Thioamide Derivatives of Cannabinoids. A Study of the Influence of the Thioamide Function on Regiochemistry in the Synthesis of Thioamide Cannabinoids from 2,4-Dihydroxybenzothioamides

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Several thiocarbamoyl derivatives of cannabinoids were obtained in the collidine-catalysed condensation of 2,4-dihydroxybenzothioamides with citral and citronellal. The thioamide function was found to change the regioselective preferences of the reaction as compared with the known cannabinoid syntheses from hydroxyacetophenones. The experimental results and theoretical (FMO theory) considerations made it possible to advance the reaction mechanism. Convenient methods were developed for the synthesis of the starting 2,4-dihydroxybenzothioamides from resorcinol and isothiocyanates in the presence of the boron trifluoride/acetic acid 1:2 complex or aluminum chloride in nitromethane.

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Introduction.

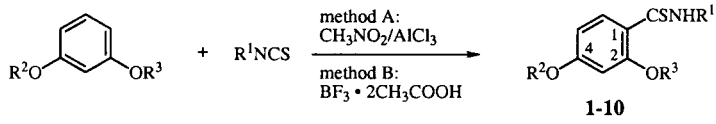
Thioamides are well known as compounds easily converted into a variety of amines [1,2], enamines [3-6], *S,N*-acetals [7,8], amides [9], and heterocycles [10-12], including a number of natural products. Introduction of the thioamide group into cannabinoid compounds, which since a long time are the subject of chemical, pharmacological, and clinical investigations, offers the opportunity to functionalise the original framework and thus obtain new compounds with potential biological activity.

Several resorcinol-derived monoterpenes occurring in *Cannabis sativa* [13] have been synthesised earlier in the pyridine- or collidine-catalysed condensation of the derivatives of resorcinol with citral [14] and citronellal [15,16]. As shown by the quoted literature data, regiochemistry of this reaction depends to a considerable extent on the substituent in the resorcinol reagent. The reactions of citral [17,18] and citronellal [16] with 2,4-dihydroxyacetophenone may serve as the most illustrative examples, particularly suitable for a comparative study. In this paper we report on the condensations starting with secondary 2,4-dihydroxybenzothioamides and on the regiospecific influence of the thioamide group on the formation of the cannabichromene-, cannabicitrane-, and hexahydrocannabinoid-type products.

Results and Discussion.

The starting *N*-substituted 2,4-dihydroxybenzothioamides **1-5** and their methyl ethers **6-10** were obtained in high yields from the appropriate isothiocyanates and resorcinol either in the Friedel-Crafts reaction carried out under conditions described for phenols [19] or in the reaction with the boron trifluoride-acetic acid 1:2 complex (Scheme 1). The latter variant proved to be a good alternative synthetic method.

Scheme 1



1-10

	1		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
R^1	Me		Et	BzI	Ph	C_6H_{11}	Et	Et	Ph	Ph	Et
R^2	H		H	H	H	H	H	Me	H	Me	Me
R^3	H		H	H	H	H	Me	H	Me	H	Me
method	A	B	B	B	B	A	B	B	B	B	B
yield (%)	66	77	82	97	81	72	28	17	22	38	93

As it may be seen, the substitution takes place only at the carbon atom *ortho* and *para* with respect to the activating groups. Since mixtures of isomers were obtained with the monomethoxy derivatives, the reaction was regioselectively controlled by neither the hydroxy nor the methoxy function.

The isomeric pairs **6-7** and **8-9** were separated by column chromatography and their structures were elucidated by ^{1}H-nmr spectroscopy. The chemical shift of the 6-H proton served here as the main identification criterion. In the *o*-methoxy derivatives **6** and **8**, it appears at lower fields (δ = 8.5) than in the *p*-methoxy analogues **7** and **9** (δ = 7.3). This may be rationalized by assuming that the 6-H proton deshielding by the O···HN hydrogen-bonded thioamide group in the *o*-methoxy compounds **6** and **8** is stronger than that by the OH···S bonded group in the *p*-methoxy isomers **7** and **9**. A similar effect of the carbonyl anisotropy on the *ortho* protons was observed earlier in aromatic amides with a stable intermolecular hydrogen bond [20].

Good evidence to support this interpretation was obtained in the 2D NOESY spectra of the *N*-ethylthioamides **6** and **7**. A cross-peak observed in the spectrum

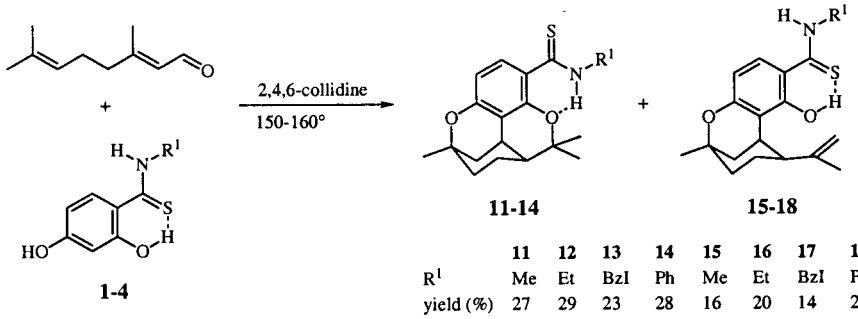
of **7** indicated an interaction of the *p*-methoxy group protons with the 5-H and 3-H aromatic protons, whereas in that of **6**, the *o*-methoxy group protons interacted only with 3-H and the thioamide NH protons. Determination of the type of the intramolecular hydrogen bonding on the base of the chemical shift of the *ortho*-protons makes it therefore possible to distinguish between the *o*-hydroxy- and *o*-alkoxy-substituted isomers of the thioamides.

On treatment with citral in collidine at 150-160°, 2,4-dihydroxybenzothioamides were converted into the mixtures of the tetracyclic cannabicitran-type compounds **11-14** and their tricyclic isomers **15-18**, (Scheme 2). They were separated by column chromatography. ^{13}C-nmr spectroscopic examination of the crude products revealed only traces (<5%) of the type-**B** regioisomers formed when the electrocyclic annulation occurred *via* the *o*-hydroxy group (*cf.* Scheme 5).

the appropriate protons and carbon atoms was presented separately [21].

It is known that the formation of chromene as the only product of the reaction of 2,4-dihydroacetophenone with citral is controlled by a strong OH···O=C chelation [17,18]. Another *o*-hydroxy group, as in 2,4,6-trihydroxyacetophenone, is required to decrease this chelating effect and thus make the formation of the type **A** and **B** citrans possible [22,23] (Scheme 5). As found presently, the thioamide group favours the formation of cannabicitrans **11-14** presumably by stabilizing the transient dienone and enforcing regioselectivity of the subsequent annulations in the intramolecular cycloaddition and Diels-Alder reactions (Scheme 5). The oxygen atom of the *o*-alkenylidenecyclohexadienone tautomer and the thiomide NH proton form the respective chelate system. The formation of the open-ring structures **15-18** seems to indicate a par-

