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Anti-ulcer Effect of Isoprenyl Flavonoids. II.[1] Synthesis and Anti-ulcer Activity of New Chalcones related to Sophoradin

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To investigate the anti-ulcer activity of the isoprenyl chalcone, sophoradin, which is present in a Chinese crude drug, Guang-dou-gen (the root of *Sophora subprostrata*), 30 related chalcones (**1**—**30**) were newly synthesized by condensation between substituted acetophenones and benzaldehydes, and their anti-ulcer activities were examined using Shay's pylorus-ligated rats, and water-immersed and restraint stress rats.

Twenty-seven chalcones were substituted with isoprenyl or isoprenyloxyl groups and two with geranyloxyl groups (**13**, **30**), with or without a carboxymethoxyl group, and one chalcone was substituted with allyloxyl group (**14**).

All the chalcones were found to be effective by both methods. Several chalcones (**2**, **3**, **8**, **10**, **11**, **12**, **15**, **17**, **22**), each having more than one isoprenyloxyl group, exhibited high inhibitory ratios by both methods. In particular, 2′,4′-dihydroxy-3′-(3-methyl-2-butenyl)-4-(3-methyl-2-butenyloxy)chalcone (**2**), 2′-hydroxy-4,4′-bis(3-methyl-2-butenyloxy)chalcone (**10**), and 2′-carboxymethoxy-4,4′-bis(3-methyl-2-butenyloxy)chalcone (**15**) exhibited very high inhibitory ratios (70—100%) by both methods, and were as potent as sophoradin.

Keywords——flavonoid; isoprenyl chalcone; isoprenyloxy chalcone; chalcone derivatives; sophoradin; anti-ulcer activity; structure–activity relationship

An isoprenyl chalcone, sophoradin (**31** in Table II), has been isolated by Komatsu *et al.*[3] in these laboratories from a Chinese crude drug, Guang-dou-gen or Shan-dou-gen, which is the root of *Sophora subprostrata* Chun *et* T. Chen (Leguminosae). Recently, we found[1] that sophoradin exhibits an anti-ulcer effect on both Shay's pylorus-ligated rats[4] and water-immersed and restraint stress rats.[5]

Among chalcones, in addition to sophoradin,[1] isoliquiritin[6] (the C-4-O-glucoside of 2′,4,4′-trihydroxychalcone) and isoliquiritigenin[6,7] have been reported to possess anti-ulcer action. On the other hand, some reports that isoprenyl unit enhances anti-ulcer activity have also appeared.[8–10]

Total synthesis of sophoradin was accomplished by Kyogoku *et al.*[11] in less than 1% yield, owing to poor yield at the step of ring isoprenylation. As a part of our investigations

1) Part I: M. Sasajima, S. Nakane, R. Saziki, H. Saotome, K. Hatayama, K. Kyogoku, and I. Tanaka, *Folia Pharmacol. Jpn.*, **74**, 897 (1978).
2) Location: *1-403, Yoshinocho, Omiya, Saitama, 330, Japan.*
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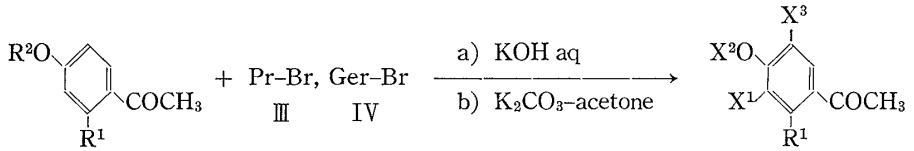
on the anti-ulcer activity of sophoradin analogs, we have synthesized 30 new chalcones (**1**—**30** in Table II), mostly substituted with an isoprenyl unit. Several chalcones having one or two isoprenyloxyl groups, with or without a carboxymethoxyl group, were found to possess anti-ulcer activities on both Shay's pylorus-ligated rats and on water-immersed and restraint stress rats; their potencies were equal to that of sophoradin.

Synthesis

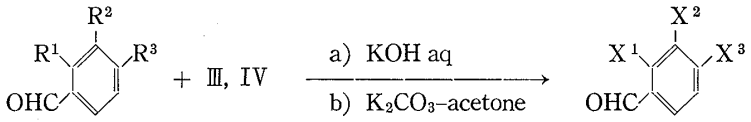
As shown in Chart 1, ring isoprenylation of I, II, or XIII with III was carried out in potassium hydroxide solution[12] to furnish V—VII,[12] VIII,[13,14] or XVII,[11] respectively, in less than 10% yield. In reacting I with III to form IX,[15] the yield was reported to be 4.6% in methanolic sodium methoxide solution, but it increased to 76% when reacted in the presence of acetone and anhydrous potassium carbonate. Similarly, II, XIII, and XIV—XVI were reacted with III in the latter mixture to give X,[13] XVIII,[16,17] and XIX—XXI, and I, II, and XIII were reacted with IV to give XI, XII, and XXII, respectively, in good yields. Methylation of VIII and XVII with dimethyl sulfate gave XXIV and XXV. Conden-



