Structure/Activity Relationship of Gemfibrozil (CI-719) and Related Compounds

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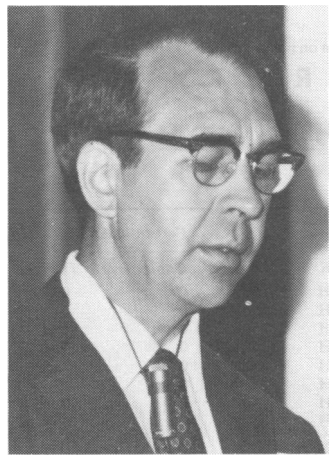

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Alkylation reactions are among the most fundamental and general procedures available to synthetic chemists for the purpose of assembling the carbon skeletons of organic molecules, but most of these methods are severely limited in sterically crowded environments.

Several years ago, dianions of carboxylic acids were reported to form in an organic solvent (Creger 1967) when carboxylate salts were treated with the strong base, lithium diisopropylamide (LDA). Subsequent treatment of the intermediate metalated carboxylic acids with epoxides (Creger 1972*a*), carbonyl compounds (Moersch & Burkett 1971, Adam *et al.* 1972) and alkyl halides (Creger 1967, 1972*b*) permitted formation of carboxylic acids with sterically crowded carbon skeletons.

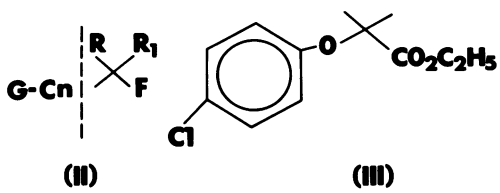
The reaction with alkyl halides is illustrated in the equation below. The procedure has been recommended as a suitable alternative for the Haller-Bauer reaction and for the malonic ester synthesis depending on whether dianions (I) are

$$HCRR_1CO_2H + 2\,LDA \longrightarrow \underset{(I)}{[CRR_1CO_2]^{2-}\,Li_2^{+}}$$

$$I + R_2X \longrightarrow R_2CRR_1CO_2H$$

formed from mono or dialkylacetic acids. Useful application of the alkylation reaction was suggested for the synthesis of structures that could display biological activity as antihyperlipidæmic agents.

A general structure (II) can be visualized which could include the structure of the hypolipidæmic agent clofibrate (III) as a single case.



(II) (III)

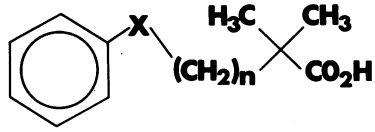
Here, R and R_1 can be substituents represented most commonly but not necessarily by a carbon fragment. Cn could represent a spacing group, either a carbon fragment or some other atomic array, and G and F are the same or different functional groups.

If the general structure could be assembled from the two halves on either side of the dashed line illustrated in (II), it is easy to recognize that the alkylation of metalated carboxylic acids could provide a great deal of synthetic control over structures where F is a carboxyl group. Finally, the carboxyl group could be converted into other functional groupings or it could be used to construct additional linkages.

This method was used, therefore, to prepare the two series of analogues shown in Table 1. The

Table 1

Effect of chain spacing on plasma lipids

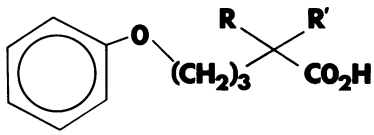


No.	X	n	Dose● (mg/kg)	Percentage reduction in plasma lipids: Cholesterol	Triglycerides
1	0	0	250	0	0
2	0	1	250	0	0
3	0	2	250	33	38
4	0	3	250	0	76
5	0	4	250	0	78
6	0	5	250	0	76
7	0	6	250	0	74
8	0	7	250	53	84
9	0	8	250	0	46
10	CH_2	0	250	0	0
11	CH_2	1	250	0	31
12	CH_2	2	250	22	50
13	CH_2	3	250	0	48
14	CH_2	4	250	29	60

● Acacia suspensions of the drugs were administered daily by gavage to groups of 10 male rats for seven days (Rodney *et al.* 1965)

Table 2

Effect of alpha-substitution on plasma lipids



No.	R	R^1	Dose● (mg/kg)	Percentage reduction in plasma lipids: Cholesterol	Triglycerides
15	H	H	250	0	0
16	CH_3	H	250	0	0
17	C_2H_5	H	250	0	51
18	$(CH_3)_2CH$	H	250	0	45
19	$(CH_3)_3C$	H	250	0	67
20	$(CH_3)_3CCH_2$	H	250	0	0
21	C_6H_5	H	250	0	0
22	CO_2H	H	250	0	0
4	CH_3	CH_3	250	0	76
23	C_2H_5	CH_3	250	0	28
24	C_2H_5	C_2H_5	250	0	39
25	—$(CH_2)_3$—		125	0	45
26	—$(CH_2)_4$—		125	0	39
27	—$(CH_2)_5$—		125	0	0

