SAR Studies in the Field of Calcium(II) Antagonists. Effect of Modifications at the Tetrasubstituted Carbon of Verapamil-like Compounds

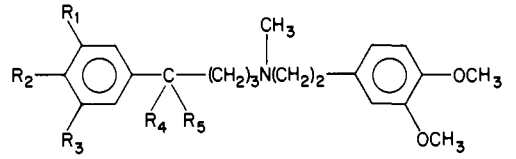
Fulvio Gualtieri,*† Elisabetta Teodori,† Cristina Bellucci,† Edilio Pesce,‡ and Giuseppe Piacenza‡

Dipartimento di Scienze Farmaceutiche, Università di Firenze, 50121 Florence, and Schiapparelli Farmaceutici, Torino, Italy.
Received January 2, 1985

A number of fluorenyl and diphenylmethane analogues of verapamil, chosen as having the same substituents arranged in different ways around the quaternary carbon, were synthesized in order to evaluate the importance of the stereoisomerism at that point of the molecule. The compounds were tested with the Langendorff technique and coronary perfusion pressure (CPP), left ventricular pressure (LVP), and heart rate (HR) were recorded. While most of the compounds were almost inactive on these parameters, three of them did show interesting cardiovascular action. In particular they produced a more pronounced decrease in CPP than verapamil, with a less marked negative inotropic effect. Structure–activity relationships and the mechanism of action of the compounds are discussed.

Despite the enormous work that has been done in the last years on the calcium antagonists,[1,2] structure–activity relationship (SAR) studies are few[3-5] if compared with the avalanche of pharmacological, physiological, and biochemical studies[6] and, because of the practical interest of this class of drugs, useful SAR information is often buried in the patent literature. However, a deeper understanding of the mechanism of action and an explanation of the amazing heterogeneity of the class may come not only from binding studies, which have been succesfully utilized to investigate the nature of calcium channels,[7,8] but also from a rational modification of each class of compounds.

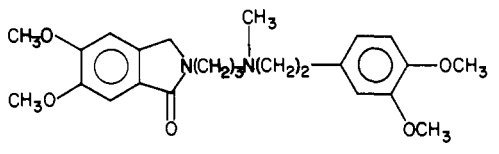
As a starting point for new research on calcium antagonists we have chosen to investigate the molecular requirements of verapamil-like compounds **1–3**, through



1 (verapamil): R_1=H; R_2=R_3=OCH_3; R_4=$CH(CH_3)_2$; R_5=CN
2 (gallapamil): R_1=R_2=R_3=OCH_3; R_4=$CH(CH_3)_2$; R_5=CN
3 (tiapamil): R_1=H; R_2=R_3=OCH_3; R_4=R_5=$-SO_2-SO_2-$

4: R_1=R_2=R_3=H; R_4=$CH(CH_3)_2$; R_5=CN

modifications of the tetrasubstituted carbon, which apparently plays a fundamental role in the interaction with the calcium channel.[9] The optical isomers of verapamil **1** and gallapamil **2**[10] show a definite enantioselectivity even if the hypothesis of a specific interaction of the two enantiomers with Ca^{2+} and Na^+ channels, respectively, has not been confirmed.[11,12] The presence of a quaternary benzylic carbon seems essential for the preservation of the biological activity, while substituents can be changed as in tiapamil **3**.[13] Nevertheless, the molecule can undergo even greater changes as is shown by the good activity of compound **5**.[14]



5

For our purposes we have synthesized and studied the compounds whose structure are reported below.

The fluorenyl and diphenylmethane series were chosen to afford analogues in which the aryl substituents are arranged in quite different ways around the quaternary carbon. By similar reasonings compound **13**, where the quaternary atom is flattened into a sp^2 carbon, and compound **12**, where the whole structure around the quaternary carbon lies on the same plane, were also prepared.

Of course, such compounds have to be considered model compounds, as they lack the methoxy groups of verapamil. Nevertheless it has been shown[3] that substituents on the benzene ring near the quaternary carbon atom are unessential for the activity of verapamil, even if they show a strong influence on the potency of the drug. As a matter of fact, although compound **4** itself has not been investigated, a verapamil derivative that is not substituted at either benzene ring differs from verapamil only in quantitative terms.[5] Therefore, while the synthesis of the methoxy derivatives is being pursued, we can usefully utilize the data of the unsubstituted compounds for SAR studies.

Chemistry

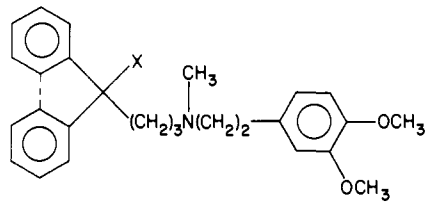
The synthetic pathways utilized to synthesize compounds **6–13** are shown in Schemes I–IV. The methods used are standard and will not be discussed in detail. Nevertheless a few points deserve comment.

In Scheme II the way eventually chosen was determined by the fact that reaction of **22** with $SOCl_2$ gives, at room temperature, the sulfite ester **37** and at higher temperature the 9-isopropylphenanthrene **38**[15,16] through a ring en-

† Università di Firenze.
‡ Schiapparelli Farmaceutici.

(1) A. Fleckenstein, *Circulation, Suppl, 52*, 3 (1983).
(2) R. A. Janis and D. J. Triggle, *J. Med. Chem.*, **26**, 775 (1983).
(3) R. Mannhold, R. Steiner, W. Haas, and R. Kaufmann, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **302**, 217 (1978).
(4) R. Rodenkirchen, R. Bayer, R. Steiner, F. Bossert, H. Meyer, and E. Moller, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **310**, 69 (1979).
(5) R. Mannhold, R. Bayer, R. Steiner, and R. Rodenkirchen, 1st Cyprus Conference on New Methods in Drug Research, Cyprus 17–23 April 1983, Abstracts.
(6) For few exemplary references, see ref 1 and 2.
(7) H. Glossmann, D. R. Ferry, F. Lubbecke, R. Mewes, and F. Hofmann, *Trends Pharmacol. Sci.*, **3**, 431 (1982).
(8) H. Glossmann, Proceeding of the XIth Congress of International Society for Heart Research, London 11–14 July 1983.
(9) H. Ramuz, *Arzneim. Forsch.*, **28**, 2048 (1978).
(10) R. Bayer, D. Kalusche, R. Kaufmann, and R. Mannhold, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **290**, 81 (1975).
(11) L. Ludwig and H. Nawrath, *Br. J. Pharmacol.*, **59**, 411 (1977).
(12) B. Muller and K. Wilsmann, *J. Cardiovasc. Pharmacol.*, **4**, 615 (1982).
(13) H. Ramuz, *Cardiology*, **69**, 26 (1982).
(14) W. Trautwein, D. Pelzer, T. F. McDonald, and W. Osterrieder, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **317**, 228 (1981).
(15) C. K. Bradsher and S. T. Amore, *J. Am. Chem. Soc.*, **63**, 493 (1941).

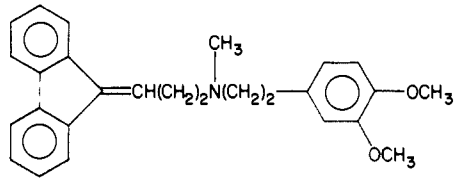
0022-2623/85/1828-1621$01.50/0



fluorenyl series diphenylmethane series

6, X = H
7, X = $CH(CH_3)_2$
8, X = CN

9, X = H
10, X = $CH(CH_3)_2$
11, X = CN



fluorenyl series **12** diphenylmethane series **13**

largement that probably follows the mechanism proposed by Greenhow.[17]

In this respect, it is interesting to note that the same reaction on the unsubstituted 9-(hydroxymethyl)fluorene gave not only 9-(chloromethyl)fluorene as reported by Wawzonek[18] but also a substantial amount of phenanthrene, which explains the low yields reported.

Compounds **26** and **27**, obtained through a Wittig reaction on **24** and **25** are the trans isomers as is shown by NMR spectra and in accordance with the literature.[19]

The Wittig reaction shown in Scheme III gives the compound with the exocyclic double bond **39** directly, while the same reaction on diphenylacetaldehyde gave the expected α, β unsaturated ester **47**. Reduction of **39** with $LiAlH_4$ afforded several products among which saturated alcohol **45** was prevalent, whereas only traces of **41** could be detected (TLC).