Scheme 2

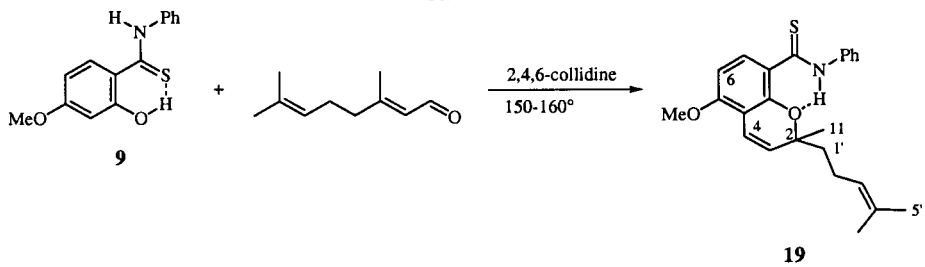


	11	12	13	14	15	16	17	18
R^1	Me	Et	BzI	Ph	Me	Et	BzI	Ph
yield (%)	27	29	23	28	16	20	14	21

Under essentially the same conditions, 2-hydroxy-4-methoxybenzothioanilide (**9**) gave a low yield (18%) of the chromene derivative **19** (Scheme 3), while attempted annulation of citral to 4-hydroxy-2-methoxybenzothioanilide (**8**) was unsuccessful and the thioamide was recovered almost unchanged.

tially ionic character of the Diels-Alder reaction. The experimental results suggest that the presence of the thioamide group facilitates annulation, in particular at the intramolecular Diels-Alder cycloaddition step, and enhances regioselectivity of the cyclisation. In order to substantiate this assumption, thioamides derived from

Scheme 3



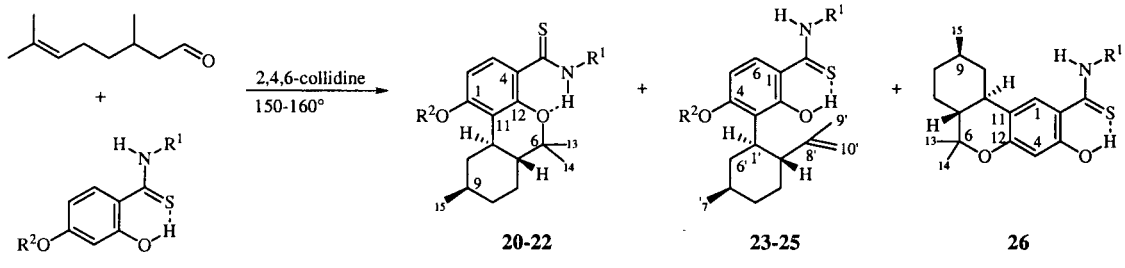
The structures of the compounds **11-14, 15-18,** and **19** were unambiguously determined by ^{1}H and ^{13}C-nmr spectroscopy. The spectra of **19**, in fact similar to those described by Crombie, *et al.* [17], are reported in detail at present in the Experimental. A detailed analysis of the other spectra with a complete assignment of all signals to

resorcinol were made to react with citronellal. Under conditions similar to those used in the reaction with citral, the cyclisations of *N*-phenyl- (**4**) and *N*-methyl-2,4-dihydroxybenzothioamide (**1**) and *N*-phenyl-2-hydroxy-4-methoxybenzothioamide (**9**) with citronellal engaged the *o*-oxygen atom to yield the compounds **20-22** (Scheme 4).

Moreover, as in the case of citral, citronellal also gives, although in lower yields, the non-annulated products **23-25** (Scheme 4). A strikingly low regioselectivity was noted with the *N*-phenyl derivative **4** which gave an 11% yield of a third product **26**.

Regioselectivity of the formation of hexahydrocannabinols from the resorcinol-derived thioamides is therefore essentially different than that from those derived from acetylresorcinol [16]. In the latter case, the oxygen atom *para* to the acetyl group is involved in the cyclisation.

Scheme 4



	20	21	22	23	24	25	26
R^1	Me	Ph	Ph	Me	Ph	Ph	Ph
R^2	H	H	Me	H	H	Me	
yield	26	33	25	5	2	2	11

The structures of the compounds **20-22** and **26** were determined with the aid of routine 1D nmr (^{1}H, ^{13}C, DEPT) and 2D nmr techniques (COSY, HETCOR). Complete assignments of the ^{1}H and ^{13}C-nmr signals are presented in the Experimental for **20**. The approximate conformational analysis based on the J_{HH} coupling constants and on the crosspeak in the NOESY spectrum suggests the configuration and conformation of **20** as shown in Figure 1. In the case of the compound **26**, the ^{1}H-nmr pattern of the aliphatic fragment of the molecule is similar as in **20**. The configuration and conformation of the cyclohexane ring in both compounds is therefore presumably identical. The orientation of substitution at 2, 3, 11 and 12 in **26** is evidenced by the occurrence of two singlet signals of the aromatic protons 1-H and 4-H.

In the case of by-products **23-25,** only **23** was isolated from the reaction mixture in a sufficient amount and purity to permit unambiguous structural analysis. A characteristic splitting of most signals in its ^{1}H and ^{13}C spectra into two sets indicates the presence of two rotamers resulting from rotational restriction about the sp^2-sp^3 bond (C-3 - C-1'). A high barrier to rotation of the bridged rings in cannabidiols was reported earlier [24]. Since many signals overlapped each other, only a few unambiguous NOE effects were found in the NOESY spectrum but coupling constants of the well separated signals of the H-6', H-1', H-2', and H-3' protons indicate their axial position (Figure 1). Structures of the trace compounds **24** and **25** were estimated by comparing their ^{1}H-nmr spectra with that of **23**.

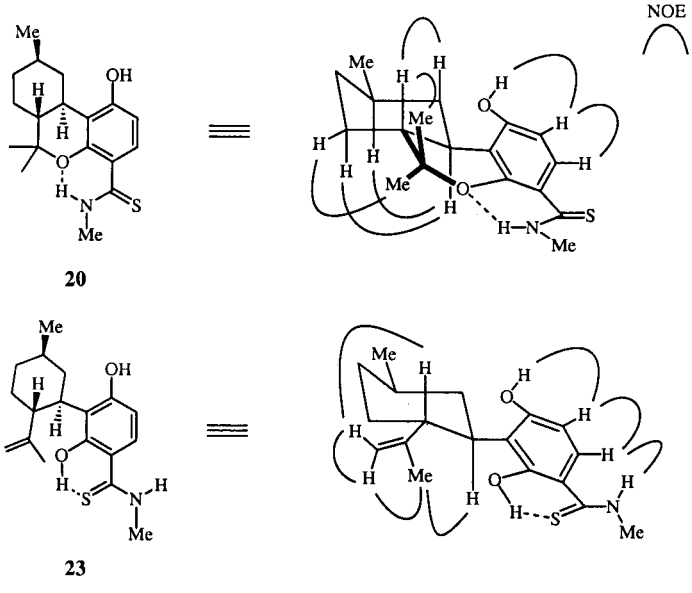


Figure 1. Configuration and conformation of compound **20** and **23**.

As far as reactivity is concerned, the reactions between citronellal and the *para* and *ortho* methoxy derivatives of thiocarbamoylresorcinol are subject to the same limitations as the reaction with citral. The *para*-methoxy derivative **9** yields the annulated product together with a small amount of an open-ring isomer, whereas the *ortho*-methoxy isomer **8** fails to react.

