Synthesis and Anticonvulsant and Sedative–Hypnotic Activity of 4-(Alkylimino)-2,3-dihydro-4*H*-1-benzopyrans and -benzothiopyrans

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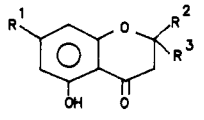
A series of 4-(alkylimino)-5-hydroxy-7-alkyl-2,3-dihydro-4*H*-1-benzopyrans and -thiopyrans were synthesized and evaluated for anticonvulsant activity. Preliminary screening of these compounds revealed that 2,2-dimethyl-4-[(2-hydroxyalkyl)imino]-5-hydroxy-7-pentyl-2,3-dihydro-4*H*-1-benzopyrans **19** and **29**, the 7-butyl analogue **34**, and the corresponding 7-pentyl-4*H*-1-benzothiopyrans **38** and **39** had the most promising anticonvulsant activity. Synthesis of both enantiomers of **29** and **39** indicated that the *R* isomers **30** and **40** were the most active and showed very good protection against MES, pentylenetetrazole, and mercaptopropionic acid induced seizures after oral administration in mice. In the Irwin test these compounds showed a generalized depressant activity but at dosages higher than those showing anticonvulsant activity, whereas acute toxicity after oral administration was low (LD_{50} higher than 400 mg/kg).

The wide range of activity of cannabinoids on the central nervous system has stimulated the search for modified analogues with selective action and increased potency but devoid of hallucinogenic properties.[1] Some considerable success, leading to compounds with antinausea and analgesic activity, has been obtained in recent years.[2]

In particular, some of these compounds show anticonvulsant activity.[3] We envisaged that possible anticonvulsant activity could be obtained by preparing hydroxyimino derivatives of chromans with the cannabinoid substitutions and the hydroxy group in a suitable position. The strong intramolecular hydrogen bond between the imino and the OH groups should keep the side chain in a more rigid situation than in the above cited compounds; moreover, a similar structural pattern is present in GABA receptor agonists with anticonvulsant activity, such as progabide.[4] We report here on the synthesis of this new class of compounds, still containing part of the cannabinoid skeleton, which showed promising anticonvulsant and sedative–hypnotic activity on animals. They are alkylimino derivatives of 5-hydroxy-7-alkyl-2,3-dihydro-4*H*-1-benzopyran-4-ones and 2,3-dihydro-4*H*-1-benzothiopyran-4-ones.

Chemistry. Convenient starting materials for the synthesis of the former series of imines are 5-hydroxy-7-alkylchromanones (**1**), easily available from the corresponding 5-alkylresorcinols and acrylic acids,[5] from 1,3-cyclohexanediones,[6] or from the appropriate acetophenones.[7]



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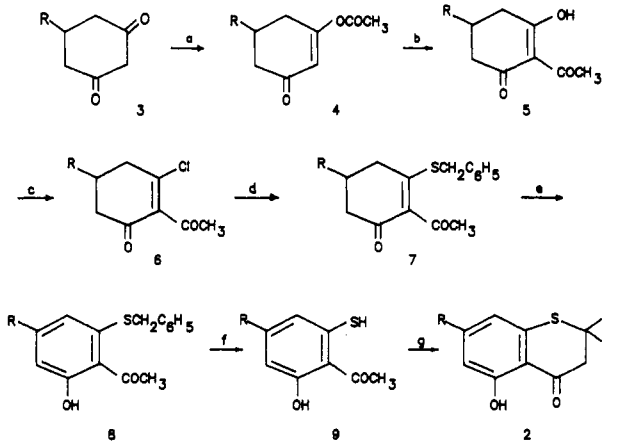
More elaborate appeared the synthesis of the corresponding thiochromanone **2**, which was prepared following a procedure first developed by Kirchlechner[8] (Scheme I).

Acetylation of the enol of 5-pentyl-1,3-cyclohexanedione (**3**), followed by Fries reaction with $AlCl_3$[9] and treatment with oxalyl chloride, gave chloro ketone **6**. Substitution of the halogen with benzyl mercaptan afforded sulfide **7**, which was dehydrogenated with *N*-bromosuccinimide and triethylamine to aromatic ketone **8**. Smooth debenzylation[8] with $AlBr_3$ gave thiol **9**, which, by reaction with acetone and pyrrolidine,[7] gave regiospecifically the expected thiochromanone **2**, in overall yield of 13% from **3**. When **8** was reacted with acetone and pyrrolidine, ring closure occurred onto the phenolic oxygen, to give thioether

Scheme I[a]



[a] (a) MeCOCl/Py; (b) $AlCl_3$; (c) $(COCl)_2$; (d) $PhCH_2SH/Et_3N$; (e) NBS/Et_3N; (f) $AlBr_3$; (g) Me_2CO/C_4H_9N. R = n-C_5H_{11}.