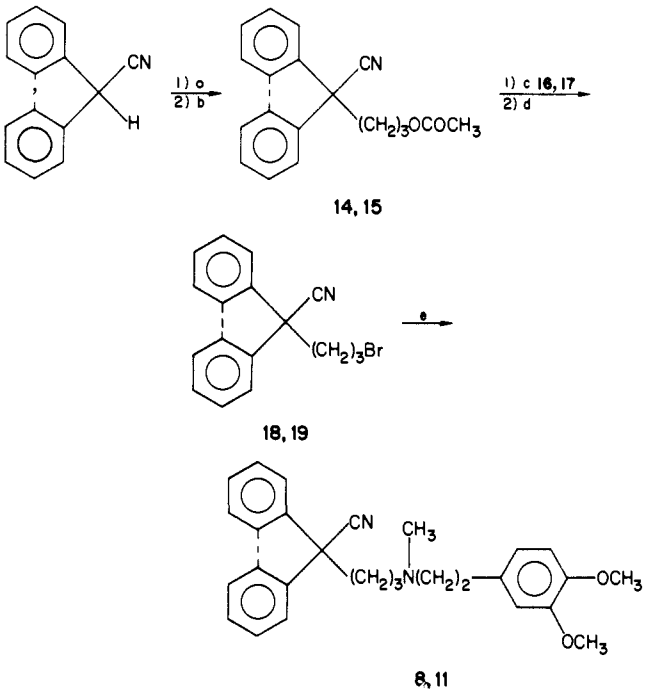
When the reduction was carried out on the acid **40**, a yield of 30% of **41** was obtained but the mixture was still very complex, so that the compound was eventually obtained from **43**.

Compounds related to **9** and **11** are cited in a few patents[20-24] but it is quite difficult to ascertain whether **9** and **11** are among the compounds synthesized in the claims. In any case, as chemical and physical data are not given, we will report such data in the Experimental Section.

Results and Discussion

The cardiovascular activity of the compounds synthesized was evaluated with the Langendorff technique as reported in the Experimental Section, and coronary perfusion pressure (CPP), left ventricular pressure (LVP), and heart rate (HR) were recorded.

Scheme I[a]



[a] Key: (a) $K/(CH_3)_3COH$; (b) $Br(CH_2)_3OCOCH_3$; (c) HCl (2 N)/CH_3COCH_3; (d) PBr_3; (e) *N*-methylhomoveratrylamine.

Compounds **7a** (sulfate), **9a** (oxalate), **10a** (oxalate), **12a** (oxalate), **13a** (oxalate), and **36a** (sulfate) were almost inactive on the different parameters at a dose as high as 5 μg/heart.

Compounds **6a** (oxalate), **8a,b** (oxalate and perchlorate), and **11a** (perchlorate), however, displayed interesting cardiovascular activities. The results are reported in Table I together with those of verapamil used as a reference compound.

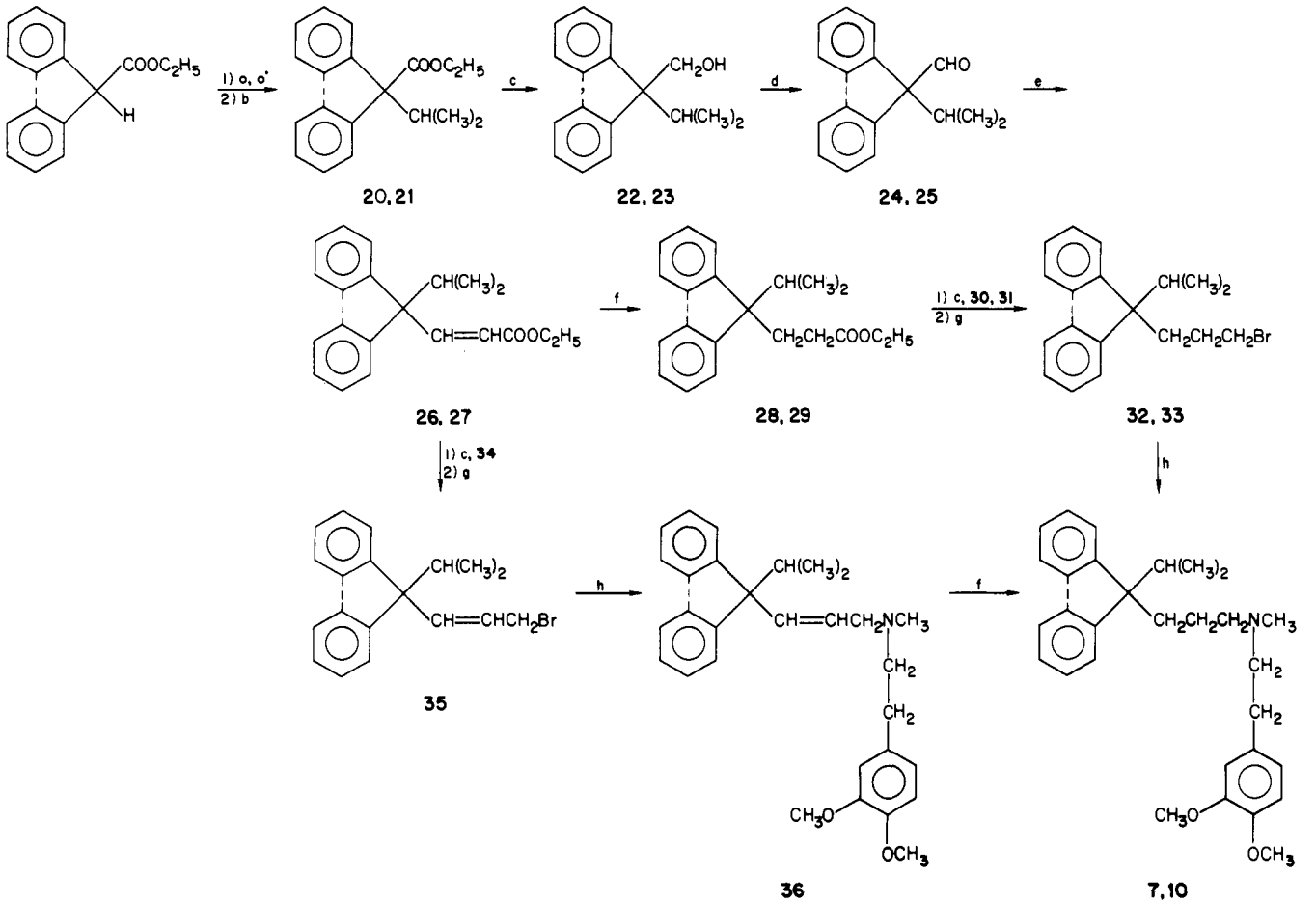
Compound **6a** produced a decrease in the CPP and an increase in LVP, whereas HR was not modified (Table I). Compound **8** produced a more pronounced decrease in CPP than Verapamil, with a less marked negative inotropic effect (Table I). Of the two salts of **8**, the perchlorate **8a** is the one that presents the most favorable ratio between coronary vasodilating activity and negative inotropic effect. In fact it produced a marked reduction of CPP associated with a reduction of LVP of only 13.4–21%, whereas verapamil produced a reduction of 43.8–71.6%.

A similar profile is shown by compound **11a**, which is even more effective than **8a** in reducing CPP, but also gave a more marked depression of contractility. These results show that when the structure is flattened as in **12** and **13**, the molecule loses both its negative inotropic and its vasodilator activities. The same happens when the carbon atom is still quaternary but the nitrile group is substituted with a phenyl group as in **7**, **10**, and **36**.

When the isopropyl group is substituted with a phenyl group (**11**), even if the structure is partially flattened (**8**), the vasodilator activity is maintained or improved while the negative inotropic activity is much lower. The same pharmacological profile is shown by compound **6**, which lacks the nitrile group. Taking into account that the nitrile is considered essential for high negative inotropic activity[26] and should be coplanar with the phenyl ring[27] our finding

(16) F. A. L. Anet and P. M. G. Bavin, *Can. J. Chem.*, **34**, 991 (1956).
(17) E. J. Greenhow, D. McNeil, and E. N. White, *J. Chem. Soc.*, 986 (1952).
(18) S. Wawzonek and E. Dufek, *J. Am. Chem. Soc.*, **78**, 3530 (1956).
(19) L. D. Bergelson and M. M. Shemyakin, *Tetrahedron*, **19**, 149 (1963).
(20) German Patent 1 158 083 (Nov 28, 1963) *Chem. Abstr.* **60**, P5403*g*.
(21) British Patent 1 201 499 (Aug 19, 1970), *Chem. Abstr.* **73**, P109531*g*.
(22) British Patent 1 201 500 (Aug 19, 1970), *Chem. Abstr.* **73**, P109532*g*.
(23) French Patent M7508 (Jan 26, 1970), *Chem. Abstr.* **77**, 19411*w*.
(24) East German Patent 122 967 (Nov 12, 1976), *Chem. Abstr.* **87**, 134458*k*.
(25) O. Langendorff, *Pfluegers Arch.*, **61**, 291 (1895).
(26) R. Mannhold, *Drugs Today*, **20**, 69 (1984).
(27) H. D. Holtje, R. Mannhold, R. Rodenkirchen, and R. Bayer, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **317**, 316 (1981).

Scheme II[a]



[a] Key: (a) $K/(CH_3)_3COH$; (a') $NaNH_2$/toluene; (b) $(CH_3)_2CH$ I; (c) $LiAlH_4$/ether; (d) $CrO_3/H_2SO_4/CH_3COCH_3$; (e) $Ph_3P^+CHCOOC_2H_5^-$; (f) H_2/Pd/C; (g) PBr_3; (h) *N*-methylhomoveratrylamine.

casts some doubts on the mechanism of action of compounds **6**, **8**, and **11**. As a matter of fact, these results could be explained with tissue selectivity but could also imply that the mechanism is not that of calcium antagonism.