The effect of the thioamide group on the regioselectivity of the investigated intramolecular Diels-Alder cycloaddition reactions was also studied by using the Frontier Molecular Orbital (FMO) theory approach [25]. In general, the FMO prediction of regioselectivity requires: i) estimation for which of the possible reactants the HOMO and LUMO energies are mostly alike; ii) estimation of the relative values of the atomic orbital coefficients on the atoms presumed

to act as the reaction centers; iii) assumption that the orbital overlap and consequent bonding preferentially takes place between the atoms with highest atomic orbital coefficients.

coefficients calculated for the LUMO of both possible tautomeric structures of the model ethylidenecyclohexadienone and for the HOMO of the dienophile are collected in

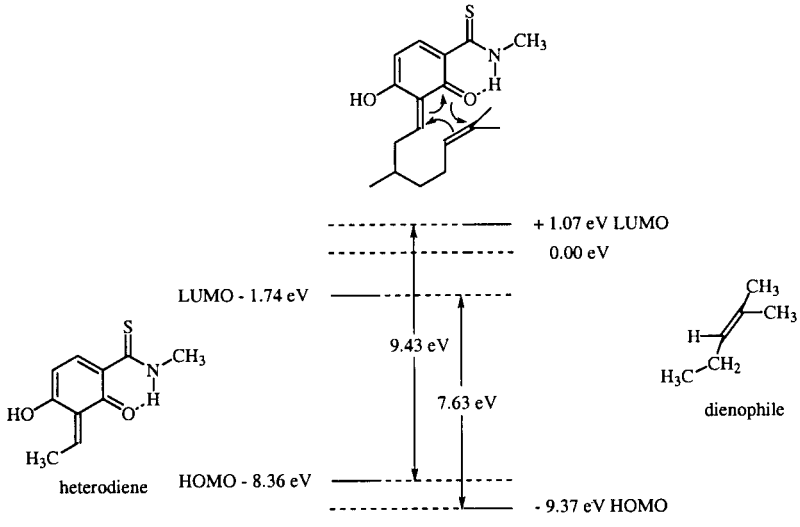


Figure 2.

Calculations of the FMO energies and the atomic orbital coefficients were performed for a somewhat simplified model system in which the thioamide derivative of *o*-ethylidenecyclohexadienone and 2-methyl-2-pentene represented the heterodiene and dienophile, respectively. The semiempirical method with PM3 parameters was used in the calculations (Figure 2) and two possible tautomers of the heterodiene were taken into consideration (Figure 3). It was assumed that these models secure estimation of the *global energy minimum* of the heterodiene molecule and thus make it possible to avoid miscalculations based on the numerous local energy minima associated with conformational flexibility of the aliphatic chain.

The results of our calculations show that the investigated reaction is prompted by the overlap of the dienophile HOMO with the heterodiene LUMO (Figure 2). It may be classified therefore, in agreement with other similar Diels-Alder cycloadditions [25], as the reaction with a reverse electron demand. The separation energy for the LUMO(heterodiene)-HOMO(dienophile) pair is 7.63 eV, and for the LUMO(dienophile)-HOMO(heterodiene) pair, 9.44 eV. The

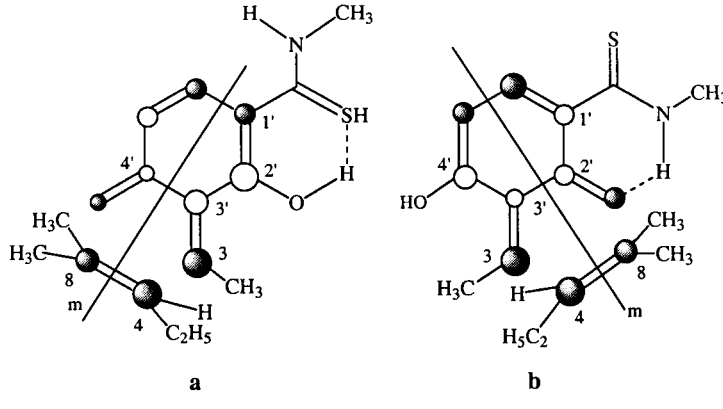


Figure 3.

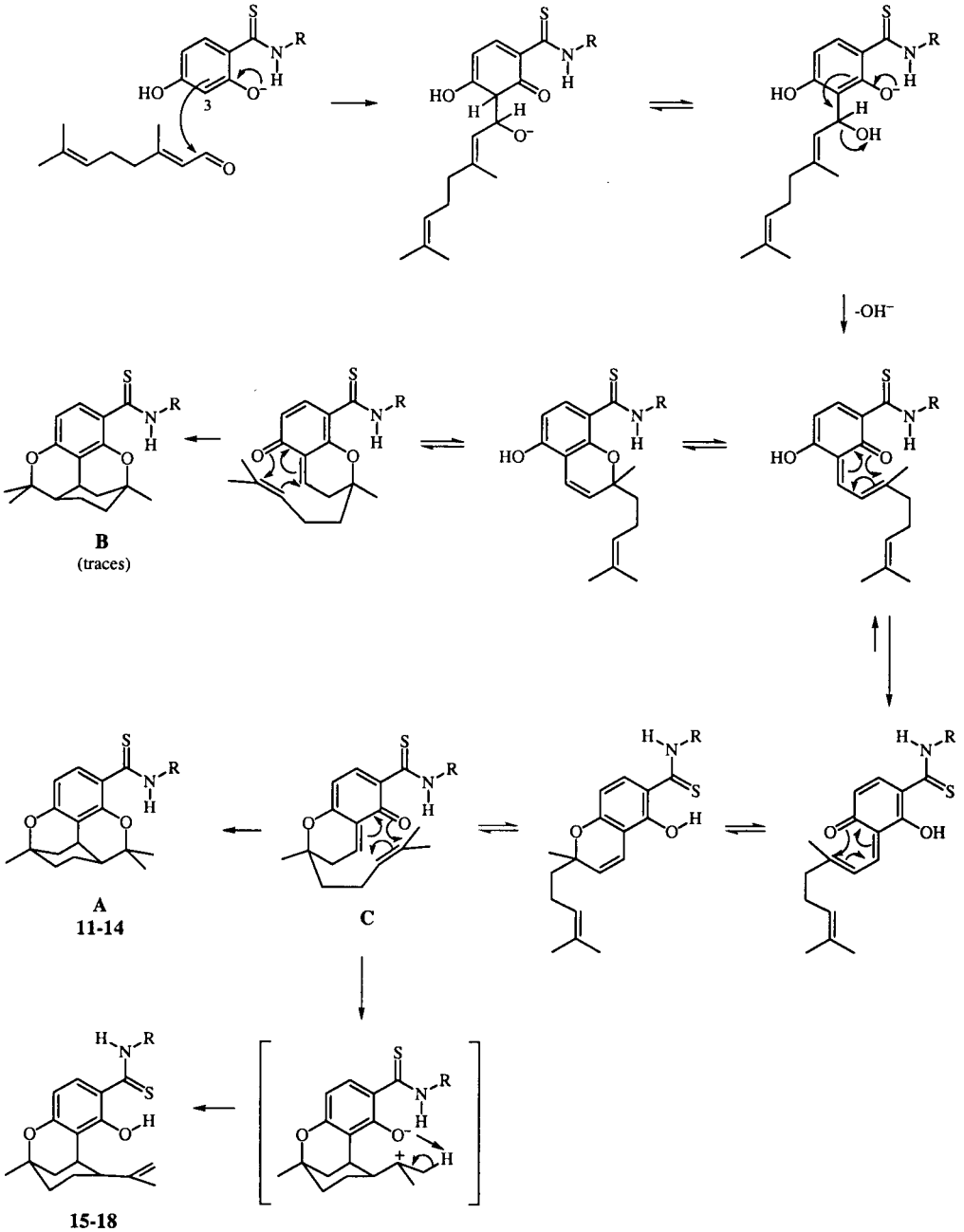
Table 1. Their graphic presentation is given in Figure 3 where the circles representing the atoms with the pz orbital lobes situated above the diagram plane are roughly proportional in size to the respective coefficient values. Filled circles represent atoms with orbitals of opposite sign.