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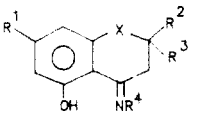
Table I. Physical Properties of Imines 13–44



no.	X	R^1	R^2	R^3	R^4	yield[a]	mp, °c (b,p)[b]	formula[c]
13	O	*n*-C_5[j]	Me	Me	Me	45	47	$C_{17}H_{25}NO_2$
14	O	*n*-C_5	Me	Me	$CH_2CH{=}CH_2$	40	67–69	$C_{19}H_{29}NO_2$
15	O	*n*-C_5	Me	Me	cyclohexyl	60	oil	$C_{22}H_{33}NO_2$
16	O	*n*-C_5	Me	Me	CH_2CH_2SH	25	91–92	$C_{18}H_{27}NO_2S$
17	O	*n*-C_5	Me	Me	CH_2CH_2NHMe	60	(130/0.1)	$C_{19}H_{30}N_2O_2$
18	O	*n*-C_5	Me	Me	$CH_2CH_2NMe_2$	80	(130/0.05)	$C_{20}H_{32}N_2O_2$
19	O	*n*-C_5	Me	Me	CH_2CH_2OH	95	108–110	$C_{18}H_{27}NO_3$
20	O	*n*-C_5	Me	Me	$CH_2(CH_2)_2OH$	70	83–86	$C_{19}H_{29}NO_3$
21	O	*n*-C_5	Me	Me	$CH_2(CH_2)_3OH$	67	112–113	$C_{20}H_{31}NO_3$
22	O	*n*-C_5	Me	Me	$CH_2CH(Me)CH_2OH$[d]	40	67–69	$C_{19}H_{29}NO_3$
23	O	*n*-C_5	Me	Me	CH_2CH_2OMe	72	(190/1)	$C_{19}H_{29}NO_3$
24	O	*n*-C_5	Me	Me	$CH_2CH_2OCH_2CH_2OH$	50	oil	$C_{20}H_{29}NO_4$
25	O	*n*-C_5	Me	Me	$CH(Et)CH_2OH$[d]	50	79–80	$C_{20}H_{31}NO_3$
26	O	*n*-C_5	Me	Me	$C(OH)C_5H_{10}$	50	92–94	$C_{23}H_{35}NO_3$
27	O	*n*-C_5	Me	Me	$CH_2CH(OH)CH_2OH$	41	127–129	$C_{18}H_{27}NO_4$
28	O	*n*-C_5	Me	Me	$CH_2(CH_2)_2COOH$	40	144–146	$C_{20}H_{29}NO_4$
29	O	*n*-C_5	Me	Me	(*RS*)-$CH_2CH(OH)Me$	79	90–92	$C_{19}H_{29}NO_3$
30	O	*n*-C_5	Me	Me	(*R*)-$CH_2CH(OH)Me$[e]	75	108–109	$C_{19}H_{29}NO_3$
31	O	*n*-C_5	Me	Me	(*S*)-$CH_2CH(OH)Me$[f]	77	102–104	$C_{19}H_{29}NO_3$
32	O	H	Me	Me	(*R*)-$CH_2CH(OH)Me$	48	126–129	$C_{14}H_{19}NO_3$
33	O	Me	Me	Me	(*R*)-$CH_2CH(OH)Me$	65	136–137	$C_{15}H_{21}NO_3$
34	O	*n*-C_4	Me	Me	(*R*)-$CH_2CH(OH)Me$	55	102–103	$C_{18}H_{27}NO_3$
35	O	DMH[i]	Me	Me	(*R*)-$CH_2CH(OH)Me$	80	91–93	$C_{23}H_{37}NO_3$
36	O	*n*-C_5	H	Me	(*R*)-$CH_2CH(OH)Me$[d]	59	113–115	$C_{18}H_{27}NO_3$
37	O	*n*-C_5	H	*n*-C_5	(*R*)-$CH_2CH(OH)Me$[d]	50	53–58	$C_{22}H_{35}NO_3$
38	S	*n*-C_5	Me	Me	CH_2CH_2OH	70	121–122	$C_{18}H_{27}NO_2S$
39	S	*n*-C_5	Me	Me	(*RS*)-$CH_2CH(OH)Me$	83	130–131	$C_{19}H_{29}NO_2S$
40	S	*n*-C_5	Me	Me	(*R*)-$CH_2CH(OH)Me$	80	136–138	$C_{19}H_{29}NO_2S$
41	S	*n*-C_5	Me	Me	(*S*)-$CH_2CH(OH)Me$	82	136–138	$C_{19}H_{29}NO_2S$
42	SO_2	*n*-C_5	Me	Me	(*R*)-$CH_2CH(OH)Me$		108–110	$C_{19}H_{29}NO_4S$
43						85	136–138	$C_{19}H_{29}NO_2S$
44						60	64–66	$C_{16}H_{25}NO_2$

