A Versatile Approach to Analogues of the Cannabinoid-like Anti-emetic Nonabine (BRL 4664)

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Analogues of the cannabinoid-like anti-emetic nonabine (BRL 4664), in which the 4-pyridinyl and 1,2-dimethylheptyl groups have been replaced by other aryl and alky groups respectively, have been synthesised from the appropriate resorcinol by a novel procedure. The route has been shown to be of general applicability, although in the case of nonabine itself the procedure does not represent a viable alternative to that previously published.

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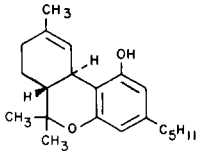
The therapeutic potential of Δ^9-tetrahydrocannabinol **1** [1-7] and cannabinoid-like compounds such as nabilone **2** [8,9], levonantradol **3** [10,11] and nonabine **4** [BRL 4664, 12] in reducing the nausea and vomiting associated with cytotoxic therapy has recently attracted considerable attention.



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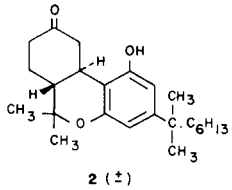

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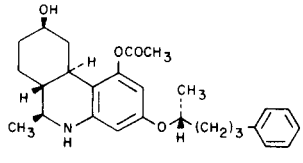

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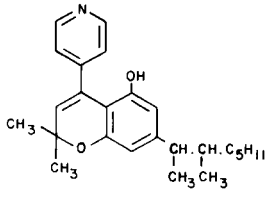
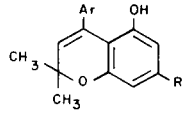


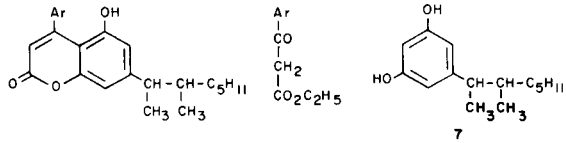
4 (±)

As part of a chemical programme designed to exploit the cannabinoid-like properties of nonabine, a series of analogues **5** was required in which the 4-pyridinyl and 1,2-dimethylheptyl groups were replaced by other aryl and alkyl groups respectively.



5 Ar = aryl, R = alkyl

The literature [13] synthesis of nonabine utilises as an intermediate the coumarin **6** which was prepared by Pechmann condensation of 5-(1,2-dimethylheptyl)resorcinol **7** with ethyl isonicotinoylacetate **8**. Coumarins such as **6** are, however, not particularly versatile intermediates since each has to be separately synthesised from the appropriate resorcinol and β-ketoester, neither of which is, in general, commercially available. Also, the coumarin route may not be of general applicability since attempts to prepare **9** by condensation of resorcinol **7** with ethyl 2-thenoylacetate **10** under normal Pechmann conditions (90% sulfuric acid, concentrated sulfuric acid/phosphorus oxychloride, phosphorus oxychloride/benzene) were unsuccessful. A more versatile alternative to the coumarin route was, therefore, sought.



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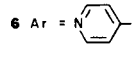
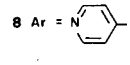


6 Ar =



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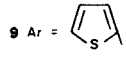

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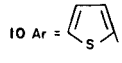
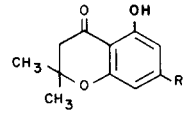
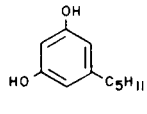


10 Ar =

Fahrenholtz *et al* [14] have described a synthesis of racemic Δ^8-tetrahydrocannabinol from the 4-chromanone **11**, the latter being prepared by condensation of olivetol **12** with 3,3-dimethylacrylic acid in the presence of boron trifluoride diethyl etherate. It appeared to us that chromanones such as **11** could represent useful intermediates to nonabine analogues since reaction of the carbonyl group with an appropriate, readily accessible, organometallic



11, R = C_5H_{11}
17, R = $CH(CH_3)C_6H_{13}$
18, R = $CH(CH_3)CH(CH_3)C_5H_{11}$



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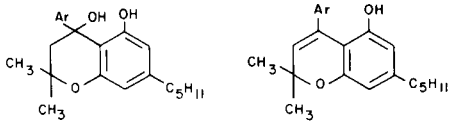
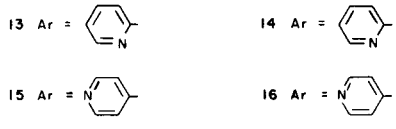
reagent, followed by dehydration of the intermediate tertiary alcohol, would afford the required final product. Although this route does not circumvent the need to separately synthesise each resorcinol, it does offer the possibility of readily incorporating a wide variety of 4-aryl groups.

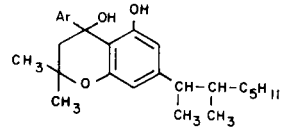
Preliminary experiments to demonstrate the viability of the route were carried out with chromanone **11**. Reaction with 4 equivalents of 2-pyridinyllithium at −65° gave the intermediate chroman-4,5-diol **13** in 58% yield which was readily dehydrated in 77% yield to the required chromen-5-ol **14** by teatment with acid (*p*-toluenesulfonic acid in benzene under reflux was particularly convenient). Alternatively, dehydration could be effected by heating neat *in vacuo* at 180-200°. The use of the less stable 4-pyridinyllithium resulted in a greatly reduced yield (28%) of the intermediate 4,5-diol **15** which on dehydration *in vacuo* yielded **16**.

