70.7° [29] only; then, however, one of the substituents occupies an unfavourable pseudo-axial position.

Experimental part

IR spectra were obtained with a Perkin-Elmer 521 spectrometer. 60 MHz PMR spectra were obtained with a Varian A-60 spectrometer. 100 MHz PMR spectra and 25.1 MHz CMR spectra were obtained with a Varian XL-100-15 spectrometer. GLC analyses were generally performed on a 50 m capillary Apiezon column at 200°. The compounds were pure according to elemental analysis, GLC analysis or both.

cis-*1,2-Bis(2-carboxy-2-propyl)cyclohexane*

A solution of 1,2-bis(2-carboxy-2-propyl)benzene[30] (3.00 g) in acetic acid (50 ml) was hydrogenated at 1 atm and 70° over reduced platinum oxide (0.2 g). The mixture was filtered, the solvent was evaporated and then the residue was recrystallized from aqueous ethanol. This gave 2.40 g (78%) of *cis*-1,2-bis(2-carboxy-2-propyl)-cyclohexane, m.p. 198–199°. Further recrystallization from aqueous ethanol raised the m.p. to 200–201° (ref. 26: 199–199.5°).

cis-*1,2-Bis[2-(methoxycarbonyl)-2-propyl]cyclohexane* (cis-**2**)

To a suspension of *cis*-1,2-bis(2-carboxy-2-propyl)cyclohexane (256 mg) in ether (5 ml), a solution of diazomethane in ether was added until a clear yellow solution resulted. Evaporation of the ether afforded 260 mg (92%) *cis*-**2** as a viscous liquid.

cis-*1,2-Bis[2-(hydroxymethyl)-2-propyl]cyclohexane* (cis-**3**)

To a solution of *cis*-1,2-bis(2-carboxy-2-propyl)cyclohexane (1.00 g) in butyl ethyl ether (35 ml), 1,35 g of $LiAlH_4$ were added. The mixture was refluxed for 15 hrs and, after cooling, poured into 2 *N*-H_2SO_4. The organic layer was separated, washed with 2 *N*-KOH and then dried over $MgSO_4$. After filtration and evaporation of the solvent, 0.87 g (98%) of crude *cis*-**3** was obtained, m.p. 128.5–130°. Crystallization from ethanol raised the m.p. to 130–131°.

trans-*1,2-Bis(2-carboxy-2-propyl)cyclohexane*

A solution of 1,2-bis(2-carboxy-2-propyl)benzene[30] (2.50 g), in acetic acid (100 ml), was hydrogenated at 1 atm and 70° over palladium (2.0 g 10% on charcoal). GLC analysis of a sample, after working-up and esterification with diazomethane, showed a *cis-trans* ratio of 1 to 3. The mixture was filtered and the resulting solution concentrated to 50 ml. After cooling, 1.03 g (40%) of *trans*-1,2-bis-(2-carboxy-2-propyl)cyclohexane were obtained, m.p. 269–270°. Recrystallization from acetic acid raised the m.p. to 270–271°.

trans-*1,2-Bis[2-(methoxycarbonyl)-2-propyl]cyclohexane* (trans-**2**)

a. *From* trans-*1,2-bis(2-carboxy-2-propyl)cyclohexane*
Following the procedure for *cis*-**2**, 200 mg *trans*-1,2-bis(2-carboxy-2-propyl)cyclohexane gave 194 mg (87%) of *trans*-**2**, m.p. 83–84°. Recrystallization from methanol raised the m.p. to 86–87°.

b. *From 1,2-Bis[2(methoxycarbonyl)-2-propyl]benzene*
Following the procedure for *trans*-1,2-bis(2-carboxy-2-propyl)cyclohexane, 2.00 g of 1,2-bis[2-(methoxycarbonyl)-2-propyl]benzene[30] gave 1.88 g of crude product. Recrystallization from methanol gave 1.03 g (50%) of *trans*-**2**, m.p. 86–87°.