To check this point we tested the calcium-blocking activity of compound **8a** on rabbit aorta and found that this compound does not behave as a calcium antagonist on this tissue.

In fact, while verapamil (10^{-6} M) decreased the maximum force of contraction, which was significantly reduced ($P < 0.05$ and $P < 0.01$) at each K^+ concentration, compound **8a** did not significantly affect the contractility of the aortic strips at a 10 times higher concentration (10^{-5} M) than that of verapamil. Taking into account that the tissues involved are different (guinea pig coronaries and rabbit aorta) and that classification of a drug as a calcium antagonist cannot rely upon data stemming from a single test procedure, more work is needed to rule out the calcium antagonistic action of **8**.

Nevertheless it seems probable from these preliminary results that the vasodilator activity of **8** is not due to calcium antagonism. In this respect it is interesting to note that compounds **6** and **8** are structurally related to calmodulin antagonists,[28] and an action of this kind could have implications in their vasodilator properties. This possibility is now under investigation.

As far as the possible clinical implications are concerned, our finding suggests that **6**, **8**, and **11** could present some advantages over verapamil in situations (i.e., myocardial infarction) in which a further depression of contractility cannot be tolerated.

Experimental Section

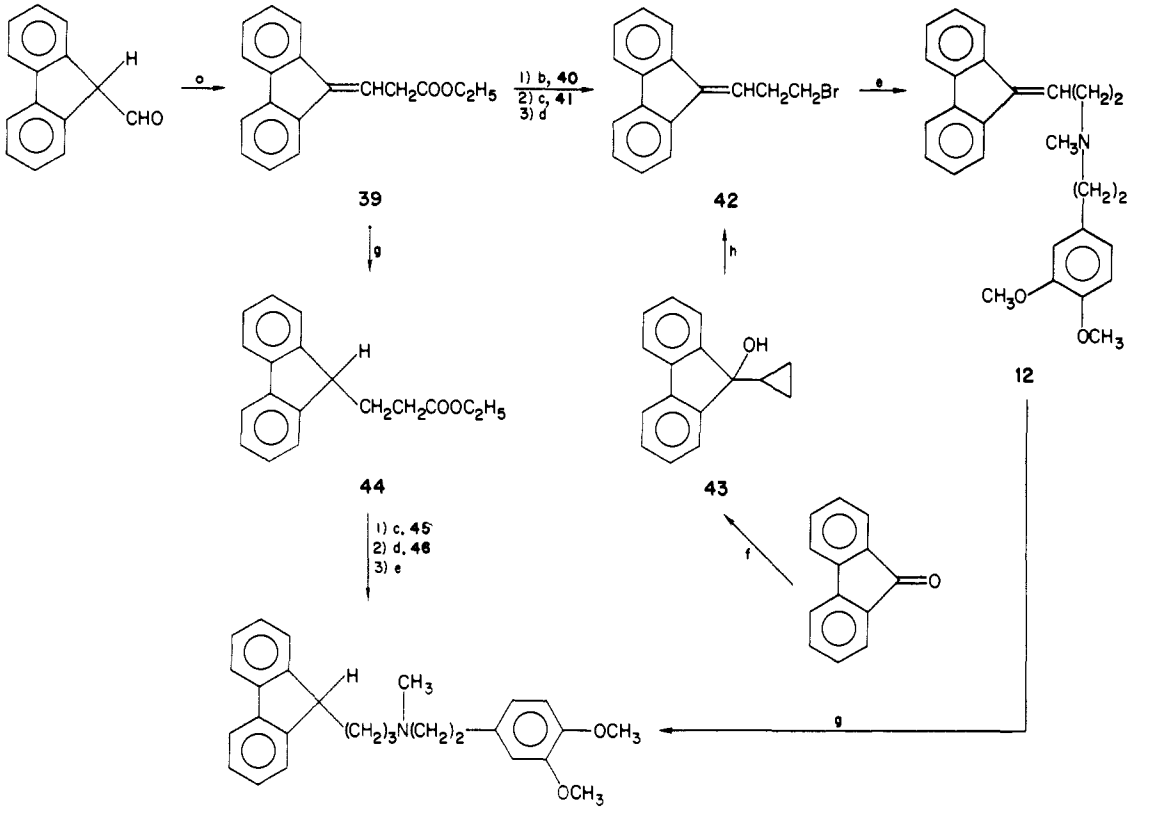
Chemistry. All melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 337 spectrophotometer in Nujol mull for solids and neat for liquids. NMR spectra were measured on a Varian EM 360L spectrometer using Me_4Si or DSS as internal standards. Chromatographic separations were performed on a silica gel column (Kieselgel 40, 0.063–0.200 mm, Merck). Where analyses are indicated by symbols, the analytical results are within ±0.4% of the theoretical values. Spectral data of only key intermediates and final compounds are included. Where spectral data are not reported, they agree with the proposed structure.

9-Cyano-9-[3-(1-acetoxypropyl)]fluorene (14). A 20-mmol portion of K was dissolved in 30 mL of anhydrous *tert*-butyl alcohol. When the K was completely dissolved, 20 mmol of 9-cyanofluorene[29] in 100 mL of *tert*-butyl alcohol were added, the solution was heated to 100 °C, and 22 mmol of 3-bromo-1-propyl acetate was slowly added. The solution was refluxed for 20 h, the excess of *tert*-butyl alcohol removed by distillation, and the residue dissolved in ether and washed with H_2O. Evaporation of the solvent left 5.2 g of an oil that was pure enough for the following reaction; yield 90%. A pure sample was obtained by column chromatography (cyclohexane–ethyl acetate 8:2): IR (neat) ν 2240 (CN), 1740 (CO) cm^{-1}; NMR ($CDCl_3$) δ 1.0–1.80 (m, 2, 2-CH_2), 1.98 (s, 3, $COCH_3$), 2.20–2.50 (m, 2, 3-CH_2), 3.90 (t, 2, 1-CH_2), 7.20–7.80 (m, 8, aromatics). Anal. ($C_{19}H_{17}NO_2$) C, H, N.

(28) B. Weiss, W. C. Prozialeck, and T. L. Wallace, *Biochem. Pharmacol.*, 31, 2217 (1982).

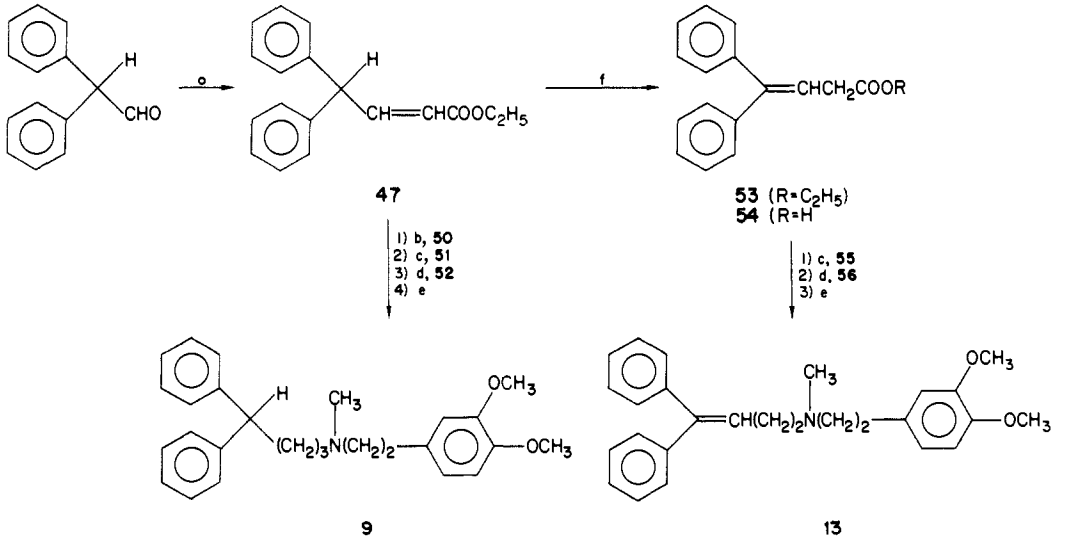
(29) D. Vorlander and A. Pritzsche, *Ber.*, 46, 115 (1974).

Scheme III[a]



[a] Key: (a) $Ph_3P^+CHCO_2C_2H_5^-$; (b) HCl (2 N); (c) $LiAlH_4$/ether; (d) PBr_3; (e) *N*-methylhomoveratrylamine; (f) Mg/  ; (g) Pd(C)/H_2; (h) CH_3COOH/HBr (30%).

Scheme IV[a]



[a] Key: (a) $Ph_3P^+CHCO_2C_2H_5^-$; (b) Pd(C)/H_2; (c) $LiAlH_4$/ether; (d) PBr_3; (e) *N*-methylhomoveratrylamine; (f) EtONa/EtOH.

