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3-*endo*-Aminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (**1**), prepared from *endo*-norborn-5-ene-2,3-dicarboxylic acid anhydride, and the analogous saturated *cis*-*exo*-amino acid (**3**) were reduced with lithium aluminum hydride to the aminoalcohols **2** and **4**; the latter were cyclized by means of arylimino ethers to methylene-bridged tetrahydro- (**6a-c**) and hexahydro-3,1-benzoxazines (**7b-d**), respectively. The *endo* (**2**) and *exo* (**4**) aminoalcohols were converted to methylene-bridged tetrahydro-3,1-benzoxazin-2-one (**9**) and hexahydro-3,1-benzoxazin-2-one (**12**) with ethyl chloroformate and sodium methoxide; treatment of the alcohols with carbon disulfide gave, *via* the dithiocarbamates, the corresponding 2-thiones (**11**, **13**). The structures were confirmed by ir and nmr spectroscopy.

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We earlier reported the synthesis of *cis*-trimethylene-, *cis*- and *trans*-tetramethylene- and pentamethylenedihydro-1,3-oxazines [2] and -tetrahydro-1,3-oxazines [3,4], 1,3-oxazin-2-ones [5,6], 1,3-oxazine-2-thiones [7,8] and 1,3-oxazin-4-ones [9,10], and the related fused-skeleton heterocycles such as pyrimidinone derivatives [11]. Conformational analysis of these compounds was effected by ^1H and ^{13}C nmr spectroscopy, and in many cases also by X-ray diffraction [2,7,12]. The above *cis* and *trans* isomeric homologous compounds were used in systematic pharmacological studies and as models in structure-activity relationship investigations [10,11].

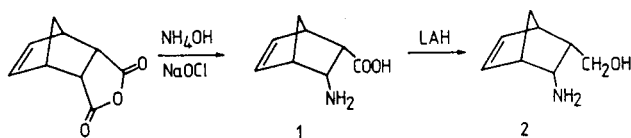
In continuation of this work, our present synthetic targets were fused-skeleton oxazine and oxazinone derivatives containing the norbornane or norbornene structural unit. Besides the stereochemical and spectroscopic interest attached to these multi-fused rigid-skeleton compounds, this research was motivated by the fact that it was always the *cis*-trimethylene derivatives which had the highest pharmacological activity [11,13] among the 5,6-trimethylene-, 5,6-tetramethylene- and 5,6-pentamethylene-1,3-oxazin-4-ones and 1,3-pyridin-4(3*H*)-ones, many of them possessing significant anti-inflammatory and analgesic actions. Hence, both stereochemical and pharmacological considerations justified the synthesis of norbornane- and norbornene-fused tricyclic derivatives which can be regarded as representatives of the earlier prepared biologically active *cis*-trimethylene fused-skeleton heterocycles, containing an ethylene bridge or ethenylene bridge (vinylene bridge) in their cyclopentane ring. Another advantage to be expected from the inclusion of the norbornane unit was that the introduction of this moiety may re-

sult in retarded pharmacological action [14].

Synthesis.

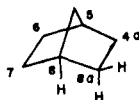
One of the isomeric starting aminoalcohols was prepared from 5-norbornene-2-*endo*-3-*endo*-dicarboxylic acid anhydride [15]. Ammonolysis of the anhydride gave 5-norbornene-3-*endo*-aminocarbonyl-2-*endo*-carboxylic acid, which was subjected without isolation, to Hofmann degradation with sodium hypochlorite [16]. After purification on an ion exchange resin, 3-*endo*-aminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (**1**) was isolated from the reaction mixture, differently from the literature result [16], where the benzoylamino acid, which had been reported previously [17], was prepared. Compound **1** was reduced with lithium aluminum hydride to 2-*endo*-amino-3-*endo*-(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene (**2**), a substance not yet described in the literature (Scheme 1).

Scheme 1



In the synthesis of the aminoalcohol **4**, chlorosulfonyl isocyanate addition to norbornene [18] afforded the *N*-chlorosulfonylazetidione, which was reduced with sulfite [19] and the resulting *exo*-3-aza-4-ketotricyclic[4.2.1.0]nonane was hydrolyzed with hydrochloric acid [18]. After removal of the hydrochloric acid on an ion-exchange resin, 3-*exo*-aminobicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (**3**) was obtained (described in the literature [20], but the

