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Cannabinoids. 1. 1-Amino- and 1-Mercapto-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyrans

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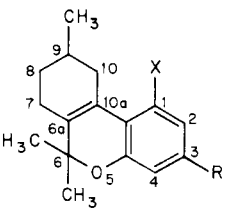
A series of 1-amino- and 1-mercapto-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyrans was synthesized and subsequently evaluated in three rodent test systems for CNS activity. The structure–activity data generated indicate that, in general, a change of the 1-hydroxy group to an amine results in a retention of pharmacological activity but that a change to sulfur results in loss of pharmacological activity. Derivatization of the 1-amino group with various functions decreased the activity of the parent compound. For optimum potency, in all series, the 3-position alkyl side chain should be either 1,1- or 1,2-dimethylheptyl. With either the 1-hydroxy- or 1-amino-7,8,9,10-tetrahydro-3-(1,1-dimethylheptyl)-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (**4c** or **10c**), preparation of the optically active antipodes did not lead to any great degree of separation of activity. Both of the antipodes possess pharmacological activity as measured in these rodent test systems.

During the 1940's, two independent groups of workers began their studies on the chemistry of the natural products from marihuana: Adams and co-workers in the United States and Todd and co-workers in England. From their investigations into the structures of the natural products from *Cannabis sativa* L., extensive programs in syntheses of 7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyrans (THDP) evolved. The resulting cannabinoid derivatives were tested in dog-ataxia and rabbit-corneal-areflexia assays for their pharmacological activity. An excellent summary of this work including tables of structure–activity data is provided by Mechoulam.[1]

A reexamination of the relative CNS potency of a series of 3-alkyl derivatives recently has been reported by Loev and co-workers.[2] Using rats as test animals, they observed structure–activity correlations that differed significantly from those reported by Adams and Todd for dogs and rabbits. Also, with specific relation to the 1 position of the synthetic THDP's, Loev and co-workers found that acetylation of the phenolic hydroxyl group diminished and methylation eliminated activity in their rat assays.

Additionally, in contrast to previously reported work,[3] Loev and co-workers reported that replacement of the 1-hydroxyl by hydrogen eliminated activity in the case where the 3-position side chain was *n*-pentyl but *not* where the 3-position side chain was 1,2-dimethylheptyl (1,2-DMH). In spite of this exception, it appears that a phenolic hydroxyl in the 1 position is a necessary requirement for pharmacological activity in most cannabinoids; removal of the hydroxyl or methylation leads to loss of activity.[2,4]

To our knowledge, no one has reported the effect on activity by replacement of the 1-position oxygen by other heteroatoms, namely, nitrogen and sulfur. We wish, therefore, to report on the synthesis and CNS activity of a series of 1-amino- and 1-mercapto-THDP's represented by the general formula



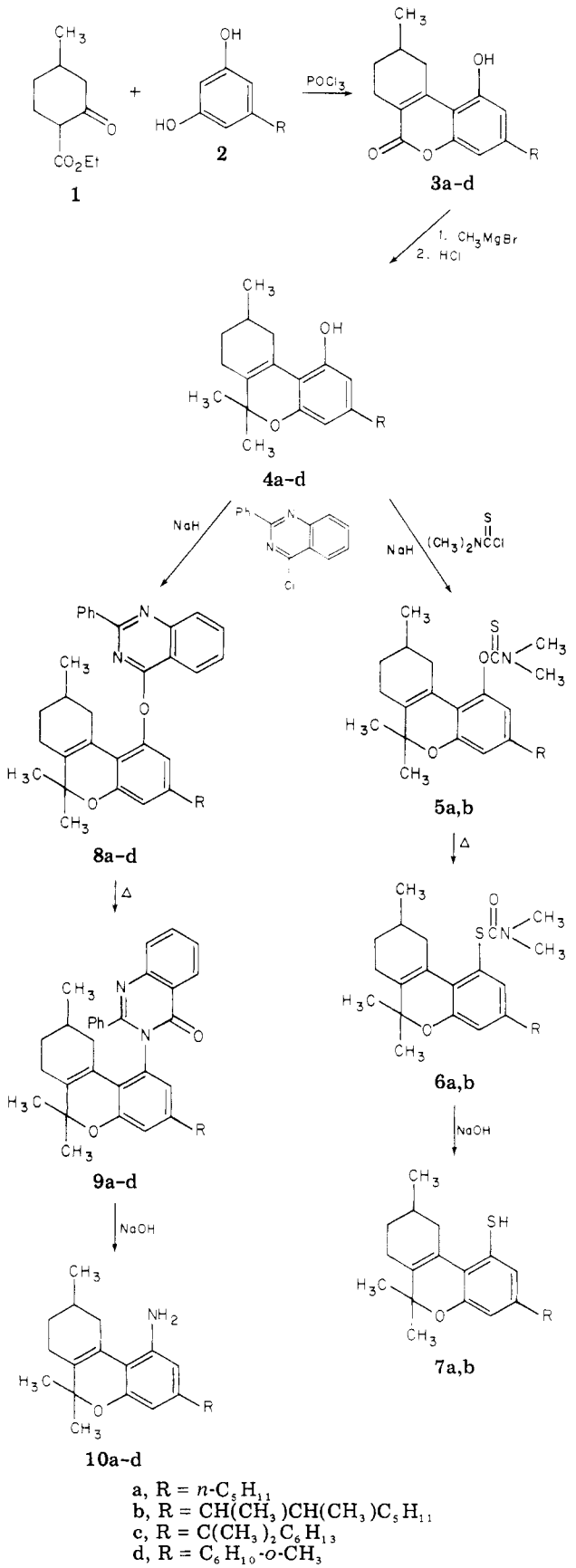
X = NR_1R_2 or SH
R = alkyl or cycloalkyl

Our choice of R was predicated on the basis of studies in our laboratories that indicated when the 1 position was substituted by a hydroxyl the greatest potency occurred when R was either 1,2- or 1,1-DMH. The same conclusion, about the relative CNS potency of 3-alkyl side chains, was reported by Loev and co-workers.[2] The cycloalkyl derivatives **4d** and **10d** were prepared in order to assess the effect of this modified side chain on CNS activity. Adams reported a significant increase in potency of the compound represented by the general formula above (X = OH and R = *n*-pentyl) when the optical center at carbon 9 was resolved.[5] From the more potent DMH side-chain structures, we reasoned that Adams' data would suggest even greater differences between isomers. Therefore, we prepared optically active antipodes of β-keto ester 1 (Scheme I) and incorporated these into 1-hydroxy- and 1-amino-3-(1,1-DMH)-THDP's.

Synthetic Chemistry. The synthetic routes to the 1-amino and 1-mercapto compounds are outlined in Scheme I. Unless otherwise indicated, all compounds are racemic when possible. Standard von Pechmann condensation of the β-keto ester **1** with the requisite resorcinols **2a–d** yielded the corresponding coumarins **3a–d** which subsequently were converted to the THDP's **4a–d** via a Grignard reaction described by Adams and co-workers.[6,7]

Conversion of the 1-hydroxy compounds **4a,b** to the 1-mercapto compounds was accomplished using Newman's method[8] for converting simple phenols to thiophenols.