Table 1
Coefficients and Energy of the Dienophile HOMO and the Heterodienes LUMO

	reagent	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-3	O=C	LUMO [eV]	$\Delta E_{LUMO(diene)-HOMO(dienophile)}$ [eV]
1.	*ortho*-heterodiene	-0.25	-0.25	-0.23	-0.35	0.20	0.37	**0.46**	**0.24**	-1.74	7.63
2.	*para*-heterodiene	0.10	-0.40	-0.15	-0.08	-0.10	0.10	**0.41**	**0.08**	-1.48	7.89
		C-4	C-8	HOMO[eV]							
3.	dienophile	0.47	0.45	-9.37							

The FMO prediction of regiospecificity is in full agreement with the experimental results. Both the energy separation values, which are lower for the *ortho* than for the *para* orientated tautomer, and low values of the orbital coefficients, particularly remarkable in the case of the oxygen atom, indicate the orbital overlapping being less effective in the *para* orientated molecule. In accordance with the Woodward-Hoffmann rule, which takes plane as the symmetry element controlling the 4+2 supra-supra cycloaddition reactions, the orbitals involved in annulation of the *o*-ethylidenecyclohexadienone heterodiene show more symmetry elements with respect to the plane *m* (Figure 3) than those of the *para* isomer. This may be observed not only for the directly overlapping orbitals but for the 2'-3' and 1'-4' orbitals as well (Figure 3). The orbital coefficients calculated for the heterodiene oxygen atom O=C and the dienophile carbon atom C-8 in the compounds orientated as in Figure 3b (0.24 and 0.46, respectively) differ from one another enough to indicate an unconcerted mechanism of the heterodiene intramolecular cycloaddition. This can explain the formation

Scheme 5
The Proposed Mechanism of Cannabicitran Formation



of the non-annulated products in the reactions with both citral and citronellal. A proposed mechanistic interpretation of the formation of the compounds **15-18** assumes an intermediate formation of a zwitterionic species *via* preferential overlapping of the carbon orbitals (Scheme 5).

The mechanism of the formation of cannabicitran (**A**) is shown in Scheme 5. Considering the earlier interpretations by Crombie [17,23], catalysis by collidine initiates a nucleophilic attack of the phenolate anion on citral with consequent hydroxyalkenylation at C-3. The subsequent cyclisation which yields a chromen structure may proceed *via* 1,2-dehydratation associated with electrocyclisation of the dienone. The final step concerns cyclisation of chromen or, what seems even more likely, its keto tautomer in an intramolecular Diels-Alder reaction yielding a thiocarbamoyl-cannabicitran.

The synthetic results show that the aldehyde group of citral and citronellal fails to react with benzothioamides in which the *ortho*-hydroxy group is methylated. This can be rationalized in terms of a resonance charge delocalization in the ion formed and consequent differences in the activation energy levels of particular mesomeric structures.

In conclusion, the presented experimental and theoretical results support the hypothesis that regioselectivity of the investigated reaction depends to a considerable extent on the presence of the thioamide function. Effective stabilization of the *o*-ethylidenecyclohexadienone intermediate (**C**, Scheme 5), which acts as a precursor in the formation of cannabicitrans and hexahydrocannabinols in the intramolecular cycloaddition reaction, explains the influence of this group.

Acknowledgements.

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EXPERIMENTAL

Melting points were determined in a digital apparatus Elektrothermal model IA9300 and are uncorrected. Infrared spectra were taken with a Specord M80 instrument in potassium bromide pellets. The ^{1}H-nmr spectroscopic measurements and the 1D-^{13}C-nmr and 2D-^{1}H, ^{1}H (COSY, NOESY), ^{13}C, ^{1}H HETCOR were performed in deuteriochloroform, deuterioacetone or deuteriodimethyl sulfoxide on a Bruker DPX apparatus (400 MHz) with tetramethylsilane as the internal standard. Calculations were performed on a PC 486 DX-50 computer with the Hyperchem 4.0 program.

The synthesis of the compounds **11-18** were described earlier [21].

General Procedure for Preparation of Thioamides of Resorcinol **1-10.**

Method A.

The appropriate isothiocyanate (0.052 mole) was added dropwise to an ice water-cooled and stirred solution of aluminium chloride (0.01 mole) in 100 ml of dry nitromethane and followed by 0.05 mole of resorcinol or its methyl ether. Stirring was continued for 1 hour at 0-5° and the mixture was then allowed to stand 3-4 hours at room temperature (tlc control), poured into ice water, and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and filtered and the solvent was evaporated. The solid product was dissolved in ethyl acetate, the solution was passed through a 10 cm thick layer of neutral aluminium oxide, the solvent was removed, and the residue was recrystallized from a suitable solvent.

Method B.

The appropriate isothiocyanate (0.052 mole) was added dropwise to an ice water-cooled and stirred solution of 40 ml of the boron trifluoride-acetic acid complex with 5.5 g (0.05 mole) of resorcinol or 0.05 mole of methyl ether. Stirring was continued for 0.5 hour at 0-5° and the mixture was then allowed to stand 3-4 hours at room temperature at 4° overnight and finally poured into ice water to precipitate a yellow solid. This was filtered and dissolved in ethyl acetate, the solution was passed through a 10 cm thick layer of neutral aluminum oxide, the solvent was removed, and the residue was recrystallized from a suitable solvent or chromatographed on silica gel; **6** and **7** were developed with *n*-hexane/ethyl acetate 6:4 and **8** and **9** were developed with benzene.

2,4-Dihydroxy-*N*-methylbenzothioamide (**1**).

This compound was obtained as off-white crystals (water), mp 121-122°; ir (potassium bromide): ν 3490 (OH), 3375, 2575 (OH, NH), 1545 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.31 (d, J = 4.9 Hz, 3H, NCH_3), 5.15 (br s, 1H, 4-OH), 6.37 (dd, J = 2.5, 8.7 Hz, 1H, aromatic 5-H), 6.46 (d, J = 2.5 Hz, 1H, aromatic 3-H), 7.21 (d, J = 8.7 Hz, 1H, aromatic 6-H), 7.58 (br s, 1H, NH), 11.78 (br s, 1H, 2-OH); ^{13}C-nmr (deuteriodimethyl sulfoxide): δ 32.6 (q, NCH_3), 102.7 (d, C-3), 107.2 (d, C-5), 115.7 (s, C-1), 131.9 (d, C-6), 157.4 (s, C-2)*, 161.1 (s, C-4)*, 193.2 (s, C=S).

Anal. Calcd. for $C_8H_9NO_2S$ (183.2): C, 52.44; H, 4.95; S, 17.50. Found: C, 52.56; H, 5.02; S, 17.38.

2,4-Dihydroxy-*N*-ethylbenzothioamide (**2**).