9-Cyano-9-[3-(1-hydroxypropyl)]fluorene (16). A 1-g portion of 14 was refluxed for 2 h with a mixture of 2 N HCl (45 mL) and acetone (15 mL). The acetone was evaporated and the solution extracted with ether and washed with H_2O. Evaporation of the solvent gave 0.93 g of an oil which was pure enough for the following reaction. A pure sample was obtained by column chromatography (cyclohexane–ethyl acetate 6:4). Anal. ($C_{17}H_{15}NO$) C, H, N.

9-Cyano-9-[3-(1-bromopropyl)]fluorene (18). A 10-mmol portion of 16 was heated with 30 mmol of phosphorus tribromide at 70 °C for 6 h. After cooling, the mixture was decomposed with ice, extracted with ether, and washed with $NaHCO_3$ and H_2O. Evaporation of the solvent gave an oil that solidified and crystallized from ethanol: yield 85%; mp 70–71 °C. Anal. ($C_{17}H_{14}BrN$) C, H, N.

9-Cyano-9-[3-(*N*-methyl-*N*-homoveratryl-1-propylamino)]fluorene (8). A mixture of 10 mmol of 18 and 20 mmol of *N*-methyl-*N*-homoveratrylamine[30] was kept at 130 °C for 6 h.

(30) R. A. W. Johnstone, D. W. Payling, and C. Thomas, *J. Chem. Soc. C*, 2223 (1969).

Table I. Effect of Bolus Injections of the Different Compounds on Left Ventricular Pressure (LVP, mmHg), Coronary Perfusion Pressure (CPP, mmHg), and Heart Rate (HR, beats/min) of the Isolated Guinea Pig Heart (Mean of Six Experiments ±SE; Numbers between Brackets Percent of Basal Value)

compd	parameter	basal	dose, μg/heart 0.005	0.05	0.5	5
verapamil	LVP	45.8 ± 4.95 (100%)	25.7 ± 4.55 (56.1%)	24 ± 4.36 (52.4%)	21.5 ± 4.09 (46.9%)	13 ± 2.08 (28.4%)
	CPP	55 ± 1.82 (100%)	51.7 ± 1.90 (94%)	50.3 ± 2.31 (91.4%)	49.7 ± 2.40 (90.4%)	48.8 ± 2.30 (88.7%)
	HR	219.8 ± 11.38 (100%)	210 ± 12.51 (95.5%)	203.8 ± 13.57 (92.7%)	200.3 ± 13.63 (91.1%)	188 ± 13 (85.5%)
6a	LVP	80 ± 4.04 (100%)	88.5 ± 7.69 (110.6%)	89.5 ± 6.89 (111.8%)	91.2 ± 8.49 (114.0%)	89.3 ± 8.45 (111.6%)
	CPP	64.3 ± 3.48 (100%)	52.0 ± 8.72 (80.9%)	52.0 ± 8.72 (80.9%)	56.0 ± 9.07 (89.1%)	51.3 ± 8.11 (79.8%)
	HR	150.0 ± 17.32 (100%)	150.0 ± 17.32 (100%)	150.0 ± 17.32 (100%)	150.0 ± 17.32 (100%)	149.3 ± 17.33 (99.5%)
7a	LVP	42.2 ± 4.46 (100%)	38.4 ± 3.95 (90.9%)	38 ± 4.21 (90%)	37 ± 4.82 (87.7%)	36 ± 4.63 (85.3%)
	CPP	81 ± 4.45 (100%)	76.4 ± 5.20 (94.3%)	78.6 ± 4.23 (97%)	78.4 ± 5.22 (96.8%)	78.4 ± 5.80 (96.8%)
	HR	215.8 ± 4.94 (100%)	211 ± 6.47 (97.7%)	209 ± 5.96 (96.8%)	207 ± 6.55 (95.9%)	204.4 ± 7.65 (94.7%)
8a	LVP	50 ± 4.42 (100%)	43.3 ± 4.27 (86.6%)	41.7 ± 4.38 (83.4%)	41.3 ± 4.72 (82.6%)	39.5 ± 4.81 (79.0%)
	CPP	49.7 ± 0.80 (100%)	44.2 ± 2.21 (88.9%)	42 ± 2.43 (84.5%)	42 ± 2.43 (84.5%)	41.2 ± 2.30 (82.9%)
	HR	215 ± 12.99 (100%)	211.5 ± 14.14 (98.4%)	209.7 ± 13.41 (97.5%)	206 ± 13.52 (95.8%)	205 ± 13.09 (95.3%)
8b	LVP	53.8 ± 6.03 (100%)	47.2 ± 4.87 (87.7%)	41.8 ± 4.42 (77.7%)	38.7 ± 5.11 (71.9%)	38.5 ± 4.97 (71.6%)
	CPP	53.7 ± 2.95 (100%)	47.7 ± 3.27 (88.8%)	45.2 ± 4.46 (84.2%)	45 ± 4.50 (83.8%)	43.8 ± 4.42 (81.6%)
	HR	216 ± 14.28 (100%)	213 ± 12.29 (98.6%)	208 ± 12.81 (96.3%)	203 ± 10.64 (93.9%)	194.8 ± 7.96 (90.2%)
9a	LVP	68.2 ± 112 (100%)	67.5 ± 11.4 (98.9%)	67.5 ± 11.4 (98.9%)	67.4 ± 10.4 (98.8%)	66.7 ± 11.2 (97.8%)
	CPP	48.7 ± 3.53 (100%)	48.0 ± 3.05 (98.6%)	48.0 ± 3.05 (98.6%)	48.7 ± 3.33 (100%)	47.3 ± 2.67 (97.1%)
	HR	152 ± 12.2 (100%)	152 ± 12.2 (100%)	152 ± 12.2 (100%)	152 ± 12.2 (100%)	152 ± 12.2 (100%)
10a	LVP	74.7 ± 7.53 (100%)	74.3 ± 9.21 (99.5%)	65.3 ± 16.2 (87.4%)	66.7 ± 14.8 (89.3%)	65.3 ± 16.2 (87.4%)
	CPP	47.0 ± 4.58 (100%)	46.3 ± 4.41 (98.5%)	50.0 ± 5.29 (106.4%)	49.3 ± 5.81 (104.9%)	49.3 ± 4.67 (104.9%)
	HR	160.0 ± 10.0 (100%)	155.3 ± 12.9 (97.1%)	154.7 ± 13.1 (96.7%)	150 0 ± 17.3 (93.7%)	150.7 ± 14.4 (94.2%)
11a	LVP	37 ± 3.6 (100%)	31.6 ± 4.3 (85.4%)	28.6 ± 5.2 (77.3%)	27.8 ± 5.7 (75.1%)	26.8 ± 5.7 (72.4%)
	CPP	88.8 ± 10.4 (100%)	73 ± 10.1 (82.2%)	72.6 ± 10.2 (81.7%)	71.2 ± 10.2 (80.2%)	68.7 ± 9.13 (77.3%)
	HR	163.3 ± 12.9 (100%)	162 ± 12.4 (99.2%)	160.2 ± 11.7 (98.1%)	159.8 ± 11.5 (97.8%)	158.3 ± 12 (96.9%)
12a	LVP	54.3 ± 12.4 (100%)	53 ± 12.5 (97.6%)	53 ± 12.5 (97.6%)	54 ± 12.5 (99.5%)	54 ± 13.7 (99.5%)
	CPP	50 ± 0 (100%)	50 ± 0 (100%)	50 ± 0 (100%)	51 ± 1.7 (102%)	51 ± 1.7 (102%)
	HR	210 ± 3.5 (100%)	210 ± 3.5 (100%)	210 ± 3.5 (100%)	208 ± 3.7 (99.1%)	208 ± 3.7 (99.1%)
13a	LVP	76.7 ± 11.5 (100%)	75.7 ± 11.3 (98.7%)	75.3 ± 11.9 (98.2%)	75.7 ± 11.3 (98.7%)	75.7 ± 11.9 (98.7%)
	CPP	51.3 ± 5.81 (100%)	48.0 ± 3.05 (93.6%)	51.0 ± 6.66 (99.4%)	47.3 ± 4.05 (92.2%)	47.3 ± 4.05 (92.2%)
	HR	150 ± 10.39 (100%)	150 ± 10.39 (100%)	150 ± 10.39 (100%)	150 ± 10.39 (100%)	150 ± 10.39 (100%)
36a	LVP	48.8 ± 2.23 (100%)	43.2 ± 3.68 (88.5%)	43.2 ± 3.17 (88.5%)	44 ± 2.60 (90.2%)	43.2 ± 2.42 (88.5%)
	CPP	80.8 ± 2.27 (100%)	83.8 ± 4.46 (103.7%)	82.4 ± 4.97 (101.9%)	77 ± 2.81 (95.3%)	74.4 ± 2.23 (92.7%)
	HR	185.2 ± 3.6 (100%)	182.6 ± 1.64 (98.6%)	177.8 ± 3.56 (96%)	180.6 ± 1.33 (97.5%)	176.6 ± 3.06 (95.4%)

After cooling, the mixture was treated with 10 mL of 2.5 N NaOH and extracted with chloroform. The solution was washed with H_2O, dried over Na_2SO_4, and evaporated to give an oil that was purified by column chromatography (chloroform–methanol 95:5): yield 2.3 g (54%); IR (neat) ν 2240 (CN) cm^{-1}; NMR ($CDCl_3$) δ 1.0–1.7 (m, 2, 2-CH_2), 2.0–2.70 (m, 8, other aliphatic protons), 2.18 (s, 3, N-CH_3), 3.90 (s, 6, OCH_3), 6.5–7.0 (m, 3, aromatics), 7.30–8.0 (m, 8, aromatics). The perchlorate **8a** crystallized from ethanol; mp 90–91 °C. Anal. ($C_{28}H_{31}ClN_2O_6$) C, H, N. The oxalate **8b** crystallized from ethanol as a white solid; mp 179–181 °C. Anal. ($C_{30}H_{32}O_6N_2$) C, H, N.