Scheme I[a]

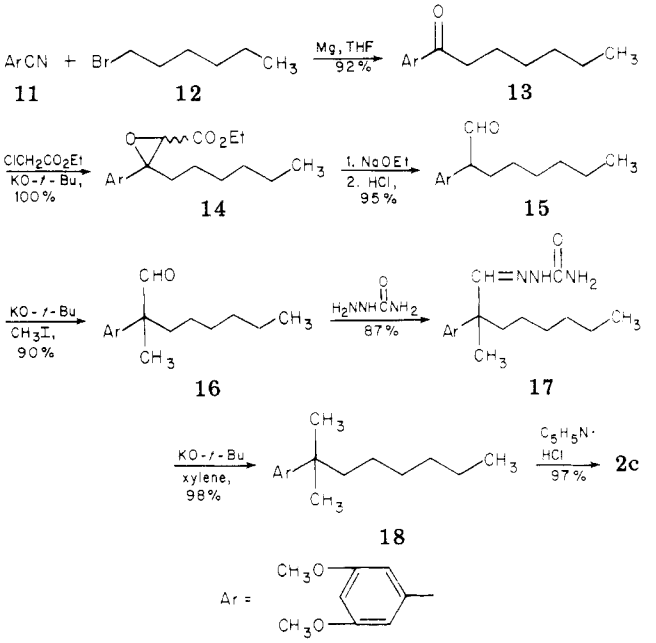


a, R = n-C_5H_{11}
b, R = $CH(CH_3)CH(CH_3)C_5H_{11}$
c, R = $C(CH_3)_2C_6H_{13}$
d, R = C_6H_{10}-o-CH_3

[a] The letters a, b, c, and d refer to the same respective side chains throughout this paper.

Their method involved thermal rearrangement of thiocarbamate intermediates **5a,b** to thiolcarbamates **6a,b**. These thiolcarbamates were hydrolyzed to the desired 1-mercapto compounds **7a,b**.

Scheme II



For preparation of the 1-amino derivatives, compounds **4a–d** were used as starting materials. The conversion was patterned on that reported by Scherrer and Beatty[9] and involved the thermal rearrangement of 2-phenylquinazolinyl derivatives **8a–d** to the 2-phenylquinazolinones **9a–d** which were hydrolyzed subsequently to the desired 1-amino compounds **10a–d**.

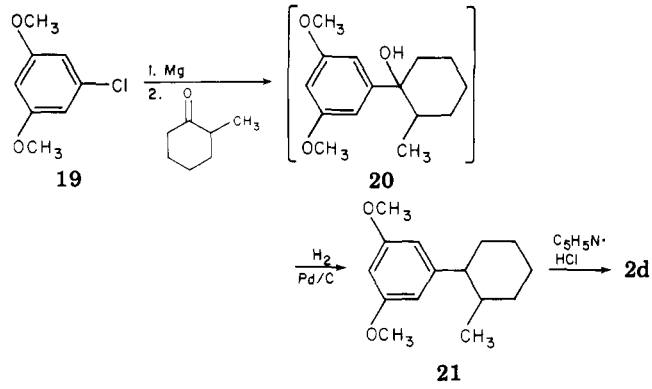
The required resorcinol starting materials **2a–d** were obtained in a variety of ways. Olivetol (**2a**) is commercially available. The 5-(1,2-DMH) homologue **2b** was prepared according to the method described by Adams and coworkers.[10] Although we initially prepared the 5-(1,1-DMH)resorcinol (**2c**) according to Adams' procedure,[10] our need for larger quantities led to the development of what we believe is a superior method outlined in Scheme II.

Combining the Grignard reagent obtained from hexyl bromide (**12**) with 3,5-dimethoxybenzonitrile (**11**) gave the heptanophenone **13**. The glycidic ester **14** preparation proceeded in quantitative yield and was used without further purification to obtain the aldehyde **15**. This aldehyde was also sufficiently pure in the crude state to be used in the next step. Methylation then yielded the aldehyde **16**. Attempts to reduce the aldehyde **16** via hydrazone formation and Wolff–Kishner reduction led to formation of large quantities of the corresponding azine and very little product **18**. However, these difficulties were circumvented by preparation of the crystalline semicarbazone **17** which was reduced with KO-t-Bu[11] to afford the dimethoxy compound **18**. Pyridine hydrochloride cleavage of the methyl ethers afforded **2c**, in an overall yield of 65%. This scheme is generally applicable for the synthesis of many 5-(1,1-dimethylalkyl)resorcinols. The 5-cycloalkylresorcinol **2d** was prepared as outlined in Scheme III.

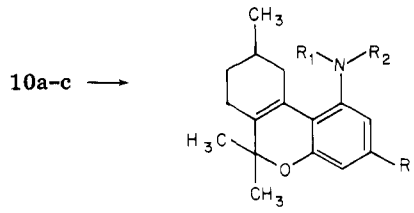
Combining the Grignard reagent prepared from 3,5-dimethoxychlorobenzene (**19**) with 2-methylcyclohexanone gave the intermediate addition product **20** which on hydrogenolysis afforded the 5-cycloalkylresorcinol dimethyl ether **21**. Again, pyridine hydrochloride cleavage of the methyl ethers afforded the required cycloalkylresorcinol **2d**.

Using the available 1-amino compounds **10a–c** as starting materials, we prepared a number of amino-sub-

Scheme III



Scheme IV



22a,b, R_1 = H; R_2 = C(=O)CH_3
23b, R_1 = H; R_2 = CH_3
24a,b, R_1 = R_2 = CH_3
25c, R_1 = H; R_2 = SO_2CH_3

stituted derivatives (Scheme IV).

The *N*-acetyl derivatives **22a,b**, *N*-methyl derivative **23b**, *N,N*-dimethyl derivatives **24a,b**, and sulfonamide **25c** were prepared according to known literature procedures.[12-14]

The optical antipodes of the 1-hydroxy derivative **4c** and 1-amino derivative **10c** were prepared from the optically active antipodes of the β-keto ester **1** (Scheme V). These optically active β-keto esters were in turn prepared from *d*- and *l*-3-methylcyclohexanone (**26**) according to the procedure reported by Adams.[5] The *d*-3-methylcyclohexanone (**26**) obtained commercially had a rotation $[\alpha]^{25}D$ +13.5°. The *l*-3-methylcyclohexanone (**26**), we prepared according to the procedure of Leonard and Boyer,[15] had a rotation $[\alpha]^{25}D$ −8.8°, despite the fact that the physical constants and rotation of the intermediates agreed with those reported.[5,15] This apparent loss of optical activity was reflected throughout the series of conversion intermediates to the desired products (Table I).

Structure–Activity Discussion. In assessing the CNS activities of cannabinoid analogues, we used three rodent test systems (see Experimental Section for a complete description of these assays). Compounds generally classified as major and minor tranquilizers were effective in taming the hyperreactivity of septal-lesioned rats. Additionally, this test differentiated between those tranquilizers (e.g., benzodiazepines and phenothiazines) and general CNS depressants such as barbiturates. Barbiturates, although exhibiting taming behavior, also decrease motor activity. At doses that show taming effects, the tranquilizers have no apparent effect on motor activity.[16] Compounds that, clinically, were effective antidepressants or appetite suppressants were found to block the killing behavior of rats in the muricidal rat assay. Finally, we measured the exploratory activity of mice placed in an activity cage. This test showed an alteration of exploratory behavior from control animals.