This compound was obtained as off-white crystals (chloroform), mp 143-145°; ir (potassium bromide): ν 3310 (OH), 3239 br, 3063 br, (OH, NH), 1545 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.37 (t, J = 7.3 Hz, 3H, CH_2CH_3), 3.81 (dd, J = 5.3 Hz, 7.3, 2 H, CH_2CH_3), 5.19 (br s, 1H, 4-OH), 6.37 (dd, J = 2.6 Hz, 8.7, 1H, aromatic 5-H), 6.45 (d, J = 2.6 Hz, 1H, aromatic 3-H), 7.20 (d, J = 8.7 Hz, 1H, aromatic 6-H), 7.42 (br s, 1H, NH), 11.81 (br s, 1H, 2-OH); ^{13}C-nmr (deuteriochloroform): δ 13.3 (q, CH_2CH_3), 40.3 (t, CH_2CH_3), 105.3 (d, C-3), 107.4 (d, C-5), 116.2 (s, C-1), 125.4 (d, C-6), 159.8 (s, C-2)*, 161.2 (s, C-4)*, 193.4 (s, C=S).

Anal. Calcd. for $C_9H_{11}NO_2S$ (197.2): C, 54.80; H, 5.62; S, 16.25. Found: C, 54.93; H, 5.74; S, 16.12.

N-Benzyl-2,4-dihydroxybenzothioamide (**3**).

This compound was obtained as yellow crystals (*n*-hexane/ethyl acetate, 7:3), mp 129-131°; ir (potassium bromide): ν 3390 (OH), 3315 br, 2486 br (OH, NH), 1519 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.93 (d, J = 5.0 Hz, 2H, CH_2), 5.35 (br. s, 1H, 4-OH), 6.34 (dd, J = 2.5 Hz, 8.8, 1H, aromatic 5H), 6.46 (d, J = 2.6 Hz, 1H, aromatic 3-H), 7.19 (d, J =

8.8 Hz, 1H, aromatic 6-H), 7.32-7.44 (m, 5H, aromatic H), 7.58 (br s, 1H, NH), 11.84 (br s, 2-OH); ^{13}C-nmr (deuteriochloroform): δ 49.6 (t, CH_2), 105.3 (d, C-3), 107.5 (d, C-5), 115.9 (s, C-1), 125.5 (d, C-6), 128.4, 128.5, 129.2, (d, aromatic CH), 135.8 (s, aromatic C), 160.0 (s, C-2)*, 161.4 (s, C-4)*, 193.4 (s, C=S).

Anal. Calcd. for $C_{14}H_{13}NO_2S$ (259.3): C, 64.84; H, 5.05; S, 12.35. Found: C, 65.01; H, 5.01; 12.28.

2,4-Dihydroxybenzothioanilide (**4**).

This compound was obtained as yellow crystals (*n*-hexane/ethyl acetate, 7:3), mp 177-179°; ir (potassium bromide): ν 3585 (OH), 3315, 2615 br, (OH, NH) 1507 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 5.28 (br s, 1H, 4-OH), 6.43 (dd, J = 2.6 Hz, 8.7, 1H, aromatic 5-H), 6.50 (d, J = 2.6 Hz, 1H, aromatic 3-H), 7.34 (tt, J = 1.3 Hz, 7.2, 1H, aromatic H), 7.42 (d, J = 8.8 Hz, 1H, aromatic 6-H), 7.46 (m, 2H, aromatic H), 7.51 (d, J = 8.0 Hz, 2H, aromatic H), 8.84 (br s, 1H, NH); ^{13}C-nmr (deuteriodimethyl sulfoxide): δ 102.6 (d, C-3), 107.3 (d, C-5), 118.0 (s, C-1), 124.4, 126.0, 128.4 (d, aromatic CH), 139.5 (s, aromatic C), 132.7 (d, C-6), 156.9 (s, C-2)*, 161.4 (s, C-4)*, 193.3 (s, C=S).

Anal. Calcd. for $C_{13}H_{11}NO_2S$ (245.3): C, 63.65; H, 4.52; S, 13.07. Found: C, 63.71; H, 4.44; S, 13.18.

N-Cycloxehyl-2,4-dihydroxybenzothioamide (**5**).

This compound was obtained as colorless crystals (*n*-hexane/ethyl acetate, 6:4), mp 136-138°; ir (potassium bromide): ν 3308 (OH), 2620 br (OH, NH), 1534 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform/deuteriodimethyl sulfoxide, 20:1): δ 1.18-1.51 (m, 5H, C_6H_{11}), 1.62-1.82 (m, 3H, C_6H_{11}), 2.05-2.16 (m, 2H, C_6H_{11}), 4.45-4.55 (m, 1H, C_6H_{11}), 6.35 (dd, J = 2.5 Hz, 8.7, 1H, aromatic 5-H), 6.45 (d, J = 2.5 Hz, 1H, aromatic 3-H), 7.31 (d, J = 8.8 Hz, 1H, aromatic 6-H), 7.97 (br d, J = 7.0 Hz, 1H, 4-OH), 9.04 (br s, 1H, NH), 11.57 (br s, 1H, 2-OH); ^{13}C-nmr (deuteriochloroform/deuteriodimethyl sulfoxide, 20:1): δ 24.8, 25.5, 31.6, (t, C_6H_{11}), 53.5 (d, C_6H_{11}), 104.7 (d, C-3), 107.9 (d, C-5), 115.8 (s, C-1), 127.1 (d, C-6), 160.4 (s, C-2)*, 161.6 (s, C-4)*, 191.9 (s, C=S).

Anal. Calcd. for $C_{13}H_{17}NO_2S$ (251.3): C, 62.12; H, 6.82; S, 12.76. Found: C, 61.98; H, 7.02; S, 12.58.

N-Ethyl-4-hydroxy-2-methoxybenzothioamide (**6**).

This compound was obtained as off-white crystals (*n*-hexane/ethyl acetate, 1:1), mp 140-143°; ir (potassium bromide): ν 3318 (OH), 3096 br (NH), 1536 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform/deuteriodimethyl sulfoxide, 20:1): δ 1.34 (t, J = 7.3 Hz, 3H, CH_2CH_3), 3.86 (qd, J = 5.1, 7.3 Hz, 2H, CH_2CH_3), 3.89 (s, 1H, OCH_3), 6.43 (d, J = 2.2 Hz, 1H, aromatic 3-H), 6.52 (dd, J = 2.3 Hz, 8.8, 1H, aromatic 5-H), 8.46 (d, J = 8.8 Hz, 1H, aromatic 6-H), 9.42 (br s, H, NH*), 9.47 (br s, 1H, OH*); ^{13}C-nmr (deuteriochloroform/deuteriodimethyl sulfoxide, 20:1): δ 13.4 (q, CH_2CH_3), 41.5 (t, CH_2), 55.9 (q, OCH_3), 98.9 (d, C-3), 108.6 (d, C-5), 118.68 (s, C-1), 137.1 (d, C-6), 157.3 (s, C-2)*, 161.7 (s, C-4)*, 194.2 (s, C=S).

Anal. Calcd. for $C_{10}H_{13}NO_2S$ (211.3): C, 56.85; H, 6.20; S, 15.17. Found: C, 57.02; H, 6.32; S, 15.05.

N-Ethyl 2-hydroxy-4-methoxybenzothioarnide (**7**).