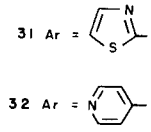




Having demonstrated the utility of the process, and in particular that intramolecular hydrogen bonding between the carbonyl and hydroxyl groups did not appear to adversely affect the reactivity of the former, attention was focussed on the preparation of analogues containing the 1-methylheptyl and 1,2-dimethylheptyl (nonabine) side-chains since previous work in both the nonabine [15] and cannabinoid [16,17] areas had demonstrated that compounds containing these side-chains possess greatly enhanced pharmacological properties compared to the corresponding *n*-pentyl derivatives. Chromanones **17** and **18** were readily prepared from the appropriate resorcinol by the Fahrenholtz, *et al* procedure [14] and their reactions with a variety of organometallic reagents were evaluated. The results are detailed in the Table [18]. In some cases the intermediate chroman-4,5-diol was not isolated and purified, the required chromen-5-ol being obtained directly from the crude organometallic reaction product either on work-up or by subsequent dehydration using methods analogous to those used for the preparation of **14** and **16**.

Acid-catalysed dehydration of the 2-thiazolyl analogue **31** proceeded smoothly to give the expected chromen-5-ol **26**. When, however, **31** was pyrolysed *in vacuo* at 180-195°, chromanone **18** (28%) was obtained in addition to **26** (72%). In a separate pyrolysis experiment, the volatile products were collected at −78° and shown by pmr spectroscopy to consist of water and thiazole, thus indicating that **18** was formed by a simple retroGrignard reaction. Although the synthetic applications of quaternary thiazolium cations as leaving groups in organic synthesis are well documented [19-21], to our knowledge the corresponding loss of an uncharged thiazole moiety has not been reported.





The 3-thienyl analogue **23** was prepared in 47% yield by reaction of 3-thienyllithium with chromanone **18** at temperatures below −10°. Under these conditions, however, an inseparable mixture (by column or thin layer chromatography) of **18** and **23** was obtained. The crude reaction mixture was, therefore, treated with an excess of hydroxylamine hydrochloride in pyridine, the required chromen-5-ol being readily separable from the chromanone oxime by column chromatography. An attempt to use a higher temperature range (−10° to 20°) in the 3-thienyllithium reaction resulted in partial isomerisation of the organometallic reagent, the resulting product containing 10-25% of the 2-thienyl analogue **22**, as well as 5-10% of **18** and the required **23**.

Several unsuccessful attempts were made to prepare nonabine from **18** and 4-pyridinyllithium using the conditions employed for the preparation of **16**. Eventually a low (19%) yield of the intermediate diol **32** was obtained by reaction of **18** with 18 equivalents of 4-pyridinyllithium at −78° in the presence of *N,N,N*^{1},*N*^{1}-tetramethylethylenediamine [22]. The corresponding yield in the absence of the ethylenediamine was only 5%. Dehydration of **32** proceeded smoothly to give nonabine which was shown to be identical with an authentic sample. Clearly, however, for nonabine itself the chromanone route is vastly inferior to the published coumarin [13] procedure.

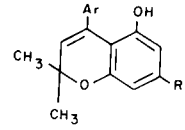
Pharmacological evaluation [15] of the analogues reported here indicates that **22, 23** and **24** are the compounds of most interest, possessing a similar profile and order of biological activity to nonabine itself.

EXPERIMENTAL

Melting points are uncorrected. Infrared (ir) spectra were recorded with a Pye-Unicam SP 200 spectrophotometer using a liquid film on sodium chloride discs. Proton magnetic resonance (pmr) spectra were recor-

Table

Chromen-5-ol Analogues of Nonabine



Compound No.	Ar	R	Organo-metallic Reagent	% Yield from Chromanone	GC Purity %	Molecular Formula	Analyses Calcd./Found C	H	N	S
14	2-pyridinyl	pentyl	Li	45	—	$C_{21}H_{25}NO_2$	78.02	7.74	4.33	—
							78.22	8.04	4.33	—
16	4-pyridinyl	pentyl	Li	18	—	$C_{21}H_{25}NO_2$	78.02	7.74	4.33	—
							77.99	7.97	4.34	—
19	2-pyridinyl	1-methylheptyl	Li	82	98	$C_{24}H_{31}NO_2$	78.90	8.49	3.84	—
							79.18	8.53	3.79	—
20	2-thienyl	1-methylheptyl	Mg	91	>98	$C_{23}H_{30}O_2S$	74.59	8.11	—	8.65
							74.67	8.45	—	8.89
21	2-pyridinyl	1,2-dimethylheptyl	Li	32	99	$C_{25}H_{33}NO_2$	79.16	8.71	3.69	—
							78.76	8.97	3.48	—
4	4-pyridinyl	1,2-dimethylheptyl	Li	11	99	$C_{25}H_{33}NO_2$	79.16	8.71	3.69	—
							78.97	8.49	3.74	—
22	2-thienyl	1,2-dimethylheptyl	Mg	74	95	$C_{24}H_{32}O_2S$	75.00	8.33	—	8.33
							74.97	8.49	—	8.28
23	3-thienyl	1,2-dimethylheptyl	Li	47	94	$C_{24}H_{32}O_2S$	75.00	8.33	—	8.33
							74.70	8.60	—	7.93
24	2-furanyl	1,2-dimethylheptyl	Li	36	95	$C_{24}H_{32}O_3$	78.26	8.70	—	—
							78.17	9.12	—	—
25	1-methyl-1*H*-pyrrol-2-yl	1,2-dimethylheptyl	Li	50	>99	$C_{25}H_{35}NO_2$	78.74	9.19	3.67	—
							78.54	9.48	3.24	—
26	2-thiazolyl	1,2-dimethylheptyl	Li	14	97	$C_{23}H_{31}NO_2S$	71.69	8.05	3.64	8.31
							72.48	8.45	3.32	8.32[a]
27	1-methyl-1*H*-pyrazol-5-yl	1,2-dimethylheptyl	Li	21	—	$C_{24}H_{34}N_2O_2$	75.39	8.90	7.33	—
							75.44	9.11	7.27	—
28	phenyl	1,2-dimethylheptyl	Mg	52	>94	$C_{26}H_{34}O_2$	82.54	8.99	—	—
							82.92	9.51	—	—[b]
29	4-fluorophenyl	1,2-dimethylheptyl	Mg	57	94	$C_{26}H_{33}FO_2$	78.79	8.33	—	—
							78.54	8.63	—	—
30	4-trifluoromethyl-phenyl	1,2-dimethylheptyl	Mg	69	98	$C_{27}H_{33}F_3O_2$	72.65	7.40	—	—
							72.72	7.67	—	—

