Stereochemical Studies. 81 [1]. Saturated Heterocycles. 69 [2]. Preparation of Methylene-bridged 3,1-Benzoxazines, 3,1-Benzoxazin-2-ones and 3,1-Benzoxazine-2-thiones

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3-*exo*-Aminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid and ethyl 3-*endo*-aminobicyclo[2.2.1]heptane-2-*endo*-carboxylate (**6**) were reduced with lithium aluminum hydride to the corresponding bicyclic aminoalcohols **3** and **4**. These and the saturated *endo-endo* and *exo-exo* *N*-methylaminoalcohols **16** and **22**, respectively, were converted to methylene-bridged tetrahydro- (**11**) and hexahydro-3,1-benzoxazin-2-ones **12, 17, 23** and 3,1-benzoxazin-2-thiones **13, 14, 18, 24**. The *exo-exo* **3** and *endo-endo* **4** aminoalcohols were cyclized by means of ethyl arylimidates to tricyclic dihydro-1,3-oxazines **7a-d, 8a-d**. The structures were confirmed by ir, ^1H and ^{13}C nmr spectroscopy.

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We earlier reported the synthesis of the 3-*endo*-aminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (**1**) and the isomeric saturated *exo* amino acid **2**, and the reduction of these to 1,3-aminoalcohols [3], from which, by cyclization, the corresponding 1,3-oxazines, 1,3-oxazin-2-ones and 1,3-oxazine-2-thiones fused with norbornene or norbornane were prepared. Starting from the 1,3-oxazines, we prepared by cycloaddition isomeric azetidinones, the structure and steric structure of which were elucidated by ^1H and ^{13}C nmr spectroscopy [4]. That work was carried out for pharmalogical purposes and to make systematic comparative stereochemical studies. As a continuation, we endeavoured to prepare further stereoisomeric 1,3-oxazines, 1,3-oxazin-2-ones and 1,3-oxazine-2-thiones fused with the norbornane skeleton. Whereas in the compounds prepared earlier the oxygen of the oxazine ring is attached to the carbocyclic unit [5], in the isomers described in the present work the nitrogen is the linking atoms.

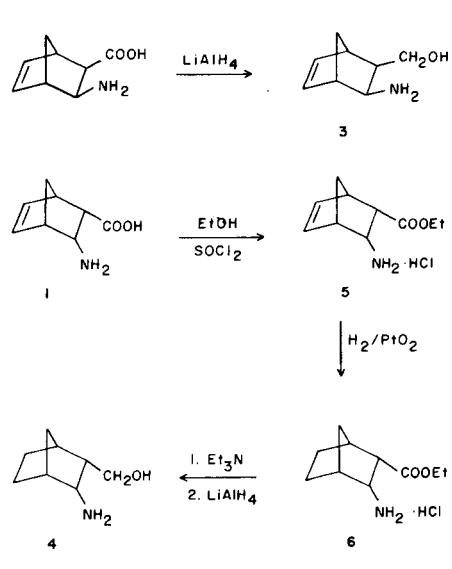
By acylation and cyclization of the *endo* amino acid **1**, tricyclic 1,3-oxazin-4-ones fused with norbornene were prepared which by retrodiene decomposition on pyrolysis furnished 6*H*-1,3-oxazin-6-ones [6], compounds difficult to obtain by other means. This reaction was also applied for the *exo*-1,3-oxazin-4-ones, and the rates of decomposition of the isomers were studied kinetically [7].

In the present work we report the preparation of further isomeric *exo-exo* 1,3-oxazines and related compounds containing norbornene as structural unit. An account is given of the saturated carbocyclic derivatives of the *endo-endo* norbornene compounds described earlier [3] and of some *N*-methyl-substituted 1,3-oxazin-2-ones and 1,3-oxazine-2-thiones.

Synthesis.