This compound was obtained as off-white crystals (*n*-heptane), mp 90-92°; ir (potassium bromide): ν 3350 (NH), 2625 br (OH), 1535 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.36 (t, J = 7.3 Hz, 3H, CH_2CH_3), 3.79 (qd, J = 5.3, 7.3 Hz, 2H, CH_2CH_3), 3.80 (s, 3H, OCH_3), 6.41 (dd, J = 2.7 Hz, 8.9, 1H, aromatic 5-H), 6.49 (d, J = 2.6 Hz, 1H, aromatic 3-H), 7.21 (d, J = 8.9 Hz, 1H, aromatic 6-H), 7.45 (br s, 1H, NH), 11.93 (br s, OH); ^{13}C-nmr (deuteriochloroform): δ 13.3 (q, CH_2CH_3), 40.3 (t, CH_2CH_3), 55.5 (q, OCH_3), 102.7 (d, C-3), 107.3 (d, C-5), 115.5 (s, C-1), 124.9 (d, C-6), 161.5 (s, C-2)*, 163.6 (s, C-4)*, 193.3 (s, C=S).

Anal. Calcd. for $C_{10}H_{13}NO_2S$ (211.3): C, 56.85; H, 6.20; S, 15.17. Found C, 56.81; H, 6.02; S, 14.98.

4-Hydroxy-2-methoxybenzothioanilide (**8**).

This compound was obtained as yellow crystals (benzene/ethyl acetate, 7:3), mp 141-142°; ir (potassium bromide): ν 3318 (NH, OH), 1513 (CN) cm^{-1}; ^{1}H-nmr (deuteriochlorofom/deuteriodimethyl sulfoxide, 20:1): δ 3.88 (s, 3H, OCH_3), 6.41 (d, J = 2.2 Hz, 1H, aromatic 3-H), 6.50 (dd, J = 2.2, 8.8 Hz, 1H, aromatic 5-H), 7.18 (t, J = 7.42 Hz, 1H, aromatic H), 7.34 (t, J = 7.7 Hz, 2H, aromatic H), 7.66 (d, J = 7.7 Hz, 2H, aromatic H), 8.42 (d, J = 8.8 Hz, 1H, aromatic 6-H), 9.51 (br s, 1H, OH), 10.94 (br s, 1H, NH); ^{13}C-nmr (deuteriochlorofom/deuteriodimethyl sulfoxide, 20:1): δ 56.0 (OCH_3), 98.7 (d, C-3), 108.8 (d, C-5), 119.6 (s, C-1), 124.5, 126.2, 128.5, 139.6 (C_6H_5), 137.3 (d, C-6), 156.8 (s, C-2)*, 162.0 (s, C-4)*, 194.0 (s, C=S).

Anal. Calcd. for $C_{14}H_{13}NO_2S$ (259.3): C, 64.84; H, 5.05; S, 12.36. Found: C, 64.67; H, 4.95; S, 12.34.

2-Hydroxy-4-methoxybenzothioanilide (**9**).

This compound was obtained as yellow crystals (*n*-hexane/ethyl acetate, 7:3), mp 165-167°; ir (potassium bromide): ν 3162, 3105 br (NH, OH), 1498 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform/deuteriodimethyl sulfoxide, 20:1): δ 3.62 (s, 3H, OCH_3), 6.27 (dd, J = 2.6, 8.7 Hz, 1H, aromatic 5-H), 6.29 (d, J = 2.6 Hz, 1H, aromatic 3-H), 7.07 (t, J = 7.4 Hz, 1H, aromatic H), 7.21 (t, J = 7.8 Hz, 2H, aromatic H), 7.39 (d, J = 7.7 Hz, aromatic H), 7.76 (d, J = 8.7 Hz, 1H, aromatic 6-H), 11.03 (br s, 1H, NH*), 11.52 (br s, 1H, OH*); ^{13}C-nmr (deuteriochloroform/deuteriodimethyl sulfoxide, 20:1): δ 55.1 (q, OCH_3), 101.7 (d, C-3), 106.15 (d, C-5), 116.5 (s, C-1), 125.1, 126.4, 128.3 (d, aromatic CH), 138.7 (s, aromatic CH), 130.2 (d, C-6), 159.5 (s, C-2)*, 163.2 (s, C-4)*, 193.3 (s, C=S).

Anal. Calcd. for $C_{14}H_{13}NO_2S$ (259.3): C, 64.84; H, 5.05; S, 12.36. Found C, 64.89; H, 5.05; S, 12.21.

N-Ethyl-2,4-dimethoxybenzothioamide (**10**).

This compound was obtained as off-white crystals (*n*-heptane), mp 72-75°; ir (potassium bromide): ν 3325 (NH), 1545 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.34 (t, J = 7.3 Hz, 3H, CH_2CH_3), 3.83 (s, 3H, 4-OCH_3), 3.87 (qd, J = 5.1, 7.3 Hz, 2H, CH_2CH_3), 3.90 (s, 3H, 2-OCH_3), 6.43 (d, J = 2.4 Hz, 1H, aromatic 3-H), 6.55 (dd, J = 2.4 Hz, 8.9, 1H, aromatic 5H), 8.59 (d, J = 8.9 Hz, 1H, aromatic 6-H), 9.32 (br s, 1H, NH); ^{13}C-nmr (deuteriochloroform): δ 13.3 (q, CH_2CH_3), 41.7 (t, CH_2CH_3), 55.6 (q, 4-OCH_3), 56.1 (q, 2-OCH_3), 98.4 (d, C-3), 105.5 (d, C-5), 120.1 (s, C-1), 137.3 (d, C-6), 157.0 (s, C-2)*, 163.2 (s, C-4)*, 194.1 (s, C=S).

Anal. Calcd. for $C_{11}H_{15}NO_2S$ (225.3): C, 58.64; H, 6.71; S, 14.23. Found: C, 58.67; H, 6.99; S, 14.34.

General Procedure for the Reaction of Thioamide Derivatives of Resorcinol with Citral and Citronellal.

The appropriate aldehyde (0.0021 mole) was added dropwise under argon to the stirred mixture of 2,4,6-collidine (0.0021

mole) and the appropriate 2,4-dihydroxybenzothioamide or its monomethylethers (0.0020 mole) at 150° for 0.5 hour. The mixture was heated for 24 hours. The next portion of citral (0.0008 mole) and 2,4,6-collidine (0.0008 mole) was then added and the mixture was heated 8 hours and finally evaporated under reduced pressure. The oily brown residue was chromatographed on silica gel (*n*-hexane:ethyl acetate, 8:2).

rac-2-Methyl-2-(4-methyl-3-pentenyl)-5-methoxy-8-(*N*-phenylcarbothio)-2*H*-benzopyran (**19**).