[a] Consistent analyses could not be obtained. Exact mass at m/e 385.2087. Calcd. for $C_{23}H_{31}NO_2S$: 385.2076. [b] Consistent analyses could not be obtained. Exact mass at m/e 378.2558. Calcd. for $C_{26}H_{34}O_2$: 378.2559.

ded at 60 MHz on either a Varian A60, or Perkin-Elmer RF12 spectrometer using solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as an internal reference. Column chromatography was carried out on Merck Kieselgel 60 (loading ratio 40:1). All organometallic reactions were carried out using dried solvents in an atmosphere of nitrogen. Magnesium sulfate monohydrate was used throughout as drying agent. Light petroleum refers to the fraction boiling between 60° and 80°.

2,3-Dihydro-2,2-dimethyl-7-pentyl-4-(2-pyridinyl)-4*H*-1-benzopyran-4,5-diol (**13**).

A solution of 2-pyridinyllithium [23] was prepared by the dropwise addition over 45 minutes of 53.43 g (338 mmoles) of 2-bromopyridine in 75 ml of ether to a cooled (−45 to −50°) stirred solution of 24.32 g (380 mmoles) of *n*-butyllithium in 225 ml of ether. To the resulting stirred solution at −45° to −50° was added over 20 minutes 22.40 g (85 mmoles) of **11** in 100 ml of ether. The temperature of the reaction mixture was then allowed to rise to −15° over 20 minutes and this temperature was maintained for a further 30 minutes. After addition of 320 ml of 1*N* sulfuric acid the ether layer was separated and extracted with 3 × 250 ml of 3*N* sulfuric acid. Neutralisation of the combined acid extracts with 0.880 ammonia solution gave an oil which was extracted into ether and dried. Removal of the ether and residual pyridine *in vacuo* yielded 26.4 g of a red oil which was crystallised from light petroleum to give 16.9 g (58%) of **13** as a colourless solid, mp 114-116°, raised to 117-118° by one further crystallisation from the same solvent; pmr: δ 0.60-2.10 (m, C_4H_9, 9H), 1.29 (s, *gem*-diCH_3, 3H), 1.46 (s, *gem*-diCH_3, 3H), 2.22 (s, pyran CH_2, 2H), 2.30-2.80 (broad t, J = 7 Hz, benzylic CH_2, 2H), 5.60-6.80 (broad hump, OH, 2H), 6.28 (d, J = 2 Hz, benzenoid CH, 1H), 6.38 (d, J = 2 Hz, benzenoid CH, 1H), 6.80-7.80 (m, β- and γ-pyridinyl CH, 3H), 8.51 (m, α-pyridinyl CH, 1H).

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.90; H, 7.92; N, 4.11. Found: C, 73.74; H, 7.88; N, 4.09.

2,2-Dimethyl-7-pentyl-4-(2-pyridinyl)-2*H*-1-benzopyran-5-ol (**14**).

A mixture of 14.6 g (43 mmoles) of **13** and 11.0 g (58 mmoles) of *p*-tolu-

enesulfonic acid monohydrate in 290 ml of dry benzene was stirred under reflux in a Dean and Stark apparatus for 9.5 hours, then left to cool overnight. The benzene solution was washed with water, aqueous sodium bicarbonate solution and water, then dried. Removal of the solvent *in vacuo* gave 13.0 g of a brown solid which was crystallised from acetonitrile to give 10.7 g (77%) of **14** as a colourless powder, mp 122-123.5°; pmr: δ 0.60-2.00 (m, C_4H_9, 9H), 1.46 (s, *gem*-diCH_3, 6H), 2.28-2.70 (broad t, J = 7 Hz, benzylic CH_2, 2H), 5.95 (s, olefinic CH, 1H), 6.31-6.38 (m, benzenoid CH, 2H), 7.10-8.00 (m, β- and γ-pyridinyl CH, 3H), 8.51 (m, α-pyridinyl CH, 1H), 13.24 (s, OH, 1H).

2,3-Dihydro-2,2-dimethyl-7-pentyl-4-(4-pyridinyl)-4*H*-1-benzopyran-4,5-diol (**15**).