Our experience with *l*-Δ^9-THC[17] and other THDP derivatives indicated that any potent agent would be effective in the rat assays at doses of 10 mg/kg po or less and in the mouse activity test at doses of 20 mg/kg po or less. Thus, these doses were chosen as screening doses; a compound was judged to be nonactive (N) for our purposes if it did not show activity at these levels. *l*-Δ^9-THC was active below the screening dose in two of the three tests, while 3-(1,2-DMH)-**4b** and 3-(1,1-DMH)-**4c** were active well below our screening doses.

Scheme V

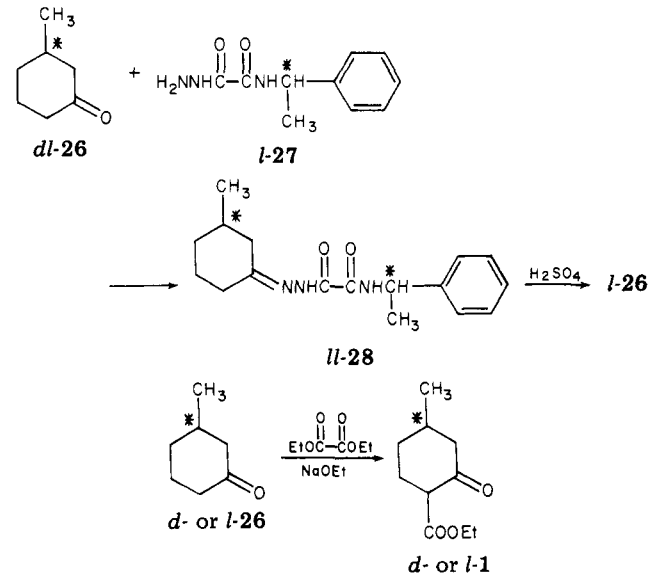


Table I. Rotations of Optical Isomers

Compd	*d*, $[\alpha]^{25}D$, deg	*l*, $[\alpha]^{25}D$, deg
26	+13.5 (neat)[a]	−8.8 (neat)
1	+92 (*neat*)[b]	−63 (*neat*)[c]
3c	+131 (*c* 0.421, EtOH)	−63 (*c* 0.426, EtOH)
4c	+142 (*c* 1.733, EtOH)	−78 (*c* 1.676, EtOH)
8c	+104 (*c* 1.463, $CHCl_3$)	−59 (*c* 1.509, $CHCl_3$)
9c	+24 (*c* 1.630, $CHCl_3$)	−13 (*c* 1.178, $CHCl_3$)
10c	+93 (*c* 1.323, $CHCl_3$)	−77 (*c* 1.346, $CHCl_3$)

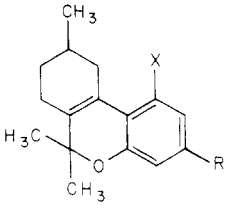
[a] Commercially available from Aldrich Chemical Co. as 98% pure. [b] Lit.[5] $[\alpha]^{20}D$ +90.8°. [c] Lit.[5] $[\alpha]^{25}D$ −84.6°.

Pharmacological testing results are tabulated in Table II. In the 1-hydroxy-THDP's **4a–c**, results show that the 3-(1,1-DMH) analogue **4c** is about four times as potent as the 3-(1,2-DMH)-**4b**. Either of these is significantly more active than the *n*-pentyl analogue **4a**. These observations are in disagreement with the original Adams' data[1] but agree quite well with Loev and co-workers,[2] who also found **4c** to be more potent than **4b** by a factor of 2 in rats.

Note, however, that in the 1-amino series, the 3-(1,2-DMH) analogue **10b** is more active than the 3-(1,1-DMH) analogue **10c**, a reversal of the former conclusion for the 1-hydroxy series.

Of further significance is the finding that the *l* isomer of **4c** in the 1-hydroxy series has about 2–4 times the potency of the *d* isomer in rats (but not in mice), while both isomers, *d* and *l*, of the 1-amino compound **10c** are approximately equal in rats at 10 mg/kg po. Thus, we tentatively conclude that conformational effects of the 9-methyl position of 1-hydroxy- or 1-amino-3-(1,1-DMH)-THDP's **4c** and **10c** have a minimal effect on the potency of these compounds in our rodent test systems. We are "tentative" about this conclusion because of our lack of success in the preparation of optically pure *l* isomers (Table I).

Table II. Pharmacological Data



Compd	X	R	Minimum effective doses: Muricidal rat[a]	Septal-lesioned rat[a]	Mouse act.[b]
l-Δ^9-THC[c]			5.0	N[d]	10.0
4a	OH	*n*-C_5H_{11}	10.0	N	N
4b	OH	$CH(CH_3)CH(CH_3)C_5H_{11}$	2.5	5.0	0.62
dl-**4c**	OH	$C(CH_3)_2C_6H_{13}$	0.62	1.25	0.62
d-**4c**	OH	$C(CH_3)_2C_6H_{13}$	5.0	2.5	0.31
l-**4c**	OH	$C(CH_3)_2C_6H_{13}$	1.25	1.25	0.31
4d	OH	C_6H_{10}-*o*-CH_3	N	N	N
7a	SH	*n*-C_5H_{11}	N	N	N
7b	SH	$CH(CH_3)CH(CH_3)C_5H_{11}$	N	N	N
10a	NH_2	*n*-C_5H_{11}	N	N	N
10b	NH_2	$CH(CH_3)CH(CH_3)C_5H_{11}$	5.0	10.0	2.5
dl-**10c**	NH_2	$C(CH_3)_2C_6H_{13}$	10.0	N	5.0
d-**10c**	NH_2	$C(CH_3)_2C_6H_{13}$	N	N	10.0
l-**10c**	NH_2	$C(CH_3)_2C_6H_{13}$	10.0	N	5.0
10d	NH_2	C_6H_{10}-*o*-CH_3	N	N	20.0
22a	$NHCOCH_3$	*n*-C_5H_{11}	N	N	N
22b	$NHCOCH_3$	$CH(CH_3)CH(CH_3)C_5H_{11}$	10.0	N	N
23b	$NHCH_3$	$CH(CH_3)CH(CH_3)C_5H_{11}$	N	N	20.0
24a	$N(CH_3)_2$	*n*-C_5H_{11}	N	N	N
24b	$N(CH_3)_2$	$CH(CH_3)CH(CH_3)C_5H_{11}$	N	N	20.0
25c	$NHSO_2CH_3$	$C(CH_3)_2C_6H_{13}$	N	N	20.0

[a] Initial testing dose, 10 mg/kg po. [b] Initial testing dose, 20 mg/kg po. [c] Kindly supplied to us by R. Mechoulam, The Hebrew University, Jerusalem, Israel. [d] N = inactive at the initial test dose.

In the unsubstituted 1-hetero series, the 3-*n*-pentyl analogues **4a**, **7a**, and **10a** were essentially devoid of activity. Our attempts to find activity in 3-cycloalkyl derivatives **4d** and **10d** were not successful. Thus, it is our conclusion that the 1,1- or 1,2-DMH 3-position side chain imparts the greatest pharmacological activity to the derivatives shown in Table II in the rodent test systems indicated.