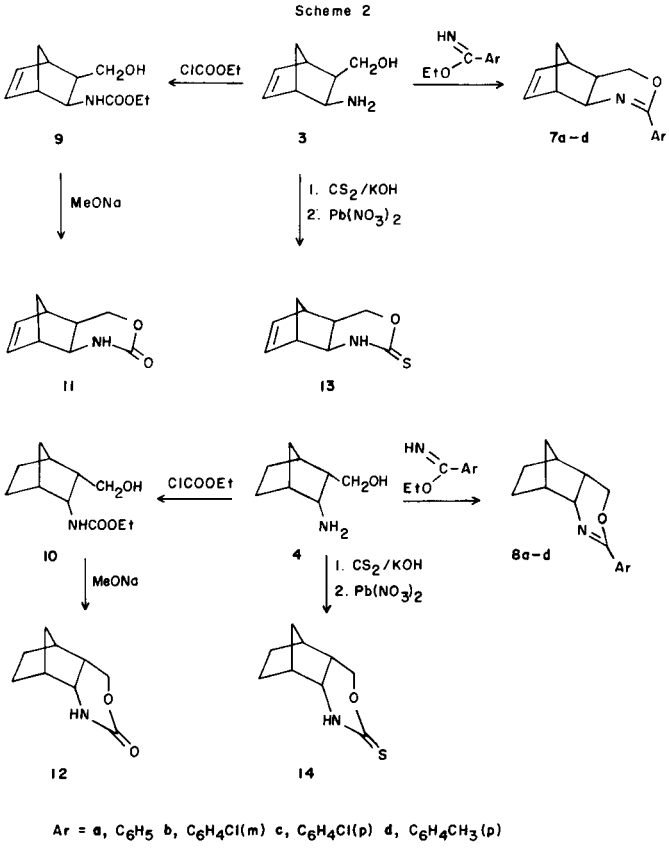
The starting aminoalcohol **3** was prepared from 3-*exo*-aminobicyclo[2.2.1]hept-1-ene-2-*exo*-carboxylic acid [7] by reduction with lithium aluminum hydride (Scheme 1). For synthesis of the bicyclic saturated aminoalcohol **4**. The *endo*-amino acid **1** [3] was esterified, the double bond of the ester salt **5** was hydrogenated, and the base liberated from the salt **6** was reduced with lithium aluminum hydride.

Scheme I



Starting from the bicyclic aminoalcohols **3** and **4**, the 5,6-methano-*r*-4a,*c*-5,*c*-8,*c*-8a-tetrahydro-4*H*-3,1-benzoxazines **7a-d** and the 5,8-methano-*r*-4a,*t*-5,6,7,*t*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazines **8a-d** were prepared with ethyl arylimidates (Scheme 2).

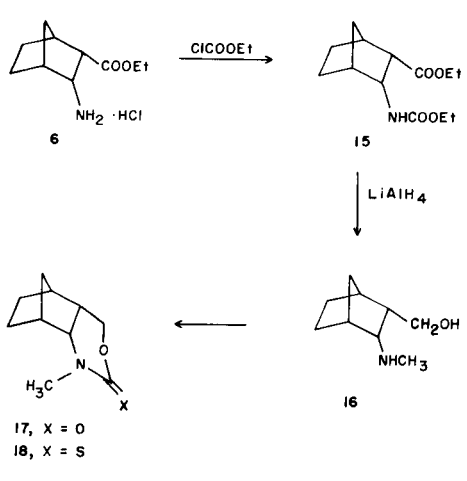
Scheme 2



Ar = a, C_6H_5 b, $C_6H_4Cl(m)$ c, $C_6H_4Cl(p)$ d, $C_6H_4CH_3(p)$

With ethyl chloroformate, the aminoalcohols **3** and **4** afforded the carbamates **9** and **10**, which were cyclized with sodium methoxide to the 5,8-methano-*r*-4a,*c*-5*c*-8,*c*-8a-tetrahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**11**) and the 5,8-methano-1-methyl-*r*-4a,*t*-5,6,7,*t*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**12**), respectively. The corresponding thiones **13** and **14** were synthesized from the aminoalcohols **3** and **4** by reaction with carbon disulphide and cyclization of the resulting non-isolated dithiocarbamates with lead(II) nitrate.