trans-*1,2-Bis[2-(hydroxymethyl)-2-propyl]cyclohexane* (trans-**3**)

a. *From* trans-*1,2-bis(2-carboxy-2-propyl)cyclohexane*
Following the procedure for *cis*-**3**, 300 mg of *trans*-1,2-bis(2-carboxy-2-propyl)cyclohexane gave 243 mg (91%) of *trans*-**3**, m.p. 104–105°. Recrystallization from petroleum ether 80–100° raised the m.p. to 107–108°.

b. *From* trans-**2**
Following the procedure for *cis*-**3**, 235 mg of *trans*-**2** gave, after recrystallization from methanol, 126 mg (67%) of *trans*-**3**, m.p. 105–106°.

Acknowledgements

Thanks are due to Mr. *J. M. van der Toorn* for measuring the NMR spectra and to Dr. *J. D. Remijnse* for helpful discussions.

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Synthesis of 2,1-benzisoxazoles (analogues of psilocine and muscimol)

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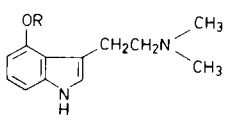
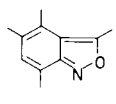
Abstract. The synthesis of several 2,1-benzisoxazoles with substituents at different positions of the six-membered ring and with a variable aliphatic side-chain at C-3 is reported. Anomalous reactions and complications, encountered in this synthesis, are dealt with.

Introduction

2,1-Benzisoxazoles (**3**) can be regarded as structural analogues of psilocybine (**1**) and psilocine (**2**), which belong to the indole derivatives, and are structurally related to muscimol (**4**) and ibotenic acid (**5**), both containing an isoxazole ring. These four natural products are pharmacologically active and possess hallucinogenic properties.



1 R = PO_3H_2
2 R = H



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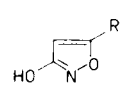


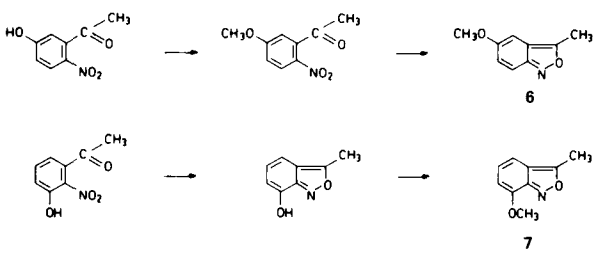
4 R = CH_2NH_2
5 R = $\underset{\underset{NH_2}{|}}{\overset{H}{|}}{C}$ - COOH

In order to investigate the possible structure to activity relation, 2,1-benzisoxazoles were synthesized with a variable aliphatic side-chain at C-3 and a methoxy group at different positions of the six-membered ring. Detailed results of the pharmacological tests will be published elsewhere[1].

Theoretical part

a. *Ring-closure reactions*

One of the basic routes, available for the synthesis of 2,1-benzisoxazoles is the partial reduction of substituted *o*-nitroacetophenones to the corresponding *o*-(hydroxyamino)acetophenones, immediately followed by dehydration leading to cyclization. This procedure is described by *Christensen* et al.[2]. Starting materials for the C-5 and C-7 substituted derivatives were 3′-hydroxy-6′-nitroacetophenone and 3′-hydroxy-2′-nitroacetophenone. These products could be synthesized by direct nitration of 3′-hydroxyacetophenone with copper(II) nitrate in a mixture of glacial acetic acid and acetic anhydride[3].
The hydroxy groups at C-5 and C-7 had to be protected by methylation before the subsequent extention of the aliphatic side-chain at C-3 could be performed. The strength of the hydrogen bonding between the hydroxy group and the acetyl or nitro group determined whether this methylation was carried out before or after ring closure (Scheme 1).