I: $R^1=OH$, $R^2=H$
II: $R^1=R^2=H$

a) V: $R^1=OH$, $X^1=Pr$, $X^2=X^3=H$; VI: $R^1=OH$, $X^1=X^2=H$, $X^3=Pr$; VII: $R^1=OH$, $X^2=H$, $X^1=X^3=Pr$; VIII: $R^1=X^2=X^3=H$, $X^1=Pr$

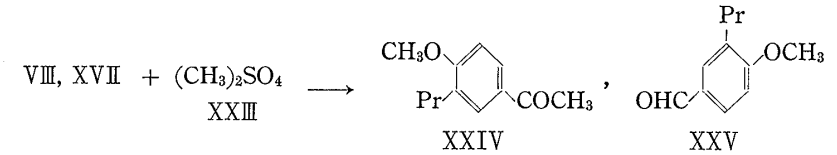
b) IX: $R^1=OH$, $X^1=X^3=H$, $X^2=Pr$; X: $R^1=X^1=X^3=H$, $X^2=Pr$; XI: $R^1=X^1=X^3=H$, $X^2=Ger$; XII: $R^1=OH$, $X^1=X^3=H$, $X^2=Ger$



XIII: $R^1=R^2=H$, $R^3=OH$
XIV: $R^1=OH$, $R^2=R^3=H$
XV: $R^1=R^3=H$, $R^2=OH$
XVI: $R^1=R^3=OH$, $R^2=H$

a) XVII: $X^1=H$, $X^2=Pr$, $X^3=OH$

b) XVIII: $X^1=X^2=H$, $X^3=OPr$; XIX: $X^1=OPr$, $X^2=X^3=H$; XX: $X^1=X^3=H$, $X^2=OPr$; XXI: $X^1=X^3=OPr$, $X^2=H$; XXII: $X^1=X^2=H$, $X^3=OGer$



V—XI, XXIV + XVIII, XIX, XXII, XXV ⟶ chalcones (**2**, **3**, **7**—**13**)

Pr:  ; Ger: geranyl

Chart 1

12) K. Kyogoku, K. Hatayama, S. Yokomori, M. Shio, and M. Komatsu, *Chem. Pharm. Bull.* (Tokyo), **21**, 1192 (1973).
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17) K. Kyogoku, K. Hatayama, S. Yokomori, T. Seki, and I. Tanaka, *Agr. Biol. Chem.* (Tokyo), **39**, 133 (1975).

sation between each of these substituted acetophenones (V—XI, XXIV) and benzaldehydes (XVIII, XIX, XXII, XXV) gave the corresponding chalcones (**2**, **3**, **7**—**13**).

As shown in Chart 2, treatment of I, II, and XIII with XXVI yielded XXVII,[11,14] XXVIII,[14] and XXIX,[11] respectively. Condensation between each of these substituted acetophenones (XXVII, XXVIII, IX, X) and benzaldehydes (XXIX, XVIII) gave five chalcones (XXXa—e), and the 1,1-dimethylpropargyloxyl group in these compounds was catalytically hydrogenated over Lindlar catalyst to afford 1,1-dimethylallyloxyl-substituted chalcones (XXXIa—e), which were converted by Claisen rearrangement to five chalcones (**1**—**5**).

As shown in Chart 3, treatment of VIII and XVII with XXXII furnished XXXIII and XXXIV, which were condensed to give XXXV. Demethoxymethylation of XXXV in

