freshly purified by preparative GLC), were dissolved in 1 ml of dry DMF at 0°C under nitrogen. Cyclopropyl methyl sulfide **2a** and 1,1-bis(methylthio)cyclopropane **3a** were formed at about the same rate ($t_{\frac{1}{2}} \approx 2$ h) in the absence of nitroxide. After the reaction was complete, the mixture contained 92% of **2a** and 8% of **3a** together with 40% (*i.e.* unreacted) di-*tert*-butyl nitroxide.

Reaction of 1-chloro-2,2-dimethylcyclopropyl methyl sulfide **9b** *with phenylhydroxylamine*

Phenylhydroxylamine[35] (1.5 mmol), potassium hydroxide (1 mmol) and 1-chloro-2,2-dimethylcyclopropyl methyl sulfide **9b** (0.5 mmol) were dissolved in 1 ml of 90% *tert*-butanol under nitrogen at 20°C. After the chloride had disappeared, its hydrolysis and butanolysis products were present, according to GLC, however the sulfide **2b** was not detected. Azobenzene was also formed but this was not due to the presence of **9b**, as was shown by a blank experiment. Similar results were obtained using methanol or DMF as solvent or with hydroquinone instead of phenylhydroxylamine.

Reaction of 2,2-dimethylcyclopropyl methyl sulfide **2b** *with base*

2,2-Dimethylcyclopropyl methyl sulfide **2b** (0.2 mmol) was dissolved in 0.6 ml CD_3ONa (1 mol/l)/CD_3OD. After 28 days at 100°C, no measurable decrease of the NMR integral at δ 1.7 was observed.

Acknowledgement

We are much indebted to Mr. *L. J. de Koning* for skilful assistance with the kinetic experiments and their interpretation.

An approach to the synthesis of [2]benzopyrano[3,4-*c*]pyrroles; alternative dopaminergic molecules

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Abstract. Benzyloxy-substituted [2]benzopyrano[3,4-*c*]pyrroles have been prepared by thermolysis of suitably substituted benzocyclobutenes, via an intramolecular Diels–Alder reaction of the quinodimethane intermediate with an aldehyde function.
Upon thermolysis of 3,4-bis(benzyloxy)-7-[[(methoxycarbonyl)(2-oxoethyl)amino]methyl]bicyclo-[4.2.0]octa-1,3,5-triene (**12**), in refluxing bromobenzene, *trans*-7,8-bis(benzyloxy)-2-(methoxycarbonyl)-1,2,3,3a,5,9b-hexahydro[2]benzopyrano[3,4-*c*]pyrrole (**13**) was isolated. Upon thermolysis of *N*-alkyl-*N*-(2-oxoethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamides (such as **19**, **29a-d** and **33a,b**) in bromobenzene, *trans/cis* mixtures of *N*-substituted-3,3a,5,9b,tetrahydro-2*H*-[2]-benzopyrano-[3,4-*c*]pyrrol-1-ones were obtained in yields of 70 to 85%. In this way, **20**, **21**, **30a-d**, **31a-d**, **34a,b** and **35a,b** have been obtained. As starting materials, suitably substituted benzocyclobutenecarboxylic acids were used (**7**, **46** and **54**). These compounds were converted into the acid chlorides and condensed with substituted 2-(hydroxyethyl)amines to afford the *N*-alkyl-*N*-(2--hydroxyethyl)benzobicyclo[4.2.0]octa-1,3,5-triene-7-carboxamides **27**, **28a-d** and **32a,b**, which were then oxidized to the required *N*-(2-oxoethyl) derivatives by means of DMSO–oxalyl chloride complex.
Reduction of the tetrahydro-2*H*-[2]benzopyrano[3,4-*c*]pyrrol-1-ones **20**, **21**, **30b**, **30c** and **35b** with borane–dimethyl sulfide complex or with $LiAlH_4$–$AlCl_3$ complex gave the hexahydro[2]benzopyrano[3,4-*c*]pyrroles **22**, **23**, **36**, **37** and **38**. Subsequently, these compounds were converted into catecholamines **24**, **25**, **39**, **40** and **41** by catalytic reduction.

Introduction

There is much evidence to show that the dopaminergic system (which plays a crucial role in locomotor behaviour, blood pressure regulation, cardiac and renal function and prolactin release) is made up of several dopamine receptor subclasses[1a-j,2].
The availability of a number of chemical structures, which have been shown to possess dopamine agonistic activity (such as 2-aminotetralins[3a-d], benzo[*h*]isoquino-

[1] For those interested in the subject of neurotransmitter classification the following references might be helpful:
[a] *S. Berthelsen* and *W. Pettinger*, Life Sci. **21**, 595 (1977);
[b] *R. P. Ahlquist*, Am. J. Physiol. **153**, 186 (1948);
[c] *A. M. Lands, A. Arnold* and *J. P. McArliff*, Nature **214**, 597 (1967);
[d] *S. Z. Langer*, Br. J. Pharm. **60**, 481 (1977);
[e] *K. P. Minneman* and *R. P. Molinoff*, Biochem. Pharmacol. **29**, 1317 (1980);
[f] *J. W. Black, W. A. M. Duncan, C. J. Durant, C. R. Ganellin* and *E. M. Parsons*, Nature **236**, 385 (1972);
[g] *S. J. Peroutka, R. M. Lebovitz* and *S. H. Snyder*, Science **212**, 827 (1981);
[h] *W. R. Martin, C. G. Eades, H. F. Fraser* and *A. Winkler*, J. Pharmacol. Exp. Ther. **197**, 517 (1976);
[i] *A. R. Cools* and *J. M. v. Rossum*, Life Sci. **27**, 1237 (1980);
[j] *J. W. Kebabian* and *D. B. Calne*, Nature **277**, 93 (1979).

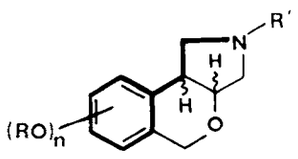
[2] *S. J. Enna* and *H. I. Yamamura*, "Neurotransmitter Receptors", part I/II, Chapman and Hall, Ed., New York, 1980.

[3a] *A. S. Horn, D. Dijkstra, M. G. P. Feenstra, C. J. Grol, H. Rollema* and *B. H. C. Westerink*, Eur. J. Med. Chem. **15**, 387 (1980);
[b] *J. D. McDermed, G. M. McKenzie* and *H. S. Freeman*, J. Med. Chem. **19**, 547 (1976);
[c] *J. G. Cannon, J. P. O'Donnell, T. Lee, C. R. Hoppin, J. P. Long, M. I. Chan, B. Costall* and *R. J. Naylor*, J. Med. Chem. **18**, 1212 (1975);
[d] *B. Costall, R. J. Naylor, J. G. Cannon* and *T. Lee*, Eur. J. Pharmacol. **41**, 307 (1977).

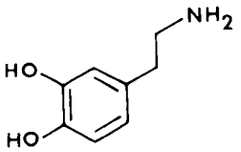
lines[4], benzo[*f*]quinolines[5a,b], pyrroloquinolines[6], benzazepines[7] and perhydroindolamines[6]) or antagonistic activity[8a,b], has provided insight into the structural requirements for interactions with the binding site of each of the dopamine receptors[9].

Nevertheless, the molecular features of the receptors, which are membrane bound proteins with a certain degree of flexibility at the binding sites, have remained largely unknown. Therefore, the development of selective dopaminergic drugs is still subject to a considerable amount of speculation.

On searching for new compounds with specific dopaminergic properties we have focused our attention on the [2]benzopyrano[3,4-*c*]pyrroles. This class of compounds, which embodies the dopamine skeleton in a rigid fashion in the molecular framework, is still largely unexplored in the chemical literature. We would therefore like to present here some details of a synthetic approach to these particular substances.



[2]Benzopyrano[3,4-*c*]pyrrole



Dopamine

Chemistry

On examination of the literature we found only one report which might provide us with an entry into the desired substituted benzopyranopyrroles[10]. Thermolysis of the benzocyclobutene derivative **1** in boiling bromobenzene had been reported to give, in a rather low yield, mixture of *trans* and *cis* amides **2a** and **2b** (Fig. 1). The low yield of such an intramolecular Diels–Alder reaction is not surprising since carbonyl groups are well known to be extremely bad dienophiles[11a,b].

Nevertheless, initially this type of reaction seemed to be convenient as a route to the required samples of hydroxylated benzopyranopyrroles, provided that suitably substituted benzocyclobutenes were readily accessible and that amide reduction could be easily accomplished in this ring system. In order to avoid unnecessary complications in this step as well as to have rapidly interchangeable functionality at nitrogen in the ultimate stages of the synthesis, it seemed to be more attractive to proceed via the urethane derivative **12** which proved to be readily obtainable (see Scheme 1) starting from 3-(2-bromo-4,5-dimethoxyphenyl)propionitrile **3**[12].

Treatment of **3** with BBr_3[13] in methylene chloride gave the catechol **4**, which was dibenzylated with benzyl bromide + K_2CO_3 in dimethylformamide to provide **5**. Ring closure of **5** into the required benzocyclobutene **6** was rapidly effected using $NaNH_2$ in liq. ammonia[14]. Basic hydrolysis of **6** with KOH in refluxing aq. ethanol gave the carboxylic acid **7**, which, upon reduction with $LiAlH_4$ in tetrahydrofuran, provided **8** as an oil. Treatment of **8** with tosyl chloride in pyridine led to the tosylate **9**, which, on heating in excess (2,2-dimethoxyethyl)amine, provided **10**.

[4] *J. G. Cannon, T. Lee, F. L. Hsu, J. P. Long* and *J. R. Flynn*, J. Med. Chem. **23**, 502 (1980).

[5a] *J. G. Cannon, G. Hatheway, J. P. Long* and *F. M. Sharabi*, J. Med. Chem. **19**, 987 (1976);

[b] *J. G. Cannon, C. Suarez-Gutierrez, T. Lee, J. P. Long, B. Costall, D. H. Fortune* and *R. J. Naylor*, J. Med. Chem. **22**, 341 (1979).

[6] *N. J. Bach, C. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorfman, J. W. Paschal, J. A. Clemens* and *E. B. Smalstig*, J. Med. Chem. **23**, 481 (1980).

[7] *J. Weinstock, J. Wilson, D. L. Ladd, C. K. Brush, F. R. Pfeiffer, G. J. Kuo, K. G. Holden, N. C. S. Jim, R. A. Hahn, J. R. Darwell, A. J. Tobia, P. E. Setler, H. M. Saran* and *P. T. Ridley*, J. Med. Chem. **23**, 973 (1980).

[8a] *N. Kumar* and *P. C. Jain*, "Agents acting on central dopamine receptors" in "Forschritte der Arzneimittel Forschung", vol. 21, Ed. Birkhäuser Verlag, Basel, 1977, pg 409 ff.;

[b] *C. Kaiser* and *P. E. Setler*, "Antipsychotic Agents" in "Burger's Medicinal Chemistry", fourth edition, part III, Ed. Wiley Interscience, New York, 1981, pg 859 ff.

[9] *G. L. Olson, Ho-Chuen Cheung, K. D. Morgan, J. F. Blount, L. Todaro, L. Berger, A. B. Davidson* and *E. Boff*, J. Med. Chem. **24**, 102 (1981) and references cited therein.

[10] *W. Oppolzer*, Angew. Chem. **84**, 1108 (1972).

[11a] *M. F. Ansell* and *A. A. Charalambides*, Chem. Commun. **739** (1972);

[b] *J. Hamer* and *J. A. Turner* in "1,4-Cycloaddition Reactions", ed. *J. Hamer*, Academic Press, New York, 1967, pg 205.

[12] *T. Kametani, K. Ogasawara* and *T. Takahashi*, Tetrahedron **29**, 73 (1973).

[13] *J. F. W. McOmie* and *D. E. West*, Org. Synth. **49**, 50 (1969).

[14] *J. A. Skorez* and *F. E. Kaminski*. Org. Synth., Coll. Vol. V. Wiley, New York, N.Y. (1973), pg 263.