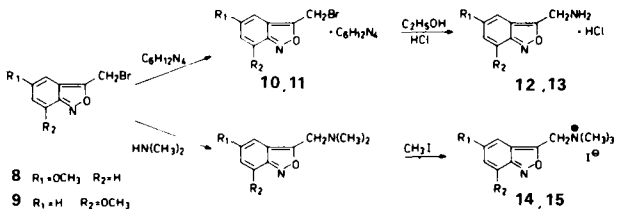


scheme 1

Photolytic decomposition of the 2,1-benzisoxazoles, as was earlier observed[4], was excluded by performing ring-closure reactions in the dark.
Due to the required excess of tin(II) chloride in concentrated hydrochloric acid for the synthesis of 2,1-benzisoxazoles, complexed compounds were rapidly formed. The products **6** and **7** could be isolated in a pure state by decomposition of the complexes with pyridine, followed by recrystallization. An alternative route for the synthesis of 2,1-benzisoxazoles through thermolytic decomposition of *o*-azidoacetophenones[5] was found to be ineffective.

b. *Reactions with 5- and 7-methoxy-2,1-benzisoxazoles*

In order to extend the aliphatic side-chain at C-3, 5- and 7-methoxy-3-methyl-2,1-benzisoxazole (**6** and **7**) were treated at first with formaldehyde and dimethylamine, analogous to the Mannich reaction with 2- and 4-methylquinoline[6]. This reaction was carried out under different conditions but in all cases only starting material could be re-isolated.
Better results were obtained by the syntheses – formulated in Scheme 2 – *via* the corresponding bromomethyl derivatives (**8** and **9**), which could be prepared in good yields by treating the 5- and 7-methoxy compounds with an equimolecular quantity of *N*-bromosuccinimide (NBS) in the presence of a trace of dibenzoyl peroxide (DBP).

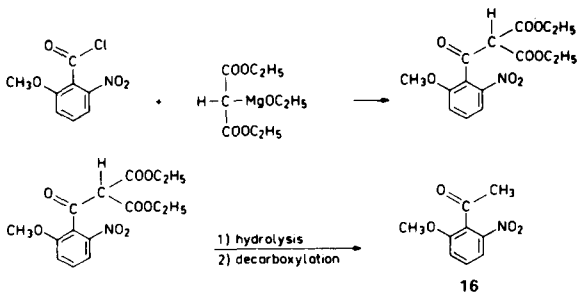


scheme 2

After complexation of **8** and **9** with hexamethylenetetramine[7] and decomposition of **10** and **11** with concentrated hydrochloric acid in ethanol[7], the hydrochlorides of the 3-aminomethyl compounds **12**, **13** were formed.
The corresponding 3-[(trimethylammonio)methyl]-2,1-benzisoxazole iodides were synthesized by treatment of the bromomethyl compounds with an excess of dimethylamine and methyl iodide.
For the elongation of the aliphatic side-chain, several routes can be considered. The 3-bromomethyl compound can be converted into the corresponding nitrile by the action of potassium cyanide, followed by reduction. The latter reaction, however, was found to be problematic and needs further investigation.

c. *Synthesis of substituted 4-methoxy-2,1-benzisoxazoles*

2-Methoxy-6-nitrobenzoic acid[8] was treated with thionyl chloride and the unpurified acid chloride converted into the corresponding methyl ketone by reaction with magnesium ethoxide/diethyl malonate, followed by hydrolysis and decarboxylation (Scheme 3).



scheme 3

The ring-closure of **16** was achieved as described under *a*[2]. Bromination of the resulting 2,1-benzisoxazole, carried out under the same conditions as with the 5- and 7-isomers, gave rise to an anomalous reaction. Instead of substitution of the C-3 methyl group, as in the 5- and 7-components, bromination now took place at C-7 of the chromophore. Only after addition of a second molecular quantity of NBS was the methyl group converted into bromomethyl (Scheme 4).
The prevalence of aromatic substitution during reaction of **17** with NBS under completely similar conditions to those applied to **6** and **7** must, therefore, be a result of the combination of the *ortho-para* directing effect of the isoxazole