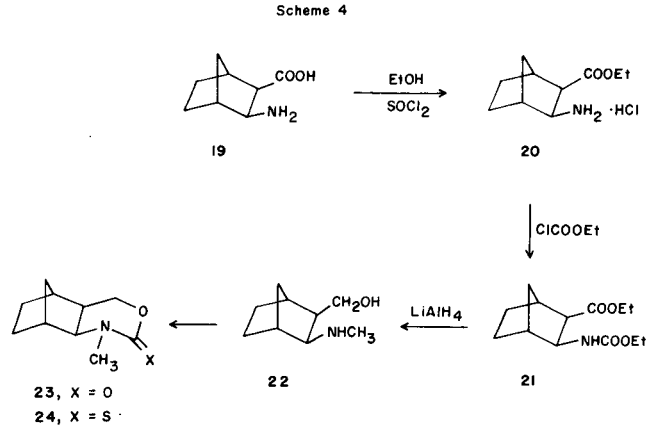
Scheme 3



The carbamate **15**, prepared from the ester salt **6**, was reduced with lithium aluminum hydride to 2-*endo*-methylamino-3-*endo*-hydroxymethylbicyclo[2.2.1]heptane (**16**). By the previous methods the aminoalcohols **16** yielded 5,8-methano-*r*-4a,*t*-5,6,7,*t*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**17**) and the corresponding 2(1*H*)-thione **18** (Scheme 3).

For preparation of the isomeric saturated *exo* *N*-methyl analogues, the 3-*exo*-aminobicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (**19**) [3] was esterified and the ester salt **20** was acylated to the carbamate **21**. The reduction of compound **21** gave the *exo* methylaminoalcohol **22**, which was transformed to 5,8-methano-1-methyl-*r*-4a,*c*-5,6,7,*c*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**23**) and 2(1*H*)-thione **24** (Scheme 4).

Scheme 4



Spectroscopic Study.

The detailed spectroscopic study of the saturated compounds **7a-d**, **11** and **13** and the unsaturated analogues **8a-d**, **12** and **14** was reported earlier [4]. The structures of the new compounds were proved by the following spectral data.

The ir spectra of compounds **11** and **12** exhibit ν 2 × NH and urethane carbonyl bands at 3325, 3300 and 3245, 3130 cm^{-1} and at 1720 and 1695 cm^{-1}, respectively. The carbonyl bands of the *N*-methyl derivatives **17** and **23** appear at 1700 and 1690 cm^{-1}. The ν 2 × NH bands of the thiones **13** and **14** are found at about 3180 cm^{-1}, and the intense characteristic thiocarbamate bands at 1550 cm^{-1}. The corresponding bands of the *N*-methyl derivatives **18** and **24** are identifiable at 1500 and 1495 cm^{-1}, respectively.

The *diexo* anellation of the hetero ring in compounds **7a-d** and **13** is proved by the doublet splitting of the H-4 signal in the region of 3.30-3.45 ppm ($J_{4,5}$ = 7.6-8.1 Hz). The H-4 signal of the *diendo* compounds **8a-d** is a double doublet at about 3.90 ppm (J = 10.5 and 4.5 Hz), which in consequence of the coupling of the H-4 and NH protons is split to 8 signals at about 3.90 ppm (J = 12, 4 and 2 Hz) in

the cases of **12** and **14**.

While the olefinic protons of the norbornene compounds **7a-d, 11** and **13** give signals in the interval 6.0-6.3 ppm, the overlapped (H-6,6',7,7',9,9') multiplets of the methylene groups in the norbornane analogues are observed at 1.0-1.8 ppm.

In the unsaturated compounds **7a-d**, the H-5 and H-8 signals appear at about 2.6 and 3.0 ppm, but in the spectra of the saturated analogues **8a-d** they are at about 2.25 and 2.6 ppm, because the −I effect of the unsaturated bond in the former compounds causes deshielding. Although the shifts change somewhat in the 2-oxo and 2-thioxo derivatives **11-14**, the deshielding in the unsaturated compounds **11** and **13** is similar.

The C-2 signal in the ^{13}C nmr spectra of compounds **7a-d** and **8a-d** can be characterized by the shifts at 156-158 ppm, and this is also the situation for the urethanes **11, 12, 17** and **23** (155.4-158.2 ppm). The thiocarbonyl carbon atom is deshielded, however, and characteristically, therefore, the C-2 signal appears in the interval 190.5-191.1 ppm for compounds **13, 14, 18** and **24**.

The C-6,7 signals could be assigned at 21-24 ppm in the norbornane derivatives **8a-d**, and at about 138.5 and 136.5 in the norbornene compounds **7a-d**. Disregarding some irregular values for the *N*-substituted analogues, no essential changes were experienced in this respect for the urethanes and thiourethanes.