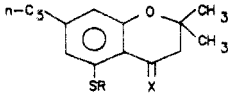
[a] Yields refer to the synthesis of the imines and are not optimized. [b] °C/mmHg. [c] All the compounds gave satisfactory C, H, and N elemental analyses. [d] Mixture of diastereoisomers. [e] $[\alpha]^{20}_D = -25.74°$ ($c = 0.09$, EtOH). [f] $[\alpha]^{20}_D = +26.24°$ ($c = 0.09$, EtOH). [g] $[\alpha]^{20}_D = -18.6°$ ($c = 0.1$, EtOH). [h] $[\alpha]^{20}_D = +18.8°$ ($c = 0.1$, EtOH). [i] DMH = 1,2-dimethylheptyl. [j] *n*-C_5 = pentyl.

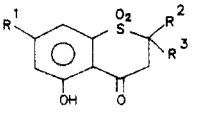
Table II. Anticonvulsant Activity of the Imines

no.	ED_{50}, mg/kg po (confidence limits) pentylenetetrazole antagonism (mice)	MES seizures antagonism (mice)	MPA antagonism (mice)	sodium pentobarbital potentiation	LD_{50} mg/kg po: orientative acute toxicity
19	19.0 (14.6–24.5)	i[a]	i	i	>800
29	24.3 (20.4–29.1)	i	i	i	>400 < 800
30	14.0 (12.2–16.3)	13.8 (8.5–22.6)	9.4 (6.2–14.2)	i	>400 < 800
34	15.5 (10.3–23.3)	i	i	14.2	>400 < 800
38	24.0 (7.6–68.4)	i	i	i	>800
39	14.3 (6.9–19.5)	i		10.0	>800
40	4.8 (4.0–5.8)	20.6 (12.5–37.2)	8.8 (7.4–10.8)	9.7	>1600
sodium valproate	200	206.2 (163.0–259.0)	200		
diazepam	0.5	1.2 (0.6–2.5)	0.7		

[a] Inactive compounds are denoted with an i.

10, which was deprotected to obtain 5-mercapto derivative **11**. Oxidation of **2** with H_2O_2 gave the corresponding sulfone **12**.





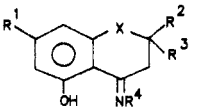
10 R = $CH_2C_6H_5$ X = O

11 R = H X = O

43 R = H X = $NCH_2CH(OH)CH_3$

12

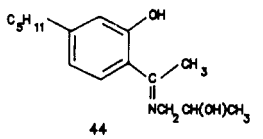
Condensation of the above said chromanones and thiochromanones with primary amines by heating in an alcoholic solvent, or by refluxing in toluene with azeotropic distillation of water, afforded in good yield imines **13–42** (Table I). 5-Mercapto derivative **11** gave imine **43**. Imine **44** was obtained similarly from 2-hydroxy-4-pentylacetophenone (**45**).



13–37 X = O

38–41 X = S

42 X = SO_2



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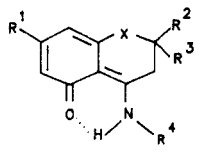
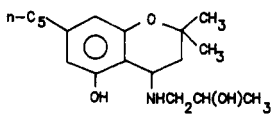
The NH group in compounds **13–44** is strongly hydrogen-bonded, as it appears from its low-field chemical shift in the NMR spectra (ca. 15 ppm). This means that hydroxyimines **13–42** may exist also in the ketoamine tautomeric forms **13b–42b**, depending on the solvent.[10]



12b–42b X = O,S

Evidence for the presence of a noticeable amount of the ketoamine tautomers comes from the coupling between protons of a hydrogen-bearing carbon of R^4 group directly linked to the nitrogen, with the NH. The low value of the coupling constant (e.g. ca. 2 Hz for **13** and **29** in DMSO-d_6) indicates a remarkable exchange between the tautomers.[10] Additional evidence comes from the high-wavelength absorption in the UV spectra in polar solvents.[11] This kind of tautomerism has been thoroughly studied by Dudek et al. Therefore, although this is the first report of such tautomerism in 4-imino-5-hydroxychromans, a detailed investigation was not extended to all the compounds prepared. In any case, in this paper the compounds will be named as imines.

