 (5 H, s).

N-(4-*Benzyloxycyclohex*-1-*enyl*)-N-[2-(3,4-*dimethoxyphenyl*)*ethyl*]-α-(*methylsulphinyl*)*acetamide* (**18**).—By the same procedure as described for the preparation of (**8**), oily *compound* (**18**) was obtained by oxidation of the sulphide (**17**) (137 mg, 0.03 mmol) with sodium metaperiodate (66.4 mg, 0.31 mmol) in 89% yield (126 mg) (Found: C, 65.7; H, 7.1; N, 3.2. $C_{26}H_{33}NO_5S$ requires C, 66.2; H, 7.05; N, 3.0%); $\nu_{max.}$($CHCl_3$) 1 640 cm^{-1}; δ($CDCl_3$) 1.7—2.5 (6 H, m), 2.6—3.0 (2 H, m), 2.61 (*ca.* 1.5 H, s), 2.64 (*ca.* 1.5 H, s), 3.4—3.9 (5 H, m), 3.80 (6 H, s), 4.53 (2 H, s), 5.4—5.6 (1 H, m), 6.68 (3 H, s), and 7.26 (5 H, s).

2-*Benzyloxy*-15,16-*dimethoxy*-7-*methylthio*-cis-*erythrinan*-8-*one* (**19a,b**).—A solution of the sulphoxide (**18**) (1.61 g, 3.41 mmol) in benzene (20 ml) containing toluene-*p*-sulphonic acid (1.17 g, 6.8 mmol) was heated under reflux for 10 min. The reaction mixture was washed successively with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel [ethyl acetate–$CHCl_3$ (1:1)]. The first eluate gave one *isomer* (**19a**) (337 mg, 22%), m.p. 119—120 °C (from benzene–n-hexane) (Found: C, 68.7; H, 6.9; N, 3.1. $C_{26}H_{31}NO_4S$ requires C, 68.85; H, 6.9; N, 3.1%); $\nu_{max.}$($CHCl_3$) 1 675 cm^{-1}; δ($CDCl_3$) 1.6—3.7 (10 H, m), 2.07 (3 H, s), 2.90 (1 H, d, *J* 6 Hz), 3.7—4.3 (2 H, m), 3.81 (6 H, s), 4.50 (2 H, s), 6.56 (1 H, s), 6.71 (1 H, s), and 7.25 (5 H, s); *m/z* 453 (M^+, 30%), 406 (30), 362 (20), 244 (100), and 164 (21). The second eluate gave another *isomer* (**19b**) (451 mg, 29%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 453.1939. $C_{26}H_{31}NO_4S$ requires M, 453.1971; $\nu_{max.}$($CHCl_3$) 1 680 cm^{-1}; δ($CDCl_3$) 1.5—3.5 (10 H, m), 2.09 (3 H, s), 3.18 (1 H, d, *J* 7 Hz), 3.6—4.4 (2 H, m), 3.81 (6 H, s), 4.56 (2 H, s), 6.53 (1 H, s), 6.82 (1 H, s), and 7.29 (5 H, s); *m/z* 453 (M^+, 52%), 406 (58), 362 (64), 244 (100), and 164 (5). The third eluate gave the benzazepinone (**12a**) (102 mg, 11%), identical with that obtained from compound (**8**).