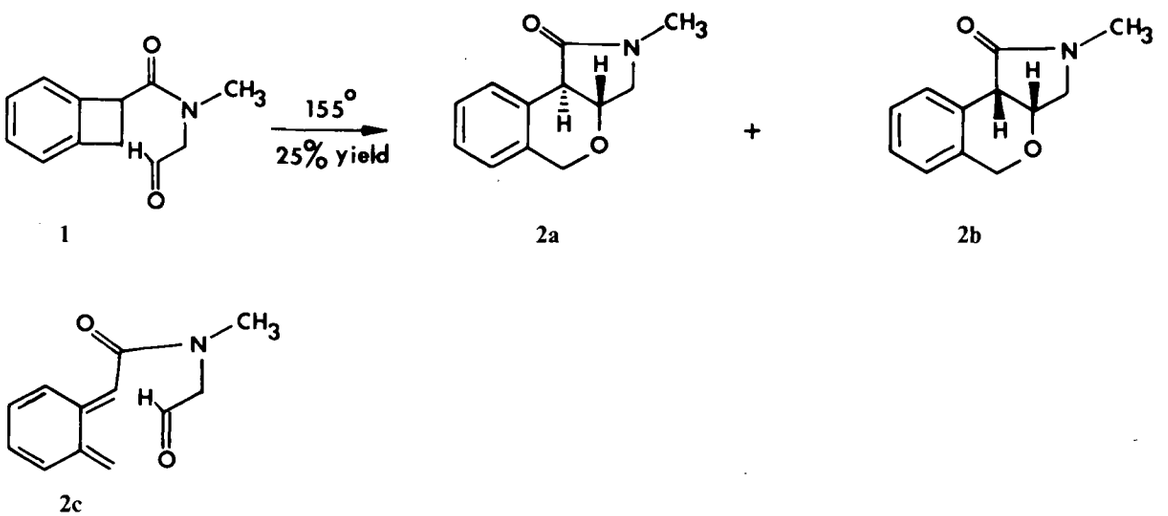
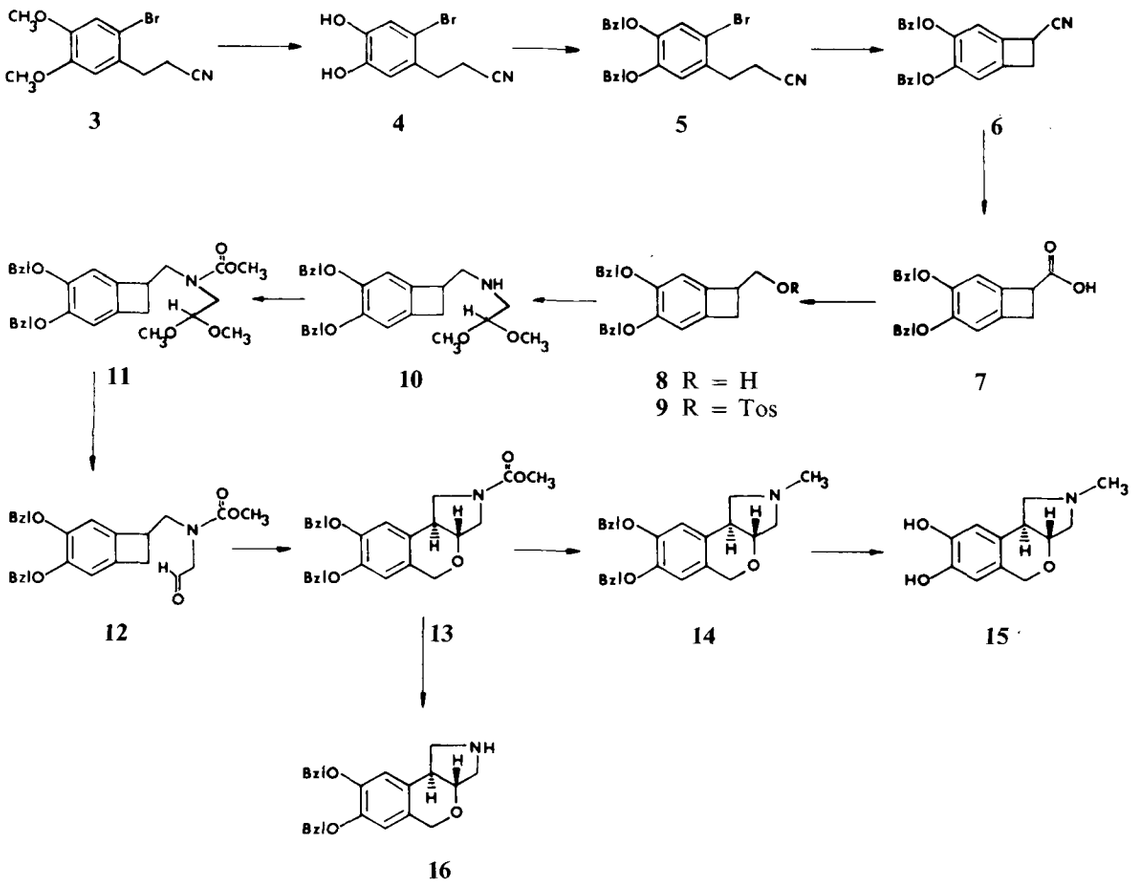


Fig. 1



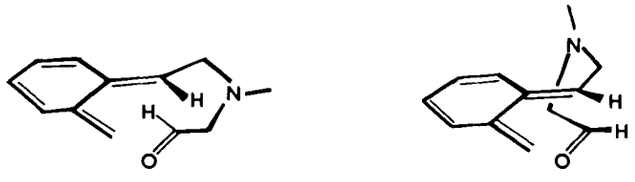
Scheme 1

The formation of the urethane **11** was effected by treatment of **10** with methyl chloroformate in the presence of several equivalents of triethylamine in ether. The liberation of the aldehyde functionality from the dimethyl acetal could be achieved by stirring **11** with $HClO_4$ in aq. dioxane to give **12** as the required strategic intermediate.

Thermolysis of **12**, by refluxing for 16 h in bromobenzene, while monitoring the reaction by TLC, provided essentially one product, **13** (together with polar materials) which could be isolated in 34% yield after chromatography.

The *trans* ring junction in **13** could be unambiguously assigned after reduction with $LiAlH_4$ to **14**. In the 90 Mhz NMR, **14** displayed a low-field double triplet (J 9 and 9.5 Hz) due to the tertiary hydrogen atom at the ring junction adjacent to the oxygen atom. The hydrogenolysis of **14** with H_2, in the presence of 10% palladium on charcoal in acetic acid, gave the catechol amine **15** as its acetate salt. The exclusive formation of the *trans*-fused ring system **13** is somewhat surprising in the light of the thermolysis of **1**.

Formally, one may assume that the thermolysis of the benzocyclobutene **12** prefers an "*exo*" transition state and is kinetically controlled[15]. This selectivity is however difficult to predict from molecular models as long as the exact transition state and the nature of the interactions, which play a role here, are not fully determined (Fig. 2).



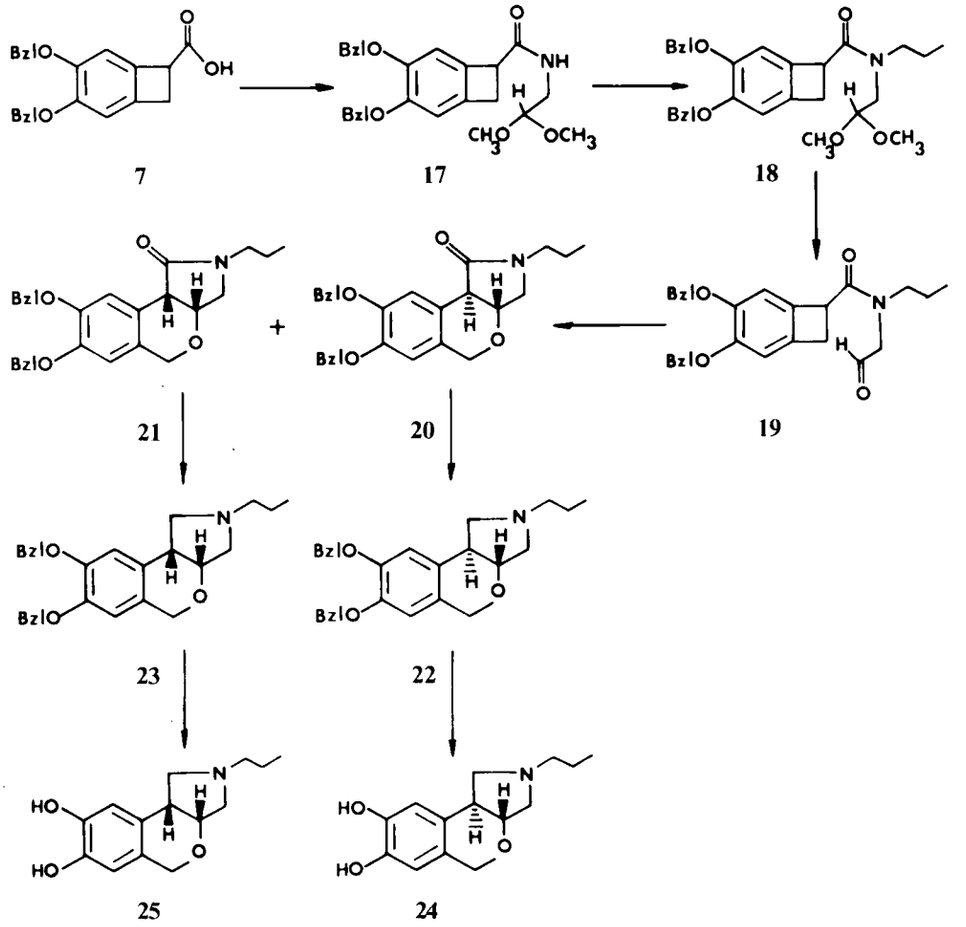
exo/trans *endo/cis*

Fig. 2

Attempts to convert **13** into the free NH compound **16** required rather harsh basic conditions and did not provide us with a pure sample of **16**. Since it was our aim to have access to a wide variety of benzopyranopyrroles, having both *trans* and *cis* ring junctions, we were only partially satisfied with this result. We therefore turned our attention once again to the cyclization (conversion of **1** into **2a,b**; see Fig. 1 and Scheme 2) initially mentioned *(vide supra)*.

Conversion of the carboxylic acid **7** into the acid chloride with $SOCl_2$ (Scheme 2), followed by condensation with (2,2-dimethoxyethyl)amine in the presence of several equivalents of triethylamine in methylene chloride, gave the amide **17**. The alkylation of **17** with propyl iodide in the presence of NaH in dimethylformamide gave, in a rather low yield, the derivative **18** (54%). A considerable amount of starting material **17** was recovered, presumably due to competitive elimination during the alkylation reaction. The next step, the acidic hydrolysis of the acetal moiety, proved to be even worse. Several attempts to deprotect the aldehyde in aqueous media in the presence of mineral acid provided us with only small amounts of the required aldehyde **19** and extensive amounts of the carboxylic acid **7** (!). Nevertheless, we succeeded in obtaining **19** in 22% yield by carrying out the hydrolysis in aq. dioxane in the presence of perchloric acid and by stopping the reaction at a suitable moment (TLC) followed by chromatography of the reaction mixture. The extensive formation of the carboxylic acid **7** is due to the marked acid sensitivity of the amide bond in the aldehyde **19**; treatment of **19** with aq. dioxane + $HClO_4$ at room temperature gave **7** quantitatively within 1 h! On the other hand, the dipropylamide **26** proved to be stable under

[15] For a recent review see: *W. Oppolzer*, Synthesis 793 (1978).



Scheme 2

these conditions, even after 24 h. We therefore propose the following mechanism for this unusually facile amide-bond hydrolysis (see Scheme 3):

As a most gratifying result, the subsequent thermolysis of **19** in bromobenzene provided the desired cyclic amides **20** and **21** in 74% isolated yield (ratio **20**/**21** = 4.5). The two isomers may be easily separated by chromatography on silica gel, since their polarities differ considerably. The *trans* isomer **20** may be converted quantitatively into the *cis* isomer **21** by treatment for 10 min with a catalytic amount of DBN in toluene at 80° (Fig. 3).

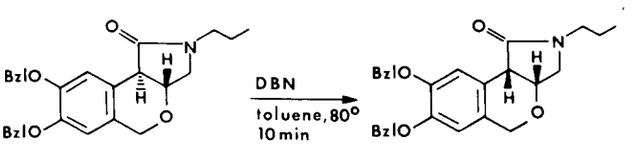
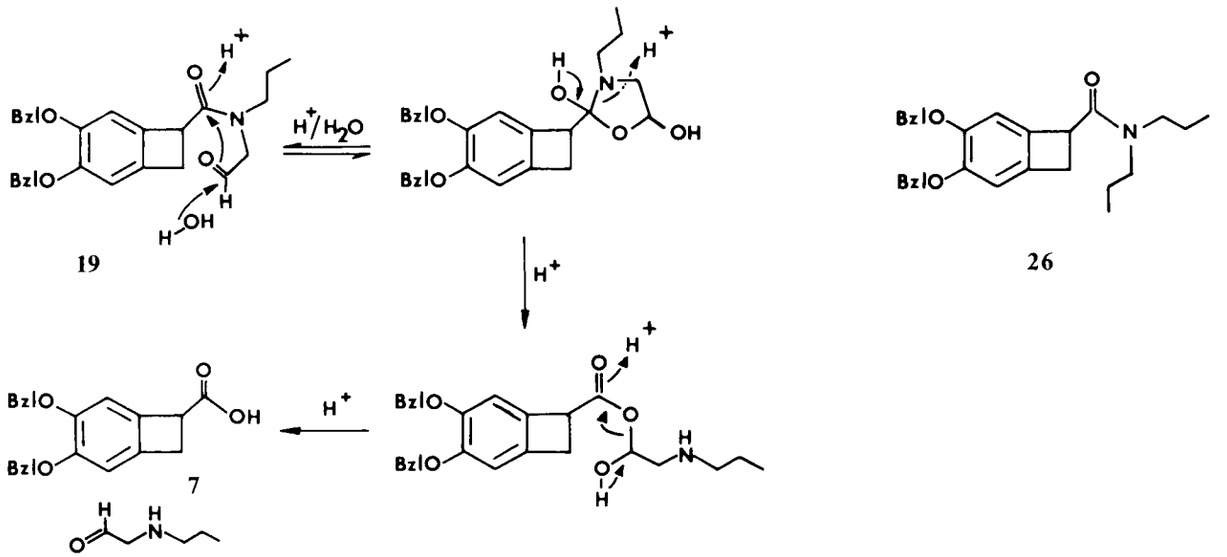
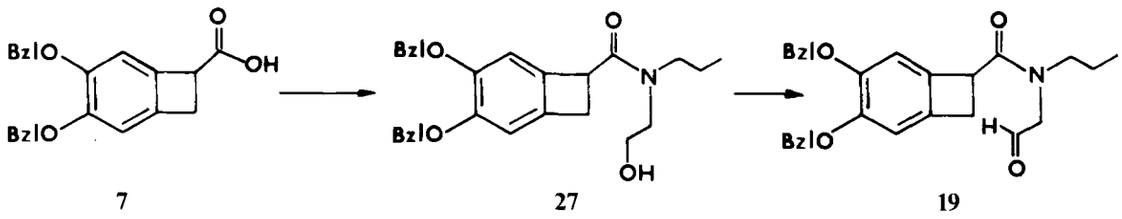


Fig. 3

The stereochemistry in the amides could be clearly determined using 90 Mhz NMR spectroscopy (see Figs. 4 and



Scheme 3



Scheme 4

5). A marked downfield shift of the aromatic hydrogen, close to the amide carbonyl (δ 7.80), was observed for the *trans* isomer, due to deshielding of the amide carbonyl group[16]. The CH_2 protons of the pyran ring (H5,6) were found at lower field (δ 4.94) for **20** than for **21** (δ 4.60). This marked effect was also always present in the other examples *(vide infra)*. In the *cis* isomer **21** the tertiary hydrogen (H2) adjacent to oxygen, has a marked down-field position (δ 4.40) and resonates as a triplet (*J* 5 Hz) due to two similar couplings with H1 and H3 and a coupling of ~ zero with H4. In the *trans* isomer on the other hand, the H2 proton resonates as a typical octet, due to three different couplings with H1, H3 and H4 (*J* 11 Hz, 9 Hz and 7 Hz).