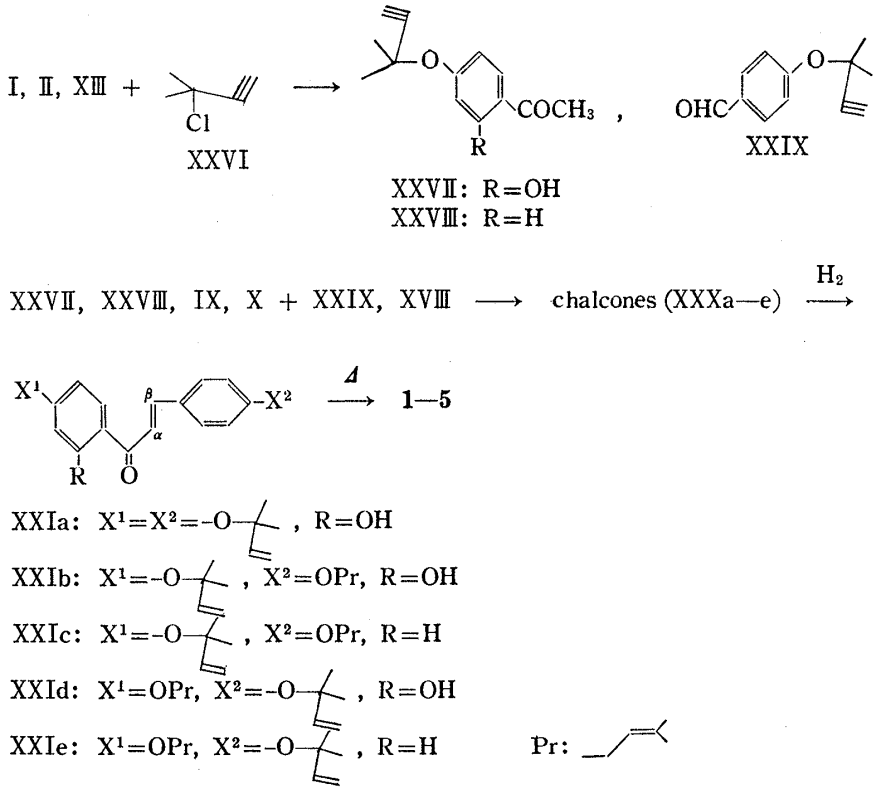


Chart 2

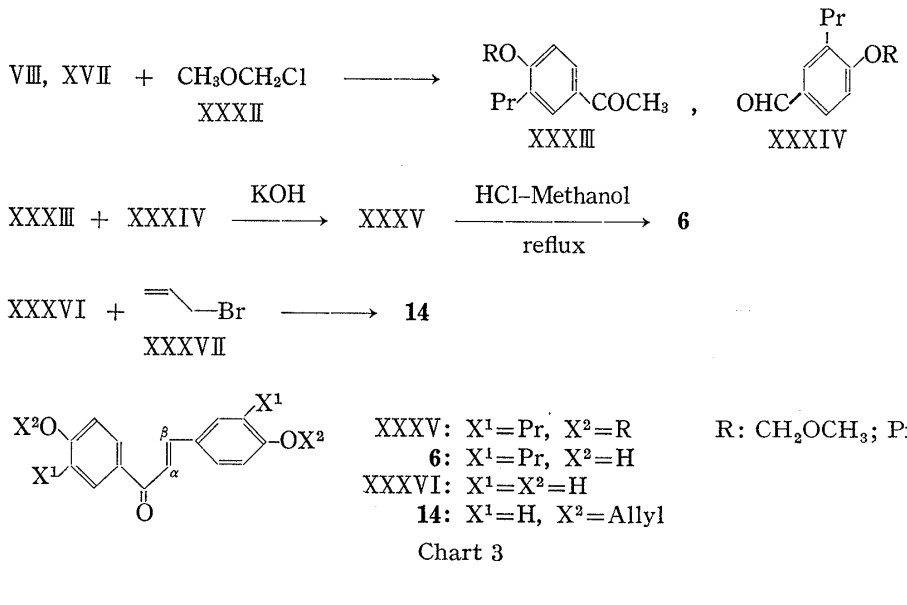


Chart 3

TABLE I. Physical and Analytical Data for the New Chalcones (**1**—**30**)