The imines could be converted into their hydrochlorides by treatment with 1:1 aqueous HCl, but the hydrochlorides were readily converted to the free bases when dissolved in dilute aqueous solutions. The imines were fairly resistant to hydrolysis to the corresponding chromanones, which, however, are inactive in the tests employed (see later). This unusual stability is certainly also due to the tautomerism discussed above. Reduction of the imines (e.g. **29**) to the corresponding amines (e.g. **46**) could be accomplished with $LiAlH_4$.



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Pharmacological Results and Discussion

All the imines reported in Table I were first evaluated for their anticonvulsant activity in mice by inhibition of pentylenetetrazole-induced maximal seizures. Having found in the early stages of the research a compound with a very low toxicity and an ED_{50} of less than 5 mg/kg, we did not consider compounds with an $ED_{50} \geq 25$ mg/kg. All the compounds were also tested for their ability to reverse reserpine-induced hypothermia and ptosis in mice and for a possible antidopaminergic activity in the apomorphine climbing test. However, all the compounds were inactive in the latter two tests.

The compounds with good activity in the pentylenetetrazole test were tested for their ability to protect mice against seizures induced by electroshock (MES), mercaptopropionic acid (MPA), bicuculline, and picrotoxin and to potentiate pentobarbital-induced sleep: they were inactive ($ED_{50} \geq 25$ mg/kg) in the bicuculline and picrotoxin tests. The other results, together with LD_{50}s, are reported in Table II.

In the Irwin test[12] the compounds that were active in the anticonvulsant test showed a generalized depressant action with lower spontaneous activity, loss of righting reflex, and diminished muscular tone but at dosages higher than those showing anticonvulsant activity.

Inspection of Table II shows that there are some structural requisites for a good anticonvulsant activity in this series of compounds. These are the presence of an alkyl chain, preferably of five carbon atoms, in position 7, and of a (hydroxyethyl)imino or, preferably, a (2-hydroxypropyl)imino group at carbon 4. However, the introduction of a hydrogen, a methyl (**32** and **33**), or a 1,2-dimethylheptyl group (**35**) in position 7, this last a common substitution in the cannabinoid series, reduced or abolished activity. The presence of two methyl groups in position 2 seems to be necessary, as with only one alkyl group (e.g. **36** and **37**) activity disappears. Substitution of the 5-OH group with the corresponding thiol group gave an inactive compound. Also the reduction of the imino double bond as in **46** eliminated the activity. The presence of a heterocyclic ring seems necessary for activity, as the open-chain analogue **44** is inactive.

Due to the much more simple chemistry, most modifications were made in the oxygen series, and only the derivatives with likely maximum activity were prepared from thiochromanone **2**. It appears that substitution of sulfur for oxygen in the heterocycle slightly increases the anticonvulsant activity in the pentylenetetrazole test; the reverse is true for the MES test. Oxidation to sulfone, although not eliminating activity, has an adverse effect on potency.

If we compare the activity of the 2*R* and 2*S* enantiomers of the (2-hydroxypropyl)imino derivatives in both the benzopyran and benzothiopyran series (**30** vs. **31**, and **40** vs. **41**), we see that most of the activity resides in the *R* isomer.

Due to its high potency and favourable toxicity, compound **40** (FCE 23819) has been selected for further pharmacological evaluation.

In conclusion, within the class of 4-(alkylimino)-2,3-dihydro-4*H*-1-benzopyrans and -benzothiopyrans, some compounds with low toxicity and high anticonvulsant and sedative activity have been found.

Experimental Section

Melting points are uncorrected. NMR spectra were measured at 80 MHz in $CDCl_3$ solutions (if not otherwise indicated) with a Bruker WP-80 instrument or at 300 MHz with a Varian instrument, with Me_4Si as internal standard. Mass spectra were measured at 70 eV with a Finnigan 4021 spectrometer, with an INCOS data system. "Flash chromatography" with Merck 60 silica gel (0.040–0.063 mm) was generally used for purification of the compounds.

Chromanones. 2,2-Dimethyl-5-hydroxychromanone,[13] 2,2,7-trimethyl-5-hydroxychromanone,[5] 2-methyl-7-pentyl-5-hydroxychromanone,[5] 2,2-dimethyl-7-pentyl-5-hydroxychromanone,[14] 2,2-dimethyl-7-(1,2-dimethylheptyl)-5-hydroxychromanone,[2d] and 2,2-dimethyl-7-phenyl-5-hydroxychromanone[5,13] were prepared according to the literature methods. 2,2-Dimethyl-7-butyl-5-hydroxychromanone [a yellow oil; NMR δ 0.92 (3 H, t, J = 6 Hz, CH_3), 1.46 (6 H, s, 2 MeCO), 2.50 (2 H, t, Ar-CH_2), 2.70 (s, H_2-3),