Having found an efficient route to the required intermediate aldehyde, together with a high-yield cyclization reaction (**19** → **20** and **21**) we focused our attention on the subsequent amide reduction (see Scheme 2). In a first attempt to reduce **21** with $LiAlH_4$ in THF, a number of undefinable polar products were isolated. However, by treatment of **21** with BH_3 + dimethyl sulfide complex[19], the reduction could be readily accomplished giving the desired product, **23**, in 78% yield. In a similar way, the *trans* amide **20** was converted into **22** in 72% yield. Hydrogenation of **22** and **23**, as their hydrochloride salts, in aq. ethanol (10% Pd-C), gave the catechol amines **24**·HCl and **25**·HCl in essentially quantitative yield. The generality of the thermolysis of benzocyclobutenes, with intramolecular capture of the quinodimethane intermediate by an aldehyde moiety, has been exemplified by the synthesis of a number of compounds in which the substituent on nitrogen has been varied (Scheme 5, **30a-d** and **31a-d**) or in which benzyloxy groups at alternative positions on the aromatic ring have been present (Scheme 5, **34a-b**, **35a-b**).

The observation that all these systems undergo, in rather unusually high yield, intramolecular Diels–Alder reactions, in which the carbonyl function acts as the dienophile, may be due to the creation of a highly reactive electron-rich diene by the strong electron-releasing benzyloxy groups.

In order to demonstrate the feasibility of this approach in the ultimate synthesis of rigid catechol amine systems, we have additionally converted a number of cyclic amides into their related catecholamine systems, as exemplified in Scheme 6 by the synthesis of **39–41**.

The methylene part of the spectrum of the *cis* isomer **21** could be completely analyzed (see spectrum; the resonance of the H1 proton is buried under the *N*-propyl resonance but is visible as two shoulders).

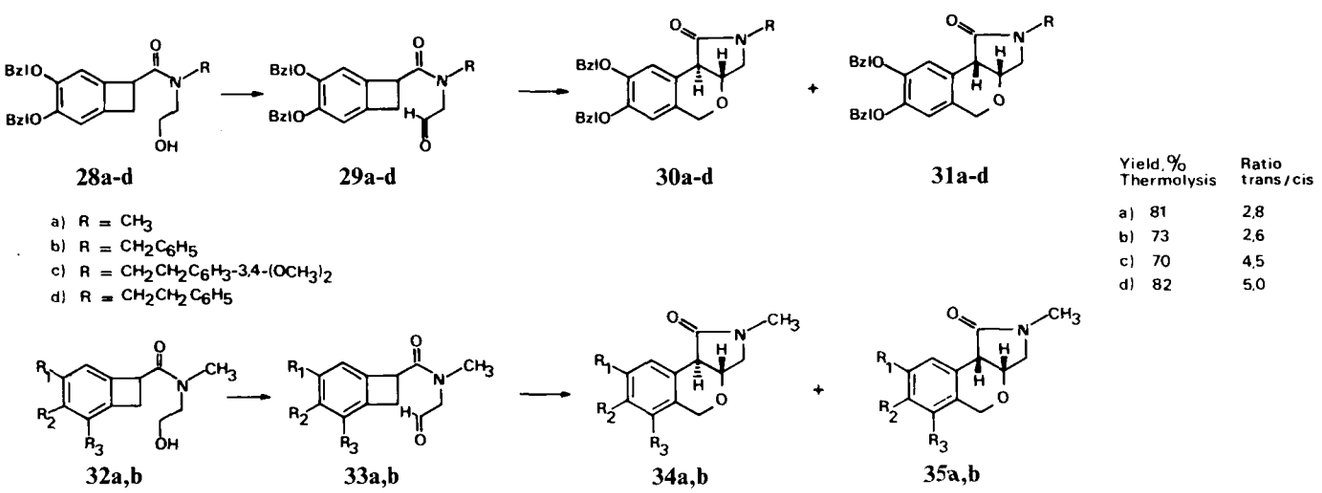
Encouraged by the high-yield cyclization reaction, which possibly provides an efficient entry into a wide variety of substituted *cis*- and *trans*-benzopyranopyrroles, we felt prompted to seek an alternative to the fairly unattractive route to the aldehyde intermediate **19**. Thus, in principle, **19** might be obtained by oxidation of an alcohol precursor.

[16] For the *cis* isomer, the shielding effect for the aromatic proton close to the carbonyl group is much less pronounced and this proton is generally buried under the aromatic protons of the benzyloxy groups (see also ref. 10).

[17] *D. F. Morrow, P. C. Johnson, H. Torabi, D. Williams, D. L. Wedding, J. W. Craig, R. F. Majewski, J. P. Braselton* and *D. C. Gallo*, J. Med. Chem. **16**, 736 (1973).

[18] *A. J. Mancuso, S. L. Huang* and *D. Swern*, J. Org. Chem. **43**, 2480 (1978).

[19] *H. C. Brown, S. Narashiman* and *Y. Moon Choi*, Synthesis 441 (1981).



Scheme 5

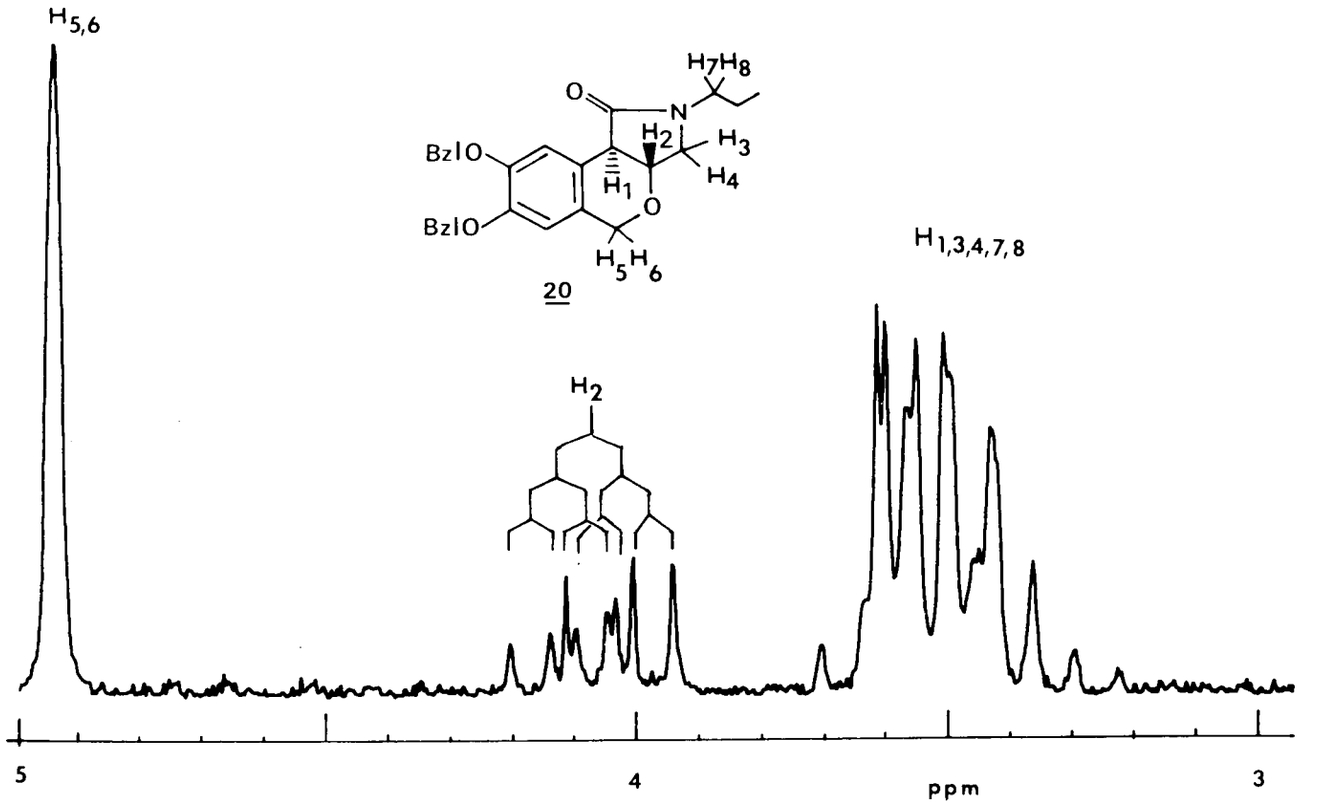


Fig. 4

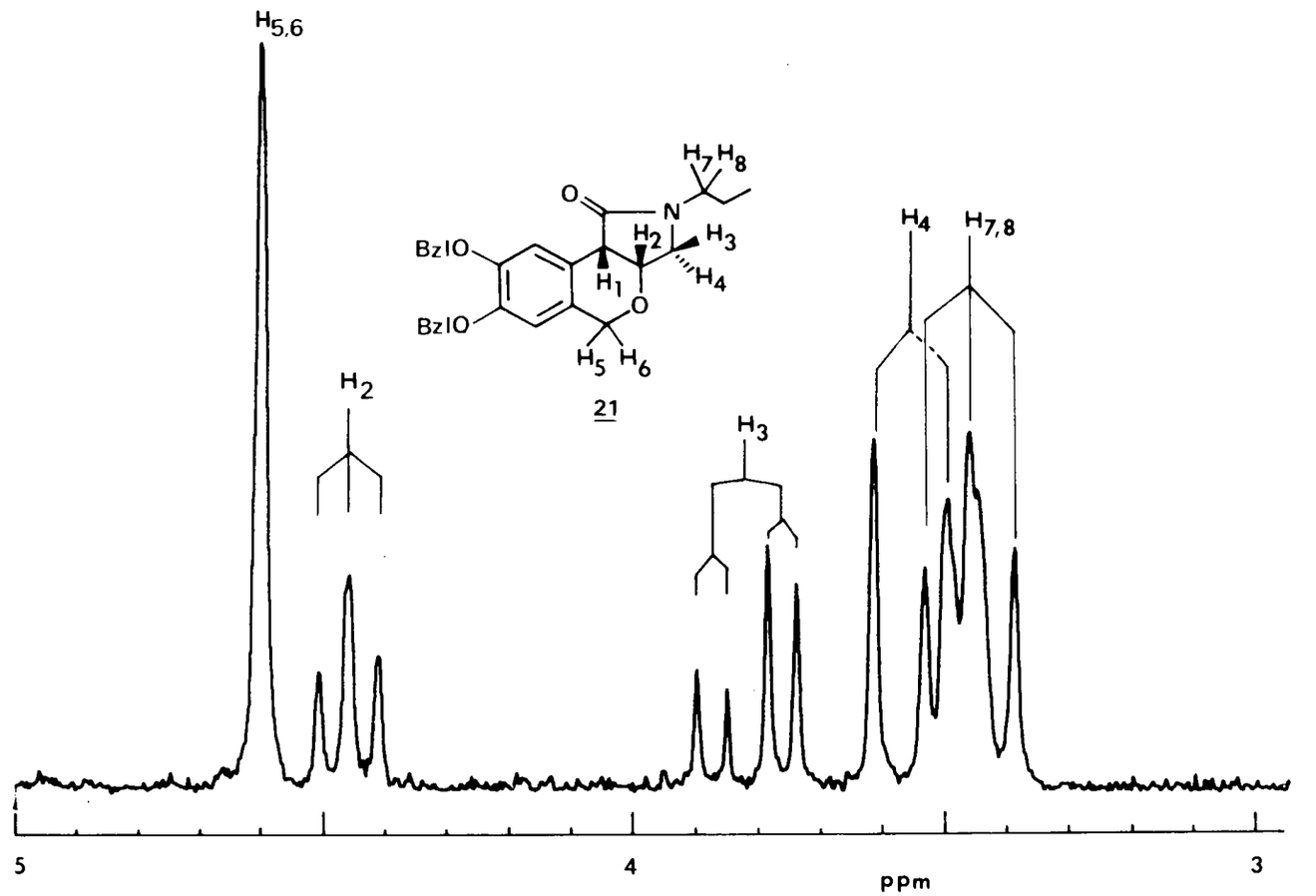


Fig. 5

The advantage of such an approach would be that one could obtain many derivatives in a convergent synthetic way, with the added bonus that β-amino alcohols are either cheap, commercially available materials or may be readily synthesized from alkylamines and ethyl (chloroformyl)-formate using simple chemical procedures[17]. Thus treatment of **7** with thionyl chloride, followed by reaction with 2-(propylamino)ethanol at $-50°$ in methylene chloride +

triethylamine, readily provided the required amide **27** (see Scheme 4). Oxidation was carried out efficiently with *Swern*'s reagent[18] (DMSO + oxalyl chloride) to provide the desired aldehyde **19** in 94% yield.