2,2-Diphenyl-5-acetoxyvaleronitrile (15). Following the procedure described for **14** and starting from diphenylacetonitrile, compound **15** was obtained in 85% yield as an oil that solidified and was crystallized from EtOH; mp 76–77 °C (lit.[31] mp 64 °C).

2,2-Diphenyl-5-hydroxyvaleronitrile (17). Following the procedure described for **16** and starting from **15**, compound **17** was obtained in 90% yield as a dense oil that was pure enough for the following reaction; bp 200–201 °C (0.1 mmHg).[31]

2,2-Diphenyl-5-bromovaleronitrile (19). Following the procedure described for **18** and starting from **17**, compound **19** was obtained in 90% yield as a yellow solid that crystallized from ethanol; mp 97–98 °C (lit.[32] mp 93–95 °C).

2,2-Diphenyl-5-(*N*-methyl-*N*-homoveratrylamino)valeronitrile (11). Following the procedure described for **8** and starting from **19**, compound **11** was obtained in 80% yield as a very dense oil that was purified by column chromatography (chloroform–methanol 9:1): IR (neat) ν 2230 (CN) cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.0 (m, 2, 4-CH_2), 2.10–3.90 (m, 8, other aliphatic protons), 2.02 (s, 3, N-CH_3), 3.85 (s, 6, OCH_3), 6.75 (m, 3, aromatics), 7.35 (m, 10, aromatics). The perchlorate (**11a**) crystallized from THF and melted at 131–132 °C. Anal. ($C_{28}H_{33}ClN_2O_6$) C, H, N.

Ethyl (9-Isopropylfluoren-9-yl)carboxylate (20). A 0.1-mol portion of K was dissolved in 160 mL of anhydrous *tert*-butyl alcohol, and then 0.1 mol of fluorene-9-carboxylic acid ethyl ester[33] in 40 mL of the same solvent was added. The solution was brought to 100 °C, and 0.12 mol of isopropyl iodide was slowly added. After refluxing for 2 h, the excess of the solvent was removed and the residue dissolved in ether and washed with H_2O. Evaporation of the solvent gave an oil that was distilled under vacuum: yield 80%; bp 148–150 °C (0.1 mmHg); IR (neat) ν 1720 (CO) cm^{-1}; NMR ($CDCl_3$) δ 0.73 (d, 6, $CH(CH_3)_2$), 1.20 (t, 3, CH_3CH_2), 2.95 (quint, 1, $CH(CH_3)_2$), 4.13 (q, 2, CH_2CH_3), 7.20–7.90 (m, 8, aromatics). Anal. ($C_{19}H_{20}O_2$) C, H.

9-Isopropyl-9-(hydroxymethyl)fluorene (22). A 10-g portion of **20** was added to a suspension of 1.36 g of $LiAlH_4$ in dry ether (100 mL) and the resultant mixture refluxed for 5 h. After cooling, 200 mL of ethyl acetate was carefully added, followed by 5 mL of H_2O. After 10 min the suspension was filtered and the solution evaporated to give an oil that was distilled under reduced pressure: bp 148–152 °C (0.5 mmHg); yield 90%.[16]

9-Isopropyl-9-formylfluorene (24). A 1.4-g sample of CrO_3 in 15 mL of 4.5 M H_2SO_4 was slowly added to an ice-cooled, stirred solution of 5 g of **22** in 100 mL of acetone. The solution turned blue. After 10 min the solution was poured into 750 mL of ether and washed twice with 25 mL of H_2O and then with $NaHCO_3$. After drying over Na_2SO_4, the solvent was removed to give an oil that was immediately chromatographed (cyclohexane–ethyl acetate 8:2). The main fraction (R_f 0.5; 65% of the mixture) was compound **24**, which is quite unstable and over 2 weeks decomposed almost completely to a complex mixture that was not investigated. IR (neat) ν 1710 (CO) cm^{-1}; NMR ($CDCl_3$) δ 0.80 (d, 6, $CH(CH_3)_2$), 2.97 (quint, 1, $CH(CH_3)_2$), 7.10–7.90 (m, 8 aromatics), 9.32 (s, 1, CHO). The 2,4-dinitrophenylhydrazone (**24b**) was obtained with a solution of 2,4-dinitrophenylhydrazine

(31) F. Salmon-Legagneur and M. Le Gall, *C.R. Hebd. Seances Acad. Sci.*, **260**, 3421 (1965).
(32) S. S. Kulp, V. B. Fish, and N. R. Easton, *J. Med. Chem.* **6**, 516 (1963).
(33) P. Friedlaender, *Ber.*, **10**, 536 (1877).

in alcohol and was recrystallized from methanol; mp 198–199 °C. Anal. ($C_{23}H_{30}N_4O_4$) C, H, N.

Ethyl 3-(9-Isopropylfluoren-9-yl)acrylate (26). A 2-g portion of **24**, 2.8 g of triphenyl(carbethoxymethylene)-phosphorane,[34] and 1 g of benzoic acid were dissolved in benzene (50 mL), and the resultant mixture was refluxed for 12 h. After cooling, 200 mL of petroleum ether was added and the solution refrigerated overnight. The solution was decanted from the gummy solid and evaporated to give an oil that was chromatographed (cyclohexane–ethyl acetate 8:2). The main fraction (1.3 g; R_f 0.37) is the trans isomer of **26**. IR (neat) ν 1710 (CO), 1640 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 0.73 (d, 6, $CH(CH_3)_2$), 1.20 (t, 3, CH_2CH_3), 2.55 (quint, 1, $CH(CH_3)_2$), 4.10 (q, 2, CH_2CH_3), 5.68 (d, 1, 2-CH=, $J_{trans} \cong 16$ Hz), 7.10–8.20 (m, 9, aromatics and 3-CH=). Anal. ($C_{21}H_{22}O_2$) C, H.

3-(9-Isopropylfluoren-9-yl)allyl Alcohol (34). Following the procedure described for **22** and starting from **26** (1.2 g), an oil was obtained that was chromatographed (cyclohexane–ethyl acetate 7:3). The main fraction (0.6 g; R_f 0.34) was **34**. Anal. ($C_{19}H_{20}O$) C, H.

9-Isopropyl-9-(3-bromoprop-1-enyl)fluorene (35). Following the procedure described for **18** and starting from **34**, compound **35** was obtained in 85% yield. Anal. ($C_{19}H_{19}Br$) C, H.

***N*-Methyl-*N*-homoveratryl-3-(9-isopropylfluoren-9-yl)-2-propen-1-amine (36).** Following the procedure described for **8** and starting from **35**, compound **36** was obtained as a very dense oil from column chromatography (chloroform–methanol 90:10): yield 70%; NMR ($CDCl_3$) δ 0.75 (d, 6, $CH(CH_3)_2$), 2.24 (s, 3, NCH_3), 2.10–2.80 (m, 5, CH_2CH_2 and $CH(CH_3)_2$), 3.0 (d, 2, 1-CH_2), 3.85 (s, 6, OCH_3), 5.42 (tt, 1, 2-CH=), 6.10 (d, 1, 3-CH=, $J_{trans} \cong 15$ Hz), 6.68 (m, 3, aromatics), 7.10–7.90 (m, 8, aromatics). The sulfate (**36a**) crystallized from H_2O and melted at 56–58 °C. Anal. ($C_{30}H_{37}NO_6S$) C, H, N.