2α- *and* 2β-*Hydroxy*-15,16-*dimethoxy*-cis-*erythrinan*-8-*one* (**20a** *and* **b**).—(a) *From* (**19b**). A solution of the sulphide (**19b**) (86 mg, 0.19 mmol) in ethanol (5 ml) containing Raney nickel W-2 (1 g) was heated under reflux for 2 h. The Raney nickel was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel (acetone). The first eluate gave 2β-hydroxy compound (**20b**) (15 mg, 25%), m.p. 197.5—198 °C (from benzene) (lit.,[5a] 196 °C) (Found: C, 68.2; H, 7.4; N, 4.4. Calc. for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3; N, 4.4%); $\nu_{max.}$($CHCl_3$) 3 600 and 1 680 cm^{-1}; δ($CDCl_3$) 1.4—3.5 (13 H, m), 3.8—4.4 (2 H, m), 3.80 (3 H, s), 3.83 (3 H, s), 6.51 (1 H, s), and 6.63 (1 H, s). The second eluate gave 2α-hydroxy compound (**20a**)[5a] (28 mg, 46%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 317.1620. Calc. for $C_{18}H_{23}NO_4$: M, 317.1625); $\nu_{max.}$($CHCl_3$) 3 600 and 1 670 cm^{-1}; δ($CDCl_3$) 1.4—2.4 (9 H, m), 2.6—3.5 (4 H, m), 3.8—4.3 (2 H, m), 3.81 (3 H, s), 3.84 (3 H, s), 6.52 (1 H, s), and 6.86 (1 H, s).

(b) *From* (**19a**). By the same procedure as described for the reduction of (**19b**) to (**20a,b**), compound (**19a**) (83 mg, 0.18 mmol) was reduced with Raney nickel to give compounds (**20b**) (15 mg, 26%), (**20a**) (20 mg, 35%) and a mixture of (**20a**) and (**20b**) (total 13 mg, 23%).

Epimerization of Alcohols (**20a**) *and* (**20b**) *in the Presence of Raney Nickel.*—A solution of the alcohol (**20a**) or (**20b**) (20 mg, 0.06 mmol) in ethanol (5 ml) containing Raney nickel W-2 (1 g) was heated under reflux for 2 h and worked up in the usual manner. T.l.c. and n.m.r. spectroscopy showed the crude product to be a mixture of the alcohols (**20a**) and (**20b**) in almost the same ratio (*ca.* 1:2) as that of the mixture obtained by reduction of the sulphide (**19a**) or (**19b**).

15,16-*Dimethoxy*-cis-*erythrinane*-2,8-*dione* (**21**).—(a) *From* (**20a**). Chromium trioxide (79 mg, 0.78 mmol) was added to a stirred solution of pyridine (123 mg, 1.56 mmol) in anhydrous CH_2Cl_2 (2 ml) at 0 °C and the mixture was stirred at room

temperature for 15 min. To the resultant mixture was added a solution of the alcohol (**20a**) (41 mg, 0.13 mmol) in CH_2Cl_2 (0.5 ml) in one portion at room temperature and the mixture was stirred at the same temperature for 15 min. The supernatant liquid was decanted from the precipitate and the precipitate was rinsed thoroughly with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed successively with dil. HCl, saturated aqueous $NaHCO_3$, and brine, and then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate) to give the dione (**21**) (24 mg, 59%), m.p. 164—165 °C (from THF) (lit.,[13] 163.5—164 °C); $\nu_{max.}$($CHCl_3$) 1 720 and 1 680 cm^{-1}; δ($CDCl_3$) 1.9—3.4 (12 H, m), 3.83 (6 H, s), 4.2—4.5 (1 H, m), 6.51 (1 H, s), and 6.62 (1 H, s).

(b) *From* (**20b**). By the same procedure as described for the oxidation of (**20a**), compound (**20b**) (41 mg, 0.13 mmol) was oxidized to give dione (**21**) (28 mg, 68%) whose physical data were identical with those of compound (**21**) obtained from (**20a**).