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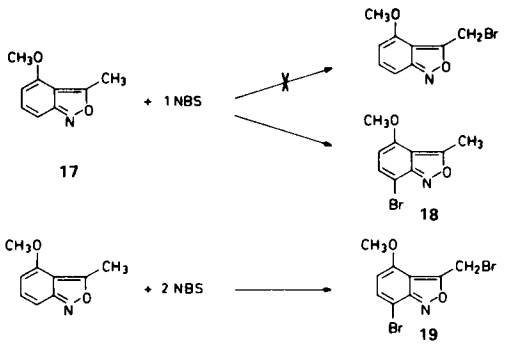

scheme 4

group[5], and the *para* directing effect of the methoxy group during electrophilic substitution.
Neither by nucleophilic nor by electrophilic or radical reaction did it seem possible to eliminate the nuclear-bound halogen atom in **19**, due to the lability of the N–O bond and the sensitivity of 2,1-benzisoxazoles to the action of reducing agents in general.
In the next stage of the synthesis the dibromo compound **19** was treated with hexamethylenetetramine and the complex formed decomposed by ethanol and hydrochloric acid, as described under *b*. The resulting compound was 3-(aminomethyl)-7-bromo-4-methoxy-2,1-benzisoxazole hydrochloride.

Preliminary pharmacological experiments with the latter compound and products **12**, **13**, **14** and **15** were carried out on mice to get some idea of their possible pharmacological activity. The hydrochlorides **12** and **13** were the most active compounds. At a dose-level of 50 mg/kg, injected intraperitoneally, they showed effects, similar to those observed with psilocin and muscimol, although the latter drugs are far more toxic and active. Weaker effects were shown by the hydrochlorides containing bromine. The quaternary iodides **14** and **15** seemed to be almost ineffective.

Experimental part

The infrared spectra were taken on a Perkin-Elmer 700 spectrometer. The NMR-spectra were run with a Varian A60 spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane ($\delta = 0$) as internal standard.
Satisfactory elementary analyses were obtained, carried out by Mr. *W. J. Buis* at the Institute for Organic Chemistry TNO, Utrecht.

1. *3'-Methoxy-6'-nitroacetophenone*

18.1 g (0.1 Mole) of 3'-hydroxy-6'-nitroacetophenone[3] were added to a stirred solution of 4 g (0.1 Mole) of NaOH in 100 ml of water. After addition of 25.2 g (0.2 Mole) of dimethyl sulfate, the mixture was kept for 20 hours at 110°.
After cooling, the reaction mixture was extracted with three 150 ml portions of ether and the combined extracts dried over anhydrous $MgSO_4$. After filtration, the ethereal solution was evaporated to dryness and the residue recrystallized from 1 l of petroleum ether 60–80. Colourless crystals (m.p. 69–70°), yield 82%.

NMR-spectrum ($DMSO-d_6$): δ CH_3 2.58(s), OCH_3 3.95(s), H_2 7.18(dd), H_4 7.25(dd) and H_5 8.19(dd).

2. *7-Hydroxy-3-methyl-2,1-benzisoxazole*

In the dark, 2.1 g (0.0116 Mole) of 3'-hydroxy-2'-nitroacetophenone[3] was added with stirring to a flask containing a solution of 13.2 g (0.058 Mole) of $SnCl_2.2H_2O$ in 18 ml of 12.4 *N*-HCl. The temperature was kept between 15 and 18°. After 30 minutes the flask was cooled to 4° and subsequently the suspension was carefully diluted with 18 ml of ice water. After coagulation, a yellowish white precipitate separated. After filtration on a glass filter G-4, the amorphous material was dried under reduced pressure over KOH.
The crude 2,1-benzisoxazole was suspended in a mixture of 15 ml of pyridine and 100 ml of chloroform, stirred for one hour at 20° and filtered. The filtrate was evaporated to dryness (the last traces of pyridine were removed by using an oil pump) and the residue – without further purification – was used for the synthesis of 7-methoxy-3-methyl-2,1-benzisoxazole (**7**).