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6.21 and 6.28 (dd, J = 2 Hz, H-6 and H-8), 11.35 (chel OH)] was prepared from 5-butylresorcinol and dimethylacrylic acid according to the method of ref 13 and purified by chromatography with hexane–AcOEt 9:1 (32% yield). 2-Spirocyclohexyl-5-hydroxychromanone [yellow oil; NMR δ 1.0–2.0 (12 H), 2.66 (H_2-3), 6.34 and 6.46 (ddd, J = 8, 2 Hz, H-6 and H-8), 7.33 (t, J = 8 Hz, H-7), 11.7 (chel OH)] was obtained in 78% yield from 2,6-dihydroxyacetophenone, cyclohexanone, and pyrrolidine according to the literature method.[7]

2-Acetyl-5-pentyl-1,3-cyclohexanedione (5). A solution of 10 g (55 mmol) of 5-pentylcyclohexanedione (**3**) in 250 mL of $CHCl_3$ was treated with 4.42 mL (55 mmol) of pyridine, added dropwise with 4.3 mL (60.5 mmol) of acetyl chloride. Stirring for 1.5 h, washing with water, aqueous 1:1 HCl, saturated, aqueous $NaHCO_3$, and water, drying with Na_2SO_4, and evaporation gave 11.3 g (92%) of a yellow oil (**4**), which was used without further purification. To 5.88 g (44 mmol) of $AlCl_3$ in 75 mL of dry 1,2-dichloroethane were added dropwise 4.93 g (22 mmol) of **4**. After stirring for 1.5 h, the reaction mixture was poured onto a mixture of 30 g of ice and 30 g of concentrated HCl and was repeatedly extracted with chloroform. On evaporation, 4.38 g of a crude product was obtained, which was dissolved in 20 mL of ether and extraced with 75 mL of 1 N NaOH; the basic solution was acidified with concentrated HCl and repeatedly extracted with ether to give 3.13 g (63%) of **5**: MS m/z 225 (100), 224 (33), 209 (17), 182 (11), 181 (13), 154 (18), 153 (35), 126 (31), 125 (24), 124 (14), 111 (38), 98 (34); NMR δ 0.87 (t, J = 6 Hz, CH_3), 1.0–2.8 (13 H), 2.58 (s, COMe), 17.7 (chel OH).

2-Acetyl-3-(benzylthio)-5-pentylcyclohex-2-en-1-one (7). A solution of 6.4 g (28.5 mmol) of **5** in 20 mL of dry $CHCl_3$ was treated dropwise with 2.7 mL (31.4 mmol) of oxalyl chloride and was refluxed for 1.7 h. Evaporation gave 7.2 g (97%) of pure **6** (GC), as an unstable oil (bp 100–110 °C/0.1 mmHg in Kugelrohr), which was directly used for the following reaction.

A solution of 6.14 g (24 mmol) of **6** in 50 mL of THF was added with 3.7 mL (26.4 mmol) of Et_3N and 2.83 mL (24 mmol) of benzyl mercaptan, with stirring. After 3 h the precipitated triethylamine hydrochloride was filtered, and the solvent was evaporated to give, after chromatography with hexane–AcOEt 3:1, 5.8 g (73%) of **7**, as a reddish oil: MS m/z 330 (0.1), 240 (14), 239 (100), 91 (47); NMR δ 0.86 (t, J = 6 Hz, CH_3), 1.0–3.1 (13 H), 2.39 (s, COMe), 4.08 (s, Ar–CH_2), 7.37 (s, 5 H arom).

2-(Benzylthio)-6-hydroxy-4-pentylacetophenone (8). A mixture of 2.28 g (6.9 mmol) of **7** and 1.23 g (6.9 mmol) of *N*-bromosuccinimide in 25 mL of CCl_4 was stirred for 3 h. Then, 1.2 mL (8.7 mmol) of Et_3N was added and the stirring was continued overnight, then the mixture was refluxed for 1 h. Filtration, evaporation, and chromatography (hexane–AcOEt 9:1) of the residue gave 1.64 g of **8**: mp 48–49 °C (from petroleum ether); MS m/z 328 (2), 310 (3), 239 (11), 238 (31), 237 (100), 91 (60); NMR δ 0.87 (t, J = 6 Hz, CH_3), 1.0–1.8 (6 H), 2.50 (t, J = 6 Hz, Ar$CH_2$$CH_2$), 2.75 (s, COMe), 4.07 (ArCH_2S), 6.62 and 6.70 (dd, J 2 Hz, H-3 and H-5), 7.26 (s, 5 H arom), 12.32 (chel OH).