The reduction of the amide bond could be achieved with either a BH_3 + dimethyl sulfide complex (**30b** → **36** or **30c** → **37**) or with a $LiAlH_4$ + $AlCl_3$ complex[20] (**34b** → **38**). Final catalytic reduction of **36**, **37** and **38** provided the required catechols **39**, **40** and **41**. It should be noted that the *N*-benzylated products may serve for the ultimate construction of the free NH derivatives (*e.g.* **39**).

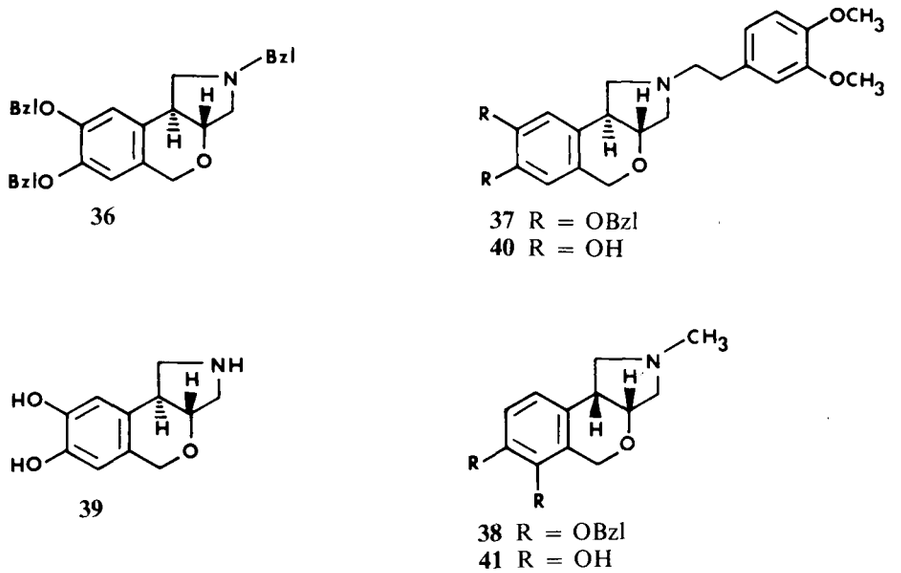
Starting materials (see Scheme 7)

The benzocyclobutene carboxylic acids **46** and **54**, which were required as additional starting materials, were easily available. Demethylation of 3-(2-bromo-4-methoxyphenyl)propionitrile (**42**)[21,22] gave **43**, which, upon ben-

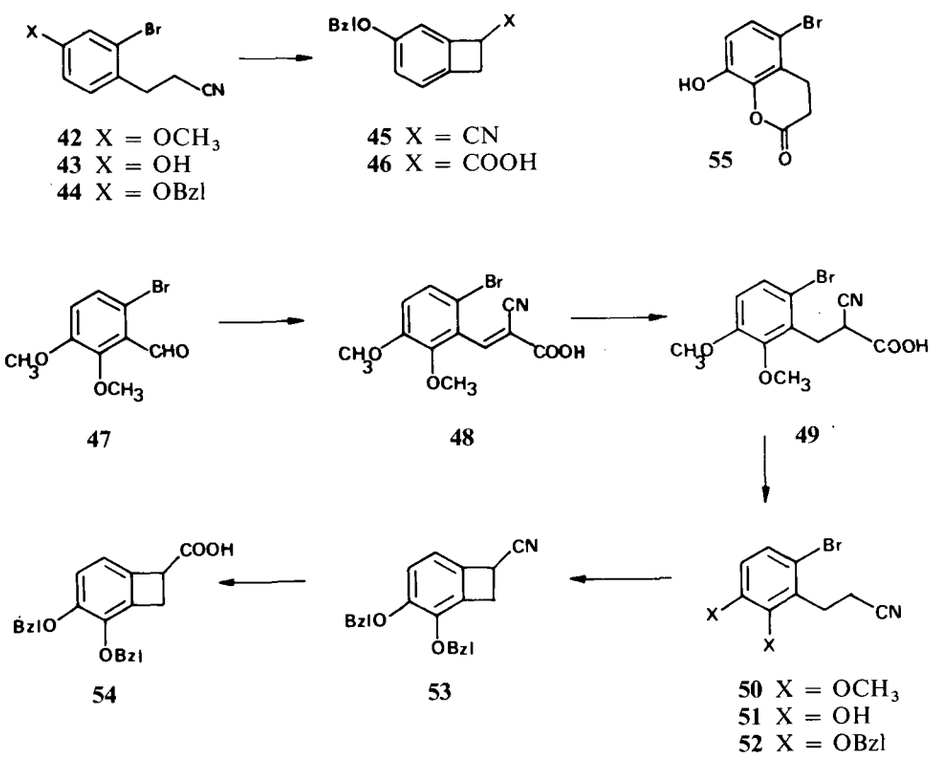
[20] *A. Hajos* in "Complex Hydrides", Elsevier Scientific Publishing Company, Amsterdam, 1979, pg 128 ff.

[21] *T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama* and *K. Fukumoto*, J. Am. Chem. Soc. **98**, 3378 (1976).

[22] *J. A. Skorcz* and *J. E. Robertson*, J. Med. Chem. **8**, 255 (1965).



Scheme 6



Scheme 7

zylation with benzyl bromide + K_2CO_3 in DMF, provided **44**. Subsequent ring closure was effected with $NaNH_2$ in liq. NH_3 (to give **45**), after which basic hydrolysis with KOH in aq. ethanol provided **46**.

The bis(benzyloxy)benzocyclobutene carboxylic acid **54** was synthesized from 2,3-dimethoxy-6-bromobenzaldehyde **47**[23]. Treatment of **47** with cyanoacetic acid in pyridine + benzene + NH_4OAc[24] led to the cinnamonitrile **48**, which was subsequently reduced ($NaBH_4$)[24] to the hydrocinnamonitrile **49**, followed by decarboxylation in refluxing dimethyl acetamide[25] to give **50**. The demethylation (BBr_3) of **50** gave **51**, accompanied by excessive amounts of the lactone **55**. On treatment of **51** with benzyl bromide + K_2CO_3, the bis(benzyloxy) compound **52** was obtained. Ring closure of **52** under standard conditions, followed by basic hydrolysis, provided the carboxylic acid **54**.

Experimental

General

Melting points were measured on a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker HX–90E spectrometer, using tetramethylsilane as internal standard, and were measured in $CDCl_3$ solutions, unless otherwise indicated; chemical shifts in ppm (ref. TMS), *J*s in Hz. Infrared spectra were obtained using a Perkin–Elmer 580 spectrometer. Organic solvents were generally dried over molecular sieves prior to use (Linde 4A). Dry THF and ether were obtained by distillation from $LiAlH_4$ prior to use. Silica gel and silica thin-layer plates were purchased from Merck (Darmstadt).

3-(2-Bromo-4,5-dihydroxyphenyl)propionitrile (**4**)

To a solution of 30 g (0.11 mol) of **3**[12] in 300 ml of methylene chloride, cooled to −60°, was added dropwise 25 ml (0.26 mol) of boron tribromide (Merck). The mixture was allowed to come to room temperature in *ca.* ½ h and stirred for an additional 3 h at ambient temperature. The reaction mixture was then poured into 300 ml of ice water and the organic layer separated. The aqueous phase was extracted once with methylene chloride. The combined organic phases were washed twice with water, dried and evaporated. The residue was triturated with ether to give 22.5 g of **4** (84%).

A sample was crystallized from toluene; m.p. 107–108°. Anal. calcd. $C_9H_8BrNO_2$: C, 44.62; H, 3.31; N, 5.78; found: C, 44.73; H, 3.31; N, 5.80. NMR ($CDCl_3$ + 20% CD_3OD): δ 2.60 (m, 2, CH_2), 2.95 (m, 2, CH_2), 6.75 (s, 1, arom. H), 7.00 (s, 1, arom. H).

3-[2-Bromo-4,5-bis(benzyloxy)phenyl]propionitrile (**5**)

To a solution of 24 g (0.1 mol) of **4** in 250 ml of dry DMF (mol sieves 4A) were added 240 g of finely powdered anh. K_2CO_3 (heated at 120° for 16 h under vacuum) and 36 g (26 ml) of benzyl bromide (0.21 mol). The mixture was efficiently stirred for 16 h. The reaction mixture was then diluted with 2 l of water and the product extracted twice with ether. The organic phase was washed three times with water, dried and evaporated. The residue was triturated with hexane to give 40.5 g (96%) of **5**; m.p. (ether) 78–80°. Anal. calcd. $C_{23}H_{20}BrNO_2$: C, 65.40; H, 4.74; N, 3.31; found: C, 65.28; H, 4.81; N, 3.43. NMR: δ 2.52 (m, 2, CH_2), 2.91 (m, 2, CH_2), 5.07 and 5.10 (s, 4, $C_6H_5CH_2$), 6.82 and 7.09 (s, 2, arom. H).

3,4-Bis(benzyloxy)bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (**6**)

A solution of $NaNH_2$ in liq. NH_3 was prepared from 7 g (0.3 at) of Na pieces in 500 ml of dry NH_3 (distilled from vessel containing excess Na), in the presence of a catalytic amount of $Fe(NO_3)_3$, at −33°. When the solution had turned grey, 20 g (0.047 mol) of powdered **5** was added. After stirring for an additional 1½ h, the excess of $NaNH_2$ was destroyed by the addition of 30 g of NH_4Cl. The ammonia was allowed to evaporate, while keeping the reaction mixture under a slow stream of nitrogen. 300 ml of water was then added and the product extracted with ethyl acetate. The residue, which was obtained after washing, drying and evaporation of the organic phase, was passed through a short silica gel column (toluene/ethyl acetate 95/5) to remove polar impurities. This provided 9.7 g (61%) of **6**; a sample was crystallized from ether/hexane; m.p. 69–71°. Anal. calcd. $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10; found: C, 80.90; H, 5.58; N, 4.06. NMR: δ 3.40 (m, 2, CH_2), 4.07 (m, 1, CH), 5.09 (s, 4, $C_6H_5CH_2$).

3,4-Bis(benzyloxy)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylic acid (**7**)

A suspension of 22 g (0.065 mol) of **6** in a solution of 40 g of KOH in 60 ml of water and 170 ml of ethanol was refluxed for 16 h. The mixture was then poured into 600 ml of water, acidified with 6 N HCl and extracted with ether; after washing, drying and evaporation, the residue was treated with diisopropyl ether to give 21 g (93%) of **7**; m.p. (toluene/hexane) 104–105°. NMR: δ 3.31 (d, 2, CH_2), 4.17 (t, 1, CH), 5.05 (s, 4, $C_6H_5CH_2O$). Anal. calcd. $C_{23}H_{20}O_4$: C, 76.65; H, 5.59; found: C, 76.59; H, 5.58.

3,4-Bis(benzyloxy)-7-(hydroxymethyl)bicyclo[4.2.0]octa-1,3,5-triene (**8**)

A solution of 9.5 g (0.026 mol) of the carboxylic acid **7** in 50 ml of THF was added dropwise with stirring to a suspension of 1.1 g (0.03 mol) of $LiAlH_4$ in 40 ml of THF. The mixture was subsequently refluxed for 1 h. Excess hydride was decomposed by successive addition of 1.1 ml of water, 1.1 ml of 15% aq. NaOH and 3.3 ml of water. After filtration of the precipitate, the filtrate was concentrated to provide 9.0 g (96%) of alcohol **8** as an essentially pure oil, which was used directly in the next step; R_f (toluene/ethanol ~9/1) 0.48. NMR: δ 2.75 and 3.15 (AB, 2, cyclobutene CH_2), 3.55 (m, 1, CH), 3.78 (d, 2, CH_2OH), 5.06 (s, 4, $C_6H_5CH_2$).

3,4-Bis(benzyloxy)-7-[(4-toluenesulfonyloxy)methyl]bicyclo-[4.2.0]octa-1,3,5-triene (**9**)

To a solution of 8.0 g (0.026 mol) of the alcohol **8** in 30 ml of pyridine was added 6.5 g (0.035 mol) of tosyl chloride. After stirring for 3 h at room temperature, the reaction was complete; 200 ml of water was then added and the product extracted with ether. The organic phase was washed twice with 100 ml of 2 N aq. HCl, twice with 10% aq. $NaHCO_3$ solution and once with water. After drying and concentrating, 12.5 g (96%) of essentially pure tosylate was obtained as an oil; single spot on TLC; R_f (toluene/ethyl acetate 95/5) 0.47. NMR: 2.40 (s, 3 CH_3), 3.64 (m, 1, cyclobutene CH), 4.19 (d, 1, CH_2OTos), 2.70 and 3.20 (AB, 2, cyclobutene CH_2), 5.06 and 5.08 (s, 4, $C_6H_5CH_2O$), 6.66 (s, 2, arom. H).

3,4-Bis(benzyloxy)-7-[[(2,2-dimethoxyethyl)amino]methyl]-bicyclo[4.2.0]octa-1,3,5-triene (**10**)

A solution of 12 g (0.024 mol) of **9** in 9 ml of (2,2-dimethoxyethyl)-amine (Aldrich) was heated for 16 h at 100–105°. The mixture was then diluted with 70 ml of water and the product extracted with ether. After washing, drying and evaporation, the crude product was chromatographed over silica gel (CH_2Cl_2/CH_3OH 97/3) to provide 8.5 g (82%) of **9** as a colourless oil; R_f (CH_2Cl_2/CH_3OH 10/1) 0.55. NMR: δ 3.37 (s, 6, OCH_3), 4.47 (t, 1, CH-$(OCH_3)_2$), 5.08 (s, 4, $C_6H_5CH_2$), 6.72 and 6.77 (s, 2, arom. H).