3. *5-Methoxy-3-methyl-2,1-benzisoxazole*

As described under (2), 3.77 g 3'-methoxy-6'-nitroacetophenone (0.02 Mole) was added to a solution of 22 g (0.1 Mole) of $SnCl_2.2H_2O$ in 30 ml 12.4 *N*-HCl. After diluting the reaction mixture with 50 ml of ice water, the coagulated precipitate was filtered off and dried.
The crude material was stirred in a mixture of 15 ml of pyridine and 100 ml of chloroform, the suspension filtered and the filtrate evaporated to dryness. The dark coloured product was recrystallized from 100 ml petroleum ether 60–80.
Yellow crystals (m.p. 86°), yield 60%.

NMR-spectrum (CD_3COCD_3): δ CH_3 2.68(s), OCH_3 3.80(s), H_4 6.72(dd), H_6 6.96(dd) and (H_7) 7.42(dd).

4. *7-Methoxy-3-methyl-2,1-benzisoxazole*

2.27 g (0.015 Mole) of the crude 7-hydroxy-3-methyl-2,1-benzisoxazole was refluxed for 18 hours in a mixture of 75 ml of methanol, 1.91 g (0.007 Mole) of $Na_2CO_3.10H_2O$ and 15 g (0.105 Mole) of methyl iodide.
After evaporation of the solvent and the excess of methyl iodide, the yellow residue was heated with 150 ml of petroleum ether 60–80° and filtered. A colourless oil was quickly separated from the filtrate and solidified upon cooling to 0°. This material was recrystallized from hexane. The yield of colourless crystals, having a characteristic lysol odour (m.p. 55–56°), was 60%.

NMR-spectrum ($CDCl_3$): δ CH_3 2.70(s), OCH_3 3.96(s), H_4, H_5 and H_6 in ABM-type multiplet.

5. *3-(Bromomethyl)-5-methoxy-2,1-benzisoxazole*

A solution of 8.15 g (0.05 Mole) of **6** in 375 ml of dry carbon tetrachloride was refluxed for four hours with 8.9 g (0.05 Mole) of NBS (recrystallized from water and dried *in vacuo* over P_2O_5) and 0.1 g of DBP. After cooling to room temperature, the succinimide was filtered off and the filtrate evaporated to dryness. The residue was recrystallized from petroleum ether 60–80. The almost colourless crystals (m.p. 149° under sublimation) had a very strong lachrymatory effect. Yield 50%.

NMR-spectrum ($CDCl_3$): δ OCH_3 3.83(s), CH_2 4.85(s), H_4 6.67(dd), H_6 7.02(dd) and H_7 7.50(dd).

6. *3-(Bromomethyl)-7-methoxy-2,1-benzisoxazole*

As described under (5), 3.26 g (0,02 Mole) of **7** was brominated with an equimolecular quantity of NBS and 0.1 g of DBP. After recrystallization of the residue from petroleum ether 60–80, bright yellow crystals (m.p. 103–104°) were isolated in a yield of 42%.

NMR-spectrum ($CDCl_3$): δ OCH_3 3.98(s), CH_2 5.19(s), H_4, H_5 and H_6 in ABM-type multiplet.

7. *3-(Aminomethyl)-5-methoxy-2,1-benzisoxazole hydrochloride*

A solution of 4.84 g (0.02 Mole) of bromomethyl compound **8** in 100 ml of chloroform was added to a solution of 3.08 g (0.022 Mole) of hexamethylenetetramine in 100 ml chloroform. The mixture was heated on a water bath for 10 minutes, cooled, and stored for 24 hours at 0°.
The colourless complex which separated, was filtered off, carefully washed with chloroform, and dried. The conversion was quantitative. 7.62 g of the isolated complex were suspended in 300 ml of 96% ethanol. While stirring, 30 ml of 12.4 *N*-HCl were added dropwise and the reaction mixture heated to 40° until the material was dissolved. The diethyl acetal – formed as a byproduct – was evaporated under a vacuum, and the syrupy residue stored for 24 hours at 0°.
After this period, an almost colourless precipitate could be isolated, which was recrystallized from 99.6% ethanol. Feather-shaped crystals (m.p. 181° under decomposition) were obtained in 86% yield.