Derivatization of the 1-amino group of compound **10c** with acetyl (**22b**), monomethyl (**23b**), or dimethyl (**24b**) functions decreased the activity of the parent compound. The methyl ether and the acetate of 3-(1,2-DMH)-**4b** were reported to be much less potent than the parent compound.[2] It was reported[14,18] that with sympathomimetic amines the alkanesulfonamido group imparts much the same biological activity as a phenolic hydroxyl group. Compound **25c** would, therefore, have been expected to possess activity similar to the phenol **4c**. The fact that the sulfonamide **25c** is far less potent than the phenol **4c** leads us to conclude that this modification also diminishes, rather than enhances, the biological activity of the parent amine **10c**.

In the 1-mercapto series, even the 3-(1,2-DMH) derivative **7b** did not have activity in our rodent test systems at the maximum screening doses. Thus, the replacement of oxygen by sulfur in the 1 position of compounds **4a** and **4b** does not lead to an improvement in pharmacological potency; indeed, in both cases the sulfur derivatives are less active.

It is important to emphasize several observations concerning these structure–activity data. (1) The screening doses chosen were very low in comparison to "normal" screening doses in rodents. Thus, many of our compounds may have had activity at higher doses than our maximum screening doses of 10 and 20 mg/kg po. (2) We selectively chose three rodent test systems because we were looking for potential CNS agents as tranquilizers or antidepressants. These hetero analogues in other test systems might possess interesting activities. We do not rule out the possibility that our rodent test systems might have overlooked potentially worthwhile CNS agents. We have, however, been able to find cannabinoid compounds that did possess potent activities in these relatively simple rodent assays and our results on the potency of *l*-Δ^9-THC and 3-(1,2-DMH)-**4b** are in agreement with others in the cannabinoid field.[1]

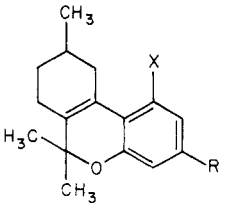
Our general conclusion about structure–activity relationships in these THDP's is that a change of the 1-hydroxy group to an unsubstituted amine results in a retention of pharmacological activity but that a change to sulfur results in loss of activity. For best potency, the 3-position alkyl side chain should be either 1,1-DMH or 1,2-DMH. And, finally, in either of the active compounds with 3-(1,1-DMH) side chains (**4c** and **10c**), preparation of the optically active antipodes does not lead to any great degree of separation of activity. Both antipodes possess pharmacological activity as measured in our rodent test systems.

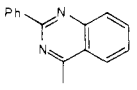
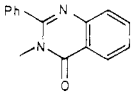
With the exception of compound **5b**, all intermediates (**5a**–**9d**, Table III) leading to the preparation of 1-amino- and 1-mercapto-THDP's were inactive in all three test systems at the screening dose. Compound **5b** had a minimum effective dose of 10 mg/kg in the muricidal rat and mouse activity tests but was inactive in the septal-lesioned rat test. This degree of activity is certainly much reduced compared to the parent 1-hydroxy compound **4b**.

Experimental Section

Biological Procedures. Compounds were dissolved in acetone and an equal volume of 1% Tween 80 was added. The acetone

Table III. 1,3-Disubstituted 6,6,9-Trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyrans



Compd	X	R	% yield[a]	Mp, °C	Formula	Analyses
4a	OH	n-C_5H_{11}	100	*b*	$C_{21}H_{30}O_2$	C, H
4b	OH	$CH(CH_3)CH(CH_3)C_5H_{11}$	99	*b*	$C_{25}H_{38}O_2$	C, H
dl-4c	OH	$C(CH_3)_2C_6H_{13}$	94	*b*	$C_{25}H_{38}O_2$	C, H
d-4c	OH	$C(CH_3)_2C_6H_{13}$	78	*b*	$C_{25}H_{38}O_2$	C, H
l-4c	OH	$C(CH_3)_2C_6H_{13}$	81	*b*	$C_{25}H_{38}O_2$	C, H
4d	OH	C_6H_{10}-*o*-CH_3	80	*b*	$C_{23}H_{32}O_2$	C, H
5a	$OC(=S)N(CH_3)_2$	n-C_5H_{11}	82	*b*	$C_{24}H_{35}NO_2S$	C, H, N, S
5b	$OC(=S)N(CH_3)_2$	$CH(CH_3)CH(CH_3)C_5H_{11}$	85	*b*	$C_{28}H_{43}NO_2S$	C, H, N, S
6a	$SC(=O)N(CH_3)_2$	n-C_5H_{11}	86	*b*	$C_{24}H_{35}NO_2S$	C, H, N, S
6b	$SC(=O)N(CH_3)_2$	$CH(CH_3)CH(CH_3)C_5H_{11}$	76	*b*	$C_{28}H_{43}NO_2S$	C, H, N, S
7a	SH	n-C_5H_{11}	94	*b*	$C_{21}H_{30}OS$	C, H, S
7b	SH	$CH(CH_3)CH(CH_3)C_5H_{11}$	75	*b*	$C_{25}H_{38}OS$	C, H, S
8a		n-C_5H_{11}	79	135-136	$C_{35}H_{38}N_2O_2$	C, H, N
8b		$CH(CH_3)CH(CH_3)C_5H_{11}$	62	*c*	$C_{39}H_{46}N_2O_2$	C, H, N
dl-8c		$C(CH_3)_2C_6H_{13}$	89	*c*	$C_{39}H_{46}N_2O_2$	C, H, N
d-8c		$C(CH_3)_2C_6H_{13}$	80	*c*	$C_{39}H_{46}N_2O_2$	C, H, N
l-8c		$C(CH_3)_2C_6H_{13}$	81	*c*	$C_{39}H_{46}N_2O_2$	H; C,[d] N[d]
8d		C_6H_{10}-*o*-CH_3	82	*c*	$C_{36}H_{40}N_2O_2$	C, H, N
9a		n-C_5H_{11}	76	*e*	$C_{35}H_{38}N_2O_2$	C, H, N
9b		$CH(CH_3)CH(CH_3)C_5H_{11}$	69	*e*	$C_{39}H_{46}N_2O_2$	C, H, N
dl-9c		$C(CH_3)_2C_6H_{13}$	79	*e*	$C_{39}H_{46}N_2O_2$	C, H, N
d-9c		$C(CH_3)_2C_6H_{13}$	75	*e*	$C_{39}H_{46}N_2O_2$	C, H, N
l-9c		$C(CH_3)_2C_6H_{13}$	74	*e*	$C_{39}H_{46}N_2O_2$	C, H, N
9d		C_6H_{10}-*o*-CH_3	65	*e*	$C_{36}H_{40}N_2O_2$	C, H, N
10a	NH_2	n-C_5H_{11}	72	*b*	$C_{21}H_{31}NO$	C, H, N
10b	NH_2	$CH(CH_3)CH(CH_3)C_5H_{11}$	73	*b*	$C_{25}H_{39}NO$	C, H, N
dl-10c	NH_2	$C(CH_3)_2C_6H_{13}$	68	*b*	$C_{25}H_{39}NO$	C, H, N
d-10c	NH_2	$C(CH_3)_2C_6H_{13}$	66	*b*	$C_{25}H_{39}NO$	C, H, N
l-10c	NH_2	$C(CH_3)_2C_6H_{13}$	70	*b*	$C_{25}H_{39}NO$	C, H, N
10d	NH_2	C_6H_{10}-*o*-CH_3	60	*b*	$C_{23}H_{33}NO$	C, H, N
22a	$NHCOCH_3$	n-C_5H_{11}	74	175-176	$C_{23}H_{33}NO_2$	C, H, N
22b	$NHCOCH_3$	$CH(CH_3)CH(CH_3)C_5H_{11}$	74	*e*	$C_{27}H_{41}NO_2$	C, H, N
23b	$NHCH_3$	$CH(CH_3)CH(CH_3)C_5H_{11}$	81	*b*	$C_{26}H_{41}NO$	C, H, N
24a	$N(CH_3)_2$	n-C_5H_{11}	76	*b*	$C_{23}H_{35}NO$	C, H, N
24b	$N(CH_3)_2$	$CH(CH_3)CH(CH_3)C_5H_{11}$	83	*b*	$C_{27}H_{43}NO$	C, H, N
25c	$NHSO_2CH_3$	$C(CH_3)_2C_6H_{13}$	47	*c*	$C_{26}H_{41}NO_3S$	C, H, N, S