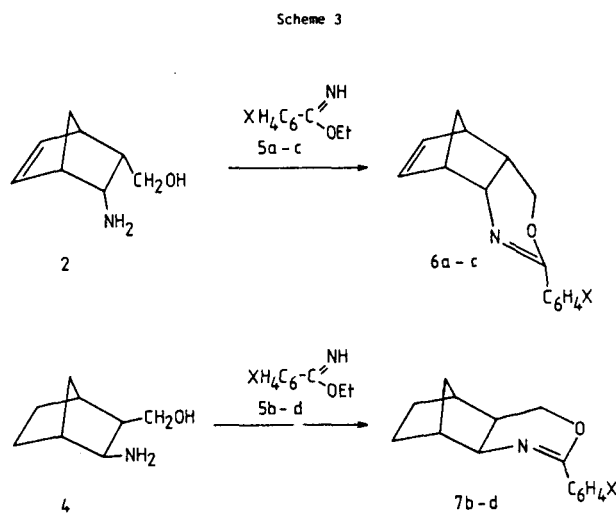
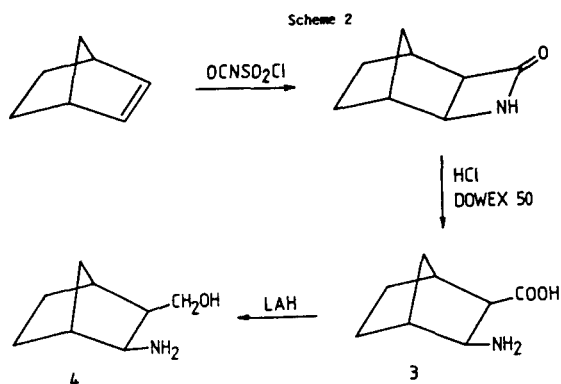
Table I
IR and ¹H-NMR Data on Compounds **6a-c**, **7b-d**, **9**, **11-13** (a)



Compound	ν C=N(O)	δ H-8a	δ H-6,7	δ ArH	ν NH
6a	1645	4.05 $2 \times d$ (4.0, 8.9) (b)	6.05 6.13 <i>m</i> (2H)	7.83 <i>m</i> (2H) (c) 7.34 <i>m</i> (3H) (d,e)	
6b	1640	4.05 $2 \times d$ (4.0, 9.0)	6.04 6.15 <i>m</i> (2H)	7.30 <i>m</i> (2H) (d,f) 7.77 <i>m</i> (2H) (c,f)	
6c	1650	4.03 $2 \times d$ (3.9, 8.8)	6.02 6.11 <i>m</i> (2H)	7.21 <i>t</i> (g), 7.31 <i>d</i> (e) 7.71 <i>d</i> (h), 7.84 <i>s</i> (i)	
7b	1645	3.47 <i>d</i> (7.7)	1.3 1.55 <i>m</i> (4H)	7.31 <i>m</i> (2H) (d,f) 7.84 <i>m</i> (2H) (c,f)	
7c	1640	3.47 <i>d</i> (7.7)	1.25, 1.5, 1.6 <i>m</i> (4H)	7.25 <i>t</i> (g), 7.34 <i>d</i> (e) 7.78 <i>d</i> (h), 7.92 <i>s</i> (i)	
7d (j)	1650	3.46 <i>d</i> (7.7)	1.25, 1.5, 1.6 <i>m</i> (4H)	7.13 <i>m</i> (2H) (d,f) 7.80 <i>m</i> (2H) (c,f)	
9	1750 (k)	3.98 $2 \times d$ ($J \equiv 5.6$)	6.14 6.26 <i>m</i> (2H)	—	3250
11	1550 (l)	3.94 $2 \times d$	6.19 6.27 <i>m</i> (2H)	—	3180
12	1750 (k)	3.35 <i>d</i> (8.1)	1.15 1.55 <i>m</i> (4H)	—	3300-3050
13	1545 (l)	3.40 <i>d</i> (8.2)	~1.3 ~1.6 <i>m</i> (4H)	—	3170

(a) Ir: potassium bromide, cm^{-1} ; ¹H nmr: deuteriochloroform, δ TMS = 0 ppm. (b) Coupling constants are given in Hz (italics). (c) H-2,6. (d) H-3,5. (e) H-4. (f) AA'BB'. (g) H-5. (h) H-6. (i) H-2. (j) δ CH₃: 2.32 s (2H). (k) ν C=O (urethane) bands. (l) ν C=N (thiourethane) bands.

melting point and the configuration were not given). Lithium aluminum hydride reduction afforded 2-*exo*-amino-3-*exo*-(hydroxymethyl)-bicyclo[2.2.1]heptane (**4**) (Scheme 2).