3,4-Bis(benzyloxy)-7-[[(2,2-dimethoxyethyl)(methoxycarbonyl)-amino]methyl]bicyclo[4.2.0]octa-1,3,5-triene (**11**)

To a solution of 8.6 g (0.02 mol) of **10** in 100 ml of ether was added 5 ml of triethylamine, followed by dropwise addition of a solution of 1.7 ml (2.11 g, 0.022 mol) of methyl chloroformate (Merck) in 10 ml ether, with the temperature being maintained at 0–5°. After stirring for an additional 15 min, 100 ml of water was added. The organic layer was separated and successively washed with 100 ml of 1 N aq. HCl, 100 ml of 10% aq. $NaHCO_3$ and 100 ml of water. After drying and evaporating the organic solvent, 9.7 g (99%) of **10** was obtained in essentially pure form as an oil; R_f (toluene/

[23] *T. Kametani, T. Honda, H. Inoue* and *K. Fukumoto*, J.C.S., Perkin I, 1221 (1976).

[24] *T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi* and *K. Fukumoto*, Chem. Pharm. Bull. Jpn **23**, 2634 (1975).

[25] *T. Kametani, M. Kajiwara* and *K. Fukumoto*, Tetrahedron 30, 1053 (1974).

ethanol 9/1) 0.56. NMR: δ 3.35 (s, 6, OCH_3), 3.68 (s, 3, $COOCH_3$), 5.08 (s, 4, $C_6H_5CH_2$), 6.70 (s, 2, arom. H).

3,4-Bis(benzyloxy)-7-[[(methoxycarbonyl)(2-oxoethyl)amino]-methyl]bicyclo[4.2.0]octa-1,3,5-triene (**12**)

To a solution of 9 g (0.018 mol) of **11** in 100 ml of dioxane was added 60 ml of water, followed by 20 ml of 70% perchloric acid. The hydrolysis was complete within 1½ h. 500 ml of 10% $NaHCO_3$ solution was then added and the product extracted with ether. After washing, drying and evaporation of the solvent, the resulting oil was passed through a short silica gel column (CH_2Cl_2/acetone ~98/2) yielding 7.9 g (98%) of **12** as a viscous oil; R_f (CH_2Cl_2/CH_3OH ~10/1) 0.85. NMR: 2.70 and 3.20 (AB, 2, cyclobutene CH_2), 3.70 (s, 3, OCH_3), 6.68 and 6.72 (s, 2, arom. H), 9.40 (s, 1, CHO).

trans-*7,8-Bis(benzyloxy)-2-(methoxycarbonyl)-1,2,3,3a,5,9b-hexahydro[2]benzopyrano[3,4-c]pyrrole* (**13**)

A solution of 8 g (0.018 mol) of **12** in 60 ml of bromobenzene was refluxed, under N_2, for 16 h. The solvent was removed using a rotary evaporator and the residue was chromatographed on silica gel (toluene/acetone ~97/3). The product solidified on treatment with hexane/ether to give 2.7 g (34%) of **13**; m.p. (toluene/hexane) 136–137°; R_f (toluene/acetone ~7/3) 0.40. Anal. calcd. $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14; found: C, 72.56; H, 6.39; N, 3.00. NMR: δ 3.72 (s, 3, OCH_3), 4.91 (s, 2, pyran CH_2), 5.08 (s, 4, $C_6H_5CH_2O$), 6.60 (s, 2, arom. H).

trans-*7,8-Bis(benzyloxy)-2-methyl-1,2,3,3a,5,9b-hexahydro[2]-benzopyrano[3,4-c]pyrrole* (**14**)

A solution of 12.7 g (0.03 mol) of **13** in 30 ml of THF was added dropwise to a suspension of 1.2 g (0.032 mol) of $LiAlH_4$ in 30 ml of THF. The mixture was refluxed for 1 h after which the aluminates were destroyed by addition of 1.2 ml of water, 1.2 ml of 15% NaOH and 3.6 ml of water. After filtration of the precipitates over Celite, the filtrate was concentrated and treated with a small volume of hexane/diisopropyl ether to give 9.4 g (89%) of **14**.

A pure sample was prepared by removal of trace impurities via acid/base extraction, followed by crystallization; m.p. (toluene/hexane) 102–104°; R_f (butanol/pyridine/acetic acid/water ~16/3/1/4) 0.44. Anal. calcd. $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49; found: C, 77.50, H, 6.77; N, 3.42. NMR: δ 3.80 (dt, 1, CH adjacent to pyran oxygen, *J* 9 and 9.5 Hz), 2.50 (s, 3, NCH_3), 4.90 (s, 2, pyran CH_2), 5.08 and 5.10 (s, 4, $C_6H_5CH_2O$), 6.49 and 6.52 (s, 2, arom. H).

trans-*2-Methyl-1,2,3,3a,5,9b-hexahydro[2]benzopyrano[3,4-c]-pyrrole-7,8-diol* (**15**) *hydrochloride*

A solution of 9.0 g (0.025 mol) of **14** in 100 ml of abs. ethanol was hydrogenated in the presence of 500 mg of 10% Pd-C. After about 10 h the reaction was complete. The catalyst was removed by filtration and the filtrate concentrated. The oily residue solidified on standing to give 4.8 g (87%) of **15** after trituration with ether. The oxidation sensitive material was taken up in a small volume of ethanol and a solution containing satd. HCl gas in isopropanol was added until the solution was slightly acidic. After a short period the hydrochloride of **15** started to crystallize from the solution; m.p. 222–223°; R_f (CH_3OH/H_2O/acetic acid ~90/10/2) 0.52. Anal. calcd. $C_{12}H_{16}ClNO_3$: C, 55.92; H, 6.26; N, 5.43; found: C, 56.14; H, 6.38; N, 5.29. NMR (DMSO-d_6): δ 2.90 (s, 3, CH_3), 4.85 (s, 2, pyran CH_2), 6.50 and 6.53 (s, 2, arom. H).

3,4-Bis(benzyloxy)-N-(2,2-dimethoxyethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (**17**)

To a solution of 3.50 g (0.01 mol) of carboxylic acid **7** in 10 ml of thionyl chloride were added three drops of DMF. The mixture was then stirred for 1 h at room temperature followed by refluxing for 15 min. Excess thionyl chloride was removed using a rotary evaporator. The remaining acid chloride was taken up in 10 ml of CH_2Cl_2 and added dropwise to a cooled (0°) solution of 1.15 g (0.011 mol) of (2,2-dimethoxyethyl)amine (Aldrich) and 2 ml of triethylamine in 50 ml of CH_2Cl_2. After stirring for a further ½ h, 100 ml of water was added. The organic layer was separated and washed twice with 100 ml of 0.5 N aq. HCl, twice with 10% aq. $NaHCO_3$ and once with water. After drying (Na_2SO_4) and concentrating, a yellowish oil was obtained, which solidified on treatment with diisopropyl ether to give 3.75 g (84%) of essentially pure **17**; m.p. (toluene/diisopropyl ether) 103–104°; R_f (toluene/ethanol ~8/2) 0.56. Anal. calcd. $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13; found: C, 72.56; H, 6.77; N, 3.04. NMR: 5.04 (m, 1, $CH(OCH_3)_2$), 4.35 (t, 1, cyclobutene CH), 3.38 (s, 6, OCH_3), 6.79 (s, 2, arom. H).

3,4-Bis(benzyloxy)-N-(2,2-dimethoxyethyl)-N-propylbicyclo-[4.2.0]octa-1,3,5-triene-7-carboxamide (**18**)

The anion of **17** was prepared by heating a solution of 3.6 g (0.008 mol) of **17** in 15 ml of dry DMF in the presence of 0.4 g of sodium (~0.009 mol; 55% dispersion in mineral oil, Fluka) for 15 min at 70–80° (at this temperature a rapid hydrogen evolution took place, which ceased after several minutes). The mixture was cooled to room temperature and 1 ml (0.01 moles) of propyl iodide in 2 ml of DMF was introduced using a syringe. After stirring for an additional 1 h, 120 ml of water was added and the product extracted with ethyl acetate. The residue, which was obtained after washing, drying and evaporation of the organic phase, was chromatographed over silica gel (CH_2Cl_2/ethyl acetate 95/5 as eluent) to give 2.1 g (54%) of **18** as a colourless oil; R_f (toluene/ethanol 9/1) 0.48. NMR: δ 0.90 (t, 3, CH_3), 3.37 (s, 6, OCH_3), 4.33 (t, 1, $CH(OCH_3)_2$), 4.50 (t, 1, cyclobutene CH), 5.10 (s, 4, $ArCH_2O$).

3,4-Bis(benzyloxy)-N-(2-oxoethyl)-N-propylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide (**19**)

To a solution of 12 g (0.025 mol) of **18** in 200 ml of dioxane was added 100 ml of water and 30 ml of 70% aq. $HClO_4$. The mixture was stirred for 1 h. 400 ml of water was then added and the products extracted with ethyl acetate. After washing, drying (Na_2SO_4) and evaporation of the organic phase, the residual oil was chromatographed over silica gel (using a gradient of toluene/ethyl acetate from 95/5 to 70/30) to give 2.2 g (21%) of the aldehyde **19** as a colourless oil and 4.6 of the carboxylic acid **7**; R_f (**19**, toluene/eth.ac. ~7/3) 0.57. NMR: 0.97 (t, 3, CH_3), 4.03 (s, 2, CH_2CHO), 4.38 (t, 1, CH), 5.08 (s, 4, $ArCH_2O$). IR (CCl_4) cm^{-1}: 1738 (C=O); 1656 (CON).

cis- *And* trans-*7,8-bis(benzyloxy)-2-propyl-3,3a,5,9b-tetrahydro-2H-[2]benzopyrano[3,4-c]pyrrol-1-one* (**21** and **20**)

A solution of 14.0 g (0.032 mol) of the aldehyde **19** in 400 ml of bromobenzene was refluxed, under a nitrogen atmosphere, for 16 h.

The bromobenzene was removed using a rotary evaporator (to which a "high vacuum" pump was connected). The residue was chromatographed over silica gel (toluene/acetone ~10/1 as eluent) to give 1.9 g of **21** and 8.4 g of **20**; total yield 74%.

For **20**: m.p. (toluene/hexane) 127–128°; R_f (toluene/acetone ~7/3) 0.63. Anal. calcd. $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16; found C, 75.80; H, 6.56; N, 3.26. NMR: δ 0.92 (t, 3, CH_3), 5.10 and 5.18 (s, 4, $C_6H_5CH_2$), 6.61 (s, 1, H-ar), 7.74 (s, 1, arom. H), 4.94 (s, 2, pyran CH_2), 4.05 (octet, 1, CH adjacent to pyran oxygen).

For **21**: m.p. (toluene/hexane) 95–96°; R_f (toluene/acetone ~7/3) 0.54. Anal. calcd. $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16; found: C, 75.72; H, 6.54; N, 3.18. NMR: δ 0.90 (t, 3, CH_3), 5.10 (s, 2, $C_6H_5CH_2$), 5.19 (AB, 2, $C_6H_5CH_2$), 6.58 (s, 1, arom. H), 4.60 (s, 2, pyran CH_2), 4.45 (t, 1, CH adjacent to pyran oxygen, *J* 5 Hz).

trans-*7,8-Bis(benzyloxy)-2-propyl-1,2,3,3a,5,9b-hexahydro[2]-benzopyrano[3,4-c]pyrrole* (**22**)

To a solution of 10.5 g (0.024 mol) of **20** in 200 ml of THF was added 16.4 ml (0.164 mol) of a 10 M solution of borane–dimethyl sulfide complex in THF (Aldrich). The mixture was stirred and refluxed for 6 h. Then, after cooling to ~5°, 50 ml of 6 N HCl was carefully added (vigorous gas evolution!) and the mixture refluxed for an additional 1½ h (this is necessary to decompose the amine–borane complex). After addition of 300 ml of satd. aq. $NaHCO_3$ solution, the product was extracted with ether. After washing, drying and evaporation of the organic solvent, the residue was chromatographed over a silica gel column (CH_2Cl_2/CH_3OH 95/5 as eluent) to give 7.4 g of **22**; m.p. (diisopropyl ether/hexane) 63–65°. A sample was converted into the hydrochloride salt; m.p. (ethanol/ether) 212–212.5°. Anal. calcd. $C_{28}H_{32}ClNO_3$: C, 72.16; H, 6.92; N, 3.01; found: C, 72.09;

H, 6.92; N, 3.04. NMR: δ 1.02 (t, 3, CH_3), 4.88 (s, 2, pyran CH_2), 5.08 (s, 4, $C_6H_5CH_2$), 6.50 (bs, 1, arom. H), 6.59 (s, 1, arom. H).

cis-7,8-Bis(benzyloxy)-2-propyl-1,2,3,3a,5,9b-hexahydro[2]-benzopyrano[3,4-c]pyrrole (**23**)

The product **23** was obtained by reduction of 1.80 g (4 m mol) of **21** with 2.80 ml (28 m mol) of BH_3–dimethyl sulfide in 45 ml of THF in essentially the same way as described for **22**. This gave 1.40 g of **23** as a white solid; m.p. (CH_2Cl_2/diisopropyl ether) 104–105°. A sample was converted into the hydrochloride salt; m.p. (ethanol/ether) 194–196°. Anal. calcd. $C_{28}H_{32}ClNO_3$: C, 72.16; H, 6.92; N, 3.01; found: C, 71.98; H, 6.91; N, 2.99. NMR: δ 1.00 (t, 3, CH_3), 1.90 (m, 2, CH_2), 4.62 (s, 2, pyran CH_2), 5.00 (s, 4, $C_6H_5CH_2$), 6.58 and 6.75 (s, 2, arom. H).

trans-2-Propyl-1,2,3,3a,5,9b-hexahydro[2]benzopyrano[3,4-c]-pyrrole-7,8-diol hydrochloride (**24**·HCl)

A solution of 6.15 g (13.2 mmol) of **22**·HCl in 480 ml of ethanol and 120 ml of water was hydrogenated, using 1.2 g of 10% Pd-C as catalyst. When the uptake of hydrogen had ceased (½ h), the catalyst was removed by filtration and the filtrate evaporated to dryness. On treatment of the residue with ether, followed by filtration, 3.43 g (93%) of **24**·HCl was obtained.
A sample was crystallized from ethanol/ether; m.p. 251–52° (dec.); R_f (butanol/pyridine/acetic acid/water ~16/3/1/4) 0.54. Anal. calcd. $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.05; N, 4.90; found: C, 58.61; H, 7.00; N, 4.67. NMR (DMSO-d_6): 0.94 (t, 3, CH_3), 1.71 (m, 2, CH_2), 4.84 (s, 2, pyran CH_2), 6.50 and 6.52 (s, 2, arom. H).

cis-2-Propyl-1,2,3,3a,5,9b-hexahydro[2]benzopyrano[3,4-c]-pyrrole-7,8-diol hydrochloride (**25**·HCl)

The preparation was carried out as described for **24**·HCl. Starting from 1.13 g (0.0024 mol) of **23**·HCl, 626 mg (90%) of **25**·HCl was obtained. A sample was crystallized from ethanol/ether; m.p. 234–35°; R_f (butanol/pyridine/acetic acid/water ~16/3/1/4) 0.52. Anal. calcd. for $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.05; N, 4.90; found: C, 58.58; H, 6.95; N, 4.72. NMR (DMSO-d_6): δ 0.90 (t, 3, CH_3), 4.35 (t, 1, CH adjacent to pyran oxygen), 4.54 (s, 2, pyran CH_2), 6.29 and 6.59 (s, 2, arom. H).