NMR-spectrum (D_2O): δ OCH_3 3.92(s), CH_2 4.81(s), NH_2 4.90(s), H_4 6.85(dd), H_6 7.09(dd) and H_7 7.50(dd).

8. *3-(Aminomethyl)-7-methoxy-2,1-benzisoxazole hydrochloride*

As described above, complexation of **9** was carried out in chloroform. 3.82 g of the complex were decomposed at room temperature in a solution of 150 ml of 96% ethanol and 30 ml 12.4 *N*-HCl.
Without evaporating the diethyl acetal, the solution was stored for 24 hours at 0°, after which the crude hydrochloride was filtered off. Recrystallization of this product from 99.6% ethanol resulted in the formation of fibrous crystals (m.p. 187° under decomposition) yield 67%.

NMR-spectrum (D_2O): δ OCH_3 4.00(s), NH_2 4.72(s), CH_2 5.06(s), H_4, H_5 and H_6 in ABM-type multiplet.

9. *5-Methoxy-3-[(trimethylammonio)methyl]-2,1-benzisoxazole iodide*

A solution of 2.42 g (0.01 Mole) (excess) of **8** in 300 ml of 99.6% ethanol was cooled to −20°. While stirring, 75 ml of dimethylamine were added, and the reaction mixture turned into a bright yellow solution. After storing for one hour at reaction temperature, the ethanol and excess dimethylamine were evaporated *in vacuo*, and the residue was exhaustedly extracted with dry ether.
An excess of methyl iodide was added to the combined extracts, and the reaction mixture refrigerated for 24 hours. After this period, the precipitate was filtered off and recrystallized from water. Brilliant colourless crystals (m.p. 228° under decomposition) were obtained in a yield of 58%.

NMR-spectrum (D_2O): δ $N(CH_3)_3$ 3.30(s), OCH_3 3.95(s), CH_2 5.15(s), H_4 6.95(dd), H_6 7.25(dd) and H_7 7.72(dd).

10. *7-Methoxy-3-[(trimethylammonio)methyl]-2,1-benzisoxazole iodide*

Starting from the bromomethyl compound **9**, this synthesis was carried out in exactly the same way as described under (9). After recrystallization of the quaternary salt from 96% ethanol, yellowish crystals (m.p. 208–211° under decomposition) were obtained in a yield of 63%.

NMR-spectrum (D_2O): δ $N(CH_3)_3$ 3.28(s), OCH_3 3.97(s), CH_2 5.42(s), H_4, H_5 and H_6 in ABM-type multiplet.

11. *2'-Methoxy-6'-nitroacetophenone*

1.9 g (0.01 Mole) of 2-methoxy-6-nitrobenzoic acid[8] were added with continuous stirring to a solution of 400 mg (0.01 Mole) of NaOH in 15 ml of water. The solvent was completely removed *in vacuo*, and the salt dried over KOH. This product, isolated in quantitative yield, was refluxed for one hour with 10 ml of thionyl chloride, after which the excess of thionyl chloride was evaporated *in vacuo*, the last traces being removed by treatment with benzene.
Due to the great instability of the acid chloride, the product was immediately suspended in 100 ml dry ether. In the meantime, the preparation of the organomagnesium reagent (Scheme 3) was started by adding 2 ml of 99.6% ethanol and five drops of carbon tetrachloride to 1.32 g of magnesium turnings. The reaction was initiated by heating the mixture at 40°; once started, 30 ml of dry ether were added, followed by a solution of 9.32 g of diethyl malonate in 5 ml of 99,6% ethanol and 5 ml of dry ether.
After heating the reaction mixture at 100° for three hours, the ethereal suspension of the acid chloride was added dropwise and very carefully to the boiling mixture, the reaction being completed by refluxing for a further hour. Stirring was no longer possible as a very viscous mass formed rapidly.
The reaction mixture was then cooled to 0° and hydrolyzed by addition of a mixture of 10 ml of concentrated H_2SO_4 and 80 ml of water. The ethereal solution was separated from the aqueous layer, the latter extracted several times with ether, and the combined extracts dried over anhydrous $MgSO_4$. After filtration and removal of the solvent from the filtrate, the residue was heated with a mixture of 32 ml of glacial acetic acid, 4 ml of concentrated H_2SO_4, and 24 ml of water. The decarboxylated product, formed after refluxing for four hours, was now treated with a 20% of NaOH solution until the pH of the reaction mixture had become 8–9. A dark brown precipitate was filtered off, carefully washed with ice water and dried *in vacuo* over KOH. After recrystallization of this product from 1500 ml petroleum ether 60–80, big yellow crystals of 2'-methoxy-6'-nitroacetophenone (m.p. 90°) were obtained in 75% yield.