2-Mercapto-6-hydroxy-4-pentylacetophenone (9). A solution of 3.8 g (11.6 mmol) of **8** in 40 mL of benzene was treated with 4.65 g (17.4 mmol) of $AlBr_3$ and was stirred 1 h. Pouring in 100 g of ice and 30 mL of HCl and extraction and ether gave, after chromatography with hexane–AcOEt 9:1, 1.98 g (71.7%) of **9**, as a yellow oil: MS m/z 238 (62), 237 (22), 224 (14), 223 (100), 182 (86), 153 (44), 151 (66), 103 (49), 101 (75); NMR δ 0.88 (t, J = 6 Hz, CH_3), 1.2–1.8 (6 H), 2.47 (t, J = 6 Hz, ArCH_2), 2.77 (s, COMe), 3.83 (SH), 6.59 and 6.66 (dd, J = 2 Hz, H-3 and H-5), 12.73 (chel OH).

2,2-Dimethyl-5-hydroxy-7-pentyl-2,3-dihydro-4*H*-1-benzothiopyran-4-one (2). A solution of 1 g (4.2 mmol) of **9** in 3 mL of toluene was added to 3.1 mL (42 mmol) of acetone, then 0.34 mL (4.2 mmol) of pyrrolidine was added dropwise and the mixture was stirred for 1 h. Addition of 6 N HCl, evaporation of acetone, and extraction with EtOAc gave, after chromatography with hexane–AcOEt 95:5, 700 mg (60%) of **2**: mp 32–33 °C; MS m/z 279 (M + 1, 11), 278 (M^+, 50), 263 (20), 223 (19), 222 (100), 179 (12), 166 (25); NMR δ 0.88 (t, J = 6, CH_3), 1.2–1.8 (6 H), 1.45 (s, 2 MeCS), 2.50 (t, J = 6 Hz, ArCH_2), 2.88 (H_2-3), 6.47 and 6.56 (dd, J = 2 Hz, H-6 and H-8), 12.65 (chel OH), free from an accompanying product, most probably (from MS 289, 236, 180) the pyrrolidinoenamine of **9**.

2,2-Dimethyl-5-(benzylthio)-7-pentyl-2,3-dihydro-4*H*-1-benzopyran-4-one (10). To a solution of 328 mg (1 mmol) of **8** in 1 mL of toluene were added 58 mg (1 mmol) of acetone and 35.5 mg (0.5 mmol) of pyrrolidine and the mixture was refluxed for 1.5 h, with further addition of 2 mmol of acetone. Addition of 2 N HCl, evaporation, extraction with AcOEt, chromatography with hexane–AcOEt 9:1, and washing with petroleum ether gave 150 mg of **10**: mp 96–97 °C; MS m/z 368 (18), 335 (28), 278 (17), 277 (100), 91 (60); NMR δ 0.87 (t, J = 6 Hz, CH_3), 1.2–1.7 (6 H), 1.42 (2 MeCS), 2.51 (t, J = 7 Hz, ArCH_2), 2.69 (H_2-3), 4.10 (ArCH_2S), 6.51 and 6.69 (dd, J = 2 Hz, H-6 and H-8), 7.2–7.6 (5 H, arom).

2,2-Dimethyl-5-mercapto-7-pentyl-2,3-dihydro-4*H*-1-benzopyran-4-one (11). A solution of 100 mg (0.36 mmol) of **10** in 1.5 mL of benzene was treated with 110 mg (0.41 mmol) of $AlBr_3$ and stirred for 1 h. Treating with iced HCl, extraction with ether, and chromatography with hexane–AcOEt 95:5 gave 15 mg of **11**, as a yellow oil: MS m/z 278 (79), 264 (19), 263 (100), 223 (65), 222 (55), 207 (14), 206 (14), 180 (15), 179 (25), 166 (96); NMR δ 0.88 (t, J = 6 Hz, CH_3), 1.2–1.7 (6 H), 1.43 (2 MeCS), 2.50 (t, J = 7 Hz, ArCH_2), 2.71 (H_2-3), 5.68 (SH), 6.50 and 6.65 (dd, J = 2 Hz, H-6 and H-8).

General Method for the Synthesis of Imines 13–44. A solution of 2 mmol of a chromanone (**1**) or thiochromanone (**2**) or of a substituted 2-hydroxyacetophenone and 4–10 mmol of the appropriate primary amine in absolute ethanol was refluxed until all or most of the starting ketone disappeared on TLC. Evaporation, taking up with EtOAc and water, washing repeatedly with water until the pH of the water layer was neutral, and evaporation gave a yellow product, which was purified by crystallization, distillation, or chromatography with hexane–EtOAc or CH_2Cl_2–MeOH. When the hydrochloride of the amine (e.g. **23**, **24**) or an amino acid (e.g. **28**) was employed, an excess of trimethylamine or sodium methoxide, respectively, was added to the reaction mixture.