A solution of 4-pyridinyllithium (**24**) was prepared by the dropwise addition over 45 minutes of 19.60 g (124 mmoles) of 4-bromopyridine in 25 ml of ether to a cooled (−65°) stirred solution of 8.90 g (139 mmoles) of *n*-butyllithium in 75 ml of ether. To the resulting stirred solution at −65° was added over 45 minutes 8.25 g (31 mmoles) of **11** in 40 ml of ether, the reaction mixture being maintained at this temperature for a further 85 minutes. After addition of 110 ml of 1*N* sulfuric acid, the ether layer was separated and washed with 3*N* sulfuric acid to give an oil, insoluble in ether and water, which crystallised to give 3.56 g of a solid, mp 125-135°. The solid was dissolved in methanol, neutralised with 0.880 ammonia solution and the resulting solution poured into water. The precipitated product was filtered, washed with water, dried and crystallised from benzene to give 2.79 g (26%) of **15** as a colourless solid, mp 175.5-176° dec; pmr: δ 0.70-1.90 (m, C_4H_9, 9H), 1.34 (s, *gem*-diCH_3, 3H), 1.48 (s, *gem*-diCH_3, 3H), 2.12 (q, J = 14 Hz, pyran CH_2, 2H), 2.28-2.70 (broad t, J = 7 Hz, benzylic CH_2, 2H), 6.28 (unresolved d, benzenoid CH, 1H), 6.37 (unresolved d, benzenoid CH, 1H), 7.31 (m, β-pyridinyl CH, 2H), 8.18 (m, α-pyridinyl CH, 2H).

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.90; H, 7.92; N, 4.11. Found: C, 73.99; H, 8.00; N, 4.02.

2,2-Dimethyl-7-pentyl-4-(4-pyridinyl)-2*H*-1-benzopyran-5-ol (**16**).

Pyrolysis of 0.15 g (0.44 mmole) of **15** *in vacuo* at 180-195° for 20 minutes yielded 0.12 g of a solid which was crystallised from benzene to give 0.10 g (70%) of **16** as a colourless solid, mp 175.5°; pmr: δ 0.70-1.90 (m, C_4H_9, 9H), 1.47 (s, *gem*-diCH_3, 6H), 2.28-2.75 (broad t, J = 7 Hz, benzylic CH_2, 2H), 5.60 (s, olefinic CH, 1H), 6.30 (unresolved d, benzenoid CH, 1H), 6.39 (unresolved d, benzenoid CH, 1H), 7.31 (m, β-pyridinyl CH, 2H), 7.75-8.75 (broad hump, OH, 1H), 8.34 (m, α-pyridinyl CH, 2H).

2,3-Dihydro-5-hydroxy-2,2-dimethyl-7-(1-methylheptyl)-4*H*-1-benzopyran-4-one (**17**).

Reaction of 5-(1-methylheptyl)resorcinol (**16**) with 3,3-dimethylacrylic acid using the procedure of Fahrenholtz, *et al* [14] yielded **17** as a yellow liquid, bp 158-180° at 0.5 mm in 75% yield. An analytical sample (gc purity >99%) boiled at 164-170° at 0.5 mm; ir 1640 cm^{-1} (C=O); pmr: δ 0.50-2.00 (m, aliphatic side-chain, 16H), 1.46 (s, *gem*-diCH_3, 6H), 2.00-2.90 (m, benzylic CH, 1H), 2.69 (s, CH_2CO, 2H), 6.23 (d, J = 2 Hz, benzenoid CH, 1H), 6.31 (d, J = 2 Hz, benzenoid CH, 1H), 11.60 (s, OH, 1H).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 75.00; H, 9.21. Found: C, 75.25; H, 9.54.

2,3-Dihydro-2,2-dimethyl-7-(1-methylheptyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-4,5-diol (**33**).

Reaction of **17** with 2-pyridinyllithium by an analogous process to that used for the preparation of **13** gave **33** as a colourless solid, mp 116° dec in 82% yield; pmr: δ 0.60-2.10 (m, aliphatic side chain, *gem*-diCH_3, 22H), 2.10-2.85 (m, benzylic CH, 1H), 2.21 (s, pyran CH_2, 2H), 5.60-6.80 (broad hump, OH, 2H), 6.28 (d, J = 2 Hz, benzenoid CH, 1H), 6.38 (d, J = 2 Hz, benzenoid CH, 1H), 6.80-7.75 (m, β- and γ-pyridinyl CH, 3H), 8.51 (m, α-pyridinyl CH, 1H).

Anal. Calcd. for $C_{24}H_{33}NO_3$: C, 75.20; H, 8.62; N, 3.66. Found: C, 75.35; H, 8.86; N, 3.64.

2,2-Dimethyl-7-(1-methylheptyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-5-ol (**19**).

Pyrolysis of **33** *in vacuo* at 180° for 1 hour yielded **19** as a pale yellow oil in quantitative yield; pmr: δ 0.60-1.80 (m, aliphatic side chain 16H), 1.47 (s, *gem*-diCH_3, 6H), 2.10-2.90 (m, benzylic CH, 1H), 5.96 (s, olefinic CH, 1H), 6.34 (d, J = 2 Hz, benzenoid CH, 1H), 6.40 (d, J = 2 Hz, benzenoid CH, 1H), 7.10-8.00 (m, β- and γ-pyridinyl CH, 3H), 8.52 (m, α-pyridinyl CH, 1H).

2,2-Dimethyl-7-(1-methylheptyl)-4-(2-thienyl)-2*H*-1-benzopyran-5-ol (**20**).

A solution of 2-thienylmagnesium bromide [25] was prepared by the dropwise addition over 30 minutes of 4.89 g (30 mmoles) of 2-bromothiophene in 10 ml of ether to a stirred suspension of 0.72 g (30 mmoles) of magnesium in 10 ml of ether, reaction being initiated by a crystal of iodine. After a further 20 minutes 3.04 g (10 mmoles) of **17** in 10 ml of ether was added dropwise over 12 minutes to the stirred solution of the Grignard reagent, the reaction mixture then being stirred at ambient temperature for 4 hours. After addition of aqueous ammonium chloride the product was extracted into ether, the ether washed with water and dried. Removal of the solvent *in vacuo* gave 3.90 g of a brown oil which was purified by column chromatography in benzene-light petroleum (1:4) to give 3.36 g (91%) of **20** as a pale yellow oil; pmr: δ 0.60-1.90 (m, aliphatic side chain, 16H), 1.42 (s, *gem*-diCH_3, 6H), 2.10-2.90 (m, benzylic CH, 1H), 5.19 (s, OH, 1H), 5.65 (s, olefinic CH, 1H), 6.29 (d, J = 2 Hz, benzenoid CH, 1H), 6.39 (d, J = 2 Hz, benzenoid CH, 1H), 6.85-7.44 (m, thienyl CH, 3H).