This compound was obtained as oil, yield 0.148 g (18%); ir (potassium bromide): ν 3295 (NH), 1495 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.47 (br s, 3H, 4'-CH_3), 1.51 (s, 3H, 2-CH_3), 1.66 (br s, 3H, 4'-CH_3), 1.78-1.85 (m, 1H, 1'-C*H*H), 2.01-2.22 (m, 3H, 1'-CH*H*, 2'-CH_2), 3.89 (s, 3H, OCH_3), 5.06 (tt, J = 1.4, 7.1 Hz, 1H, 3'-H), 5.63 (d, J = 10.1 Hz, 1H, 3-H), 6.58 (d, J = 9.2 Hz, 1H, 6-H), 6.77 (d, J = 10.1 Hz, 1H, 4-H), 7.27 (tt, J = 1.1, 7.3 Hz, 1H, aromatic H), 7.43 (t, J = 7.4 Hz, 2H, aromatic H), 7.78 (dd, J = 1.1, 8.9 Hz, 2H, aromatic H), 8.63 (d, J = 9.2 Hz, 1H, 7-H), 11.39 (br s, 1H, NH); ^{13}C-nmr (deuteriochloroform): δ 17.6 (q, C-5'), 22.9 (t, C-2), 25.6 (q, C-5'), 26.5 (q, C-11), 41.1 (t, C-1'), 55.9 (q, OCH_3), 81.2 (s, C-2), 104.1 (d, C-6), 109.8 (s, C-10), 117.6 (d, C-4), 120.1 (s, C-8), 123.2 (d, C-3') 124.2, 126.5, 128.4 (d, aromatic CH), 127.1 (d, C-3), 132.6 (s, C-4'), 136.9 (d, C-7), 139.7 (s, aromatic C), 149.8 (s, C-9)*, 157.9 (s, C-5)*, 193.3 (C=S).

Anal. Calcd. for $C_{24}H_{27}NO_2S$ (393.5): C, 73.25; H, 6.92; S, 8.15. Found: C, 73.16; H, 7.02; S, 7.99.

rac-(6aα,9α,10aβ)-1-Hydroxy-6,6,9-trimethyl-4-(*N*-methylcarbothio)-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran (**20**).

This compound was obtained as yellow crystals (acetone), mp 180-182°; ir (potassium bromide): ν 3370, 3325 br (OH, NH), 1542 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.68 (q, J = 11.5 Hz, 1H, 10-H_{ax}), 0.94 (d, J = 6.6 Hz, 3H, 9-CH_3), 1.08 (qd, J = 3.6, 12.7 Hz, 1H, 8-H_{ax}), 1.12 (s, 3H, 6-CH_3), 1.16 (qd, J = 3.1, 12.8 Hz, 1H, 7-H_{ax}), 1.46 (s, 3H, 6-CH_3), 1.52 (td, J = 2.3, 11.3 Hz, 1H, 6a-H_{ax}), 1.58-1.72 (m, 1H, 9-H_{ax}), 1.84 (br d, J = ca. 11.7 Hz, 1H, 7-H_{eq}), 1.87 (br d, J = ca. 12.0 Hz, 1H, 8-H_{eq}), 2.50 (td, J = 2.4, 11.1 Hz, 1H, 10a-H_{ax}), 3.07 (br d, J = 12.8 Hz, 1H, 10-H_{eq}), 6.43 (d, J = 8.8 Hz, 1H, aromatic 2-H), 7.68 (br s, 1H, OH), 8.48 (d, J = 8.8 Hz, 1H, aromatic 3-H), 9.99 (br s, 1H, NH); ^{13}C-nmr (deuteriochloroform): δ 19.2 (q, C-13), 22.5 (q, C-15), 27.8 (q, C-14), 27.9 (t, C-7), 32.8 (d, C-9), 33.5 (q, NCH_3), 35.4 (t, C-8), 35.7 (d, C-10a), 38.7 (t, C-10), 48.8 (d, C-6a), 79.7 (s, C-6), 108.5 (d, C-2), 112.6 (s, C-11), 118.6 (s, C-4), 134.9 (d, C-3), 152.4 (s, C-1)*, 159.1 (s, C-12)*, 195.9 (s, C=S).

Anal. Calcd. for $C_{18}H_{25}NO_2S$ (319.5): C, 67.68; H, 7.89; S, 10.04. Found: C, 67.81; H, 8.00; S 10.14.

rac-(6aα,9α,10aβ)-1-Hydroxy-6,6,9-trimethyl-4-(*N*-phenylcarbothio)-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran (**21**).

This compound was obtained as yellow crystals (*n*-hexane/ethyl acetate), mp 58-61°; ir (potassium bromide): ν = 3324 (OH), 2990 br (NH), 1544 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.73 (q, J = 12.3 Hz, 1H, 10-H_{ax}), 0.95 (d, J = 6.6 Hz, 3H, 9-CH_3), 1.15-1.24 (m, 2H, 7-H_{ax}, 8-H_{ax}), 1.18 (s, 3H, 6-CH_3), 1.53 (s, 3H, 6-CH_3), 1.59 (td, J = ca. 2.3, 11.4 Hz, 1H, 6a-H_{ax}), 1.61-1.71 (m, 1H, 9-H_{ax}), 1.87 (br d, J = *ca.* 11.0 Hz, 1H, 7-H_{eq}), 1.89 (br d, J = *ca.* 11.6 Hz, 1H, 8-H_{eq}), 2.53 (td, J = 2.3, 11.1 Hz, 1H, 10a-H_{ax}), 3.02 (br d, J = 12.9 Hz, 1H, 10-H_{eq}), 6.21 (br s, 1H, OH), 6.40 (d, J = 8.8 Hz, 1H, aromatic 2-H), 7.25 (t, J = 7.5 Hz, 1H, aromatic H), 7.42 (t, J = 8.1 Hz, 2H, aromatic H), 7.77 (d, J = 8.7 Hz, 2H, aromatic H), 8.47 (d, J = 8.8 Hz, 1H, 3-H), 11.49 (br s, 1H, NH); ^{13}C-nmr (deuteriochloroform): δ 19.32 (q, C-14), 22.5 (q, C-15), 27.8 (q, C-13), 27.9 (t, C-7), 32.9 (d, C-9), 35.4 (t, C-8), 35.7 (d, C-10a), 38.8 (t, C-10), 48.7 (d, C-6a), 80.4 (s, C-6), 108.7 (d, C-2), 112.7 (s, C-11), 120.8 (s, C-4), 124.2, 126.4, 128.8 (d, aromatic CH), 139.8 (s, aromatic C), 135.4 (d, C-3), 151.8 (s, C-1), 158.1 (s, C-12), 194.2 (s, C=S).

Anal. Calcd. for $C_{23}H_{27}NO_2S$ (381.5): C, 72.41; H, 7.13; S, 8.40. Found: C, 72.32; H, 7.00; S, 8.32.

rac-(6aα,9α,10aβ)-1-Methoxy-6,6,9-trimethyl-4-(*N*-phenylcarbothio)-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran (**22**).

This compound was obtained as pale yellow crystals (toluene/*n*-hexane), mp 163-165.5°; ir (potassium bromide): ν 3250 (NH), 1495 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.70 (q, J = 11.5 Hz, 1H, 10-H_{ax}), 0.96 (d, J = 6.6 Hz, 3H, 9-CH_3), 1.04-1.25 (m, 2H, 7-H_{ax}, 8-H_{ax}), 1.17 (s, 3H, 6-CH_3), 1.53 (s, 3H, 6-CH_3), 1.60 (td, J = 2.2 Hz, 11.3, 1H, 6a-H_{ax}), 1.61-1.71 (m, 1H, 9-H_{ax}), 1.86 (br d, J = *ca.* 11.2 Hz, 1H, 7-H_{eq}), 1.90 (br d, J = *ca.* 10.7 Hz, 1H, 8-H_{eq}), 2.51 (td, J = 2.4, 11.0 Hz, 1H, 10a-H_{ax}), 2.92 (br d, J = 12.6 Hz, 1H, 10-H_{eq}), 3.87 (s, 3H, OCH_3), 6.56 (d, J = 9. 1 Hz, 1H, aromatic 2-H), 7.25 (t, J = 7.5 Hz, 1H, aromatic H), 7.42 (t, J = 7.6 Hz, 2H, aromatic H), 7.80 (d, J = 7.7 Hz, 2H, aromatic H), 8.62 (d, J = 9.1, 1H, aromatic 3-H), 11.49 (br s, 1H, NH); ^{13}C-nmr (deuteriochloroform): δ 19.2 (q, C-14), 22.6 (q, C-15), 27.8 (q, C-13), 28.0 (t, C-7), 32.9 (d, C-9), 35.4 (t, C-8), 35.9 (d, C-10a), 39.1 (t, C-10), 48.9 (d, C-6a), 55.4 (q, OCH_3), 81.1 (s, C-6), 103.5 (d, C-2), 114.2 (s, C-11), 121.0 (s, C-4), 124.1, 126.3, 128.8 (d, aromatic CH), 139.9 (s, aromatic C), 135.6 (d, C-3), 151.1 (s, C-1)*, 161.6 (s, C-12)*, 194.2 (C=S).