[a] Based on immediate precursor. [b] Isolated by silica gel chromatography as a viscous oil. Single spot on TLC (10% EtOAc-PhH). [c] Isolated by chromatography as an immobile glass. Single spot on TLC. [d] C: calcd, 81.49; found, 80.80. N: calcd, 4.87; found, 4.37. [e] Isolated by chromatography as an amorphous solid. Single spot on TLC.

was then flash evaporated leaving a suspension of compound in 1% Tween 80 and the concentration adjusted so that the animals received the same volume per kilogram body weight, regardless of dose. Vehicle controls were run on the same "volume of injection" basis.

Septal-Lesioned Rat Test. We used rats with septal lesions as one of our tests for behavior altering drugs. The hyperreactivity of the animals will be depressed by compounds classed as tranquilizers and this test can readily differentiate between general CNS depressants, such as barbiturates, that cause ataxia and tranquilizers of the class of benzodiazepines and phenothiazines that inhibit affect with apparent inhibition of motor activity.[16]

Rats were made hyperreactive by destruction of an area in the septal region of the brain.[19] Mechanical lesions were made using a 26-gauge hypodermic needle with a 0.75-mm burr at a right angle to the shaft.

The A-P and lateral coordinates for the mechanical lesions were $A = 7.5$ and $L = 0.0$, using the coordinates of deGroot.[20] The animals were not used for at least 2 weeks postoperatively.

A behavioral rating of from 0 to 2 for seven parameters was used, similar to that used by Harrison and Lyon.[21] Thus, 14 represented a maximum rating. A score of 0 represented no reaction; 1, a weak reaction; and 2, a marked, well-developed reaction. The seven parameters or reactions measured, and the order in which they were presented, were (1) startle reaction to a loud handclap; (2) startle reaction to a puff of air on the back of the neck; (3) attempting to bite an object in contact with the fur on the side of the neck; (4) biting an object approaching the nose or held near the nose; (5) following or biting an object moved in front of the nose; (6) following or biting an object moved about in contact with the vibrissae; (7) hopping and attempting to bite an object rubbed on the back adjacent to the tail. Animals with a rating of 11 or higher were considered hyperreactive. This is an arbitrary value used in our laboratory.

The data obtained are reported in two ways: (1) a *P* value, which is an index of the effectiveness of a compound in reducing the reactivity of the rats at each of the five test periods, and (2) an *E* value, which is an index of the effectiveness of a compound

in reducing the reactivity of the rats over a 5-h period.

P values were computed for the 30-, 60-, 120-, 240-, and 300-min periods after drug. The computation was done as follows. Each group of rats served as its own control. The sum of the postdrug rating for each time period for each group (T) was divided by the sum of the predrug control rating (C). This fraction when substracted from 1.0 is the *P* value. Thus, increasing drug effects yield higher *P* values.

$$P = 1.0 - T/C$$

The *P* value may be computed until this value has returned to a 0. This procedure is most useful for drugs with a long period of onset and/or a long duration of action.

The *E* values were computed as follows. The sum of the ratings for each group of rats for each 30-min period following drug for 300 min (or ten periods) is averaged. Since only six actual measurements were used, the values for the remaining four periods were obtained by interpolation. This average sum for each group of rats (T) was divided by the sum of the predrug control rating (C). This fraction when substracted from 1.0 is the *E* value. Thus, increasing drug effects and/or increasing duration of action yield higher *E* values.

$$E = 1.0 - \text{av } T/C$$

Arbitrarily, an *E* value greater than 0.150 or, alternatively, two consecutive *P* values greater than 0.150 were considered significant. These criteria gave *p* values of <0.01 based on a Student's *t* test. Any compound not causing significant behavioral changes at a dose as high as 10 mg/kg po was classified as inactive.

Muricidal Rat Test. Some rats have an innate tendency to kill a mouse introduced to its home cage. This mouse-killing behavior is called muricide. Obviously, any compound that alters this by increasing the latency to kill has an effect on behavior. We used this test for identifying CNS-active drugs.

An animal is not used in this assay unless its control "kill-time" is less than 5 s. An objective scoring system is used in the evaluation of compounds blocking muricide by rats. The scoring is as follows: 0 = kill time of 0–59 s; 1 = kill time of 60–120 s; 2 = kill time of greater than 120 s.

Groups of three rats per dose level were used each time. The effect of drug on muricide was measured 15, 30, 60, 120, 180, 240, 300, and 360 min postdosing.

Activity of a compound is based upon comparison of the drug to the effect of vehicle in blocking muricide. The protection afforded by drug (or vehicle) is converted to a percent protection score and a Student's *t* test used to establish significant protection against muricide. Any compound not affording significant protection or blockade of muricide at a dose as high as 10 mg/kg po was considered inactive.

Mouse Activity Test. Mice will show active exploratory behavior for up to 30 min after being placed in an activity cage and essentially no activity after that for at least 2 h. CNS depressants often decrease the early exploratory behavior although barbiturates, at very low doses, cause increased activity. CNS stimulants usually increase activity throughout the experimental period in a dose-dependent manner. Other classes of CNS-active agents may decrease the early exploratory activity but increase the activity in the later period. Alteration of the pattern and/or degree of exploratory behavior of mice placed in an activity cage is used as a measure of drug activity and classification.

Groups of five mice each were placed in activity cages, 90 min after dosing with the compound, to be studied. The activity cages were doughnut-shaped with six photoelectric cells and use filtered infrared as a light source, invisible to the mice and, because of the filter arrangement, not a source of heat. As the animals move about, the beams of light are broken and the frequency of this is recorded on cumulative counters (one counter per activity cage). The number of counts for each cage is recorded at 30, 60, 90, and 120 min after placing the animals in the activity cages, and, as well, the total counts for the entire 120 min are recorded. Thus, the first reading is at 120 min postdosing and the last reading is at 210 min postdosing. The postdrug data are compared against those following vehicle injection. Compounds not causing a change in activity at a dose as high as 20 mg/kg po were considered inactive.