7-(1,2-Dimethylheptyl)-2,3-dihydro-5-hydroxy-2,2-dimethyl-4*H*-1-benzopyran-4-one (**18**).

Reaction of 5-(1,2-dimethylheptyl)resorcinol (**17**) with 3,3-dimethylacrylic acid using the procedure of Fahrenholtz, *et al* [14] yielded **18** as a yellow liquid (gc purity >99%) bp 174-184° at 0.9 mm in 59% yield; ir: 1640 cm^{-1} (C=O); pmr: δ 0.50-2.00 (m, aliphatic side chain, 18H), 1.48 (s, *gem*-diCH_3, 6H), 2.00-2.90 (m, benzylic CH, 1H), 2.72 (s, CH_2CO, 2H), 6.24 (unresolved d, benzenoid CH, 1H), 6.32 (unresolved d, benzenoid CH, 1H), 11.60 (s, OH, 1H).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.47; H, 9.43. Found: C, 75.55; H, 9.54.

7-(1,2-Dimethylheptyl)-3,4-dihydro-2,2-dimethyl-4-(2-pyridinyl)-2*H*-1-benzopyran-4,5-diol (**34**).

Reaction of 12.70 g (40 mmoles) of **18** in 50 ml of ether with 13.60 g (160 mmoles) of 2-pyridinyllithium in 150 ml of ether was carried out as for the preparation of **13**. After decomposition of the reaction mixture with 145 ml of 1*N* sulfuric acid, the ether layer was separated, washed with 100 ml of water then four 100 ml portions of 3*N* sulfuric acid. Addition of a further 100 ml of water to the ether layer resulted in the separation of three layers, the middle one of which was collected and partitioned between aqueous sodium bicarbonate and ether. The organic layer was separated and dried and the solvent removed *in vacuo* to yield 13.20 g of waxy solid which was crystallised twice from light petroleum to give 6.33 g (40%) of **34** as a colourless powder, mp 81.5-83°; pmr: δ 0.10-1.85 (m, aliphatic side chain, *gem*-diCH_3, 24H), 1.90-2.80 (m, benzylic CH, 1H), 2.20 (s, pyran CH_2, 2H), 5.60-6.20 (broad hump, OH, 2H), 6.28 (partially resolved d, benzenoid CH, 1H), 6.38 (partially resolved d, benzenoid CH, 1H), 6.80-7.80 (m, β- and γ-pyridinyl CH, 3H), 8.53 (m, α-pyridinyl CH, 1H).

Anal. Calcd. for $C_{25}H_{35}NO_3$: C, 75.57; H, 8.82; N, 3.53. Found: C, 75.46; H, 8.90; N, 3.49.

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-(2-pyridinyl)-2*H*-1-benzopyran-5-ol (**21**).

Pyrolysis of **34** *in vacuo* at 180° for 1.5 hours, followed by column chromatography of the resulting red oil in benzene-light petroleum (1:1), yield **20** as a pale orange oil in 80% yield; pmr: δ 0.60-2.00 (m, aliphatic side chain, 18H), 1.45 (s, *gem*-diCH_3, 6H), 2.10-2.75 (m, benzylic CH, 1H), 5.98 (s, olefinic CH, 1H), 6.32 (unresolved d, benzenoid CH, 1H), 6.38 (unresolved d, benzenoid CH, 1H), 7.15-7.95 (m, β- and γ-pyridinyl CH, 3H),

8.50 (m, α-pyridinyl CH, 1H), 10.50-13.00 (broad hump, OH, 1H).

7-(1,2-Dimethylheptyl)-3,4-dihydro-2,2-dimethyl-4-(4-pyridinyl)-2*H*-1-benzopyran-4,5-diol (**32**).

To a stirred solution of 8.96 g (140 mmoles) of *n*-butyllithium in 85 ml of ether at ambient temperature was added dropwise over 3 minutes a solution of 3.66 g (32 mmoles) of *N,N,N*^{1},*N*^{1}-tetramethylethylenediamine [22] in 5 ml of ether. After a further 15 minutes at ambient temperature the resulting solution was cooled to −68 to −70° and a solution of 19.8 g (125 mmoles) of 4-bromopyridine in 60 ml of ether was added dropwise over 65 minutes. After a further 20 minutes a solution of 2.10 g (6.6 mmoles) of **18** in 10 ml of ether was added dropwise over 12 minutes, the temperature of the reaction mixture then being allowed to rise to −40° over 45 minutes. After 10 minutes at −40° the reaction mixture was allowed to attain ambient temperature over 30 minutes and this temperature was maintained for a further 1 hour. The reaction mixture was then decomposed by the addition of 1*N* sulfuric acid until the aqueous layer was neutral, the ether layer then being separated and washed with 5*N* hydrochloric acid (2 × 100 ml). Further washing of the ether layer with water gave a turbid two-phase system which after several hours separated into three distinct layers. The middle layer was separated, neutralised and extracted with ether. The ether extract was dried and the solvent removed *in vacuo* to give 0.65 g of a yellow solid which was purified by column chromatography. Elution with benzene gave 0.15 g of **18**; further elution with chloroform gave 0.48 g (18%) of **32** as a colourless powder, mp 163-165°, raised to 167-167.5° by two crystallisations from ether-light petroleum; pmr: δ 0.60-1.85 (m, aliphatic side chain, gem-diCH_3, 24H), 2.10 (q, J = 14 Hz, pyran CH_2, 2H), 2.15-2.80 (m, benzylic CH, 1H), 3.50-4.50 (broad hump, OH, 1H), 6.30 (s, benzenoid CH, 1H), 6.38 (s, benzenoid CH, 1H), 7.20 (m, β-pyridinyl CH, 2H), 8.14 (m, α-pyridinyl CH, 2H).