No.	mp (°C)	MS *m/e* (M^+)	Formula	Analysis (%) Calcd. (Found) C	Analysis (%) Calcd. (Found) H	IR cm^{-1} $\nu C{=}O$ (KBr)	Solv.[a]	NMR (δ) C-α-H	NMR (δ) C-β-H
1	Oil	392	$C_{25}H_{28}O_4$			1630[c]	A	7.42 (1H, d, J=15.0)	7.76 (1H, d, J=15.0)
2	167—168.5	392	$C_{25}H_{28}O_4$	76.50 (76.53)	7.19 (7.37)	1625	A	7.37 (1H, d, J=15.0)	7.85 (1H, d, J=15.0)
3	145—147	376	$C_{25}H_{28}O_3$	79.75 (79.77)	7.50 (7.47)	1665	A	7.39 (1H, d, J=15.0)	7.72 (1H, d, J=15.0)
4	147—149	392	$C_{25}H_{28}O_4$	76.50 (76.45)	7.19 (7.23)	1625	A	6.25—7.80 (8H, m, C-α,β-H, Ar[b]–H×6)	
5	140—140.5	376	$C_{25}H_{28}O_3$	79.75 (79.77)	7.50 (7.50)	1638[c]	A	6.40—7.90 (9H, m, C–α,β-H, Ar–H×7)	
6	Oil	376	$C_{25}H_{28}O_3$				B	6.80—7.90 (8H, m, C–α,β-H, Ar–H×6)	
7	Oil	404	$C_{27}H_{32}O_3$				C	6.60—7.90 (8H, m, C–α,β-H, Ar–H×6)	
8	145—146	392	$C_{25}H_{28}O_4$	76.50 (76.42)	7.19 (7.37)	1632	A	7.33 (1H, d, J=15.0)	7.90 (1H, d, J=15.0)
9	56—58	460	$C_{30}H_{36}O_4$	78.23 (78.25)	7.88 (8.00)	1630	C	7.30 (1H, d, J=15.0)	7.64 (1H, d, J=15.0)
10	87—88.5	392	$C_{25}H_{28}O_4$	76.50 (76.54)	7.19 (7.16)	1632	B	7.79 (2H, s, C–α,β-H)	
11	95—96	376	$C_{25}H_{28}O_3$	79.75 (79.77)	7.50 (7.48)	1665	A	7.45 (1H, d, J=15.0)	7.76 (1H, d, J=15.0)
12	63	376	$C_{25}H_{28}O_3$	79.75 (79.75)	7.50 (7.51)	1654	C	6.70—8.00 (10H, m, C–α,β-H, Ar–H×8)	
13	69—70	512	$C_{35}H_{44}O_3$	81.99 (81.91)	8.65 (8.69)	1625	C	7.37 (1H, d, J=15.0)	7.63 (1H, d, J=15.0)
14	77—78	320	$C_{21}H_{20}O_3$	78.72 (78.67)	6.29 (6.21)	1653	C	7.29 (1H, d, J=15.0)	7.65 (1H, d, J=15.0)
15	143—144	450	$C_{27}H_{30}O_6$	71.98 (71.93)	6.71 (6.76)	1639	A	7.18 (1H, d, J=15.0)	7.68 (1H, d, J=15.0)
16	126—127	450	$C_{27}H_{30}O_6$	71.98 (72.11)	6.71 (6.62)	1650	A	6.45—7.80 (9H, m, C–α,β-H, Ar–H×7)	
17	77—79	450	$C_{27}H_{30}O_6$	71.98 (72.01)	6.71 (6.68)	1683	A	6.50—8.17 (9H, m, C–α,β-H, Ar–H×7)	
18	148—150	382	$C_{22}H_{22}O_6$	69.10 (69.08)	5.80 (5.84)	1616	A	6.50—8.20 (9H, m, C–α,β-H, Ar–H×7)	
19	112—114	366	$C_{22}H_{22}O_5$	72.11 (72.14)	6.05 (6.05)	1645	A	6.50—7.90 (10H, m, C–α,β-H, Ar–H×8)	
20	171—173	382	$C_{22}H_{22}O_6$	69.10 (69.14)	5.80 (5.81)	1648	B	8.05 (1H, d, J=15.0)	8.27 (1H, d, J=15.0)
21	154—157[d]	366	$C_{22}H_{22}G_5$	72.11 (71.90)	6.05 (6.18)	1642	D	6.90—8.20 (10H, m, C–α,β-H, Ar–H×8)	
22	147—148	366	$C_{22}H_{22}O_5$	72.11 (71.98)	6.05 (6.15)	1644	B	6.85—8.20 (10H, m, C–α,β-H, Ar–H×8)	
23	81—83	450	$C_{27}H_{30}O_6$	71.98 (72.05)	6.71 (6.66)	1639	A	6.43—8.20 (9H, m, C–α,β-H, Ar–H×7)	
24	141—142	366	$C_{22}H_{22}O_5$	72.11 (72.18)	6.05 (6.00)	1652	A	6.79—7.85 (10H, m, C–α,β-H, Ar–H×8)	
25	80—81	366	$C_{22}H_{22}O_5$	72.11 (72.02)	6.05 (6.10)	1640	A	6.78—7.80 (10H, m, C–α,β-H, Ar–H×8)	
26	148—150	450	$C_{27}H_{30}O_6$	71.98 (72.08)	6.71 (6.61)	1645	A	6.40—8.10 (9H, m, C–α,β-H, Ar–H×7)	
27	163—164	382	$C_{22}H_{22}O_6$	69.10 (69.21)	5.80 (5.71)	1624	E	7.80 (2H, s, C–α,β-H)	
28	140.5—142	382	$C_{22}H_{22}O_6$	69.10 (69.19)	5.80 (5.78)	1622	A	6.40—8.22 (9H, m, C–α,β-H, Ar–H×7)	
29	109—112	366	$C_{22}H_{22}O_5$	72.11 (72.01)	6.05 (6.08)	1647	B	6.95—8.20 (10H, m, C–α,β-H, Ar–H×8)	
30	102—103	586	$C_{37}H_{46}O_6$	75.74 (75.89)	7.90 (7.79)	1642	A	7.21 (1H, d, J=15.0)	7.70 (1H, d, J=15.0)

a) Solvent: A=$CDCl_3$; B=$(CD_3)_2CO$; C=CCl_4; D=DMSO-d_6; E=$(CD_3)_2CO$+DMSO-d_6,
b) Ar: aromatic, *c*) Nujol, *d*) dec.