All the imines show very similar NMR mass and UV spectra, consistent with their structure. As examples, data for **39** and **29** are reported.

39: MS m/z 336 (M + 1, 10), 335 (M^+, 55), 320 (21), 292 (19), 290 (36), 280 (16), 279 (100), 222 (21); NMR (80 MHz, $CDCl_3$) δ 0.87 (t, J = 6 Hz, CH_3CH_2), 1.2–1.7 (10 H), 1.33 (d, J = 6 Hz, CH_3CHOH), 1.42 (s, Me_2-2), 2.47 (t, J = 7 Hz, ArCH_2), 2.87 (s, H_2-3), 3.52 (d, J = 6 Hz, NCH_2CHOH), 4.12 (m, CHOH), 6.42 and 6.47 (dd, H-6 and H-8), 10.2 (br, chel OH); UV (C_6H_{12}) λ 228 (ϵ 14 300), 246 (18 000), 297 (8600), 350 (3650) nm; (MeOH) λ 214 (19 200), 244 (21 200), 330 (8400), 410 (4600) nm.

29: NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 6 Hz, CH_3CH_2), 1.13 (d, J = 6 Hz, CH_3 CHOH), 1.20–1.35 (4 H), 1.32 (s, 2 CH_3), 1.51 (q, $CH_2CH_2CH_2$), 2.38 (t, J = 6 Hz, ArCH_2), 2.83 (s, CH_2-3), 3.44 (dd, J = 2, 5 Hz, NCH_2), 3.86 (m, CHOH), 4.82 (d, J = 6 Hz, OH), 5.95 and 6.08 (dd, J = 2Hz, H-6 and H-8), 15.66 (t, J = 2 Hz, NH); UV (C_6H_{12}) λ 234 (ϵ 17 100), 280 (16 000), 332 (3100) nm; (MeOH) λ 207 (18 200), 222 (22 400), 306 (14 900), 403 (4100) nm. Hydrochloride (from 6 M HCl): mp 159–161 °C.

2,2-Dimethyl-4-[(2-hydroxypropyl)amino]-5-hydroxy-7-pentyl-2,3-dihydro-4*H*-1-benzopyran (46). To 76 mg (2 mmol) of $LiAlH_4$ suspended in 5 mL of dry ether was added 319 mg (1 mmol) of imine **29** in 20 mL of dry ether, and the mixture was stirred for 5 h. Addition of 10% aqueous NaOH, extraction with ether, evaporation of the solvent, and chromatography with hexane–EtOAc 3:7 gave 320 mg (62%) of **46**, as a diastereoisomeric mixture: NMR δ 0.89 (t, J = 6 Hz, CH_3), 1.8–3.0 (20 H), 2.43 (t, J = 6 Hz, ArCH_2), 3.8–4.2 (m, 2 H, C*H*OH and C*H*NH), 5.6 (br, 2 H, OH and NH), 6.13 and 6.22 (dd, J = 2 Hz, H-6 and H-8). Hydrochloride (from ether): mp 165–167 °C.

2-Hydroxy-4-pentylacetophenone (45). 3-Pentylphenol[15] (1 g, 6.1 mmol) was refluxed 1 h with 3 mL of acetic anhydride and 0.5 g of sodium acetate. Evaporation, taking up with water, extraction with EtOAc, and chromatography with hexane–EtOAc 9:1 gave 970 mg (77%) of 3-acetoxy-1-pentylbenzene, as an oil: NMR ($CDCl_3$) δ 0.91 (t, J = 6 Hz, CH_3), 1.2–1.9 (6 H), 2.31 (AcO), 2.62 (t, ArCH_2), 6.8–7.3 (4 H, arom). A mixture of 900 mg of 3-acetoxy-1-pentylbenzene and $AlCl_3$ (1.1 g) was heated for 2 h

(15) Carvalho, C. F.; Sargent, M. V. *Aust. J. Chem.* **1986**, *39*, 1765.

at 130 °C. Taking up with aqueous HCl, extraction with EtOAc, and chromatography with hexane–EtOAc 9:1 gave **45** (450 mg), as an oil; NMR δ 0.88 (t, J = 6 Hz, CH_3), 1.2–1.8 (6 H), 2.60 (MeCO), 2.60 (t, $ArCH_2$), 6.70 (H-5), 7.27 (H-3), 7.62 (H-6), ca. 12 (br, chel OH).