3,4-Bis(benzyloxy)-N,N-*dipropylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**26**)

The acid chloride, prepared from 350 mg (1 mmol) of **7** and 3 ml of thionyl chloride (see preparation of **17**), was taken up in 2 ml of methylene chloride and added dropwise to a solution of 2 ml of di-*n*-propylamine in 10 ml of methylene chloride. After stirring for ½ h at room temperature, 10 ml of 2 N HCl was added to the reaction mixture. The organic phase was separated and washed with 2 N HCl, 10% aq. $NaHCO_3$ solution and water. After drying and evaporation, the residue was passed through a short silica gel column (toluene/acetone ~8/2 as eluent). This gave 0.39 g (91%) of **26** as a colourless oil; R_f (toluene/acetone 7/3) 0.67. NMR: δ 4.29 (t, 1, cyclobutene CH), 5.09 (s, 4, $C_6H_5CH_2O$), 6.71 and 6.80 (s, 2, arom. H), 0.90 (dt, 6, CH_3). IR (CCl_4) cm^{-1}: 1680 (CO).

3,4-Bis(benzyloxy)-N-*(2-hydroxyethyl)*-N-*propylbicyclo[4.2.0]-octa-1,3,5-triene-7-carboxamide* (**27**)

A solution of 10 g (~0.03 mol) of **7** in 50 ml of thionyl chloride was stirred for 1 h at room temperature (several drops of DMF were added to promote the reaction) and then refluxed for ½ h. Excess thionyl chloride was removed using a rotary evaporator.
The acid chloride was taken up in 50 ml of methylene chloride and added dropwise to a cooled solution (−50°) of 4.6 g (0.045 mol) of 2-(propylamino)ethanol and 10 ml of triethylamine in 60 ml of methylene chloride. The mixture was stirred for ½ h at −50° and then for 1 h at ambient temperature. 200 ml of water was then added and the organic layer separated. After several washings with 2 N HCl and 10% aq. $NaHCO_3$ solution, the organic layer was dried and concentrated to give 12.0 g of rather pure **27**.
Chromatography over silica gel (CH_2Cl_2/acetone ~4/1) provided 10.5 g (79%) of **27** as a colourless oil; R_f (CH_2Cl_2/acetone 2/1) 0.65. NMR: δ 0.95 (m, 3, CH_3), 4.36 (m, 1, cyclobutene CH), 5.09 (s, 4, $C_6H_5CH_2$), 6.75 and 6.84 (s, 2, arom. H).

3,4-Bis(benzyloxy)-N-*(2-oxoethyl)*-N-*propylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**19**) by oxidation of **27**

The oxidant was prepared by dropwise addition of a solution of 5 ml of DMSO in 30 ml of methylene chloride to a cooled solution (−60°) of 4 ml (0.045 mol) of oxalyl chloride in 100 ml of methylene chloride. The mixture was stirred for 10 min at −60°, after which period a solution 15 g (0.034 mol) of **27** in 50 ml of methylene chloride was added dropwise over 10 min.
The mixture was stirred for a further 20 min and 30 ml of triethylamine was then added dropwise. After warming to room temperature, the reaction mixture was stirred for ½ h and 300 ml of water was then added. The organic layer was separated and washed several times with 2 N HCl followed by 5% aq. $NaHCO_3$. The crude product which remained after drying and evaporation of the organic solvent was chromatographed over silica gel (toluene/acetone ~4/1) to give 14.0 g (94%) of aldehyde **19** as a colourless oil, which was identical to the product obtained by hydrolysis of **18**.

2,3-Bis(benzyloxy)-N-*(2-hydroxyethyl)*-N-*methylbicyclo[4.2.0]-octa-1,3,5-triene-7-carboxamide* (**28a**)

The product was prepared from the carboxylic acid **7** and 2-(methylamino)ethanol (Aldrich), as described for **27**, in 73% yield; m.p. (acetone/diisopropyl ether) 116–18°. Anal. calcd. $C_{26}H_{27}NO_4$: C, 74.87; H, 6.52; N, 3.36; found: C, 74.87; H, 6.70; N, 3.24. NMR: δ 3.12 and 2.89 (s, 3, CH_3 rotamers), 3.32 (d, 2, cyclobutene CH_2, *J* 4 Hz), 3.50 (m, 2, NCH_2), 3.70 (m, 2, CH_2OH), 4.31 (t, 1, cyclobutene CH, *J* 4 Hz), 5.08 (s, 4, $C_6H_5CH_2O$), 6.72 and 6.85 (s, 2, arom. H).

3,4-Bis(benzyloxy)-N-*benzyl*-N-*(2-hydroxyethyl)bicyclo[4.2.0]-octa-1,3,5-triene-7-carboxamide* (**28b**)

Reaction of **7** with 2-(benzylamino)ethanol (Aldrich), as described for **27**, gave **28b** in 77% yield; m.p. (CH_2Cl_2/ether) 100–101°; R_f (CH_2Cl_2/acetone ~10/1) 0.42. Anal. calcd. $C_{32}H_{31}NO_4$: C, 77.86; H, 6.33; N, 2.84; found: C, 78.05; H, 6.57; N, 2.69. NMR: δ 4.32 (m, 1, cyclobutene CH), 4.98 (AB, 2, $C_6H_5CH_2O$), 5.05 (s, 2, $C_6H_5CH_2O$), 4.62 (m, 2, N–$CH_2C_6H_5$, rotamers).

3,4-Bis(benzyloxy)-N-*[2-(3,4-dimethoxyphenyl)ethyl]*-N-*(2-hydroxyethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**28c**)

The 2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]ethanol, which was required for the preparation of **28c**, was prepared along the lines indicated for the synthesis of 2-(propylamino)ethanol[17] and was obtained as a solid; m.p. (CH_2Cl_2/hexane) 62–64°. The preparation along the lines indicated for **27** provided **28c** in 60% yield; R_f (toluene/acetone ~7/3) 0.30; m.p. (toluene/hexane) 110–114°. Anal. calcd. $C_{35}H_{37}NO_6$: C, 74.05; H, 6.57; N, 2.47; found: C, 74.16; H, 6.60; N, 2.43. NMR: δ 2.82 (t, 2, $ArCH_2CH_2$), 4.09 (t, 1, cyclobutene CH, *J* 4 Hz), 5.08 (s, 4, $C_6H_5CH_2O$), 3.83 (s, 6, OCH_3), 3.24 (t, 2, CH_2 cyclobutene).

3,4-Bis(benzyloxy)-N-*phenethyl*-N-*(2-hydroxyethyl)bicyclo-[4.2.0]octa-1,3,5-triene-7-carboxamide* (**28d**)

The 2-(phenethylamino)ethanol, required for the preparation of **28d**, was prepared from phenethylamine as described for the synthesis of 2-(propylamino)ethanol and obtained as a viscous oil; b.p. (0.2 mm) 130–135°. Preparation of **28d**, along the lines indicated for **27** was achieved in 89% yield; m.p. (CH_2Cl_2/ether) 160–161°; R_f (toluene/acetone ~7/3) 0.52. Anal. calcd. $C_{33}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.77; found: C, 78,25; H, 6.33; N, 6.25. NMR: δ 4.08 and 4.47 (t, 1, CH cyclobutene, rotamers), 5.08 (s, 4, $C_6H_5CH_2O$), 6.75 (s, 2, arom. H).

2,3-Bis(benzyloxy)-N-*methyl*-N-*(2-oxoethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**29a**)

The aldehyde **29a** was obtained as a colourless oil in 94% yield by oxidation of **28a** along the lines indicated for the conversion of **27** into **19**; R_f (toluene/acetone ~7/3) 0.32. NMR: δ 3.17 (s, 3, NCH_3), 3.40 (d, 2, cyclobutene CH_2, *J* 4 Hz), 4.17 (s, 2, CH_2CHO), 4.42 (t, 1, cyclobutene CH), 5.10 (s, 4, $C_6H_5CH_2O$) 9.58 (s, 1, CHO).

2,3-Bis(benzyloxy)-N-*benzyl*-N-*(2-oxoethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**29b**)

Oxidation of **28b**, as indicated for the conversion of **27** to **19**, provided **29b** in 90% yield as an oil; R_f (toluene/acetone ~7/3) 0.50. NMR: δ 9.38 (s, 1, CHO), 6.70 (s, 2, arom. H), 4.66 (s, 2, $CH_2C_6H_5$), 5.02 (s, 2, $C_6H_5CH_2O$), 4.97 (AB, 2, $C_6H_5CH_2O$), 4.39 (t, 1, cyclobutene CH), 4.00 (AB, 2, NCH_2CHO). IR (CCl_4) cm^{-1}: 1650 (CON), 1737 (CO).

2,3-Bis(benzyloxy)-N-*[2-(3,4-dimethoxyphenyl)ethyl]*-N-*(2-oxoethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**29c**)

Oxidation of **28c** provided **29c** as a colourless oil in 98% yield; R_f (toluene/acetone ~7/3) 0.45. NMR: δ 2.80 (t, 2, CH_2CH_2Ar), 3.27 (d, 2, cyclobutene CH_2), 4.15 (t, 1, cyclobutene CH), 4.00 (s, 2, CH_2CHO), 3.80 (s, 6, OCH_3), 5.04 (s, 4, $OCH_2C_6H_5$), 9.43 (s, 1, CHO). IR (CCl_4) cm^{-1}: 1735 (HC=O), 1650 (CON).

2,3-Bis(benzyloxy)-N-*(2-oxoethyl)*-N-*phenethylbicyclo[4.2.0]-octa-1,3,5-triene-7-carboxamide* (**29d**)

Treatment of **28d** with Swern's oxidant, as described above, provided **29d** as a colourless oil in 80% yield; R_f (toluene/acetone ~7/3) 0.52. NMR: δ 4.00 (s, 2, CH_2CHO), 4.15 (t, 1, cyclobutene CH, *J* 4 Hz), 5.05 (s, 4, $C_6H_5CH_2O$), 9.42 (s, 1, CHO). IR (CH_2Cl_2) cm^{-1}: 1731 (CHO), 1641 (CON).

trans *And* cis *7,8-Bis(benzyloxy)-2-methyl-3,3a,5,9b-tetrahydro-2H-[2]benzopyrano[3,4-c]pyrrol-1-one* (**30a** and **31a**)

Thermolysis of 19 g (0.046 mol) of **29a** in 300 ml of refluxing bromobenzene, as described for **20**, gave 11.3 g of **30a** and 4.0 g of **31a**.
For **30a**: m.p. (toluene/hexane) 108–109°; R_f (toluene/acetone ~7/3) 0.56. Anal. calcd. $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37; found: C, 75.18; H, 6.19; N, 3.18. NMR: δ 2.90 (s, 3, NCH_3), 4.00 (octet, 1, H adjacent to pyran oxygen, *J* 10, 9 and 7 Hz), 4.93 (s, 2, pyran CH_2), 6.60 (s, 1, arom. H), 7.80 (s, 1, arom. H).
For **31a**: m.p. (toluene/hexane) 119–120°; R_f (toluene/acetone ~7/3) 0.34. Anal. calcd. $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37; found: C, 74.87; H, 6.16; N, 3.25. NMR: δ 2.86 (s, 3, NCH_3), 4.38 (t, 1, CH adjacent to pyran oxygen, *J* 5 Hz), 4.53 (s, 2, pyran CH_2), 5.08 (s, 2, $C_6H_5CH_2O$), 5.17 (AB, 2, $C_6H_5CH_2O$).

trans *And* cis-*7,8-bis(benzyloxy)-2-benzyl-3,3a,5,9b-tetrahydro-2H-[2]benzopyrano[3,4-c]pyrrol-1-one* (**30b** and **31b**)