In both the ^1H and the ^{13}C nmr spectra, aromatic signals appear for compounds **7a-d** and **8a-d** and, of course, are absent from the spectra of the 2-oxo and 2-thioxo derivatives.

The C-methyl signals for compounds **7d** and **8d** and the analogous signals for the *N*-methyl derivatives are identifiable in both the ^1H nmr (2.35 and 3.30 ppm, in **17** 2.84 ppm) and the ^{13}C nmr (21.3 and about 33-34 ppm) spectrum.

The above spectral data unambiguously prove the presumed structures and purity of the compounds. Use of the spectral data on the earlier-reported analogues will allow a comparison of the *exo-exo* and *endo-endo* anellated saturated and unsaturated compounds. These studies and the detailed spectroscopic data will be published later.

EXPERIMENTAL

The ir spectra were recorded in potassium bromide with Specord 75 (Jena GDR) or Bruker IFS-113v FT spectrometers. The ^1H and ^{13}C nmr spectra were obtained in deuteriochloroform at room temperature with Bruker WH-250 or Bruker WP 80-SY spectrometers, locked on the deuterium signal of the solvent and using TMS as internal standard.

Ethyl 3-*endo*-Aminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate Hydrochloride (**5**) and Ethyl 3-*exo*-aminobicyclo[2.2.1]heptane-2-*exo*-carboxylate Hydrochloride (**20**).

Thionyl chloride (8 ml, 0.11 mole) was added dropwise with stirring to absolute ethanol (90 ml) at −10°. 3-*endo*-Aminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (15.3 g, 0.1 mole) (**1**) [3] or 3-*exo*-aminobicyclo-[2.2.1]heptane-2-*exo*-carboxylic acid (15.5 g, 0.1 mole) (**19**) [3] was added in portions to the mixture, which was stirred for 30 minutes at 0°. After standing for 3 hours at room temperature, the mixture was refluxed for 1 hour and evaporated. The residue gave 16.2 g (75%) colorless crystals of **5**, mp 178-180° and 13.4 g (62%) **20**, mp 171-173° from ethanol.

Anal. (**5**) Calcd. for $C_{10}H_{16}ClNO_2$: C, 55.17; H, 7.41; N, 6.43. Found: C, 54.86; H, 7.54; N, 6.68.

Anal. (**20**) Calcd. for $C_{10}H_{18}ClNO_2$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.85; H, 8.42; N, 6.22.

Ethyl 3-*endo*-Aminobicyclo[2.2.1]heptane-2-*endo*-carboxylate Hydrochloride (**6**).

Table I

Physical and Analytical Data on the Compounds Prepared (**7a-d, 8a-d, 11-14, 17, 18, 23, 24**)

Compound	Mp (°C)	Yield (%)	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
7a	46-47	42	$C_{15}H_{15}NO$	79.97	6.71	6.22	79.91	6.54	6.36
7b	65-67	43	$C_{15}H_{14}ClNO$	69.36	5.43	5.39	69.18	5.20	5.31
7c	84-86	48	$C_{15}H_{14}ClNO$	69.36	5.43	5.39	69.45	5.50	5.33
7d	59-61	40	$C_{16}H_{17}NO$	80.30	7.16	5.85	80.55	7.25	6.01
8a	146-148 [a]	34	$C_{15}H_{17}NO$	79.26	7.54	6.16	79.21	7.48	6.27
8b	66-67	36	$C_{15}H_{16}ClNO$	68.83	6.16	5.35	68.70	6.04	5.51
8c	85-87	45	$C_{15}H_{16}ClNO$	68.83	6.16	5.35	68.80	6.12	5.37
8d	71-73	45	$C_{16}H_{19}NO$	79.63	7.94	5.80	79.72	8.02	5.87
11	87-89	34	$C_9H_{11}NO_2$	65.43	6.71	8.48	65.24	6.53	8.44
12	93-95	32	$C_9H_{13}NO_2$	64.65	7.84	8.38	64.81	7.96	8.30
13	123-125	54	$C_9H_{11}NOS$	59.64	6.12	7.73	59.45	6.03	7.50
14	161-163	49	$C_9H_{13}NOS$	58.98	7.15	7.64	59.14	7.26	7.67
17	122-124 [a]	30	$C_{10}H_{15}NO_2$	66.27	8.34	7.73	66.21	8.32	7.90
18	68-69	34	$C_{10}H_{15}NOS$	60.87	7.66	7.10	60.93	7.70	7.08
23	128-130 [a]	30	$C_{10}H_{15}NO_2$	66.27	8.34	7.73	66.40	8.43	7.87
24	98-100	33	$C_{10}H_{15}NOS$	60.87	7.66	7.10	60.71	7.58	7.23

[a] Colorless oil, bp (400 Pa).