N-(*Cyclohex*-1-*enyl*)-N-[2-(*cyclohex*-1-*enyl*)*ethyl*]-α-(*methylthio*)*acetamide* (**24**).—By the same procedure as described above for the preparation of the amide (**7**), compound (**24**) was obtained from 2-(cyclohex-1-enyl)ethylamine[16] (220 mg, 1.73 mmol), cyclohexanone (170 mg, 1.73 mmol), and α-(methylthio)acetic anhydride (663 mg, 3.4 mmol) in 60% yield (304 mg) as an *oil*, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 293.1812. $C_{17}H_{27}NOS$ requires *M*, 293.1812); $\nu_{max.}$($CHCl_3$) 1 630 cm^{-1}; δ($CDCl_3$) 1.4—2.3 (18 H, m), 2.22 (3 H, s), 3.22 (2 H, s), 3.45 (2 H, m), 5.40 (1 H, m), and 5.67 (1 H, m).

N-(*Cyclohex*-1-*enyl*)-N-[2-(*cyclohex*-1-*enyl*)*ethyl*]-α-(*methylsulphinyl*)*acetamide* (**25**).—By the same procedure as described for the preparation of the sulphoxide (**8**), compound (**24**) (2.98 g, 10.1 mmol) was oxidized with sodium metaperiodate to give the *sulphoxide* (**25**) (2.56 g, 84%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 309.1760. $C_{17}H_{27}NO_2S$ requires *M*, 309.1760); $\nu_{max.}$($CHCl_3$) 1 630 cm^{-1}; δ($CDCl_3$) 1.4—2.3 (18 H, m), 2.77 (3 H, s), 3.45 (2 H, m), 3.65, 3.95 (1 H each, AB q, *J* 14 Hz), 5.39 (1 H, m), and 5.68 (1 H, m).

Perhydro-7-*methylthio*-cis-*erythrin*-11-*en*-8-*one* (11,12-*Didehydroperhydro*-7-*methylthio*-cis-*erythrinan*-8-*one*) (**26**) *and* 14,15,16,17-*Tetrahydro*-7-*methylthio*-cis-*erythrinan*-8-*one* (**27**).—Compound (**25**) (1.73 g, 5.6 mmol) was treated under almost the same conditions as described above for the preparation of the erythrinanone (**11**) from the sulphoxide (**8**) and the crude products were separated by chromatography on silica gel [benzene–diethyl ether (1:1)]. The first eluate gave the 11-ene (**26**) (70 mg, 4%) as an oil, which was characterized by its conversion into the desulphurized product (**28**) (see below); $\nu_{max.}$ 1 665 cm^{-1}; δ($CDCl_3$) 1.1—2.9 (19 H, m), 2.27 (3 H, s), 3.18 (1 H, d, *J* 8 Hz), 3.9—4.2 (1 H, m), and 5.66 (1 H, m). The second eluate gave the 12-*ene* (**27**) (213 mg, 13%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 291.1668. $C_{17}H_{25}NOS$ requires *M*, 291.1658); $\nu_{max.}$($CHCl_3$) 1 665 cm^{-1}; δ($CDCl_3$) 1.2—2.4 (19 H, m), 2.18 (3 H, s), 2.7—3.1 (1 H, m), 3.25 (1 H, d, *J* 10 Hz), and 4.08 (1 H, ddd, *J* 13, 7, and 3 Hz); *m/z* 291 (M^+, 36%) 245 (40), 244 (100), 234 (42), and 202 (13).

Perhydro-cis-*erythrin*-11-*en*-8-*one* (11,12-*Didehyrdoperhydro*-cis-*erythrinan*-8-*one*) (**28**).—A solution of the sulphide (**26**) (63 mg, 0.22 mmol) in ethanol (5 ml) containing Raney nickel W-2 (1 g) was heated under reflux for 1 h. After the usual work-up, the crude product was purified by silica gel chromatography (ethyl acetate) to give the enone (**28**)[15] (37 mg, 70%) as an oil, pure by t.l.c. and n.m.r. spectroscopy (Found: M^+, 245.1776. Calc. for $C_{16}H_{23}NO$: *M*, 245.1777); $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1}; δ($CDCl_3$) 1.2—2.9 (21 H, m), 3.9—4.2 (1 H, m), and 5.65 (1 H, m).