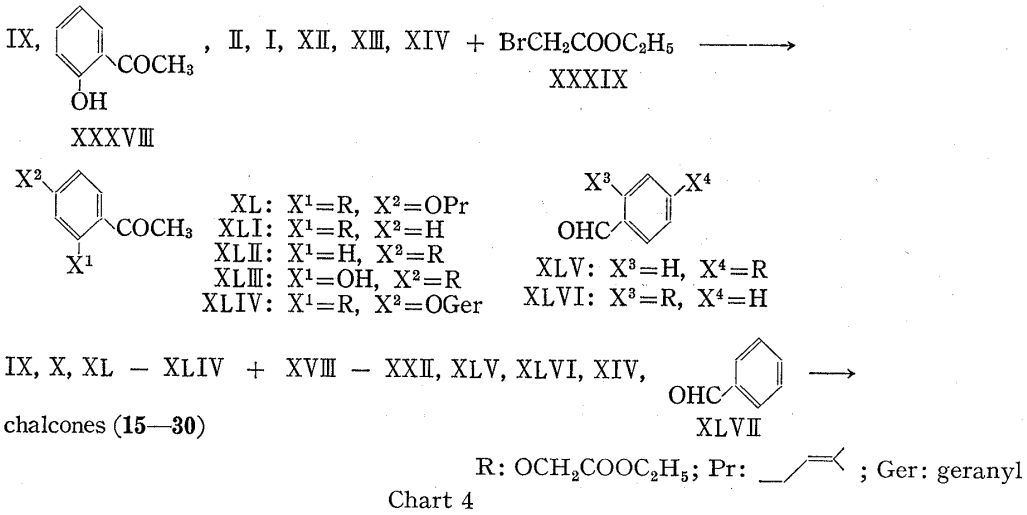
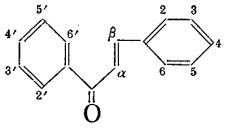


Chart 4

TABLE II. Anti-ulcer Activity of the New Chalcones on Shay's Pylorus-ligated Rats and Water-immersed and Restraint Stress Rats



No.	C-2′	C-3′	C-4′	C-5′	C-2	C-3	C-4	C-5	Inhibitory ratio	
									Shay's rats	Stress rats
1	OH	Pr	OH	H	H	Pr	OH	H	##	##
2	OH	Pr	OH	H	H	H	OPr	H	###	###
3	H	Pr	OH	H	H	H	OPr	H	##	###
4	OH	H	OPr	H	H	Pr	OH	H	##	##
5	H	H	OPr	H	H	Pr	OH	H	##	+
6	H	Pr	OH	H	H	Pr	OH	H	##	##
7	H	Pr	OCH_3	H	H	Pr	OCH_3	H	+	##
8	OH	H	OH	Pr	H	H	OPr	H	###	##
9	OH	Pr	OH	Pr	H	H	OPr	H	##	##
10	OH	H	OPr	H	H	H	OPr	H	###	###
11	H	H	OPr	H	H	H	OPr	H	##	###
12	H	H	OPr	H	OPr	H	H	H	###	##
13	H	H	OGer	H	H	H	OGer	H	+	+
14	H	H	OAlly	H	H	H	OAlly	H	+	+
15	OR	H	OPr	H	H	H	OPr	H	###	###
16	OR	H	OPr	H	H	OPr	H	H	##	+
17	OR	H	OPr	H	OPr	H	H	H	###	##
18	OR	H	OPr	H	OH	H	H	H	##	##
19	OR	H	OPr	H	H	H	H	H	##	+
20	OH	H	OPr	H	OR	H	H	H	##	##
21	H	H	OPr	H	H	H	OR	H	##	##
22	H	H	OPr	H	OR	H	H	H	###	+
23	OR	H	H	H	OPr	H	OPr	H	+	+
24	OR	H	H	H	H	H	OPr	H	+	+
25	OR	H	H	H	OPr	H	H	H	+	+
26	H	H	OR	H	OPr	H	OPr	H	+	+
27	OH	H	OR	H	H	H	OPr	H	+	##
28	OH	H	OR	H	OPr	H	H	H	+	+
29	H	H	OR	H	OPr	H	H	H	+	+
30	OR	H	OGer	H	H	H	OGer	H	+	+
31	OH	Pr	OH	H	H	Pr	OH	Pr	###	###

31: Sophoradin.
Dose: 100 mg/kg; route: *i.p.*; No. of rats: 5; +: 11—40%; ##: 41—70%; ###: 71—100%; Pr: ; Ger: geranyl; Ally: allyl; R: CH_2COOH.

methanolic hydrochloric acid solution with refluxing gave a chalcone (**6**). Treatment of XXXVI with XXXVII also gave a chalcone (**14**).

As shown in Chart 4, treatment of IX, XXXVIII, II, I, XII, XIII and XIV with ethyl bromoacetate gave XL—XLIV, XLV, and XLVI. Condensation between each of these substituted acetophenones (IX, X, XL—XLIV) and benzaldehydes (XVIII—XXII, XLV, XLVI, XIV, XLVII) in potassium hydroxide solution, with hydrolysis, furnished the corresponding carboxymethoxy-substituted chalcones (**15**—**30**).

Physical and analytical data for **1**—**30** are recorded in Table I.

Anti-ulcer Effect

Anti-ulcer effect was examined using Shay's pylorus-ligated rats, and water-immersed and restraint stress rats. Samples were given intraperitoneally (*i.p.*). As shown in Table II, the inhibitory ratio is expressed as + (11—40%), ++ (41—70%), and +++ (71—100%).