Anal. Calcd. for $C_{25}H_{35}NO_3$: C, 75.57; H, 8.82; N, 3.53. Found: C, 75.43; H, 8.99; N, 3.59.

When the reaction was carried out in the absence of the ethylenediamine, the yield of **32** dropped to 5%.

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-(4-pyridinyl)-2*H*-1-benzopyran-5-ol (Nonabine, **4**).

Pyrolysis of 0.12 g (0.30 mmole) of **32** at 185° for 1 hour yielded a brown gum which was purified by column chromatography on silica in benzene-chloroform (1:1) to give 0.07 g (61%) of **4**, mp 89-94°, lit [13] mp 80-85°, after crystallisation from light petroleum. This material was shown by ir, uv, pmr and gc to be identical with an authentic sample of nonabine.

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-(2-thienyl)-2*H*-1-benzopyran-5-ol (**22**).

Reaction of **18** with 2-thienylmagnesium bromide by an analogous method to that described for the preparation of **19** yielded **22** as a pale yellow oil in 74% yield; pmr: δ 0.60-2.10 (m, aliphatic side chain, 18H), 1.42 (s, *gem*-diCH_3, 6H), 2.10-2.80 (m, benzylic CH, 1H), 5.14 (s, OH, 1H), 5.67 (s, olefinic CH, 1H), 6.29 (partially resolved d, benzenoid CH, 1H), 6.38 (partially resolved d, benzenoid CH, 1H), 6.92-7.45 (m, thienyl CH, 3H).

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-(3-thienyl)-2*H*-1-benzopyran-5-ol (**23**).

A solution of 3-thienyllithium [26] was prepared by the dropwise addition over 1.25 hours of 8.43 g (52 mmoles) of 3-bromothiophene in 25 ml of ether to a cooled (−70°) stirred solution of 3.60 g (56 mmoles) of *n*-butyllithium in 18 ml of hexane. After a further 45 minutes at −70° a solution of 3.18 g (10 mmoles) of **18** in 15 ml of ether was added dropwise over 25 minutes and the resulting reaction mixture was then stirred at −70° for 2.5 hours, at −40° for 1.5 hours and finally at −10° for 1.25 hours. After neutralisation with 5*N* sulfuric acid, the organic layer was separated, washed with water and dried. Removal of the solvent gave 3.80 g of a black oil containing an inseparable mixture of **18** and the required product **23**. The crude product was therefore dissolved in 15 ml of pyridine and treated with 2.0 g of hydroxylamine hydrochloride, the resulting solution being heated at 100° for 6 hours. After being cooled the solution was poured into water and extracted with ether. The ether extract was washed with 5*N* hydrochloric acid, water, dried and the solvent removed *in vacuo* to give 3.70 g of a black oil which was purified by column chromatography in benzene-light petroleum (1:4) to give 1.80 g (47%) of **23** as a pale yellow oil; pmr: δ 0.60-1.90 (m, aliphatic side chain, 18H), 1.45 (s, *gem*-diCH_3, 6H), 2.10-2.80 (m, benzylic CH, 1H), 4.89 (s, OH, 1H), 5.57 (s, olefinic CH, 1H), 6.23 (partially resolved d, benzenoid CH, 1H), 6.37 (partially resolved d, benzenoid CH, 1H), 6.95-7.60 (m, thienyl CH, 3H).

7-(1,2-Dimethylheptyl)-4-(2-furanyl)-2,2-dimethyl-2*H*-1-benzopyran-5-ol (**24**).

2-Furanyllithium [27] was prepared by the dropwise addition over 10 minutes of 2.72 g (40 mmoles) of furan in 10 ml of ether to a stirred solution of 2.56 g (40 mmoles) of *n*-butyllithium in 17 ml of hexane at −20°. The resulting solution was allowed to attain ambient temperature over 20 minutes and then heated at 35-40° for 2.5 hours. A solution of 3.18 g (10 mmoles) of **18** in 10 ml of ether was added dropwise over 10 minutes to this hot solution of 2-furanyllithium, heating and stirring being continued for a further 2.5 hours. Acid work-up, followed by column chromatography in benzene-light petroleum (1:1) yielded 1.32 g (36%) of **24** as a colourless oil which rapidly darkened on exposure to air; pmr (carbon tetrachloride): δ 0.60-1.90 (m, aliphatic side-chain, 18H), 1.39 (s, *gem*-diCH_3, 6H), 2.00-2.80 (m, benzylic CH, 1H), 5.10 (s, OH, 1H), 5.81 (s, olefinic CH, 1H), 6.18 (broad s, β-furanyl CH, 2H), 6.40 (d, benzenoid CH, 2H), 7.40 (broad t, α-furanyl CH, 1H).

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-1-benzopyran-5-ol (**25**).