Anal. Calcd. for $C_{24}H_{29}NO_2S$ (395.6): C, 72.87; H, 7.39; S, 8.10. Found: C, 72.85; H, 7.35; S, 8.25.

rac-(2'α,5'α,1'β)-*N*-Methyl-2,4-dihydroxy-3-(2-isopropenyl-5-methylcyclohexyl)benzothioamide (**23**). - A 1:1 Mixture of Rotamers.

This compound was obtained as colorless crystals (additionally purified on a preparative tlc-plate), mp 160-167°; ^{1}H-nmr (deuterioacetone): δ 0.91 (d, J = 6.4 Hz, 3H, 7'-CH_3) and 0.92 (d, J = 6.4 Hz, 3H, 7'-CH_3), 1.08 (qd, J = 5.6, 12.9 Hz, 1H, 3'-H_{ax}) and 1.12 (qd, J = 5.6, 12.9 Hz, 1H, 3'-H_{ax}), 1.38-1.60 (m, 3H, 4'-H_{eq}, 5'-H_{ax}, 6'-H_{eq}), 1.57 (t, J = 0.6 Hz, 8-CH_3), 1.69 (qd, J = 3.3, 12.8 Hz, 1H, 4'-H_{ax}) and 1.71 (qd, J = 3.3, 12.8 Hz, 1H, 4'-H_{ax}), 1.75 (m, 1H, 3'-H_{eq}) and 1.78 (m, 1H, 3'-H_{eq}), 1.78 (q, J = 12.0 Hz, 1H, 6'-H_{ax}) and 1.90 (q, J = 12.0 Hz, 1H, 6'-H_{ax}), 3.13 (td, J = 3.3, 11.6 Hz, 1H, 2'-H_{ax}) and 3.19 (td, J = 3.3, 11.6 Hz, 1H, 2'-H_{ax}), 3.20 (d, J = 4.7, 3H, NCH_3) and 3.21(d, J = 4.7 Hz, 3H, NCH_3), 3.36 (dd, J = 3.3, 11.6 Hz, 1H, 1'-H_{ax}) and 3.46 (dd, J = 3.3, 11.6 Hz, 1H, 1'-H_{ax}), 4.34-4.37 (m, 1H, =CH*H*), 4.61-4.64 (m, 1H, =CH*H*), 6.30 (d, J = 8.8 Hz, 1H, aromatic 5-H) and 6.36 (d, J = 8.8 Hz, 1H, aromatic 5-H), 7.20 (d, J = 8.8 Hz, 1H, 6-H) and 7.22 (d, J = 8.8 Hz, 1H, 6-H), 8.75 (s, 1H, OH or NH), 9.26 (s, 1H, NH or OH), 12.25 (s, 1H, OH) and 12.33 (s, 1H, OH); ^{13}C-nmr (deuterioacetone): δ [19.2 and 19.4 (q, C-9')], 22.3 (q, C-7'), [32.5 and 32.5 (q, NCH_3)], 38.9 (t, C-4'), [34.1 and 34.2 (d, C-5')], 36.1 (C-3'), [38.5 and 39.2 (C-1')], [39.3 and 39.5 (C-6')], [47.4 and 47.7 (C-2')], [107.3 and 108.1 (C-5)], [109.9 and 109.9 (C- 10')], [116.0 and 116.5 (C-3)], [120.3 and 120.5 (C-1)], [124.4 and 124.5 (C-6)], [150.36 and 150.44

(C-8')], [159.3 and 159.3 (C-2)]*, [160.9 and 161.0 (C-4)]*, [195.4 and 195.5 (C=S)].

Anal. Calcd. for $C_{18}H_{25}NO_2S$ (319.5): C, 67.68; H, 7.89; S, 10.04. Found: C, 67.55; H, 7.72; S 9.91.

rac-(6aα,9α,10aβ)-3-Hydroxy-6,6,9-trimethyl-2-(*N*-phenylcarbothio)-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran (**26**).

This compound was obtained as pale yellow crystals (*n*-hexane/ethyl acatate), mp 204.5-206.5°; ir (potassium bromide): 3275, 2645 br (OH, NH), 1493 (CN) cm^{-1}; ^{1}H-nmr (deuterioacetone): δ 0.71 (q, J = 12.4 Hz, 1H, 10-H_{ax}), 0.84 (d, J = 6.6 Hz, 3H, 9-CH_3), 0.92 (qd, J = 3.7, 12.7 Hz, 1H, 8-H_{ax}), 1.04 (s, 3H, 6-CH_3), 1.15 (qd, J = 3.4, 12.8 Hz, 1H, 7-H_{ax}), 1.23 (td, J = 2.9, 11.5 Hz, 1H, 6a-H_{ax}), 1.26 (s, 3H, 6-CH_3), 1.41-1.54 (m, 1H, 9-H_{ax}), 1.67-1.72 (m, 2H, 7-H_{eq}, 8-H_{eq}), 2.31 (td, J = 3.2, 11.6 Hz, 1H, 10a-H_{ax}), 2.37 (br d, J = *ca* 12.9 Hz, 1H, 10-H_{eq}), 6.15 (s, 1H, aromatic 4-H), 7.17 (tt, J = 2.4, 7.0 Hz, 1H, aromatic H), 7.30 (tt, J = 2.6, 6.9 Hz, 2H, aromatic H), 7.50 (d, J = 7.7 Hz, 2H, aromatic H), 7.77 (s, 1H, 1-H), 10.7 (b s, 1H, NH), 11.3 (br s, 1H, OH); ^{13}C-nmr (deuterioacetone): δ 20.7 (q, C-13), 22.9 (q, C-15), 28.1 (t, C-7) 28.2 (q, C-14), 33.0 (d, C-9), 35.4 (t, C-8), 35.9 (d, C-10a), 40.3 (t, C-10), 47.8 (d, C-6a), 79.4 (s, C-6), 105.7 (d, C-4), 117.6 (s, C-2), 118.4 (s, C-11), 126.9 (d, C-1), 126.5, 127.5, 129.5 (d, aromatic CH), 140.2 (s, aromatic C), 159.0 (s, C-3)*, 159.4 (s, C-12)*, 195.1 (s, C=S).

Anal. Calcd. for $C_{23}H_{27}NO_2S$ (381.5): C, 72.41; H, 7.13; S, 8.40. Found: C, 72.23; H, 7.25; S, 8.46.

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