Ester salt **5** (15.24 g, 0.07 mole) with platinum oxide catalyst (0.15 g) in ethanol (300 ml) was hydrogenated at room temperature and atmospheric pressure, with stirring. After completion of the reduction (4-6 hours) the catalyst was filtered off and the solvent was evaporated. The residue (13.9 g, 90%) gave colorless crystals from ethanol, mp 177-179°.

Anal. Calcd. for $C_{10}H_{18}ClNO_2$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.77; H, 8.49; N, 6.20.

Ethyl 3-*endo*-Aminobicyclo[2.2.1]heptane-2-*endo*-carboxylate (**6a**).

Ester salt **6** (2.20 g, 0.01 mole) and triethylamine (1.0 g, 0.01 mole) in acetone (20 ml) was chilled to 10° for 10 minutes and the solid was filtered off. The filtrate was evaporated and the residue was subjected to fractional distillation to yield **6a** as a colorless oil (1.1 g, 60%), bp 94-96° (400 Pa).

3-*exo*-Hydroxymethylbicyclo[2.2.1]hept-5-enyl-2-*exo*-amine (**3**) and 3-*endo*-Hydroxymethylbicyclo[2.2.1]heptyl-2-*endo*-amine (**4**).

Lithium aluminum hydride (14.0 g, 0.37 mole) was added in portions, with stirring and cooling, to dry tetrahydrofuran (700 ml). The 3-*exo*-aminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (20.60 g, 0.133 mole) [7] or the ethyl 3-*endo*-aminobicyclo[2.2.1]heptane-2-*endo*-carboxylate (**6a**) (24.37 g, 0.133 mole) was added to the mixture, which was stirred and refluxed for 20 hours. After cooling to 0°, the excess lithium aluminum hydride was decomposed by adding water (30 ml) dropwise, and the mixture was stirred at room temperature until it became completely white. The precipitate was filtered off with suction and repeatedly washed with hot tetrahydrofuran and then with ethanol, and the oily residue was subjected to fractional distillation to yield **3** and **4** as colorless oils. The aminoalcohol **3** [12.2 g, 65%, bp 96-98° (400 Pa)] became crystalline on standing at 4°.

Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.81; H, 9.35; N, 10.31.

Aminoalcohol **4** had bp 90-92° (400 Pa), yield 13.5 g (72%).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.70; N, 9.92. Found: C, 67.92; H, 10.63; N, 9.84.

2-*endo*-Methylamino-3-*endo*-hydroxymethylbicyclo[2.2.1]heptane (**16**) and 2-*exo*-Methylamino-3-*exo*-hydroxymethylbicyclo[2.2.1]heptane (**22**).

Ethyl chloroformate (1.3 g, 0.012 mole) was added dropwise to a mixture of ester salt **6** or **20** (0.01 mole), sodium hydrogen carbonate (2.52 g, 0.03 mole) and water (30 ml). The mixture was stirred for 2 hours, and after 10 hours the solid **15** (2.1 g, 82%) in the case of **6** was filtered off with suction, washed with water and dried. Colorless crystals from *n*-hexane, mp 64-66°.

Anal. Calcd. for $C_{13}H_{12}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.36; H, 8.40; N, 5.28.

In the case of **20**, the oily product **21** was extracted with chloroform, and the extract was washed with water, dried (sodium sulfate) and evaporated. The oily residue was reduced without any purification.

Lithium aluminum hydride (2.0 g) was suspended in dry tetrahydrofuran (100 ml) and the product **15** or **21** was added in portions, with stirring. The mixture was refluxed for 1 hour and the excess lithium aluminum hydride was decomposed with water (5 ml). After the usual working-up, colorless oily products were obtained: **16**, bp 94-96° (400 Pa; 1.18 g, 76% calcd. for **6**) and **22**, bp 96-98° (400 Pa; 1.10 g, 71% calcd. for **20**). For analytical purposes the hydrochlorides were prepared.