Some intresting tendencies can be seen in Table II. Although three chalcones (**1**, **6**, **7**), each having two isoprenyl groups, exhibited + or ++ effects, several chalcones (**2**, **3**, **8**, **10**, **11**, **12**, **15**, **17**, **22**), each having more than one isoprenyloxyl group, exhibited +++ effects in either method. Compound **2** and C-4,4'-diisoprenyloxyl type (**10**, **15**) exhibited +++ effects in both methods, being equipotent with sophoradin. Among the C-4,4'-diether compounds, an isoprenyloxyl group (**10**, **11**, **15**) seemed to be much more effective than geranyloxyl (**13**, **30**) or allyloxyl (**14**) groups.

Chalcones (**18**—**22**, **24**, **25**, **27**—**29**) with one carboxymethoxyl and one isoprenyloxyl group exhibited +, ++, or +++ effects. In our preliminary examination with water-immersed and restraint stress rats, using oral instead of *i.p.* administration, the inhibitory ratio of **15** with one carboxymethyloxyl group was ++, while that of **11** was +. Further work in progress in these laboratories is centered on characterizing the anti-ulcer effect of **15** (code No. SU-88).

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a Jasco DS-701 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken at 60 MHz with tetramethylsilane as an internal standard, using a Hitachi-Perkin-Elmer R-20 spectrometer. The chemical shifts are given in δ values, and the unit (Hz) of coupling constants (J) is omitted. Mass spectra were obtained on a Shimadzu LKB GCMS-9000 machine. RT stands for room temperature. The chromatography column was packed with silica gel.

Ring Isoprenylation of I, II, and XIII to give V—VII, VIII, and XVII——i) III (24.5 g) was added dropwise into I (30 g) dissolved in 10% KOH solution (30 ml), and the mixture was agitated for 3 hr at RT. After addition of H_2O (300 ml), the solution was adjusted to pH 2 with dil. HCl and extracted with ether. The ether layer was washed with H_2O, and dried over Na_2SO_4, then the solvent was evaporated off. The residue was column-chromatographed, eluting with benzene to yield V[12] (yield, 7%), VI[12] (yield, 5%), and VII[12] (yield, 4%).

ii) Treatment of II and III in a similar manner furnished VIII[13,14] (yield, 8%).

iii) III (25 g) was added dropwise into XIII (10 g) dissolved in 10% KOH solution (120 ml) and the mixture was agitated for 48 hr at RT. The reaction solution was adjusted to pH 2 with dil. HCl and extracted with ether. The ether layer was extracted with 2% Na_2CO_3 solution to recover unreacted XIII, and the ether layer was dried over Na_2SO_4. Removal of ether left a residue, which was column-chromatographed using hexane–$(CH_3)_2CO$ (12: 1) to give XVII[11] (yield, 3%).

Isoprenyloxyl Derivatives (IX, X, and XVIII—XXI)——i) Compound III (13 g) was added dropwise to a mixture of I (10 g) and anhyd. K_2CO_3 (11 g) in $(CH_3)_2CO$ (200 ml), and the mixture was agitated for 3 hr at RT then filtered. Removal of $(CH_3)_2CO$ from the filtrate left a residue, which was recrystallized from ether–petroleum ether to give 11 g of colorless needles (IX),[15] mp 46—47°. IR ν_{max}^{KBr} cm^{-1}: 1620 (CO). NMR (CCl_4) δ: 2.47 (3H, s, $COCH_3$), 4.47 (2H, d, J=6.8, OCH_2), 5.39 (1H, t, J=6.8, $OCH_2C\underline{H}$=), 6.27 (1H, dd, J=2.2, J=9.5, C-5-H), 7.45 (1H, d, J=9.5, C-6-H), 12.48 (1H, s, C-2-OH).

ii) A similar reaction of II with III followed by recrystallization from MeOH gave colorless plates (X)[13] (yield, 81%), mp 45—46°.

iii) A similar reaction of XIII with III followed by distillation of the residue *in vacuo* gave a colorless clear liquid (XVIII),[16,17] bp 92—94° (0.9 Torr) (yield, 84%). IR $\nu_{max}^{liq.}$ cm^{-1}: 1690 (CHO). NMR (CCl_4) δ: 1.82 (6H, s, $(CH_3)_2$), 4.58 (2H, d, J=7.0, OCH_2), 5.48 (1H, t, J=7.0, CH_2–$C\underline{H}$=).

iv) A similar reaction of XIV with III followed by column chromatography of the residue with hexane–$(CH_3)_2CO$ (19: 1) gave a colorless oily product (XIX), bp 110—112° (0.6 Torr) (yield, 65%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1663 (CHO). NMR (CCl_4) δ: 1.78—1.81 (6H, m, $CH_3\times2$), 4.58 (2H, d, $J=7.0$, $OC\underline{H}_2CH=$), 5.47 (1H,t, $J=7.0$, $OCH_2C\underline{H}=$).