Chemical Syntheses. Melting points (Thomas-Hoover capillary melting point apparatus) and boiling points are uncorrected. Uv spectra were run on a Cary Model 15 recording spectrometer. NMR spectra were recorded on a Varian T-60 using Me_4Si as an internal standard. Mass spectra were recorded with either a Varian Mat 731 or CEC-110 instrument. Optical rotations were run on a Franz Schmidt and Haensch instrument. Unless otherwise indicated, analytical results were within ±0.4% of theoretical values. TLC experiments were performed on 0.25-mm E. Merck precoated silica gel plates (No. 5765). Materials on plates were detected with I_2 vapor. Column chromatography procedures were performed using Woelm activity I silica gel.

Resorcinols 2a–d. Olivetol (**2a**) was purchased from Saber Labs. 5-(1,2-Dimethylheptyl)resorcinol (**2b**) was prepared as described by Adams et al.[10] The 5-(1,1-dimethylheptyl)- and 5-(2-methylcyclohexyl)resorcinols (**2c** and **2d**) were prepared as described below.

Coumarins 3a–d. Coumarins **3a–c** were prepared as described by Adams et al.[6,10] Using their procedure, courmarin **3d** was prepared in 46% yield from **2d**: mp 265–266 °C (recrystallized from CH_3OH); NMR ($CDCl_3$) δ 0.70 (d, 3 H, cyclohexane methyl), 6.65 (s, 2 H, aromatic), 9.50 (d, 1 H, OH); mass spectrum *m/e* 326 (M^+). Anal. ($C_{21}H_{26}O_3$) C, H.

Optical isomers of **3c** were prepared by the same procedure.

1-Hydroxy-3-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyrans (4a–d). Pyrans **4a–c** were prepared as described by Adams et al.[6,10] Compound **4d** was prepared in an analogous fashion in 80% yield from **3d**: NMR ($CDCl_3$) δ 0.65 (d, 3 H, cyclohexane CH_3), 5.30 (s, 1 H, OH), 6.10, 6.35 (d, d, 2 H, aromatic); mass spectrum *m/e* 340 (M^+).

The optical isomers of pyran **4c** were prepared in the same manner as the racemate.

Ethyl 2,3-Epoxy-3-(3,5-dimethoxyphenyl)nonanoate (14). To a vigorously stirred solution consisting of 25.0 g (100 mmol) of ketone **13**,[22] 18.4 g (150 mmol) of ethyl chloroacetate, and 25 ml of benzene, cooled to between −5 and 0 °C, was added 16.8 g (150 mmol) of KO-*t*-Bu in several portions over a 1.5-h period. The resultant dark solution was stirred at room temperature for 2 h after which it was poured onto 200 g of ice. The aqueous layer was extracted with benzene and the combined benzene layer washed successively with 2 × 100 ml of water and 100 ml of water containing 3 ml of AcOH. Drying the benzene extracts with Na_2SO_4 and evaporating under reduced pressure afforded **14**, 33.6 g (100%) of a crude product as a viscous liquid: NMR ($CDCl_3$) δ 3.40, 3.65 (s, s, 1 H, methine proton), 3.95, 4.30 (q, q, 2 H, ester CH_2–), 3.80 (s, 6 H, OCH_3), 6.40 (m, 1 H, C-4 aromatic), 6.55 (m, 2 H, C-2, C-6 aromatic). GC (3% SE-30 at 200 °C) analysis revealed a mixture of diastereomers. This crude material was used without further purification.

2-(3,5-Dimethoxyphenyl)octanal (15). After preparing a solution of NaOEt from 200 ml of EtOH and 10.0 g (0.44 mol) of Na, 135 g (0.40 mol) of glycidic ester **14** was added and the resultant dark solution stirred at room temperature for 4 h. The solution was cooled to 15 °C and 10 ml water was added. Most of the EtOH was removed under reduced pressure and the amorphous solid obtained was heated on a steam bath for 2 h with 36 ml of concentrated HCl and 200 ml of water. The organic material was extracted with ether and the ether layer washed successively with water, saturated $NaHCO_3$, and water. Drying over Na_2SO_4 and concentrating under reduced pressure yielded **15**, 100.0 g (95%), as a reddish liquid: NMR ($CDCl_3$) δ 3.40 (m, 1 H, methine), 3.80 (s, 6 H, OCH_3), 6.35 (s, 3 H, aromatic), 9.60 (d, 1 H, aldehyde). GC (3% SE-30 at 200 °C) indicated a single peak. This material was used without further purification.

2-(3,5-Dimethoxyphenyl)-2-methyloctanal (16). A solution of 395 g (1.42 mol) of **15**, 1800 ml of benzene, and 940 ml of CH_3I was cooled to −2 °C. To this stirred solution was added slowly 173 g (1.54 mol) of KO-*t*-Bu while the temperature was maintained at −2 °C. The mixture was stirred an additional 2 h at 0 °C after which it was poured onto 1900 ml of cold water. The organic material was extracted with ether; the ether layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a crude viscous oil. Distillation through a Vigreux column yielded **16**: 357.5 g (90%); bp 134–143 °C (0.1

mm); NMR ($CDCl_3$) δ 1.40 (s, 3 H, C-2 methyl), 3.80 (s, 6 H, OCH_3), 6.40 (s, 3 H, aromatic), 9.40 (s, 1 H, aldehyde); mass spectrum m/e 278 (M^+). Anal. ($C_{17}H_{26}O_3$) C, H.

2-(3,5-Dimethoxyphenyl)-2-methyloctanal Semicarbazone (17). To a solution of 143 g (1.28 mol) of semicarbazide hydrochloride dissolved in 643 ml of water was added 357.5 g (1.28 mol) of **16** and 2570 ml of CH_3OH, a two-phase system resulting. To this was added 103 ml (1.28 mol) of pyridine and a solution quickly formed. After a few minutes, the semicarbazone began to precipitate. Cooling the mixture in ice followed by suction filtering gave **17**, 375.7 g (87%), as a white crystalline solid: mp 133–135 °C; NMR ($CDCl_3$) δ 1.40 (s, 3 H, C-2 methyl), 3.70 (s, 6 H, OCH_3), 6.30 (m, 3 H, aromatic), 7.10 (s, 1 H, methine); mass spectrum m/e 335 (M^+). Anal. ($C_{18}H_{29}N_3O_3$) C, H, N.

5-(1,1-Dimethylheptyl)resorcinol Dimethyl Ether (18). A mixture of 375 g (1.12 mol) of semicarbazone **17**, 3600 ml of xylene, and 250 g (2.24 mol) of KO-*t*-Bu was stirred and heated to reflux for 21 h. The mixture was poured onto 3600 ml of 2 N HCl and the layers were separated. The aqueous layer was extracted with ether and the combined organic layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to a liquid. Distillation through a Vigreux column afforded **18**: 291 g (98%); bp 113–118 °C (0.02 mm) [lit.[10] bp 161–163 °C (0.5 mm)]; NMR ($CDCl_3$) δ 1.25 (s, 6 H, C-1 methyls), 3.80 (s, 6 H, OCH_3), 6.25 (t, 1 H, C-2 aromatic), 6.50 (d, 2 H, C-4, C-6 aromatic); mass spectrum m/e 264 (M^+). Anal. ($C_{17}H_{28}O_2$) C, H.