Thermolysis of 32 g (0.065 mol) of **29b** in 400 ml of bromobenzene, as described for **20**, gave 17.0 g of **30b** and 6.5 g of **31b**, after chromatography over silica gel (toluene/ethyl acetate ~9/1).
For **30b**: m.p. (toluene/hexane) 112–113°; R_f (toluene/acetone ~7/3) 0.69. Anal. calcd. $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85; found: C, 78.28; H, 6.15; N, 2.64. NMR: δ 4.49 (AB, 2, $NCH_2C_6H_5$), 4.90 (s, 2, pyran CH_2), 5.08 and 5.18 (s, 4, $OCH_2C_6H_5$); 6.58 (s, 1, arom. H), 7.80 (s, 1, arom. H), 3.92 (octet, 1, H adjacent to pyran oxygen, *J* 6, 9 and 11 Hz).
For **31b**: m.p. (CH_2Cl_2/ether) 140–141°; R_f (toluene/acetone ~7/3) 0.56. Anal. calcd. $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85; found: C, 78.28; H, 6.15; N, 2.64. NMR: δ 6.57 (s, 1, arom. H), 5.17 (AB, 2, $C_6H_5CH_2O$), 5.08 (s, 2, $C_6H_5CH_2O$), 4.52 (s, 2, $NCH_2C_6H_5$), 4.49 (AB, 2, pyran CH_2), 4.37 (t, 1, H adjacent to pyran oxygen, *J* 5 Hz).

trans *And* cis-*7,8-bis(benzyloxy)-2-(3,4-dimethoxyphenethyl)-3,3a,5,9b-tetrahydro-2H-[2]benzopyrano[3,4-c]pyrrol-1-one* (**30c** and **31c**)

Thermolysis of 22 g (0.039 mol) of **29c** in 400 ml of bromobenzene, as described for **20**, gave 12.5 g of **30c** and 2.8 g of **31c**, after chromatography of the product over silica gel (CH_2Cl_2/ethyl acetate ~9/1).
For **30c**: m.p. (CH_2Cl_2/diisopropyl ether) 90–92°; R_f (toluene/acetone ~7/3) 0.65. Anal. calcd. $C_{35}H_{35}NO_6$: C, 74.31; H, 6.34; N, 2.48; found: C, 74.19; H, 6.24; N, 2.48. NMR: δ 3.86 (s, 6, OCH_3), 4.90 (s, 2, pyran CH_2), 5.09 and 5.18 (s, 4, $C_6H_5CH_2O$), 7.78 (s, 1, arom. H).
For **31c**: obtained as a viscous oil; R_f (toluene/acetone ~7/3) 0.54. NMR: δ 3.80 and 3.81 (s, 6, OCH_3), 4.51 (s, 2, pyran CH_2), 5.08 (s, 2, $C_6H_5CH_2O$), 5.20 (AB, 2, $C_6H_5CH_2O$), 4.32 (t, 1, CH adjacent to pyran oxygen, *J* 5 Hz).

trans *And* cis-*7,8-bis(benzyloxy)-2-phenethyl-3,3a,5,9b-tetrahydro-2H-[2]benzopyrano[3,4-c]pyrrol-1-one* (**30d** and **31d**)

Thermolysis of 21 g (0.042 mol) of **29d** in 400 ml of refluxing bromobenzene gave 14.7 g of **30d** and 2.5 g of **31d**, after chromatography over silica gel (toluene/ethyl acetate ~9/1).
For **30d**: m.p. (CH_2Cl_2/ether) 134–135°; R_f (toluene/acetone ~7/3) 0.68. Anal. calcd. $C_{33}H_{31}NO_4$: C, 78.39; H, 6.18; N, 2.77; found: C, 78.48; H, 6.24; N, 2.73. NMR: δ 3.82 (octet, 1, CH adjacent to pyran oxygen), 4.89 (s, 2, pyran CH_2), 5.06 and 5.14 (s, 4, $C_6H_5CH_2O$), 7.77 (s, 1, arom. H).
For **31d**: m.p. (CH_2Cl_2/ether) 94–95°; R_f (toluene/acetone ~7/3) 0.55. Anal. calcd. $C_{33}H_{31}NO_4$: C, 78.39; H, 6.18; N, 2.77; found: C, 78.14; H, 6.24; N, 2.79. NMR: δ 4.38 (t, 1, CH adjacent to pyran oxygen, *J* 5 Hz), 5.10 (s, 2, $C_6H_5CH_2O$), 5.19 (AB, 2, $C_6H_5CH_2O$), 6.58 (s, 1, arom. H).

4-(Benzyloxy)-N-*methyl*-N-*(2-hydroxyethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**32a**)

This oily compound was prepared in 95% yield from carboxylic acid **46** and 2-(methylamino)ethanol, as described for **27**; R_f (toluene/acetone ~1/1) 0.45. NMR: δ 2.95 and 3.18 (s, 3, NCH_3 rotamers), 3.38 (d, 2, cyclobutene CH_2), 4.40 and 4.50 (t, 1, CH cyclobutene rotamers), 5.00 (s, 2, $C_6H_5CH_2O$).

4-(Benzyloxy)-N-*methyl*-N-*(2-oxoethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**33a**)

Oxidation of **32a** with *Swern*'s oxidant afforded **33a** in 82% yield, after chromatography over silica gel (methylene chloride/acetone ~8/2); R_f (hexane/acetone ~7/3) 0.20. NMR: δ 3.16 (s, 3, CH_3), 4.18 (s, 2, CH_2CHO), 5.00 (s, 2, $C_6H_5CH_2O$), 9.56 (s, 1, CHO), 4.48 (m, 1, cyclobutene CH).

trans *And* cis-*8-(benzyloxy)-2-methyl-3,3a,5,9b-tetrahydro-2H-[2]benzopyrano[3,4-c]pyrrol-1-one* (**34a** and **35a**)

Thermolysis of 7.4 g of **33a** (0.024 mol) in 100 ml of bromobenzene afforded 3.7 g of **34a** and 2.4 g of **35a**, after chromatography over silica gel (CH_2Cl_2/acetone ~95/5); both were oily materials.
For **34a**: R_f (CH_2Cl_2/acetone 95/5) 0.47. NMR: δ 2.90 (s, 3, NCH_3), 4.97 (s, 2, pyran CH_2), 5.07 (s, 2, $C_6H_5CH_2O$), 3.87–4.15 (octet, 1, CH adjacent to pyran oxygen, *J* 10.5, 9 and 7 Hz).
For **35a**: R_f (CH_2Cl_2/acetone ~95/5) 0.29. NMR: δ 2.90 (s, 3, NCH_3), 4.61 (s, 2, pyran CH_2), 5.09 (s, 2, $C_6H_5CH_2O$), 4.42 (t. 1, *J* 5 Hz, H adjacent to pyran oxygen).

2,3-Bis(benzyloxy)-N-*(2-hydroxyethyl)*-N-*methylbicyclo[4.2.0]-octa-1,3,5-triene-7-carboxamide* (**32b**)

This compound was prepared in 84% yield from the carboxylic acid and 2-(methylamino)ethanol; R_f (toluene/ethanol ~3/1) 0.54; m.p. (diisopropyl ether) 100–105°. Anal. calcd. $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.36; found: C, 74.46; H, 6.53; N, 3.30. NMR: δ 2.90 and 3.15 (s, 3, NCH_3, rotamers), 4.35 (m, 1, cyclobutene CH), 5.03 and 5.20 (s, 4, $C_6H_5CH_2O$), 6.72 (AB, 2, arom. H).

2,3-Bis(benzyloxy)-N-*methyl*-N-*(2-oxoethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide* (**33b**)

Oxidation of **32b** with *Swern*'s oxidant gave **33b** in 81% yield as a white solid; m.p. (CH_2Cl_2/ether) 91–94°. NMR: δ 3.29 (s, 3, CH_3), 4.18 (AB, 2, CH_2CHO), 4.42 (m, 1, cyclobutene CH), 5.05 and 5.22 (s, 4, $C_6H_5CH_2O$), 9.52 (s, 1, CHO). IR (CH_2Cl_2) cm^{-1}: 1736 (CO), 1649 (CON).

trans *And* cis-*6,7-bis(benzyloxy)-2-methyl-3,3a,5,9b-tetrahydro-2H-[2]benzopyrano[3,4-c]pyrrol-1-one* (**34b** and **35b**)

A solution of 4 g (0.0096 mol) of **33b** in 80 ml of 1,2-dichlorobenzene was refluxed for 4 h. This provided, after chromatography, 1.5 g of **34b** and 1.92 g of **35b**.
For **34b**: m.p. (methylene chloride/diisopropyl ether 152–154°. Anal. calcd. $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37; found: C, 75.20; H, 6.18; N, 3.31. NMR: δ 2.88 (s, 3, CH_3), 3.85 (octet, 1, CH adjacent to pyran oxygen), 4.90 (s, 2, pyran CH_2), 5.01 and 5.09 (s, 4, $C_6H_5CH_2O$), 7.75 and 6.91 (AB, 2, arom. H).
For **35b**: m.p. (methylene chloride/diisopropyl ether) 169–171°. Anal. calcd. $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37; found: C, 74.90; H, 5.92; N, 3.36. NMR: δ 2.90 (s, 3, NCH_3), 4.35 (t,

l, CH adjacent to pyran oxygen, *J* 5 Hz), 4.37 and 4.92 (AB, 2, pyran CH_2), 4.93 and 5.10 (AB, 2, $C_6H_5CH_2O$), 5.12 (s, 2, $C_6H_5CH_2O$).

trans-*2-Benzyl-7,8-bis(benzyloxy)-1,2,3,3a,5,9b-hexahydro[2]-benzopyrano[3,4-c]pyrrole* (**36**)

To a solution of 16 g (0.033 mol) of **30b** in 150 ml of THF was added 15 ml of a 10 M borane + dimethyl sulfide solution in THF (Aldrich). The mixture was refluxed for 6 h after which the excess borane was destroyed by careful addition of 60 ml of 6 N HCl (caution, vigorous foaming!). The mixture was then refluxed for $1\frac{1}{2}$ h to destroy the amine–borane complex. After cooling to room temperature, 300 ml of 10% aq. $NaHCO_3$ solution was added and the product extracted with ether. The crude product obtained after washing, drying and evaporation of the organic phase was chromatographed over silica gel (CH_2Cl_2/acetone ~10/1).
The resulting oily product solidified on treatment with hexane and diisopropyl ether to give 10.1 g (65%) of **36**; m.p. (CH_2Cl_2/diisopropyl ether) 94–95°. Anal. calcd. $C_{32}H_{31}NO_3$: C, 80.47; H, 6.54; N, 2.93; found: C, 80.15; H, 6.52; N, 2.99. NMR: δ 3.80 (double t, 1, H adjacent to pyran oxygen, *J* 8 and 10 Hz), 3.83 (s, 2, $NCH_2C_6H_5$), 4.90 (s, 2, pyran CH_2), 5.08 (s, 4, $C_6H_5CH_2O$), 6.55 and 6.61 (s, 2, arom. H).

trans-*1,2,3,3a,5,9b-Hexahydro[2]benzopyrano[3,4-c]pyrrole-7,8--diol, acetate* (**39**·CH_3COOH)

A solution of 8 g (0.018 mol) of **36** in 150 ml of glacial acetic acid was hydrogenated in the presence of 1 g of 10% Pd on charcoal. Hydrogen uptake took ~10 hr (~1100 ml). The catalyst was removed by filtration and the resulting light green filtrate was concentrated and treated with a small amount of ether to give 4.4 g (92%) of **39** as the acetate salt; R_f (butanol/pyridine/acetic acid/water ~16/3/1/4) 0.47; m.p. (96% ethanol/ether) 181–183°. Anal. calcd. $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24; found: C, 58.49; H, 6.53; N, 5.10. NMR (DMSO-d_6): 4.80 (s, 2, pyran CH_2), 6.40 and 6.44 (s. 2. arom. H).

trans-*7,8-Bis(benzyloxy)-2-(3,4-dimethoxyphenethyl)--1,2,3,3a,5,9b-hexahydro[2]benzopyrano[3,4-c]pyrrole* (**37**)

To a solution of 10.4 g (0.018 mol) of **30c** in 150 ml of dry THF was added 13 ml of 10 M borane + dimethyl sulfide. The solution was then refluxed for 6 h after which the mixture was stirred overnight at room temperature; excess borane was destroyed by careful addition of 40 ml of 6 N aq. HCl. The mixture was refluxed for a further $1\frac{1}{2}$ h and subsequently neutralized by addition of 200 ml of 10% aq. $NaHCO_3$ solution. The product was extracted with ether. After washing, drying and evaporation of the solvent, the resulting oil was chromatographed over silica gel (CH_2Cl_2/acetone ~3/1) to give an oily product which solidified on treatment with 30 ml of diisopropyl ether; yield 8.0 g (79%); m.p. (diisopropyl ether) 82–83°; R_f (CH_2Cl_2/acetone ~7/3) 0.40. Anal. calcd. $C_{35}H_{37}NO_5$: C, 76.20; H, 6.75; N, 2.54; found: C, 75.69; H, 6.90; N, 2.46. NMR: δ 3.85 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 4.90 (s, 2, pyran CH_2), 5.08 and 5.09 (s, 4, $C_6H_5CH_2$).

trans-*2-(3,4-Dimethoxyphenethyl)-1,2,3,3a,5,9b-hexahydro[2]-benzopyrano[3,4-c]pyrrole-7,8-diol, acetate* (**40**·CH_3COOH)

A solution of 6.0 g (0.011 mol) of **37** in 150 ml of acetic acid was hydrogenated in the presence of 700 mg of 10% Pd on charcoal. After $1\frac{1}{2}$ h the reaction was complete. The catalyst was removed by filtration and the filtrate concentrated. Upon treatment of the residue with a small amount of ether, 4.1 g (87%) of **40**·CH_3COOH was obtained. A sample was crystallized from ethanol/ether and melted at 174–176°. Anal. calcd. $C_{23}H_{29}NO_7$: C, 64.11; H, 6.90; N, 3.01; found: C, 64.02; H, 6.77; N, 3.25. NMR (DMSO-d_6): 3.70 and 3.72 (s, 6, OCH_3), 4.78 (s, 2, pyran CH_2).