v) A similar reaction of XV with III followed by column chromatography of the residue with hexane–$(CH_3)_2CO$ (10: 1) gave a colorless oily product (XX) (yield, 88%). MS *m/e*: 190 (M^+ for $C_{12}H_{14}O_2$). NMR (CCl_4) δ: 1.73 (6H, s, $CH_3\times2$), 4.44 (2H, d, $J=7.5$, OCH_2), 5.33 (1H, t, $J=7.5$, $OCH_2C\underline{H}=$).

vi) A similar reaction of XVI with III followed by column chromatography of the residue with hexane–$(CH_3)_2CO$ (7: 3) gave a colorless oily product (XXI) (yield, 57%). MS *m/e*: 274 (M^+ for $C_{17}H_{14}O_2$). NMR (CCl_4) δ: 4.48 (4H, d, $J=7.0$, $OCH_2\times2$), 5.40 (2H, t, $J=7.0$, $OCH_2C\underline{H}=\times2$).

Geranyl Bromide (IV) and Geranyloxyl Derivatives (XI, XII, XXII)——i) PBr_3 (7 g) was added dropwise to a solution of geraniol (10 g) and anhyd. pyridine (1 g) with stirring at −10°, then the mixture was agitated for 1 hr, and allowed to stand overnight at RT. The reaction mixture was adjusted to pH 10 with Na_2CO_3 solution and extracted with petroleum ether. The petroleum ether layer was washed with dil. H_2SO_4, $NaHCO_3$ solution, and H_2O, then dried over $MgSO_4$. Removal of the solvent left an oily product (IV) (10 g). NMR (CCl_4) δ: 3.93 (2H, d, $J=8.0$, $Br–CH_2–$).

ii) Reaction of II with IV in a manner similar to that described for the formation of isoprenyloxyl derivatives (IX) and column chromatography of the residue with hexane–$(CH_3)_2CO$ (19: 1) gave a colorless oily product (XI) (yield, 50%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (CO). NMR (CCl_4) δ: 1.59, 1.65, 1.75 (each 3H, each s, $CH_3\times3$), 2.05—2.10 (4H, br, m, $CH_2\times2$), 4.52 (2H, d, $J=7.0$, OCH_2), 5.02 (1H, br, $_H\rangle C=\langle$), 5.41 (1H, t, $J=7.0$, $_H\rangle=\langle$).

iii) Reaction of I with IV in a manner similar to that described in ii) gave a colorless oily product (XII) (yield, 56%).

iv) A similar reaction of XIII with IV gave a colorless oily product (XXII) (yield, 40%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (CHO). NMR (CCl_4) δ: 9.78 (1H, s, CHO).

Methylation of VIII and XVII to give XXIV and XXV——i) A mixture of VIII (506 mg), $(CH_3)_2SO_4$ (1 g), anhyd. K_2CO_3 (5 g), and $(CH_3)_2CO$ (20 ml) was agitated for 2 hr at RT. The reaction mixture was filtered and $(CH_3)_2CO$ was evaporated off. H_2O was added to the residue and this was extracted with ether. The ether layer was washed with 1% Na_2CO_3 solution and H_2O, then dried over Na_2SO_4. Removal of ether left a residue, which was column-chromatographed with benzene, giving 360 mg of a faintly yellow oily product (XXIV). IR $\nu_{max}^{liq.}$ cm^{-1}: 1675 (CO). NMR (CCl_4) δ: 2.41 (3H, s, $COCH_3$), 3.84 (3H, s, OCH_3).

ii) A similar reaction of XVII with $(CH_3)_2SO_4$ gave a faintly yellow oily product (XXV) (yield, 58%). IR $\nu_{max}^{liq.}$ cm^{-1}: 1688 (CO). NMR (CCl_4) δ: 3.92 (3H, s, OCH_3), 9.78 (1H, s, CHO).

Condensation between Acetophenones and Benzaldehydes to give Chalcones (2, 3, 7—13)——i) A solution of V (440 mg) and XVIII (380 mg) dissolved in EtOH (5 ml) was treated with 50% KOH solution (20 ml), and the solution was agitated for 8 hr at RT. After removal of EtOH, H_2O was added to the residue, and the solution was adjusted to pH 2 with dil. HCl then extracted with ether. The ether layer was washed with H_2O and dried over Na_2SO_4. Removal of ether left a residue, which was column-chromatographed using benzene, followed by recrystallization from hexane–$(CH_3)_2CO$ to give 2′,4′-dihydroxy-3′-(3-methyl-2-butenyl)-4-(3-methyl-2-butenyloxy)chalcone (**2**) (75 mg) as yellow needles. NMR ($CDCl_3$) δ: 1.77, 1.82 (each 6H, each s, $CH_3\times4$), 3.46 (2H, d, $J=7.0$, $C\underline{H}_2CH=$), 4.55 (2H, d, $J=7.0$, $OC\underline{H}_2CH=$), 5.10—5.70 (2H, m, $CH=C\langle\times2$), 6.19 (C-4′-OH), 6.39 (1H, d, $J=9.0$, C-5′-H), 6.90 (2H, d, $J=9.0$, C-3,5-H), 7.58 (2H, d, $J=9.0$, C-2,6-H), 7.70 (2H, d, $J=9.0$, C-6′-H), 13.86 (1H, s, C-2′-OH). Physical and other analytical data are recorded in Table I.