NMR-spectrum ($CDCl_3$): δ CH_3 2.58(s), OCH_3 3.88(s), H_3 7.30(dd), H_4 7.55(dd) and H_5 7.79(dd).

12. *4-Methoxy-3-methyl-2,1-benzisoxazole*

As already described under (2) and (3), 5.6 g (0.028 Mole) of **16** was added to a solution of 32 g (0.14 Mole) of $SnCl_2.2H_2O$ in 35 ml of 12.4 *N*-HCl. The reaction mixture was diluted with 35 ml of ice water, stirred for another 30 minutes in the dark, after which the coagulated precipitate was filtered off and dried.
Decomplexation of the crude 2,1-benzisoxazole was carried out under the usual conditions. After recrystallization of the pyridine-free residue from petroleum ether 60–80, colourless needles (m.p. 82°) were isolated in 68% yield.

NMR-spectrum (CD_3COCD_3): δ CH_3 2.84(s), OCH_3 3.94(s), H_5 6.22 (dd), H_6 7.00(dd) and H_7 7.28(dd).

13. *7-Bromo-4-methoxy-3-methyl-2,1-benzisoxazole*

To a solution of 864 mg (0,05 Mole) of **17** in 60 ml of carbon tetrachloride an equimolecular quantity of NBS was added, and the reaction mixture refluxed for 24 hours. After cooling, filtration and evaporation of the solvent, the residue was recrystallized from petroleum ether 60–80. Beige coloured, fibrous crystals (m.p. 100°) were obtained in a yield of 46%.
Note: when a trace of DBP was added to the reaction mixture the same product was isolated, only in a lower yield (40%).

NMR-spectrum ($CDCl_3$): δ CH_3 2.87(s), OCH_3 3.96(s), H_5 6.06(d) and H_6 7.42(d).

14. *7-Bromo-3-(bromomethyl)-4-methoxy-2,1-benzisoxazole*

The reaction was carried out as already described under (13), only a double molecular quantity of NBS and 50 mg of DBP were added to the solution of **17** in carbon tetrachloride. After recrystallization from hexane, a yellow crystalline product (m.p. 146°) was obtained in a yield of 52%.

NMR-spectrum ($CDCl_3$): δ OCH_3 4.05(s), CH_2 5.08(s), H_5 6.25(d) and H_6 7.57(d).

15. *3-(Aminomethyl)-7-bromo-4-methoxy-2,1-benzisoxazole hydrochloride*

Complexation of **19** with hexamethylenetetramine was similarly carried out as described earlier under (7). The bright yellow coloured complex was isolated in quantitative yield.
2.30 g of this complex, suspended in 35 ml of 96% ethanol, was treated with 6 ml of 12.4 *N*-HCl, and the resulting solution stored for 24 hours in an ice box. The precipitate was filtered off and recrystallized from 96% ethanol. Colourless crystals (m.p. 199°), yield 70%.

NMR-spectrum (D_2O): δ OCH_3 3.96(s), NH_2 4.68(s), CH_2 4.82(s), H_5 6.20(d) and H_6 7.41(d).

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