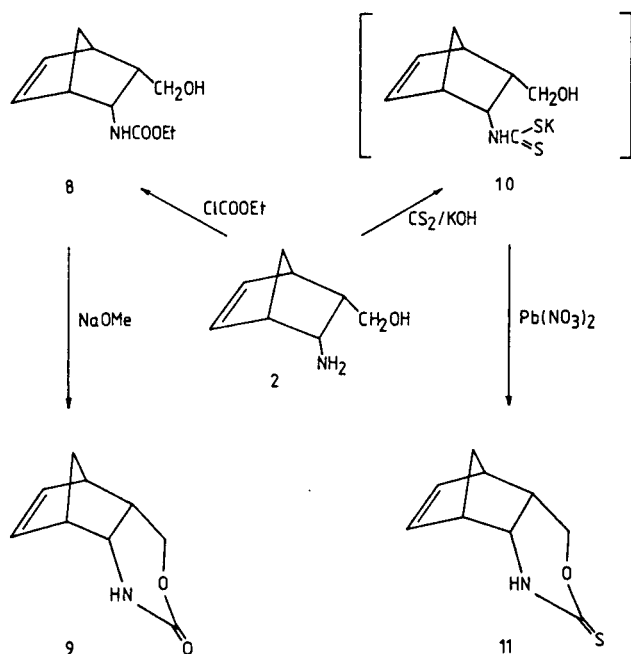


X: a = H; b = *p*-Cl; c = *m*-Cl; d = *p*-CH₃

The tricyclic fused-skeleton compounds, the 5,8-methano-4*ar*,5*t*,8*t*,8*ac*-tetrahydro-4*H*-3,1-benzoxazines **6a-c** were obtained from the *endo*-aminoalcohol **2** by treatment with arylimino ethers (**5a-c**) (Scheme 3). Similarly, the reactions of the *exo*-aminoalcohol **4** with the imino ethers **5b-d** gave the 5,8-methano-4*ar*,5*c*,6,7,8*c*,8*ac*-hexahydro-4*H*-3,1-benzoxazines (**7b-d**) (Scheme 3).

The ethyl carbamate **8** was prepared from the *endo*-aminoalcohol **2** with ethyl chloroformate, and the product was cyclized with sodium methoxide to give 5,8-methano-4*ar*,5*t*,8*t*,8*ac*-tetrahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (**9**) (Scheme 4). The corresponding thione (**11**) was synthesized

Scheme 4

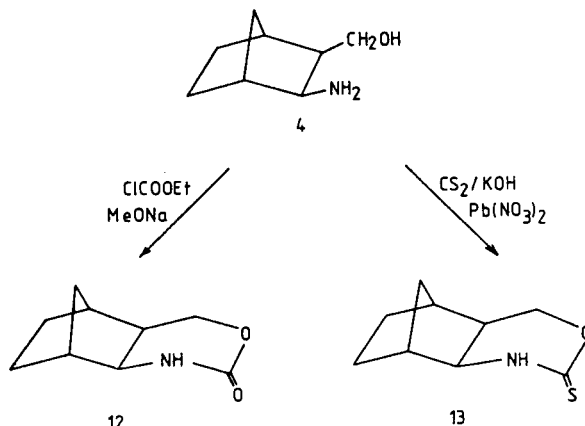


ed from the aminoalcohol **2** by reaction with carbon disulfide, and cyclization of the resulting dithiocarbamate (**10**) with lead(II) nitrate. A similar reaction path led from the *exo*-aminoalcohol **4** to 5,8-methano-4a,5c,6,7,8c,8ac-hexahydro-4H-3,1-benzoxazin-2(1H)-one (**12**) and the corresponding -2(1H)-thione (**13**) (Scheme 5).

Structure Confirmation by IR and NMR.

The detailed ^1H and ^{13}C nmr investigations of the new compounds are reported elsewhere [21]. The most important ir and ^1H nmr data supporting the structures are listed in Table I.

Scheme 5



In respect of the annelation of the norbornane skeleton and the hetero ring, the multiplicity of the H-8a proton resonance signal is of decisive importance, since the dihedral angle between the $\text{C}_8\text{-H}$ and $\text{C}_{8a}\text{-H}$ bonds is about 50° for the *diendo* compounds **6a-c**, **9** and **11**, whereas for the *diexo* analogs **7b-d**, **12** and **13** it is about 90° . Therefore, in the former group the 8,8a spin-spin interaction is expected to give rise to a considerable splitting of the signal, while the coupling constant to be expected for the *diexo* compound is smaller than 1 Hz, and hence is non-significant. Accordingly, the H-8a signal is a doublet in the spectra of the *diexo* derivatives (the splitting of about 8 Hz being caused by the 4a,8a coupling), whereas for the *diendo* compounds it is a doublet of doublets. The 8,8a coupling is represented by a splitting of about 4 Hz.