5-(1,1-Dimethylheptyl)resorcinol (2c). A mixture of 291 g (1.10 mol) of **18** and 700 g of pyridine hydrochloride was heated to reflux for 5.5 h. After cooling to room temperature, the mixture was diluted with 2 l. of water and extracted with ether. The ether was washed with 1 N HCl and water, dried over Na_2SO_4, treated with charcoal, and evaporated under reduced pressure to afford **2c**, 253 g (97%), as a viscous oil which solidified: mp 91–92 °C; NMR ($CDCl_3$) δ 1.20 (s, 6 H, C-1 methyls), 6.25 (t, 1 H, C-2 aromatic), 6.35 (d, 2 H, C-4, C-6 aromatic); mass spectrum m/e 236 (M^+). Anal. ($C_{15}H_{24}O_2$) C, H.

5-(2-Methylcyclohexyl)resorcinol Dimethyl Ether (21). To facilitate aryl Grignard formation, a small amount of methyl Grignard first was formed by adding 1.2 g of CH_3I to a suspension of 10.35 g (0.42 mol) of Mg turnings in 25 ml of THF. After stirring 1 h, 60.0 g (0.35 mol) of 3,5-dimethoxychlorobenzene (**19**) in 185 ml of THF was added and the mixture refluxed 24 h. Then, 47.6 g (0.42 mol) of 2-methylcyclohexanone in 70 ml of THF was added and the mixture refluxed an additional 16 h. The reaction was cooled and treated successively with 60 ml of NH_4Cl and 50 ml of 1 N HCl. Most of the THF was removed under reduced pressure, and the organic material was extracted with ether, dried over Na_2SO_4, and evaporated to afford a crude oil containing the intermediate alcohol **20**.

Crude alcohol **20** above was dissolved in 500 ml of EtOAc containing 5 ml of concentrated H_2SO_4 and 10 g of 5% Pd/C and hydrogenated at an initial pressure of 50 psi for 1 h (50–60 °C). After filtration and evaporation of the solvent under reduced pressure, the residue was distilled to yield **21**: 26.8 g (33%); bp 125–128 °C (0.25 mm); NMR ($CDCl_3$) δ 0.70 (d, 3 H, CCH_3), 3.80 (s, 6 H, OCH_3), 6.30 (s, 3 H, aromatic); mass spectrum m/e 234 (M^+). Anal. ($C_{15}H_{22}O_2$) C, H.

5-(2-Methylcyclohexyl)resorcinol (2d). This was prepared from **21** in 97% yield analogous to that of **2c**: mp 95–98 °C; NMR ($CDCl_3$) δ 0.60 (d, 3 H, CCH_3), 6.25 (s, 3 H, aromatic); mass spectrum m/e 206 (M^+). Anal. ($C_{13}H_{18}O_2$) C: calcd, 75.69; found, 75.09; H: calcd, 8.80; found, 7.96.

1-(*N,N*-Dimethylthiocarbamoyloxy)-3-(1,2-dimethylheptyl)-7,8,9,10-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran (5b). To a solution of 3.7 g (10.0 mmol) of **4b** in 50 ml of anhydrous DMF was added 1.0 g (20 mmol) of a 50% dispersion of NaH in mineral oil. After the bubbling had subsided, 2.4 g (30 mmol) of *N,N*-dimethylthiocarbamoyl chloride was added all at once and the mixture stirred and heated to 85–95 °C for 1 h. After cooling to room temperature, the mixture was decomposed with 100 ml of cold water and extracted with ether. The ether layer was washed with 1 N HCl, 1 N NaOH, and water. Drying over Na_2SO_4 and concentrating the product afforded a crude viscous oil. Purification was achieved by elution on a silica gel column (150 g) with benzene. Combining appropriate fractions, **5b**, 3.88 g (85%) of a clear yellow oil, was obtained: NMR ($CDCl_3$) δ 3.30 (s, 3 H, NCH_3), 3.45 (s, 3 H, NCH_3), 6.30, 6.50 (broad singlets, 2 H, aromatic); mass spectrum m/e 457 (M^+), 442.

Homologue **5a** was prepared by the same procedure.

1-(*N,N*-Dimethylcarbamoylthio)-3-(1,2-dimethylheptyl)-7,8,9,10-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran (6b). A sample of 7.53 g (16.5 mmol) of thiocarbamate **5b** was heated neat to 300 °C under N_2 for 30 min. Purification was achieved on a silica gel column (250 g) eluted with 1–2% EtOAc–PhH to afford **6b**, 5.75 g (76%), as a viscous oil: NMR ($CDCl_3$) δ 3.00 [s, 6 H, $N(CH_3)_2$], 6.70, 6.80 (broad singlets, 2 H, aromatic); mass spectrum m/e 457 (M^+), 442.

Homologue **6a** was prepared by the same procedure.

1-Mercapto-3-(1,2-dimethylheptyl)-7,8,9,10-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran (7b). To a solution of 5.0 g (10.9 mmol) of thiocarbamate **6b** dissolved in 200 ml of ethanol was added 75 ml of 2 N NaOH. The resultant solution was heated on a steam bath under N_2 for 16 h after which most of the ethanol was removed under reduced pressure. The aqueous solution containing a viscous insoluble oil was acidified with 1 N HCl to pH 1 and extracted with ether. After drying the ether solution with Na_2SO_4 and evaporating under reduced pressure, a crude viscous oil was obtained. Purification on a silica gel column (100 g) and elution with 2% EtOAc–PhH afforded **7b**, 3.18 g (75%), as a yellow oil: NMR ($CDCl_3$) δ 3.45 (s, 1 H, SH), 6.45, 6.55 (broad singlets, 2 H, aromatic); mass spectrum m/e 386 (M^+), 371.

Homologue **7a** was prepared by the same procedure.

7,8,9,10-Tetrahydro-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-1-[(2-phenyl-4-quinazolinyl)oxy]-6*H*-dibenzo[*b,d*]pyran (8b). To a solution of anhydrous DMF containing 19.8 g (53.5 mmol) of **4b** was added 3.1 g (64.2 mmol) of a 50% dispersion of NaH in mineral oil. After stirring at room temperature for 1 h, 14.2 g (58.8 mmol) of 2-phenyl-4-chloroquinazoline was quickly added and the mixture heated at 150–160 °C for 2 h. The reaction mixture was poured onto 800 ml of cold water and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to afford a viscous oil. Purification was achieved by chromatography over 1 kg of silica gel eluted with benzene to yield **8b**, 19.0 g (62%), as a virtually immobile glass: NMR ($CDCl_3$) δ 6.65 (m, 2 H, C-2, C-4 aromatic), 7.20–8.50 (m, 9 H, quinazoline aromatic); λ_{max}^{MeOH} 212 nm (ε 23 000), 257 (19 200); mass spectrum m/e 574 (M^+), 559.

Homologues **8a** and **8d**, isomer **8c**, and optical isomers of **8c** were prepared by the same procedure.

7,8,9,10-Tetrahydro-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-1-[4(3*H*)-oxo-2-phenyl-3-quinazolinyl]-6*H*-dibenzo[*b,d*]pyran (9b). In a round-bottom flask was placed 6.02 g (10.45 mmol) of quinazoline **8b** which was heated neat under N_2 at 330 °C for 3 h. The resultant glassy residue was purified by chromatography over 250 g of silica gel eluted with 1% EtOAc–PhH to afford **9b**, 4.14 g (69%), as an amorphous yellow solid: NMR ($CDCl_3$) δ 6.65 (m, 2 H, C-2, C-4 aromatic), 6.85–8.50 (m, 9 H, quinazoline aromatic); λ_{max}^{MeOH} 205 nm (ε 59 000), 227 (46 400), 261 (24 000); mass spectrum m/e 574 (M^+), 559.