2-Lithio-1-methylpyrrole [28] was prepared by the dropwise addition over 10 minutes of 3.24 g (40 mmoles) of 1-methylpyrrole in 10 ml of ether to a stirred solution of 2.56 g (40 mmoles) of *n*-butyllithium in 17 ml of hexane and the resulting solution was stirred at 40° for 20 hours. A solution of 3.18 g (10 mmoles) of **18** in 10 ml of ether was then added dropwise over 10 minutes to the heated solution, heating and stirring then being maintained for a further 6 hours. Acid work-up followed by pyrolysis of the crude product *in vacuo* at 180° for 1 hour yielded a brown oil which was purified by chromatography in benzene-light petroleum (1:1) to give 1.90 g (50%) of **25** as an almost colourless oil; pmr (carbon tetrachloride): δ 0.60-1.80 (m, aliphatic side chain, 18H), 1.43 (s, *gem*-diCH_3, 6H), 2.00-2.80 (m, benzylic CH, 1H), 3.37 (s, NCH_3, 3H), 4.98 (s, OH, 1H), 5.46 (s, olefinic CH, 1H), 6.00-6.30 (m, benzenoid CH, β-pyrrolyl CH, 4H) 6.61 (broad t, α-pyrrolyl CH, 1H).

7-(1,2-Dimethylheptyl)-3,4-dihydro-2,2-dimethyl-4-(2-thiazolyl)-2*H*-1-benzopyran-4,5-diol (**31**).

2-Lithiothiazole [29] was prepared by the dropwise addition over 1.25 hours of 8.43 g (51 mmoles) of 2-bromothiazole in 25 ml of ether to a stirred solution of 3.60 g (56 mmoles) of *n*-butyllithium in 18 ml of hexane at −70°. A solution of 3.18 g (10 mmoles) of **18** in 12 ml of ether was added dropwise over 30 minutes to the cooled solution of the lithio derivative, the temperature being maintained at −70° for a further 3 hours then allowed to rise to −10° over one hour. The resulting black solution was neutralised with 5*N* sulfuric acid and the precipitated black solid filtered and discarded. The organic layer was washed with water, dried and evaporated *in vacuo* to give a black solid. Two crystallisations from ether-light petroleum (charcoal) gave 0.80 g (20%) of **31** as a colourless solid, mp 143-144°; pmr: δ (d_6-dimethyl sulfoxide) 0.50-1.70 (m, aliphatic side chain, *gem*-diCH_3, 24H), 2.00-2.70 (m, benzylic CH, 1H), 2.18 (s, pyran CH_2, 2H), 6.10 (s, benzenoid CH, 2H), 7.45 (d, J = 2 Hz, thiazolyl CH, 1H), 7.55 (d, J = 3 Hz, thiazolyl CH, 1H).

Anal. Calcd. for $C_{23}H_{33}NO_3S$: C, 68.49; H, 8.19; N, 3.47; S, 7.94. Found: C, 68.34; H, 8.22; N, 3.48; S, 8.00.

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-(2-thiazolyl)-2*H*-1-benzopyran-5-ol (**26**).

A solution of 1.30 g (3.2 mmoles) of **31** and 0.12 g (0.63 mmoles) of *p*-toluenesulfonic acid monohydrate in 25 ml of benzene was boiled under reflux for 45 minutes then cooled and poured into water. The organic layer was separated, dried and the solvent removed *in vacuo* to give a yellow oil. Purification by chromatography in benzene-light petroleum (3:7) gave 0.90 g (72%) of **26** as a pale yellow oil; pmr (carbon tetrachloride): δ 0.60-1.90 (m, aliphatic side chain, 18H), 1.47 (s, *gem*-diCH_3, 6H), 2.00-2.70 (m, benzylic CH, 1H), 6.33 (unresolved d, benzenoid CH, 1H), 6.38 (s, olefinic CH, 1H), 6.42 (unresolved d, benzenoid CH, 1H), 7.25 (d, J = 3 Hz, 5-thiazolyl CH, 1H), 7.74 (d, J = 3 Hz, 4-thiazolyl CH, 1H), 12.84 (s, OH, 1H).

When **31** was pyrolysed *in vacuo* at 185-200° for 30 minutes, a mixture of **26** (72%) and **18** (28%) was obtained.

7-(1,2-Dimethylheptyl)-3,4-dihydro-2,2-dimethyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2*H*-1-benzopyran-4,5-diol (**33**).

5-Lithio-1-methylpyrazole [30] was prepared by the dropwise addition over 10 minutes of 16.40 g (200 mmoles) of 1-methylpyrazole in 100 ml of ether to a stirred solution of 12.80 g (200 mmoles) of *n*-butyllithium in 85 ml of hexane at 20°, a yellow precipitate being formed. The resulting suspension was then stirred at 10-20° for a further 3.75 hours. A solution of 15.90 g (50 mmoles) of **18** in 50 ml of ether was added dropwise over 10 minutes to the stirred solution of the lithio derivative, the yellow precipitate gradually dissolving to form a red solution. After 17.5 hours at ambient temperature, acid work-up yielded 19.25 g of a brown solid which, on trituration with light petroleum yielded 8.73 g of a yellow solid. Crystallisation of this solid from light petroleum yielded 4.79 g (24%) of **33** as a colourless solid, mp 154-157°; pmr: δ (d_6-dimethyl sulfoxide) 0.40-1.60 (m, aliphatic side chain, *gem*-diCH_3, 24H), 2.00-2.70 (m, benzylic CH, 1H), 2.17 (s, pyran CH_2, 2H), 3.50 (s, NCH_3, 3H), 5.20 (s, OH, 1H), 5.89 (partially resolved d, 4-pyrazolyl CH, 1H), 6.14 (s, benzenoid CH, 2H), 7.16 (partially resolved d, 3-pyrazolyl CH, 1H), 9.28 (s, OH, 1H).