Ethyl 3-(9-Isopropylfluoren-9-yl)propionate (28). A solution of 2.0 g of **26** in 100 mL of ethanol and 0.4 g of 10% Pd over C was hydrogenated in a Parr apparatus at 44 psi during 12 h. The suspension was then filtered and the solvent removed to give 95% of an oil that is suitably pure for the following reaction. A pure sample was obtained by column chromatography (cyclohexane–ethyl acetate 9:1): IR (neat) ν 1700 (CO) cm^{-1}; NMR ($CDCl_3$) δ 0.75 (d, 6, $CH(CH_3)_2$), 1.1 (t, 2, CH_2CH_3), 1.20–1.65 (m, 2, 2-CH_2), 2.0–2.9 (m, 3, 3-CH_2 and $CH(CH_3)_2$), 3.94 (q, 2, CH_2CH_3), 7.20–7.90 (m, 8, aromatics). Anal. ($C_{21}H_{24}O_2$) C, H.

3-(9-Isopropylfluoren-9-yl)propan-1-ol (30). Following the procedure already described for **20** and starting from **28**, compound **30** was obtained in 80% yield as a dense oil. Anal. ($C_{19}H_{22}O$) C, H.

9-Isopropyl-9-(3-bromoprop-1-yl)fluorene (32). Following the procedure described for **18** and starting from **30**, compound **32** was obtained in 90% yield as a dense oil. Anal. ($C_{19}H_{21}Br$) C, H.

***N*-Methyl-*N*-homoveratryl-3-(9-isopropylfluoren-9-yl)-propan-1-amine (7).** (A) Following the procedure described for **8** and starting from **32**, compound **7** was obtained in 60% yield after column chromatography (chloroform–methanol 9:1) as a dense oil: NMR ($CDCl_3$) δ 0.7 (d, 6, $CH(CH_3)_2$), 0.7–1.4 (m, 2, 2-CH_2), 1.8–2.9 (m, 9, other aliphatic protons), 2.04 (s, 3, N-CH_3), 3.83 (s, 6, OCH_3), 6.5–6.85 (m, 3, aromatics), 7.1–7.8 (m, 8, aromatics). The sulfate (**7a**) crystallized from THF and melted at 89–91 °C. Anal. ($C_{30}H_{39}NO_6S$) C, H, N.

(B) Compound **7** was also obtained by hydrogenation of **36** under the conditions described for **28**, in nearly quantitative yield.

Ethyl 2,2-Diphenyl-3-methylbutanoate (21). A 40-mmol portion of ethyl diphenyl acetate in dry toluene (20 mL) were added to a suspension of $NaNH_2$ in toluene (3.5 mL of a 50% suspension) and refluxed for 15 min. Then, 45 mmol of isopropyl iodide was added and the mixture refluxed for 20 h. After cooling, the mixture was poured into 20 mL of H_2O and the organic layer was separated and dried. The residue obtained after evaporation of the solvent was distilled under reduced pressure to give 75% of an oil that distilled at 133–135 °C (0.2 mmHg): IR (neat) ν 1715 (CO) cm^{-1}; NMR ($CDCl_3$) δ 0.80 (d, 6, $CH(CH_3)_2$), 1.05 (t, 3, CH_2CH_3), 3.38 (quint, 1, $CH(CH_3)_2$), 4.08 (q, 2, CH_2CH_3), 7.30 (s, 10, aromatics). Anal. ($C_{19}H_{22}O_2$) C, H.

2,2-Diphenyl-3-methylbutan-1-ol (23). Following the procedure described for **22** and starting from **21**, compound **23** was obtained as an oil in 90% yield. Anal. ($C_{17}H_{20}O$) C, H.

2,2-Diphenyl-3-methylbutyraldehyde (25). Following the procedure described for **24** and starting from **23**, compound **25** was obtained in 70% yield as an oil that was purified by column chromatography (cyclohexane–ethyl acetate 7:3): IR (neat) ν 1720 (CO) cm^{-1}; NMR ($CDCl_3$) δ 0.85 (d, 6, $CH(CH_3)_2$), 3.23 (quint, 1, $CH(CH_3)_2$), 7.0–7.50 (m, 10, aromatics), 9.62 (s, 1, CHO). Anal. ($C_{17}H_{18}O$) C, H.

Ethyl 4,4-Diphenyl-5-methyl-2-hexene-1-carboxylate (27). Following the procedure described for **26** and starting from **25**, compound **27** was obtained by refluxing the reaction mixture for 80 h in toluene. Even after such a long time the reaction was not complete and some starting material was present. The resulting mixture was chromatographed (cyclohexane–ethyl acetate 9:1) and **27** was isolated in 50% yield as a white solid that crystallized from petroleum ether: mp 85–86 °C; IR (Nujol) ν 1720 (CO), 1640 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 0.9 (d, 6, $CH(CH_3)_2$), 1.27 (t, 3, CH_2CH_3), 2.98 (quint, 1, $CH(CH_3)_2$), 4.18 (q, 2, CH_2CH_3), 5.65 (d, 1, 2-CH=, $J_{trans} \cong 16$ Hz), 7.23 (s, 10, aromatics), 7.60 (d, 1, 3-CH=). Anal. ($C_{21}H_{24}O_2$) C, H.

Ethyl 4,4-Diphenyl-5-methylhexanoate (29). Following the procedure described for **28** and starting from **27**, compound **29** was obtained as a dense oil in nearly quantitative yield. Anal. ($C_{21}H_{26}O_2$) C, H.

4,4-Diphenyl-5-methylhexan-1-ol (31). Following the procedure described for **22** and starting from **29**, compound **31** was obtained in 90% yield. Anal. ($C_{19}H_{24}O$) C, H.

1-Bromo-4,4-diphenyl-5-methylhexane (33). Following the procedure described for **18** and starting from **31**, compound **33** was obtained as a very dense oil in 70% yield. Anal. ($C_{19}H_{23}Br$) C, H.

***N*-Methyl-*N*-homoveratryl-4,4-diphenyl-5-methylhexan-1-amine (10).** Following the procedure described for **8** and starting from **33**, compound **10** was obtained as a very dense oil after column chromatography (chloroform–methanol 9:1) in 65% yield: NMR ($CDCl_3$) δ 0.78 (d, 6, $CH(CH_3)_2$), 0.8–1.30 (m, 2, 2-CH_2), 1.8–3.0 (m, 9, other aliphatic protons), 2.08 (s, 3, NCH_3), 3.78 (s, 6, OCH_3), 6.62 (m, 3, aromatics), 7.18 (m, 10, aromatics). The oxalate (**10a**) crystallized from EtOH and melted at 160–161 °C. Anal. ($C_{32}H_{41}NO_6$) C, H, N.

Reaction of 22 with $SOCl_2$. **22** (8 g) was dissolved in 30 mL of $SOCl_2$. After a few minutes the starting material disappeared (TLC). Careful evaporation of the solvent gave an oil (**37**) that was soluble in petroleum ether from which it crystallized as a white solid: yield 90%; mp 98–100 °C.

Heated with acids, **37** gave back **22**. From its chemical and physical characteristics it was identified as bis(9-isopropylfluoren-9-yl)methyl sulfite **37**: NMR ($CDCl_3$) δ 0.65 (dd, 6, $CH(CH_3)_2$), 2.48 (quint, 1, $CH(CH_3)_2$), 3.98 (q, 2, CH_2O), 7.0–7.90 (m, 8, aromatics). Anal. ($C_{34}H_{34}O_3S$) C, H.

When the $SOCl_2$ solution was heated to reflux for 4 h, the solvent removed under vacuum, and the residue distilled under reduced pressure, 9-isopropylphenanthrene (**38**) (bp = 168–170 °C (1 mmHg); mp 41 °C[15,16]) was obtained as the only product.

In a similar reaction 9-(hydroxymethyl)fluorene gave, at room temperature, bis(9-fluorenyl)methyl sulfite,[18] while at a higher temperature and after vacuum distillation a mixture of phenanthrene and 9-(chloromethyl)fluorene (50:50) was obtained.[18]

Ethyl 3-(Fluoren-9-ylidene)propionate (39). Following the procedure described for **26** and starting from 9-formylfluorene,[35] compound **39** was obtained after few hours at room temperature as a solid that was crystallized from EtOH: yield 70%; mp 72–73 °C (lit.[35] mp 75–76 °C).

3-(Fluoren-9-ylidene)propionic Acid (40). A 1-g portion of **39** was refluxed for 1 h in 20 mL of CH_3COOH and 2 mL of concentrated HCl. After cooling, compound **40** crystallized as yellow needles: yield 95%; mp 202 °C (lit.[36] mp 201–202 °C).

3-(Fluoren-9-ylidene)propan-1-ol (41). Following the procedure described for **22**, compound **40** was reduced at room

(34) D. B. Denney and S. T. Ross, *J. Org. Chem.*, **27**, 998 (1962).

(35) I. Von and E. C. Wagner, *J. Org. Chem.*, **9**, 155 (1944).

(36) A. Sieglitz and H. Troster: *Ber.*, **96**, 2577 (1963).

temperature with $LiAlH_4$. The residue was dissolved in ether and **41** precipitated as a solid that crystallized from EtOH: yield 30%; mp 165 °C; IR (Nujol ν 3340 (OH) cm^{-1}; NMR ($CDCl_3$) δ 1.20 (s, 1, OH), 2.05–2.40 (m, 2, 2-CH_2), 3.55 (t, 2, 1-CH_2), 7.20–7.80 (m, 9, 3-CH= and aromatics). Anal. ($C_{16}H_{14}O$) C, H.