Pharmacological Methods. All tests were conducted on male mice (Crl:CD^R (ICR)BR, 22–25-g body weight) or on male rats (Crl:CD^R (SD)BR, 110–130-g body weight). The compounds were administered orally by gavage as a suspension in 0.5% methylcellulose and 0.1% Tween 80 in a volume of 0.5 mL/100 g. Statistical evaluations were made by using the probits method according to Finney.[16]

Pentylenetetrazole Antagonism. The compounds were tested for their effect on the maximal extensor seizures induced in mice by pentylenetetrazole given by iv injection at a dose of 50 mg/kg. This dose of pentylenetetrazole induces clonic and flexor–extensor tonic convulsions in 100% of the control animals. The test compounds were administered at different dosages 60 min before treatment with pentylenetetrazole, starting from the screening dose of 25 mg/kg, in order to obtain the dose–response curves. Groups of 10 animals per dose were used and one group of 10 animals served as a control group. From the dose–response curves the ED_{50} was calculated as the dose which prevents the onset of flexor–extensor tonic convulsions in 50% of the treated animals.

Maximal Electroshock Seizures (MES). The seizures were elicited with a 100-cycle alternating current of a 25-mA intensity, delivered for 0.5 s via auricular electrodes, with at least four doses and 10 mice at each dose. Protection in this test was defined as the abolition of the hind-limb tonic extension component of the seizure.

3-Mercaptopropionic Acid (MPA), Bicuculline, and Picrotoxin Antagonism. Male mice (CD_1, Charles River Italy, Crl:CD-1^R (ICR)BR) weighing 18–20 g were housed in groups of 50 in a stabularium on a 12-h light–dark cycle (from 6 a.m. to 6 p.m.) for a week, the final weight was 22–24 g. The compounds were suspended in 5% methocel (400 cps, Dow Chemicals, AM 17B018) and administered by gavage to 10 animals per dose in a volume of 0.5 mL/100 g of body weight.

After 1 h mice were injected sc with 60 mg/kg MPA (Sigma) dissolved in distilled water, in a volume of 0.5 mL/100 g of body weight.

In a similar experiment, after 1 h mice were injected sc with 3 mg/kg of bicuculline (Fluka) dissolved in 0.01 N HCl in a volume of 0.5 mL/100 g of body weight.

In a similar experiment, after 1 h mice were injected sc with 4 mg/kg picrotoxin (BDH) dissolved in distilled water, in a volume of 0.5 mL/100 g of body weight.

This dose was the minimum dose required to induce clonic convulsions, tonic extensions, and death in all the placebo-treated animals. The animals were put in individual cages and observed for 1 h after the injection of the convulsant. From the dose–response curves obtained, the doses were calculated which prevented 50% of the treated animals from tonic convulsions (ED_{50}).

Pentobarbital Sleep Potentiation. The compounds were tested for their capacity to increase sleeping time of male rats treated with sodium pentobarbital. The animals were fasted 9 h before the experiment took place. The compounds were administered 60 min before ip injection of sodium pentobarbital (30 mg/kg). Groups of eight animals were used for each dose tested and a group of 16 served as a control group. From the dose–response curve the ED_{50} was calculated as the dose which increased sleeping time by 50% compared with that of the control group.

Reserpine Antagonism. The reserpine antagonism test was performed in male mice as described elsewhere.[17]

Climbing Behavior. Male mice [CD^R-1 (ICR) BR, 22–25-g body weight] were present from the evening before in the same room in which the steady was conducted. In the morning they were randomly assigned into groups of 10 animals each. At time zero, control groups were treated orally with vehicle (0.5% methocel) and haloperidol, respectively, at a dose of 0.2 mg/kg in a fixed volume of 0.5 mL/100 g of body weight and the other groups were treated with different doses of the compounds to be tested. Sixty minutes later, all animals were injected subcutaneously with 1.3 mg/kg apomorphine (0.1% ascorbic acid) in the same volume of 0.5 mL/100 g of body weight. Immediately after treatment, the animals were put into cylindrical individual cages (12 cm diameter, 14 cm height) with walls of vertical metal bars (2 mm diameter, 1 cm apart) with smooth surfaces. After a 5-min period of exploratory behavior, the saline-treated animals tend to adopt a vertical position, holding the bars for at least 30 min and climbing up. This behavior was scored as follows: four paws on the floor = 0, forefeet holding the wall = 1, four paws holding the wall = 2. The animals were observed twice, 10 and 20 min after injection, and the scores were evaluated according to the method of Protais.[18]

Orientative Acute Toxicity. This information (ca. LD_{50}) was obtained in the course of the Irwin's test,[12] performed on all the tested compounds in order to have their symptomatologic profile. All the compounds were tested at least at six dose levels on four animals per dose with careful observation for 60 min after treatment. Deaths occurring in 7 days after drug administration were registered.

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