Anal. Calcd. for $C_{24}H_{36}N_2O_3$: C, 72.00; H, 9.00; N, 7.00. Found: C, 72.13; H, 9.22; N, 6.98.

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2*H*-1-benzopyran-5-ol (**27**).

Pyrolysis of 4.02 g (10 mmoles) of **33** *in vacuo* at 180-190° for 40 minutes yielded 3.77 g of a solid which was crystallised from light petroleum to give 3.22 g (84%) of **27** as a colourless solid, mp 149-150°; pmr: δ 0.60-2.00 (m, aliphatic side chain, 18H), 1.45 (s, *gem*-diCH_3, 6H), 2.00-2.70 (m, benzylic CH, 1H), 3.44 (s, NCH_3, 3H), 5.59 (s, olefinic CH, 1H), 6.20 (d, J = 2 Hz, 4-pyrazolyl CH, 1H), 6.32 (s, benzenoid CH, 2H), 7.41 (d, J = 2 Hz, 3-pyrazolyl CH, 1H), 8.00-8.30 (broad hump, OH, 2H).

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-phenyl-2*H*-1-benzopyran-5-ol (**28**).

A solution of phenylmagnesium bromide was prepared from 4.71 g (30 mmoles) of bromobenzene and 0.80 g (33 mmoles) of magnesium in 30 ml of ether. To the stirred solution of the Grignard reagent at ambient temperature was added dropwise over 20 minutes 3.18 g (10 mmoles) of **18** in 10 ml of ether, stirring being continued for a further 3 hours. Work-up with aqueous ammonium chloride yielded 4.37 g of crude 7-(1,2-dimethylheptyl)-3,4-dihydro-2,2-dimethyl-4-phenyl-2*H-1-benzopyran-4,5-diol which, without purification, was dehydrated with 1.80 g (9.5 mmoles) of* *p*-toluenesulfonic acid monohydrate in 100 ml of benzene under reflux in a Dean and Stark apparatus for 1.25 hours. The *p*-toluenesulfonic acid was removed by washing the cooled benzene solution with aqueous sodium bicarbonat, the organic layer yielding 4.02 g of an oil which was purified by chomatography in benzene-light petroleum (1:4) to give 1.97 g (52%) of **28** as a colourless oil which darkened on exposure to air; pmr: δ 0.60-2.00 (m, aliphatic side chain, 18H), 1.45 (s, *gem*-diCH_3, 6H), 2.10-2.80 (m, benzylic CH, 1H), 4.51 (s, OH, 1H), 5.49 (s, olefinic CH, 1H), 6.23 (unresolved d, benzenoid CH, 1H), 6.39 (unresolved d, benzenoid CH, 1H), 7.40 (s, phenyl CH, 5H).

7-(1,2-Dimethylheptyl)-4-(4-fluorophenyl)-2,2-dimethyl-2*H*-benzopyran-5-ol (**29**).

Reaction of **18** with 4-fluorophenylmagnesium bromide by an analogous method to that described in the preparation of **28** yielded 57% of **29** as a pale yellow oil; pmr: δ 0.60-2.10 (m, aliphatic side chain, 18H), 1.46 (s, *gem*-diCH_3, 6H), 2.10-2.80 (m, benzylic CH, 1H), 4.48 (s, OH, 1H), 5.48 (s, olefinic CH, 1H), 6.25 (unresolved d, benzenoid CH, 1H), 6.42 (unresolved d, benzenoid CH, 1H), 6.90-7.70 (m, 4-F-phenyl CH, 4H).

7-(1,2-Dimethylheptyl)-2,2-dimethyl-4-(4-trifluoromethylphenyl)-2*H*-1-benzopyran-5-ol (**30**).

Reaction of **18** with 4-trifluoromethylphenylmagnesium bromide by an analogous method to that described in the preparation of **28** yielded 69% of **30** as a pale yellow gum; pmr: δ 0.60-1.90 (m, aliphatic side chain, 18H), 1.43 (s, *gem*-diCH_3, 6H), 2.10-2.80 (m, benzylic CH, 1H), 4.63 (s, OH, 1H), 5.53 (s, olefinic CH, 1H), 6.16 (unresolved d, benzenoid CH, 1H), 6.38 (unresolved d, benzenoid CH, 1H), 7.28-7.76 (broad q, 4-CF_3-phenyl CH, 4H).

Attempted Preparation of 7-(1,2-Dimethylheptyl)-5-hydroxy-4-(2-thienyl)-2*H*-1-benzopyran-2-one (**9**).

(1) A mixture of 4.72 g (20 mmoles) of **7** and 3.96 g (20 mmoles) of **10** in 10 ml of 90% sulfuric acid was stirred at ambient temperature for 18 hours (no reaction by tlc) then heated at 60° for 24 hours. The resulting blue viscous solution was shown by tlc to contain no starting β-keto ester but aqueous work-up yielded none of the required **9**.

(2) A mixture of 1.18 g (5 mmoles) of **7** and 0.99 g (5 mmoles) of **10** in 1.5 ml of phosphorus oxychloride and 2.5 ml of concentrated sulfuric acid [31] was stirred at ambient temperature for 7 days. Aqueous work-up yielded only starting material.

[3] A mixture of 4.72 g (20 mmoles) of **7** and 3.96 g (20 mmoles) of **10** in 20 ml of phosphorus oxychloride and 40 ml of sodium-dry benzene was stirred at ambient temperature for 18 hours (no reaction by tlc) then boiled under reflux for 2 days. After aqueous work-up none of the required **9** was isolated.

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