14,15,16,17-*Tetrahydro*-cis-*erythrinan*-8-*one* (**29**).—By the same procedure as described for the preparation of compound (**28**), its isomer (**29**) was obtained from the sulphide (**27**) (213 mg, 0.73 mmol) in 81% yield (145 mg), m.p. 75.5—76.0 °C (from n-hexane) (lit.,[15] 74—75 °C) (Found: C, 78.25; H, 9.7; N, 5.65. Calc. for $C_{16}H_{23}NO$: C, 78.3; H, 9.45; N, 5.7%); $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1}; δ($CDCl_3$) 1.2—2.5 (21 H, m), 2.7—3.1 (1 H, m), and 4.07 (1 H, ddd, *J* 13, 8, and 1 Hz); *m/z* 245 (M^+, 24%), 216 (2), 202 (100), 189 (20), and 188 (11).

References

1 N. H. Andersen, Y. Yamamoto, and A. D. Denniston, *Tetrahedron Lett.*, 1975, 4547; V. L. Mizyuk and A. V. Semenovsky, *ibid.*, 1978, 3603; R. S. Brinkmeyer, *ibid.*, 1979, 207; L. N. Mander and P. H. C. Mundill, *Synthesis*, 1981, 620; B. M. Trost and E. Murayama, *J. Am. Chem. Soc.*, 1981, **103**, 6529; B. M. Trost and E. Murayama, *Tetrahedron Lett.*, 1982, **23**, 1047.

2 Y. Tamura, H. Maeda, S. Akai, K. Ishiyama, and H. Ishibashi, *Tetrahedron Lett.*, 1981, **22**, 4301.

3 A part of this work has appeared as a preliminary communication, Y. Tamura, H. Maeda, S. Akai, and H. Ishibashi, *Tetrahedron Lett.*, 1982, **23**, 2209.

4 A. Mooradian, C. J. Cavallito, A. J. Bergman, E. J. Lawson, and C. M. Suter, *J. Am. Chem. Soc.*, 1949, **71**, 3372.

5 (*a*) A. Mondon, K. F. Hansen, K. Boehme, H. P. Faro, H. J. Nestler, H. G. Vilhuber, and K. Böttcher, *Chem. Ber.*, 1970, **103**, 615; (*b*) A. Mondon and P.-R. Seidel, *ibid.*, 1971, **104**, 2937.

6 O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Am. Chem. Soc.*, 1970, **92**, 5686.

7 W. N. Speckamp, in 'Stereoselective Synthesis of Natural Products,' eds W. Bartmann and E. Winterfeldt, Elsevier, Amsterdam, 1979, p. 50.

8 A. Mondon, *Justus Liebigs Ann. Chem.*, 1959, **628**, 123.

9 A. Mondon, H. P. Faro, K. Boehme, K. F. Hansen, and P.-R. Seidel, *Chem. Ber.*, 1970, **103**, 1286.

10 M. Haruna and K. Ito, *J. Chem. Soc., Chem. Commun.*, 1976, 345.

11 D. A. Prins, *Helv. Chim. Acta*, 1957, **40**, 1621.

12 E. G. Peppiatt and R. J. Wicker, *J. Chem. Soc.*, 1955, 3122; E. L. Eliel and S. H. Schroeter, *J. Am. Chem. Soc.*, 1965, **87**, 5031.

13 A. Mondon, H. J. Nestler, H. G. Vilhuber, and M. Ehrhardt, *Chem. Ber.*, 1965, **98**, 46.

14 A. Mondon, H. G. Vilhuber, C. Fischer, M. Epe, B. Epe, and C. Wolff, *Chem. Ber.*, 1979, **112**, 1110.

15 A. Mondon and B. Neffgen, *Chem. Ber.*, 1970, **103**, 3050.

16 O. Schneider and J. Hellerbach, *Helv. Chim. Acta*, 1950, **33**, 1437.

Received 9th July 1984; *Paper* 4/1177