● Acacia suspensions of the drugs were administered daily by gavage to groups of 10 male rats for seven days (Rodney *et al.* 1965)

structures correspond to (II) where G is phenyl or phenoxy and Cn is an aliphatic chain. These models were examined initially to assess the effect of chain spacing on lipid levels in normal rats (VanHandel & Zilversmit 1957). When the drugs were administered by gavage (Rodney *et al.* 1965), good activity was displayed in compounds **4–8** when the phenoxy and isobutyric acid fragments were spaced by three or more carbon atoms (Creger 1972*b*). Moderate activity was obtained for analogues **12–14** in which the ether oxygen atom was replaced by a methylene group. In the rat, the biological effect was restricted primarily to a reduction in serum triglyceride levels, and that effect continued to be manifested at much lower doses.

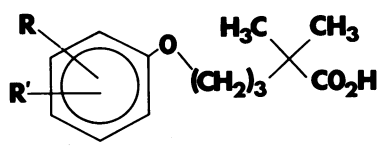
There are significant synthetic advantages associated with the chain spacing (Cn) of three carbon atoms in **4** and, given no clear biological advantages from the initial data for alternative spacings, that fragment was chosen for incorporation into models designed to evaluate variations in alpha substituents.

Table 2 summarizes these results. Increased branching in singly substituted examples enhanced the activity, and a maximum effect was revealed for a *tert*-butyl substituent (**19**). Examples containing other alkyl or functional substitution were devoid of activity. All disubstituted models (**23–27**) were less active than the dimethyl substituted example (**4**), which was also more active than the most active singly substituted analogue (**19**).

A few of many examples of substituent variations on the aromatic ring are presented in Table 3. Single substituents (not shown) failed to produce analogues with activities greater than (**4**). Examples containing single electronegative substituents were devoid of activity or displayed a greatly reduced capacity to affect serum triglyceride levels in rats. Among disubstituted derivatives, activity patterns indicated that 2,5- and 3,5- substitution produced a maximum response where both substituents were methoxy or chloro (not shown) as well as the dimethyl analogues shown in Table 3. The dimethyl substituted congeners shown, displayed greatest activity (Creger 1972*a*). Trimethyl substituted

Table 3

Effect of aromatic substitution on plasma lipids

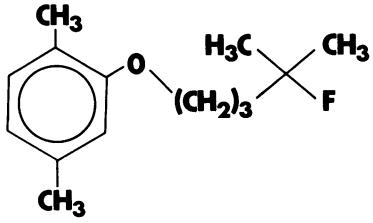


No.	Positions	R	R^1	Dose● (mg/kg)	Percentage reduction in plasma lipids: Cholesterol	Triglycerides
28	2,3	CH_3	CH_3	250	0	65
29	2,4	CH_3	CH_3	125	0	34
30	2,5	CH_3	CH_3	250	0	88
31	2,6	CH_3	CH_3	250	0	50
32	3,4	CH_3	CH_3	125	0	0
33	3,5	CH_3	CH_3	250	0	88

● Acacia suspensions of the drugs were administered daily by gavage to groups of 10 male rats for seven days (Rodney *et al.* 1965)

Table 4

Effect of functional changes on plasma lipids



No.	F	Dose● (mg/kg)	Percentage reduction in plasma lipids	
			Cholesterol	*Triglycerides*
30	CO_2H	75	0	70
34	CO_2Et	75	0	58
35	CHO	50	0	68
36	CH_2OH	75	0	60
37	CH_2OCH_3	25	0	54
38	$COCH_3$	250	0	39
39	$CHOHCH_3$	100	0	0
40	CN	250	0	38

● Acacia suspensions of the drugs were administered daily by gavage to groups of 10 male rats for seven days (Rodney *et al.* 1965)

analogues (not shown) were significantly less active, and mixed methyl-alkyl and methyl-chloro derivatives (not shown) likewise displayed lower effects than (**30**) (**33**) or (**4**).

Earlier work in another series of compounds indicated that ester or carboxyl functions are not necessary for activity in antihyperlipidæmic agents (Creger 1966). Accordingly, the functional derivatives shown in Table 4 were prepared and examined with regard to their effects on serum lipids. Simple oxygenated functions (**35–37**) (Creger & Neuklis 1972, 1973, 1974) displayed effects that were approximately equivalent to those that obtained for the corresponding carboxylic acid (**30**) or simple alkyl ester derivatives (**34**).

Finally, optimum aryl substitution (2, 5- and 3,5-xylyloxy) in (**30**) and (**33**) was retained and the spacing group was varied, then the alpha substituents were systematically changed. All of the analogues so produced (not shown) were considerably iess active than (**33**) and gemfibrozil (**30**). It seems likely, therefore, that the structure of gemfibrozil (**30**) reflects optimum substituent variations in each of the four fragments of the molecule that are amenable to change.

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