From the ether solution, among several minor products, the saturated alcohol **45** was obtained by column chromatography (cyclohexane–ethyl acetate (7:3) in 30% yield.

When the reduction was carried out on the ester **39**, the main product obtained was **45** (45%) and only a minor amount of **41** was obtained with other side products.

9-(3-Bromoprop-1-ylidene)fluorene (42). (A) Following the procedure described for **18** and starting from **41**, compound **42** was obtained in 60% yield.

(B) A 4-g portion of **43** was heated at 100 °C for 30 min in 100 mL of CH_3COOH/HBr (30%). The solvent was removed under reduced pressure, and water added to the residue that was then extracted with ether. Evaporation of the solvent gave a solid that crystallized from EtOH: yield 85%; mp 86–87 °C; NMR ($CDCl_3$) δ 3.1–3.8 (m, 4, CH_2CH_2), 6.60 (t, 1, 3-CH=), 7.0–7.90 (m, 10, aromatics). Anal. ($C_{16}H_{13}Br$) C, H.

9-Hydroxy-9-cyclopropylfluorene (43). 9-Fluorenone (27 mmol) was added to an ether solution of 54 mmol of the Grignard reagent obtained from cyclopropyl bromide and Mg and the mixture refluxed for 19 h. After cooling, H_2O and dilute HCl were added, and the organic layer was separated and dried over Na_2SO_4. The oily residue contained some starting material that was eliminated by column chromatography (chloroform–methanol (95:5)): yield 75%; IR (neat) ν 3380 (OH) cm^{-1}; NMR ($CDCl_3$) δ 0.3–0.8 (m, 4, CH_2CH_2), 0.9–1.4 (m, 1, CH), 2.1 (s, 1, OH), 7.10–7.80 (m, 8, aromatics). Anal. ($C_{16}H_{14}O$) C, H.

***N*-Methyl-*N*-homoveratryl-3-(fluoren-9-ylidene)propan-1-amine (12).** Following the procedure described for **18** and starting from **42**, compound **12** was obtained as a very dense oil in 55% yield after column chromatography purification (chloroform–methanol (85:15)): NMR ($CDCl_3$) δ 2.45 (s, 3, NCH_3), 2.1–3.4 (m, 8, aliphatic protons), 3.85 (s, 6, OCH_3), 6.68 (m, 4, aromatics and 3-CH=), 7.1–8.0 (m, 8, aromatics). The oxalate (**12a**) crystallized from EtOH; mp 165–166 °C. Anal. ($C_{29}H_{31}NO_6$) C, H, N.

Ethyl 3-(Fluoren-9-yl)propionate (44). Following the procedure described for **28** and starting from **39**, compound **44** was obtained as a white oil in nearly quantitative yield.[33] Saponification of the product with 2 N NaOH gave the carboxylic acid as a solid that crystallized from EtOH/H_2O and melted at 144–146 °C.[37]

3-(Fluoren-9-yl)propan-1-ol (45). Following the procedure described for **22** and starting from **44**, compound **45** was obtained in 85% yield as a white solid; mp 55–56 °C (lit. mp[34] 60 °C). As reported above the same product was obtained in low yield during reduction of **39** and **40** with $LiAlH_4$.

9-(3-Bromoprop-1-yl)fluorene (46). Following the procedure described for **18** and starting from **45**, compound **46** was obtained in 60% yield; mp 43–44 °C (lit. mp[38] 46 °C).

***N*-Methyl-*N*-homoveratryl-3-(fluoren-9-yl)propan-1-amine (6).** (A) Following the procedure described for **8** and starting from **46**, compound **6** was obtained in 50% yield after column chromatography (chloroform–methanol (9:1)): NMR ($CDCl_3$) δ 0.9–1.6 (m, 2, 2-CH_2), 1.8–2.8 (m, 8, other aliphatic protons), 2.10 (s, 3, NCH_3), 3.74 (s, 6, OCH_3), 3.90 (t, 1, 9-H), 6.60 (m, 3, aromatics), 7.0–7.8 (m, 8, aromatics). The oxalate (**6a**) crystallized from THF and melted at 131–133 °C. Anal. ($C_{29}H_{33}NO_6$) C, H, N.

(B) The same compound was obtained by reduction of **12** in EtOH with Pd/C/H_2 at 40 psi in a Parr device.

Ethyl 3,3-Diphenylacrylate (47). Following the procedure described for **26**, triphenyl(carbethoxymethylene)phosphorane and diphenylacetaldehyde gave **47** as an oil that distilled at 198–204 °C (0.2 mmHg): yield 85%; IR (neat) ν 1720 (CO), 1650 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.2 (t, 3, CH_2CH_3), 4.10 (q, 2, CH_2CH_3), 4.75 (dd, 1, 9-H), 5.65 (dd, 1, 2-CH, $J_{trans} \cong 16$ Hz), 6.90–7.60 (m, 9, aromatics and 3-CH). Anal. ($C_{18}H_{18}O_2$) C, H.

Ethyl 4,4-Diphenyl-3-butenoate (53). A 3-g sample of **47** was refluxed in absolute ethanol containing 100 mg of Na for 18 h. After the solvent was removed, the residue was treated with HCl and extracted with ether. The organic solution was extracted with $NaHCO_3$ and washed with H_2O. Removal of the solvent gave 1.3 g of **54** as a yellow oil.[39] The $NaHCO_3$ solution, acidified and extracted with ether, gave 1.1 g of 4,4-diphenyl-3-butenoic acid (**54**), mp 116–117 °C (lit.[40] mp 115–116, °C).

4,4-Diphenyl-3-buten-1-ol (55). Following the procedure already described for **22** and starting from **53**, compound **55** was obtained in 80% yield as a thick oil.[41]

1,1-Diphenyl-4-bromo-1-butene (56). Following the procedure described for **18** and starting from **55**, compound **56** was obtained as a thick oil in 65% yield.[41]

***N*-Methyl-*N*-homoveratryl-4,4-diphenyl-3-buten-1-amine (13).** Following the procedure described for **8** and starting from **56**, compound **13** was obtained after column chromatography (chloroform–methanol (9:1)) as a very thick oil in 58% yield: NMR ($CDCl_3$) δ 2.28 (s, 3, NCH_3), 2.0–3.0 (m, 8, aliphatic protons), 3.85 (s, 6, OCH_3), 6.10 (t, 1, 3-CH), 6.72 (m, 3, aromatics), 7.0–7.6 (m, 10, aromatics). The oxalate (**13a**) crystallized from ethanol and melted at 162–167 °C. Anal. ($C_{29}H_{33}NO_6$) C, H, N.

Ethyl 4,4-Diphenylbutanoate (50). Following the procedure described for **28** and starting from **47**, compound **50** was obtained as a white oil in nearly quantitative yield. Anal. ($C_{18}H_{20}O_2$) C, H.

4,4-Diphenyl-1-butanol (51). Following the procedure described for **18** and starting from **50**, compound **51** was obtained as a white oil in 90% yield.[38]

1-Bromo-4,4-diphenylbutane (52). Following the procedure described for **18** and starting from **51**, compound **52** was obtained in 70% yield; mp 39–41 °C (lit.[38] mp 42 °C).

***N*-Methyl-*N*-homoveratryl-4,4-diphenylbutan-1-amine (9).** Following the procedure already described for **8** and starting from **52** compound **9** was obtained in 60% yield after column chromatography (chloroform–methanol (9:1)): NMR ($CDCl_3$) δ 1.2–1.86 (m, 2, 2-CH_2), 2.15 (s, 3, NCH_3), 1.8–3.0 (m, 8, other aliphatic protons), 3.84 (s, 6, OCH_3), 3.60 (m, 1, 4-H), 6.72 (m, 3, aromatics), 7.25 (m, 10, aromatics). The oxalate (**9a**) crystallized from EtOH and melted at 156–158 °C. Anal. ($C_{29}H_{35}NO_6$) C, H, N.

Pharmacology. (a) Guinea Pig Heart. Guinea pigs (400–500 body weight) were sacrificed by cervical dislocation and their hearts rapidly excised and immediately suspended for retrograde aortic perfusion of the coronary arteries with a modified Krebs–Henseleit buffer solution (pH 7.4).

The hearts were perfused with the Langendorff[25] technique at 37 °C at a constant flow rate of 20 mL/min supported by a Watson–Marlow rotary pump (MHRE 100). Left ventricular pressure (LVP) was monitored by an HP 1290/A transducer connected with a liquid-filled balloon introduced into the left ventricle.[42] Coronary perfusion pressure (CPP) was monitored in the aortic inflow cannula by an HP 1290/A pressure transducer. Heart rate (HR) was derived from the LVP tracing. Following an initial 30-min stabilization period the drugs, dissolved in the perfusion liquid, were injected via a side arm of the aortic inflow cannula at doses of 0.005, 0.05, 0.5, and 5 μg/heart, at the constant injection volume of 0.5 mL and in the constant injection time of 1 min. As a reference compound, verapamil (Isoptin, Knoll) was injected at the same doses as the test substances. Each compound was tested on six different preparations.