The multiplet due to the two olefinic protons in the unsaturated *diendo* compounds is found between 6.0 and 6.3 ppm. The corresponding methylene signals of the saturated *diexo* derivatives are multiplets of 4H intensity appearing between 1.1 and 1.6 ppm.

Table II

Physical and Analytical Data on the Compounds Prepared (**6a-c**, **7b-d**, **9**, **11-13**)

Compound	Mp $^\circ\text{C}$	Yield %	Formula	Calcd. %			Found %		
				C	H	N	C	H	N
6a	45-47 (a)	32	$\text{C}_{15}\text{H}_{15}\text{NO}$	79.97	6.71	6.22	79.64	6.50	6.10
6b	104-105 (b)	35	$\text{C}_{15}\text{H}_{14}\text{ClNO}$	69.37	5.43	5.39	69.34	5.66	5.60
6c	61-63 (c)	48	$\text{C}_{15}\text{H}_{14}\text{ClNO}$	69.37	5.43	5.39	69.66	5.13	5.37
7b	82-84 (b)	38	$\text{C}_{15}\text{H}_{16}\text{ClNO}$	68.83	6.16	5.35	69.27	6.48	5.05
7c	61-62 (d)	27	$\text{C}_{15}\text{H}_{16}\text{ClNO}$	68.83	6.16	5.35	68.48	6.39	5.36
7d	49-51 (d)	30	$\text{C}_{16}\text{H}_{19}\text{NO}$	79.63	7.94	5.80	79.90	8.04	5.75
9	62-64 (e)	24	$\text{C}_9\text{H}_{11}\text{NO}_2$	65.44	6.71	8.48	65.62	6.72	8.26
11	136-138 dec (f)	24	$\text{C}_9\text{H}_{11}\text{NOS}$	59.64	6.12	7.73	59.44	6.30	7.65
12	89-91 (b)	28	$\text{C}_9\text{H}_{13}\text{NO}_2$	64.65	7.84	8.38	64.36	8.01	8.30
13	147-149 (b)	25	$\text{C}_9\text{H}_{13}\text{NOS}$	58.98	7.15	7.94	58.59	7.39	7.34

(a) From benzene-petroleum ether. (b) From ethanol-petroleum ether. (c) From petroleum ether. (d) From ethyl acetate-petroleum ether. (e) From ethyl acetate. (f) From ethanol-ethyl acetate.

The ^1H nmr spectra of compounds **6a-c** and **7b-d**, containing aromatic substituents, have the aromatic proton signals between 7.2 and 7.9 ppm, with the expected multiplicities and intensities. Compounds **9-13** give no proton resonance signal in this region, but the ir spectra have well identifiable bands, that of the urethane carbonyl being situated at about 1750 cm^{-1} in the case of **9** and **12**, and the thiourethane $\nu\text{ C}=\text{N}$ vibration band at 1545 and 1550 cm^{-1} in **11** and **13**. All four spectra display a broad $\nu\text{ NH}$ band with maximum at about 3200 cm^{-1} . These bands are missing from the spectra of **6a-c** and **7b-d**; instead, the $\nu\text{ C}=\text{N}$ band of the imino ether group can readily be identified between 1640 and 1650 cm^{-1} .

EXPERIMENTAL

The ^1H nmr spectra were obtained at 250 MHz , in deuteriochloroform at room temperature with a Bruker WM-250-FT spectrometer using tetramethylsilane as internal standard.

3-endo-Aminobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic Acid (**1**).

endo-Norborn-5-ene-2,3-dicarboxylic acid anhydride (30 g, 0.18 mole) was added in portions, at 0° , to a stirred 6% solution of ammonium hydroxide (250 ml). At this temperature, a cooled solution of sodium hydroxide (22 g, 0.55 mole) in water (100 ml) was added dropwise. Excess ammonia was removed at 40° using a water suction pump, the mixture was diluted with water (300 ml), and 2.04 M sodium hypochlorite solution (90 ml) was added dropwise over a period of 1 hour, with stirring and cooling. After stirring for another 10 minutes, the solution was maintained at 70° for 5 minutes, then cooled and adjusted to $\text{pH } 7$ with concentrated hydrochloric acid. It was next evaporated to dryness *in vacuo* and the residue was extracted with hot ethanol. The solvent was evaporated off, and the residue was dissolved in water and applied onto a column of Dowex 50 ion-exchange resin (in acid form). The column was washed with water until neutral, and the amino acid **1** was eluted with a 1:1 mixture (2000 ml) of concentrated ammonium hydroxide and water. The residue obtained after evaporation of the eluate was dissolved in water, filtered, and acetone was added to the solution until turbidity appeared. Crystallization at $+4^\circ$ gave 14.5 g (53%) of the product as a pale beige powder, mp $274\text{--}276^\circ\text{ dec}$.

Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{NO}_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.50; H, 7.45; N, 9.13.

3-endo-Amino-2-endo-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (**2**) and 3-exo-Amino-2-exo-(hydroxymethyl)bicyclo[2.2.1]heptane (**4**).

Lithium aluminum hydride (14.0 g , 0.37 mole) was added in portions, with stirring and cooling, to dry tetrahydrofuran (700 ml). The amino acid **1** (20.37 g , 0.133 mole) or **3** (20.6 g) 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 30 ml of water 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. The solvents were evaporated from the combined filtrate and the oily residue was subjected to fractional distillation to yield **2** as a colorless oil (13.5 g , 73%), bp $116\text{--}120^\circ$ (4 mm), picrate, mp $193\text{--}195^\circ$.

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}_8$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.30; H, 4.61; N, 14.98.

The aminoalcohol **4** was a colorless oil, bp $106\text{--}108^\circ$ (4 mm), which became crystalline on standing at $+4^\circ$, yield, 15.0 g (80%), picrate, mp $178\text{--}180^\circ$.

Anal. Calcd. for $\text{C}_{11}\text{H}_{18}\text{N}_4\text{O}_8$: C, 45.41; H, 4.90; N, 15.13. Found: C, 45.64; H, 4.99; N, 15.36.

2-Aryl-5,8-methano-4ar,5t,8t,8ac-tetrahydro-4H-3,1-benzoxazines (**6a-c**)

and 2-Aryl-5,8-methano-4ar,5c,6,7,8c,8ac-hexahydro-4H-3,1-benzoxazines (**7b-d**).

The aminoalcohol **2** or **4** (1.4 g , 0.01 mole) and the arylimino ether (0.01 mole : 1.5 g of **5a**; 1.84 g of **5b** or **5c**; 1.63 g of **5d**) were dissolved in ethanol (20 ml), one drop of ethanol saturated with hydrogen chloride was added and the mixture was refluxed. The progress of the reaction was monitored by thin-layer chromatography (silica gel; chloroform-benzene 9:1, detection in iodine vapor). After the reaction was complete (6-10 hours), the mixture was concentrated under reduced pressure and the residue was crystallized. Data on the prepared compounds are listed in Table II.

5,8-Methano-4ar,5t,8t,8ac-tetrahydro-4H-3,1-benzoxazin-2(1H)-one (**9**) and 5,8-Methano-4ar,5c,6,7,8c,8ac-hexahydro-4H-3,1-benzoxazin-2(1H)-one (**12**).

Ethyl chloroformate (0.55 g , 5 mmoles) was added dropwise to a mixture of the *endo*-aminoalcohol **2** (0.7 g , 5 mmoles), water (5 ml) and sodium hydrogen carbonate (0.55 g , 5 mmoles). The mixture was stirred and refluxed for 5 minutes and then concentrated under reduced pressure. The residual oil crystallized at $+4^\circ$. This product was heated with sodium methoxide at 120° for 20 minutes on 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 aluminum oxide (neutral, activity grade 2) column, and eluted with benzene and then with chloroform. After evaporation of the chloroform the residue gave **9** as colorless, shining needles from ethyl acetate.

On starting from the *exo*-aminoalcohol **4** (0.7 g , 5 mmoles), a similar procedure gave compound **12**.

The melting points, yields and analyses of compounds **9** and **12** are shown in Table II.

5,8-Methano-4ar,5t,8t,8ac-tetrahydro-4H-3,1-benzoxazine-2(1H)-thione (**11**) and 5,8-Methano-4ar,5c,6,7,8c,8ac-hexahydro-4H-3,1-benzoxazine-2(1H)-thione (**13**).

The *endo*-aminoalcohol **2** (2.3 g , 0.0165 mole) in a solution (10 ml) of potassium hydroxide (1.1 g) was cooled to 0° then carbon disulfide (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 precipitated lead sulfide 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 of **11**.

In a similar way, the *exo*-aminoalcohol **4** afforded the thione **13**.

The data on compounds **11** and **13** are shown in Table II.

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