Homologues **9a** and **9d**, isomer **9c**, and optical isomers of **9c** were prepared by the same procedure.

1-Amino-7,8,9,10-tetrahydro-3-(1,2-dimethylheptyl)-6,6,-9-trimethyl-6*H*-dibenzo[*b,d*]pyran (10b). To a solution consisting of 100 g of KOH dissolved in 1400 ml of ethylene glycol and 70 ml of water was added 12.5 g (21.8 mmol) of quinazolinone **9b**. The mixture was stirred vigorously and heated to 150 °C for 16 h. After cooling to room temperature, it was poured onto 1400 ml of water and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure to yield a crude dark residue. Purification over 500 g of silica gel eluted with benzene afforded **10b**, 5.87 g (73%), as a viscous oil: NMR ($CDCl_3$) δ 3.75 (br, 2 H, $-NH_2$), 6.05, 6.15 (d, d, 2 H, aromatic); mass spectrum m/e 369 (M^+), 354.

Homologues **10a** and **10d**, isomer **10c**, and optical isomers of **10c** were prepared by the same procedure.

1-Acetamido-7,8,9,10-tetrahydro-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran (22b). To a 0 °C solution of 738 mg (2.0 mmol) of **10b** dissolved in 10 ml of THF was added 212 mg (2.1 mmol) of Et_3N. To this was added 165 mg (2.1 mmol) of acetyl chloride in 10 ml of THF and the mixture allowed to

stand at room temperature for 16 h. Water (10 ml) was added and the THF removed under reduced pressure. The aqueous layer was extracted with ether and the ether layer dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude gum. Purification over 50 g of silica gel, eluted with 2% EtOAc–PhH, yielded **22b**, 610 mg (74%), as a white amorphous solid: NMR ($CDCl_3$) δ 2.15 [s, 3 H, $-C(=O)CH_3$], 6.4–7.0 (m, 2 H, aromatic); mass spectrum m/e 411 (M^+), 396.

The corresponding 3-*n*-pentyl homologue **22a** was similarly prepared.

7,8,9,10-Tetrahydro-1-methylamino-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (23b). To a solution of 738 mg (2.0 mmol) of **10b** dissolved in 20 ml of THF was added 600 mg (6.0 mmol) of formylimidazole and the resultant solution stirred at room temperature for 16 h. Evaporation of the solvent under reduced pressure afforded a crude gum. Purification over 50 g of silica gel, eluted with 3–4% EtOAc–PhH, yielded 210 mg (26%) of a viscous oil: mass spectrum m/e 397 (M^+), 382.

The above formyl derivative, 210 mg (0.55 mmol), was dissolved in 5 ml of benzene and to this was added a solution of 8 ml of benzene containing 3 ml of a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride. After stirring at room temperature for 1 h, the solution was decomposed with 20 ml of 10% HCl. The layers were separated and the aqueous layer was extracted with ether. The combined ether layer was washed with 1 N NaOH and water, dried over Na_2SO_4, and evaporated under reduced pressure to afford a crude gum. Purification over 50 g of silica gel and elution with benzene afforded **23b**, 170 mg (81%), as an oil: NMR ($CDCl_3$) δ 2.85 (s, 3 H, $-NCH_3$), 6.05, 6.15 (d, d, 2 H, aromatic); mass spectrum m/e 383 (M^+), 368.

7,8,9,10-Tetrahydro-1-(dimethylamino)-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (24b). A solution of 738 mg (2.0 mmol) of **10b** dissolved in 50 ml of 95% EtOH containing 125 mg of 10% Pd/C and 2 ml of formalin (37% solution) was hydrogenated at an initial pressure of 50 psi for 16 h. After filtration and evaporation under reduced pressure, the crude residue was purified over 50 g of silica gel eluted with benzene to yield **24b**, 660 mg (83%), as a viscous oil: NMR ($CDCl_3$) δ 2.60 [s, 6 H, $N(CH_3)_2$], 6.35 (m, 2 H, aromatic); mass spectrum m/e 397 (M^+), 382.

Homologue **24a** was similarly prepared in 76% yield.

7,8,9,10-Tetrahydro-1-methylsulfonamido-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (25c). To a solution consisting of 1.0 g (2.71 mmol) of **10c**, 20 ml of benzene and 274 mg (2.71 mmol) of Et_3N, quickly, was added 310 mg (2.71 mmol) of methanesulfonyl chloride. After stirring 5 h at room temperature, TLC (10% EtOAc–PhH) revealed the starting amine was still present; therefore, an additional 274 mg of Et_3N and 310 mg of mesyl chloride were added and the solution was stirred 16 h at room temperature. The reaction was decomposed with 20 ml of water and the organic material extracted with ether. The ether layer was washed with 1 N HCl, saturated $NaHCO_3$, and H_2O, dried over Na_2SO_4, and evaporated under reduced pressure to yield a crude oil. Purification over 30 g of silica gel eluted with 1% EtOAc–PhH afforded **25c**, 570 mg (47%), as a gummy residue: NMR ($CDCl_3$) δ 2.90 (s, 3 H, $-SO_2CH_3$), 6.30 (broad, 1 H, NH), 6.80 (m, 2 H, aromatic); mass spectrum m/e 447 (M^+), 432.

***l*-5-(α-Methylbenzyl)semioxamazide (27)** was prepared as described by Leonard and Boyer:[15] mp 167–168 °C (reported mp 167–168 °C); $[\alpha]^{25}D$ –118° ($CHCl_3$) (reported $[\alpha]^{25}D$ –102°). Anal. ($C_{10}H_{13}N_3O_2$) C, H, N.

***l*-3-Methylcyclohexanone *l*-5-(α-methylbenzyl)semioxamazone (28)** was prepared in 23% yield from *dl*-**25** and *l*-**27** as described by Leonard and Boyer:[15] mp 176–177 °C (reported mp 179–180 °C); $[\alpha]^{25}D$ –124° ($CHCl_3$) (reported $[\alpha]^{25}D$ –115°).

***l*-3-Methylcyclohexanone (26)** was prepared in 68% yield from **28** as described by Leonard and Boyer:[15] bp 167–168 °C (lit.[5] bp 164–168 °C); $[\alpha]^{25}D$ –8.8° (neat) (reported[5] $[\alpha]^{20}D$ –12.6°).

***d*- and *l*-ethyl 4-methyl-2-oxo-1-cyclohexanecarboxylate (1)** was prepared as described by Adams et al.[5] The *d* isomer was isolated in 62% yield: bp 116–118 °C (15 mm) [reported bp 122–124 °C (15 mm)]; $[\alpha]^{25}D$ +92° (neat) (reported $[\alpha]^{20}D$ +90.8°). Anal. ($C_{10}H_{16}O_3$) C, H. The *l* isomer was isolated in 55% yield: bp 117–125 °C (12 mm) [reported bp 126–130 °C (17 mm)]; $[\alpha]^{25}D$ –63° (neat) (reported $[\alpha]^{25}D$ –84.6°). Anal. ($C_{10}H_{16}O_3$) H; C: calcd, 65.19; found, 64.67.

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