cis-*6,7-Bis(benzyloxy)-2-methyl-1,2,3,3a,5,9b-hexahydro[2]-benzopyrano[3,4-c]pyrrole* (**38**)

The reduction mixture was prepared by addition of a solution of 692 mg (5.2 mmol) of $AlCl_3$ in 7 ml of dry ether to a suspension of 346 mg (9.4 mmol) of $LiAlH_4$ in 7 ml of ether. The mixture was stirred for 15 min, cooled to −70° and then further diluted with 14 ml of dry CH_2Cl_2. A solution of 0.96 g (2.4 mmol) of **35b** in 10 ml of CH_2Cl_2 was introduced dropwise over 5 min. After stirring for an additional 15 min, 4.8 ml of water was added and the mixture allowed to come to room temperature. 5 g of sodium sulfate was then added and, after an additional stirring period of 15 min, the precipitates were filtered over Celite and the filtrate evaporated. The residue was passed through a short silica gel column (CH_2Cl_2/CH_3OH ~10/1) to give 0.84 g of **38**, as an oil, which solidified on treatment with hexane. The solid was treated with 10 ml of ether and filtered over Celite to remove traces of gummy material. The filtrate was concentrated and the residue crystallized from diisopropyl ether/hexane to give 0.42 g (45%) **38** as a fine white crystalline material; m.p. 81–82°. Anal. calcd. $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49; found: C, 77.65; H, 6.75; N, 3.33. NMR: δ 2.40 (s, 3, CH_3), 5.00 (AB, 2, $C_6H_5CH_2$), 5.09 (s, 2, $C_6H_5CH_2$), 6.85 (s, 2, arom. H), 4.30 and 4.92 (AB, 2, pyran CH_2O).

cis-*2-Methyl-1,2,3,3a,5,9b-hexahydro[2]benzopyrano[3,4-c]-pyrrole-6,7-diol hydrochloride* (**41**·HCl)

A solution of 438 mg (1 mmol) of **38**·HCl in 60 ml of 80% aq. ethanol was hydrogenated in the presence of 80 mg of 10% Pd on charcoal. After 15 min the hydrogenation was complete. The catalyst was removed by filtration and the filtrate concentrated. The residual water was removed by repeated coevaporation with abs. ethanol. Treatment of the residue with ether gave 230 mg of **41**; m.p. 257–60°; R_f (butanol/pyridine/acetic acid/water ~$4/\frac{3}{4}/\frac{1}{4}$/1) 0.40. NMR (DMSO-$d_6$): 2.80 (s, 3, CH_3), 4.45 and 4.82 (AB, 2, pyran CH_2), 6.48 and 6.70 (AB, 2, arom. H).

3-(Benzyloxy)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylic acid (**46**)

Treatment of 3-(2-bromo-4-methoxyphenyl)propionitrile (**42**)[21] with BBr_3 in CH_2Cl_2, as described for **4**, gave 3-(2-bromo-4--hydroxyphenyl)propionitrile (**43**) in 81% yield; m.p. (toluene) 119–120°. Anal. calcd. C_9H_8BrNO: C, 47.81; H, 3.57; N, 6.20; found: C, 47.93; H, 3.67; N, 6.00.
On benzylation of **43**, as described for **5**, the required 3-[4(benzyl-oxy)-2-bromophenyl]propionitrile **44** was obtained in 89% yield; m.p. (ether/hexane) 43–45°. Anal. calcd. $C_{16}H_{14}BrNO$: C, 60.77; H, 4.46; N, 4.43; found: C, 61.07; H, 4.53; N, 4.39. NMR: δ 4.98 (s, 2, $C_6H_5CH_2$).
Cyclization of **44**, under standard conditions ($NaNH_2$ in liq. NH_3)[14,25], yielded 3-(benzyloxy)bicyclo[4.2.0]octa-1,3,5-triene--7-carbonitrile (**45**) in 48% yield; m.p. (diisopropyl ether) 111–113°. Anal. calcd. $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95; found: C, 81.62; H, 5.75; N, 5.95. NMR: δ 4.16 (m, 1, CHCN), 3.50 (m, 2, cyclobutene CH_2), 5.00 (s, 2, $C_6H_5CH_2O$).
The final hydrolysis of **45** was performed with KOH in aq. ethanol, as described for **6**, and gave **46** in essentially quantitative yield; m.p. (CH_2Cl_2/diisopropyl ether) 116–117°. Anal. calcd. $C_{16}H_{13}O_3$: C, 75.57; H, 5.55; found: C, 75.59; H, 5.66. NMR: δ 3.40 (d, 2, cyclobutene CH_2, *J* 4 Hz), 4.27 (t, 1, cyclobutene CH, *J* 4 Hz), 5.00 (s, 2, $C_6H_5CH_2O$).

3-(6-Bromo-2,3-dimethoxyphenyl)propionitrile (**50**)

Condensation of 6-bromo-2,3-dimethoxybenzaldehyde[23] **47** with cyanoacetic acid, essentially as described[12] for the isomeric 2-bromo-4,5-dimethoxybenzaldehyde, afforded 2-cyano-3-(2,3--dimethoxy-6-bromophenyl)propenoic acid (**48**) in 95% yield; m.p. (toluene) 139–142°. Anal. calcd. $C_{12}H_{12}BrNO_4$: C, 46.17; H, 3.23; N, 4.49; found: C, 46.40; H, 3.28; N, 4.56. NMR: δ 3.89, 3.93 (s, 6, OCH_3), 6.90, 7.30 (AB, 2, arom. H), 8.30 (s, 1, olefin H). The reduction of **48**, leading to 2-cyano-3-(6--bromo-2,3-dimethoxyphenyl)propionic acid (**49**), was performed using $NaBH_4$ in aq. $NaHCO_3$[12] (**49**) in 95% yield; m.p. (ether/hexane) 132–134°. Anal. calcd. $C_{12}H_{12}BrNO_4$: C, 45.88; H, 3.85; N, 4.46; found: C, 45.89; H, 3.94; N, 4.45. NMR: δ 4.08 (dd, 1, CHCN), 3.88 and 3.94 (s, 6, OCH_3), 6.80 and 7.28 (AB, 2, arom. H).
The subsequent decarboxylation of **49** was carried out in refluxing *N,N*-dimethylacetamide[12] (Baker Chemicals) to give the required **50** as a viscous oil in 85% yield; b.p. 135–144° (0.6 mm). NMR ($CDCl_3$): 2.58 (t, 2, CH_2CN), 3.18 (t, 2, $ArCH_2$), 3.83 and 3.90 (s, 6, OCH_3), 6.72 and 7.25 (AB, 2, arom. H).

3-(2-Bromo-5,6-dihydroxyphenyl)propionitrile (**51**)

To a cooled (−60°) solution of 30 g (0.11 mol) of **50** in 800 ml of CH_2Cl_2 was added 25 ml (66.2 g, 0.26 mol) of BBr_3.
After stirring for $\frac{1}{2}$ h at −60°, the mixture was allowed to come to room temperature and stirred overnight. It was then poured into

1 l of ice-water and the organic layer was separated, washed three times with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed over silica gel (toluene/ethanol ~98/2) to give 9.5 g (36%) of **51** and 10.8 g (40%) of **55**.
For **51**: m.p. (diisopropyl ether/hexane) 94–96°; R_f (toluene/acetone ~7/3) 0.48. Anal. calcd. for $C_9H_8BrNO_2$: C, 44.65; H, 3.33; N, 5.70; found: C, 44.99; H, 3.42; N, 5.69. NMR: δ 2.60 (t, 2, CH_2), 3.17 (t, 2, CH_2), 6.60 and 6.89 (AB, 2, arom. H).
For **55**: m.p. (CH_2Cl_2/diisopropyl ether) 176–178°; R_f (toluene/acetone ~7/3) 0.66. Anal. calcd. $C_9H_7BrO_3$: C, 44.47; H, 2.90; found: C, 44.33; H, 2.93. NMR: δ 2.80 (m, 2, CH_2), 3.10 (m, 2, CH_2), 6.72 and 7.17 (AB, 2, arom. H). IR (KBr) cm^{-1}: 1760 (C=O).

2,3-Bis(benzyloxy)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylic acid (**54**)

Benzylation of **51** with benzyl bromide + K_2CO_3 in DMF, as described for **5**, gave 3-[2,3-bis(benzyloxy)-6-bromophenyl]-propionitrile (**52**) in 86% yield; m.p. (ethyl acetate/hexane) 63–65°. Anal. calcd. $C_{23}H_{20}BrNO_2$: C, 65.41; H, 4.37; N, 3.32; found: C, 65.60; H, 4.18; N, 3.33. NMR: δ 5.08 (s, 4, $C_6H_5CH_2$).

Cyclization of **52** with $NaNH_2$ in liq. NH_3, as described for **6**, gave 2,3-bis(benzyloxy)bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (**53**) in 73% yield; m.p. (CH_2Cl_2/diisopropyl ether) 90–91°. Anal. calcd. $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10; found: C, 80.74; H, 5.52; N, 3.97. NMR: δ 3.48 (m, 2, cyclobutene CH_2), 4.07 (m, 1, CHCN), 5.09 and 5.08 (s, 4, $C_6H_5CH_2O$), 6.70 and 6.88 (AB, 2, arom. H).
Hydrolysis of **53** with KOH in aq. ethanol, as described for **7**, gave the required carboxylic acid **54** in 96% yield; m.p. (CH_2Cl_2/diisopropyl ether) 142–144°. NMR: δ 3.47 (m, 2, cyclobutene CH_2), 4.17 (m, 1, cyclobutene CH), 5.09 and 5.20 (s, 4, $C_6H_5CH_2O$), 6.65 and 6.85 (AB, 2, arom. H). Anal. calcd. $C_{23}H_{20}O_4$: C, 76.65; H, 5.59; found: C, 76.11; H, 5.61.

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Reaction of 1-alkynyl thiocyanates with nucleophilic reagents. Synthesis of 2,4-disubstituted 1,3-thiazoles

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Abstract. Reaction of 1-alkynyl thiocyanates RC≡C–S–C≡N (**1**) with alcohols, phenol or thiols or secondary aliphatic amines in the presence of anhydrous zinc chloride or boron trifluoride diethyl etherate gives mixtures of 2,4-disubstituted 1,3-thiazoles (**2**), thiocarbonyl compounds (**3**) (thiono esters, dithio esters or thioamides) and 2-alkylidene-1,3-dithioles (**4**). In all cases, the 1,3-thiazoles can be obtained in good yields if the proper reaction conditions are applied. Interaction between **1** and lithium dialkylamides $LiNR'_2$ gives the compounds $RC{\equiv}C{-}S{-}NR'_2$ (**5**) (attack on sulfur). With alkoxides $R'O^{\ominus}$, the primary attack is on C≡N, the intermediary alkynethiolate $RC{\equiv}C{-}S^{\ominus}$ subsequently reacts with the alkyl cyanate R'OC≡N to afford 1-alkynyl sulfides $RC{\equiv}C{-}SR'$ (**6**).

Introduction

1-Alkynyl thiocyanates RC≡C–S–C≡N were synthesized for the first time in our laboratory about ten years ago[1]. Structurally they resemble 1-(acylthio)-1-alkynes RC≡C–S–C(=O)R' because of the presence of an electronegative grouping linked to sulfur.
The acyl compounds have been studied in detail by *Drenth* et al.[2], who used them in the synthesis of 1,3-oxathiole derivatives. With this analogy in mind, we undertook a study of the properties of 1-alkynyl thiocyanates, the main objective being their use in a synthesis of 1,3-thiazole derivatives. As the starting compounds can be easily prepared from acetylenes, such a synthesis would provide a good alternative to the well known methods of *Hantzsch*, *Tcherniac*, *Traumann* and *Gabriel* (compare ref. 3).

[1] *J. Meijer* and *L. Brandsma*, Recl. Trav. Chim. Pays-Bas **91**, 1098 (1971).
[2] *W. Drenth* and *G. H. E. Nieuwdorp*, Recl. Trav. Chim. Pays-Bas **88**, 307 (1969).
[3] *J. V. Metzger*, "Thiazole and its Derivatives" in "The Chemistry of Heterocyclic Compounds", Vol. 34, Part I, Chapter 2, p. 166–271, John Wiley and Sons, New York, 1979.

Results and discussion

a. Reaction of 1-alkynyl thiocyanates with alcohols

As in the synthesis of 1,3-oxathioles from (acylthio)-alkynes[2], we heated solutions of **1** (R = CH_3) in methanol or ethanol under reflux. After a 2–3 day period, all the starting material had disappeared and a mixture of the thiazole **2** and thiono ester **3** (R = CH_3, R' = OCH_3, OC_2H_5) was obtained in a low (~30%) yield.

The slow formation of **2**, as compared with the easy cyclisation of (acylthio)alkynes with alcohols to oxathioles[2], may be explained by a lower rate of addition of alcohols across the less polar C≡N bond. To promote this primary addition the use of Lewis-acid catalysts was considered, since they are able to coordinate to nitrogen giving rise to an increase in the polarity.
We carried out a large number of experiments in different solvents (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane) at 20°C and at higher temperatures, using anhydrous zinc chloride as a catalyst and varying the amount of alcohol. In all cases $ZnCl_2$ was found to exert a distinct catalytic effect upon the formation of the desired 1,3-thiazole, **2**. However, especially at elevated temperatures