Anal. Calcd. for $C_9H_{18}ClNO$: C, 56.39; H, 9.46; N, 7.30. Found: (**16**) C, 56.44; H, 9.29; N, 7.37. Found: (**22**) C, 56.27; H, 9.30; N, 7.44.

2-Aryl-5,8-methano-*r*-4a,*c*-5,*c*-8a-tetrahydro-4*H*-3,1-benzoxazines (**7a-d**) and 2-Aryl-5,8-methano-*r*-4a,*t*-5,6,7,*t*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazines (**8a-d**).

The aminoalcohol **3** or **4** (1.4 g, 0.01 mole) and the imidate [Ar = C_6H_5: 1.5 g, Ar = C_6H_4Cl (*m* or *p*), 1.83 g, Ar = $C_6H_4CH_3$(*p*), 1.63 g] were dissolved in ethanol (20 ml), one drop of ethanol saturated with hydrogen chloride was added, and the mixture was refluxed. After the reaction was complete (6-8 hours), the mixture was concentrated and the residue was crystallized from ethanol-petroleum ether. Data on the prepared colorless crystalline compounds are listed in Table I.

5,8-Methano-*r*-4a,*c*-5,*c*-8,*c*-8a-tetrahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**11**), 5,8-Methano-*r*-4a,*t*-5,6,7,*t*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**12**), 5,8-Methano-1-methyl-*r*-4a,*c*-5,6,7,*c*-8a-hexahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**17**) and 5,8-Methano-1-methyl-*r*-4a,*t*-5,6,7,*t*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**23**).

Ethyl chloroformate (1.1 g, 0.01 mole) was added dropwise to a mixture of aminoalcohol (**3**: 1.40 g, **4**: 1.42 g, **16** and **22**: 1.56 g, 0.01 mole), water (10 ml) and sodium hydrogen carbonate (0.9 g, 0.01 mole). The mixture was stirred and refluxed for 5 minutes and then concentrated. The dry residue was heated with sodium methoxide at 120° for 20 minutes in an oil bath. After cooling, the mixture was repeatedly extracted with hot ethyl acetate, the extracts were combined and the solvent was evaporated. The residue was transferred onto an aluminium oxide (neutral, activity grade 2) column, and eluted with benzene and then with chloroform. After evaporation of the chloroform, the residue gave colorless crystals (**11** and **12**) from ethyl acetate-petroleum ether, or colorless oils (**17** and **23**).

The mp's, yields and analyses of compounds **11**, **12**, **17** and **23** are listed in Table I.

5,8-Methano-*r*-4a,*c*-5,*c*-8,*c*-8a-tetrahydro-4*H*-3,1-benzoxazine-2(1*H*)-thione (**13**), 5,8-Methano-*r*-4a,*t*-5,6,7,*t*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazine-2(1*H*)-*thione* (**14**), 5,8-Methano-1-methyl-*r*-4a,*c*-5,6,7,*c*-8a-hexahydro-4*H*-3,1-benzoxazine-2(1*H*)-thione (**18**) and 5,8-Methano-1-methyl-*r*-4a,*t*-5,6,7,*t*-8,*c*-8a-hexahydro-4*H*-3,1-benzoxazine-2(1*H*)-thione (**24**).

The aminoalcohol (**3**: 2.30 g, **4**: 2.34 g, **16** and **22**: 2.57 g, 0.0165 mole) in a solution (10 ml) of potassium hydroxide (1.1 g) was cooled to 0°, carbon disulphide (1.3 g) in dioxane (8 ml) was added and the mixture was stirred for 5 minutes. Potassium hydroxide (0.55 g) in water (10 ml) and then an aqueous solution (30 ml) of lead(II) nitrate (5.5 g) were added, followed by stirring at 60° for 10 minutes. The lead sulphide was filtered off, washed with hot water and extracted with hot ethanol. The aqueous filtrate and the ethanolic extracts were combined and evaporated to dryness. The residue gave colorless crystals from ethanol.

The data on compounds **13**, **14**, **18** and **24** are listed in Table I.

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