Means, SE, and percent of the basal value were calculated for each dose.

(b) Rabbit Aorta. Male adult rabbits were killed by cervical dislocation. The aorta was rapidly excised and placed in physiological Krebs solution gassed with 95% O_2 + 5% CO_2. After the connective tissue was cleaned away, the aorta was cut into

(37) W. Wislicenus and W. Mocker, *Ber.*, **46**, 2791 (1913).
(38) A. Maerker and M. Passlack, *Chem. Ber.*, **116**, 710 (1983).
(39) V. K. Kausal and A. P. Bhaduri, *Z. Naturforsch.*, **34b**, 1567 (1979).
(40) W. S. Johnson, J. W. Peterson, and W. P. Schneider, *J. Am. Chem. Soc.*, **69**, 74 (1947).
(41) S. H. Graham and A. J. S. Williams, *J. Chem. Soc.*, 4066 (1959).
(42) G. Arnold, F. Kosche, E. Messner, A. Neitzert, and W. Lochener, *Pfluegers Arch.* **299**, 339 (1968).

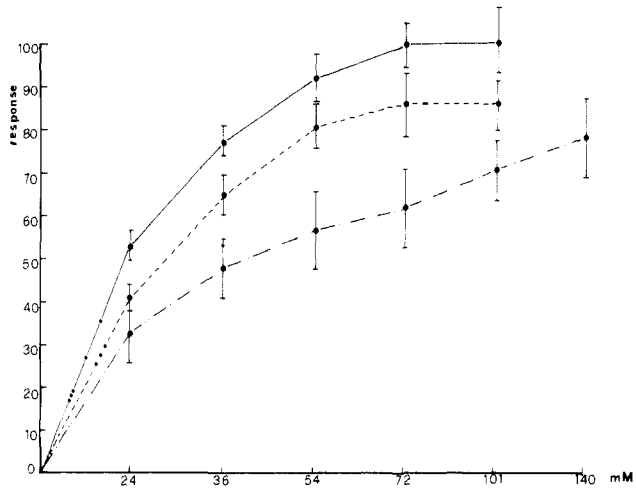


Figure 1. Variation of the maximal force of contraction of rabbit aorta with KCl (—) alone and in the presence of 1×10^{-5} M **8a** (- - -) and 1×10^{-6} M of verapamil (–··–). $p < 0.05$ for the first two points, and $p < 0.01$ for the other ones of Verapamil. The variation in presence of **8a** is not significative.

strips 5 cm long that were suspended (at 3-g resting tension) in a muscle chamber containing Krebs solution gassed as above at pH 7.38 and 37 °C. Isometric tension was measured and recorded on a recording microdynamometer, Model, 7003 (U. Basile).

After 60-min stabilization the strips were stimulated cumulatively with elevated K^+ concentrations (24, 36, 54, 72, 101, 140 mM), and cumulative dose–response curves were obtained in the presence and absence of **8a** (10^{-5} M) and verapamil (10^{-6} M).

Each curve was obtained on five different preparations. Means and standard errors of the means were calculated and significance was tested by means of a Student's t-test.

Registry No. **6**, 97634-44-1; **6a**, 97634-45-2; **7**, 97634-26-9; **7a**, 97634-27-0; **8**, 97634-10-1; **8a**, 97634-11-2; **8b**, 97634-12-3; **9**, 97634-49-6; **9a**, 97634-50-9; **10**, 97634-35-0; **10a**, 97634-36-1; **11**, 96275-88-6; **11a**, 97634-13-4; **12**, 97634-41-8; **12a**, 97634-42-9; **13**, 97634-47-4; **13a**, 97634-48-5; **14**, 97634-07-6; **15**, 1705-77-7; **16**, 97634-08-7; **17**, 1705-68-6; **18**, 97634-09-8; **19**, 14078-27-4; **20**, 97634-14-5; **21**, 97634-28-1; **22**, 97634-15-6; **23**, 97634-29-2; **24**, 97634-16-7; **24b**, 97634-17-8; **25**, 97634-30-5; **26**, 97634-18-9; **27**, 97634-31-6; **28**, 97634-23-6; **29**, 97634-32-7; **30**, 97634-24-7; **31**, 97634-33-8; **32**, 97634-25-8; **33**, 97634-34-9; **34**, 97634-19-0; **35**, 97634-20-3; **36**, 97634-21-4; **36a**, 97634-22-5; **37**, 97634-37-2; **38**, 17024-04-3; **39**, 95156-69-7; **40**, 4440-26-0; **41**, 97634-39-4; **42**, 39633-87-9; **43**, 97634-40-7; **44**, 90033-35-5; **44** (carboxylic acid), 97634-43-0; **45**, 25789-95-1; **46**, 85322-70-9; **47**, 97634-46-3; **50**, 10347-28-1; **51**, 56740-71-7; **52**, 36265-55-1; **53**, 72936-07-3; **54**, 7498-88-6; **55**, 76694-24-1; **56**, 6078-95-1; 9-cyanofluorene, 1529-40-4; 3-bromo-1-propyl acetate, 592-33-6; *N*-methyl-*N*-homoveratrylamine, 3490-06-0; diphenylacetonitrile, 86-29-3; fluorene-9-carboxylic acid ethyl ester, 26878-12-6; isopropyl iodide, 75-30-9; triphenyl(carbethoxymethylene)phosphorane, 1099-45-2; ethyl diphenylacetate, 3468-99-3; 3-(hydroxymethyl)fluorene, 24324-17-2; bis(9-fluorenyl)methyl sulfite, 97634-38-3; phenanthrene, 85-01-8; 9-(chloromethyl)fluorene, 36375-77-6; 9-formylfluorene, 20615-64-9; 9-fluorenone, 486-25-9; cyclopropyl bromide, 4333-56-6; diphenylacetaldehyde, 947-91-1.

Pseudosymmetry and Bioisosterism in Biaryl Pyridyl Competitive Histamine H_2-Receptor Antagonists

Christopher A. Lipinski,* John L. LaMattina, and Lyle A. Hohnke[1]

Central Research, Pfizer Inc., Groton, Connecticut 06340. *Received January 15, 1985*

A process of drug design has previously been described that led to the synthesis of 3-amino-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole (4), a competitive histamine H_2-receptor antagonist structurally unrelated to, but more potent than, cimetidine. A QSAR study on a subset of analogues closely related to 4 showed that gastric acid antisecretory activity increased with decreasing lipophilicity. An SAR study about 4 focused on (1) pyridine substitution compatible with both unidentate and bidentate hydrogen bonding, (2) exploration of the pseudosymmetry of 4, and (3) examination of triazole and imidazole bioisosterism. This SAR study led to a definition of the minimum structural features required for antagonist activity. The pyridylamino group is not essential for activity since replacement with a methyl group results in a decrease but not loss of activity. The triazole amino group is also not essential since replacement of the triazole amino group by methyl results in very similar activity. A triazole ring nitrogen N-1 can be replaced by a CH as in imidazole **20**. The same methylimidazole in **20** when appended to a methyl pyridine as in **22** produces a competitive antagonist with Schild plot slope of unity. In summary compound **22** displays the minimum features required for antagonist activity, namely a 4-substituted pyridine appended to a 4(5)-substituted imidazole ring with single nitrogen to amidine nitrogen pair distances of 5.16 and 6.42 Å.

The discovery of biaryl pyridyltriazoles that are competitive histamine H_2-receptor antagonists by a process of bioisosteric drug design has been previously described.[2] Exploration of the structure–activity relationships of derivatives related to the original lead was influenced by the rationale used to discover the original lead. Accordingly, in addition to the standard techniques of modifying aromatic substitution according to the Topliss operational scheme and a QSAR study that we describe here, we focused particular attention on substituent effects on hydrogen bonding, the possibility that the pseudosymmetry of the lead might extend to the SAR pattern and the likelihood that imidazoles might function as triazole bioisosteres. This report provides data allowing us to define the minimum structural features required for activity in this series of histamine H_2-receptor antagonists, indicates that these derivatives exhibit a pseudosymmetrical SAR pattern, and illustrates that extended lipophilic side chains are consistent with in vitro activity but lead to antisecretory reduction at one position of the histamine H_2-receptor site.

Chemistry

The syntheses of the various 3-amino-5-(4-pyridyl)-1,2,4-triazole derivatives were straightforward. Four general routes were employed (Scheme I). In method A the appropriate isonicotinic acid hydrazide is condensed with *S*-methylpseudothiourea sulfate to give the intermediate amidinohydrazide, which was thermally closed to afford

(1) Department of Medicine, University of Connecticut Health Center, Farmington, CT 06032.

(2) Lipinski, C. A. *J. Med. Chem.* **1983**, *26*, 1–6.

0022-2623/85/1828-1628$01.50/0