Similar condensation were carried out to give chalcones (**3**, **7**—**13**) as follows; their physical and analytical data are recorded in Table I.

ii) Condensation between VIII and XVIII and purification of the product by column chromatography using hexane–$(CH_3)_2CO$ (7: 1), followed by recrystallization from hexane–$(CH_3)_2CO$ gave 4′-hydroxy-3′-(3-methyl-2-butenyl)-4-(3-methyl-2-butenyloxy)chalcone (**3**) as yellow scales (yield, 34%).

iii) Condensation between XXIV and XXV and purification of the product by column chromatography using hexane–$(CH_3)_2CO$ (10: 1) gave 4,4′-dimethoxy-3,3′-bis(3-methyl-2-butenyl)chalcone (**7**) as a faintly yellow, viscous oily product (yield, 71%).

iv) Condensation between VI and XVIII and purification of the product by column chromatography using benzene, followed by recrystallization from hexane–$(CH_3)_2CO$, gave 2′,4′-dihydroxy-5′-(3-methyl-2-butenyl)-4-(3-methyl-2-butenyloxy)chalcone (**8**) as orange-yellow needles (yield, 24%).

v) Condensation between VII and XVIII and purification of the product by column chromatography using benzene gave 2′,4′-dihydroxy-3′,5′-bis(3-methyl-2-butenyl)-4-(3-methyl-2-butenyloxy)chalcone (**9**) as orange-yellow needles (yield, 17%).

vi) Condensation between IX and XVIII and purification of the product by reacrystallization from $(CH_3)_2CO$–MeOH gave 2′-hydroxy-4,4′-bis(3-methyl-2-butenyloxy)chalcone (**10**) as yellow needles (yield, 73%).

vii) Condensation between X and XVIII and purification of the product by recrystallization from $(CH_3)_2CO$–MeOH gave 4,4′-bis(3-methyl-2-butenyloxy)chalcone (**11**) as slightly yellow needles (yield, 78%).

viii) Condensation between X and XIX and purification of the product by recrystallization from MeOH gave 2,4′-bis(3-methyl-2-butenyloxy)chalcone (**12**) as faintly yellow needles (yield, 70%).

ix) Condensation between XI and XXII and purification of the product by recrystallization from $(CH_3)_2CO$–MeOH gave 4,4′-digeranyloxychalcone (**13**) as light yellow scales (yield, 49%).

1,1-Dimethylpropargyloxyl Derivatives (XXVII—XXIX)——i) A mixture of I (1.5 g), anhyd. K_2CO_3 (1.7 g), and dimethylformamide (DMF) (8 ml) was agitated for 5 hr at RT under an N_2 atmosphere, and XXVI (3.3 g) was added dropwise. This mixture was agitated for 7 hr at 75° and filtered. H_2O was added to the filtrate, which was adjusted to pH 2 with dil. HCl, and extracted with ether. The ether layer was washed with dil. HCl, dil. $NaHCO_3$ solution, H_2O, and saturated NaCl solution, then dried over Na_2SO_4. Removal of ether left a residue, which was column-chromatographed using petroleum ether to give 11 g of a light yellow crystalline product (XXVII),[11,14] mp 64.5—65°. NMR ($CDCl_3$) δ: 2.67 (1H, s, C≡CH).

ii) A similar reaction of II with XXVI and purification of the residue by distillation *in vacuo* gave a faintly yellow oily product (XXVIII),[14] bp 116—118° (1 Torr) (yield, 65%). NMR (CCl_4) δ: 2.59 (1H, s, C≡CH).

iii) XXVI (45 g) was added dropwise to a solution of XIII (15 g), KOH (18 g), and MeOH (135 ml). This mixture was agitated for 4 hr at 70° under an N_2 atmosphere, then filtered. The procedures described above were carried out, and the residue was purified by distillation *in vacuo*, giving a faintly oily product (XXIX),[11] bp 107—109° (3 Torr) (yield, 59%). NMR (CCl_4) δ: 2.80 (1H, s, C≡CH).

Condensation between Acetophenones and Benzaldehydes to give Chalcones (XXXa—e)——i) Condensation between XXVII and XXIX in a manner similar to that described for the formation of chalcone (**2**) and purification of the product by column chromatography using benzene gave a yellow oily product (XXXa) (yield, 58%). IR $\nu_{max}^{liq.}$ cm^{-1}: 3300 (C≡CH), 1630 (CO). NMR (CCl_4) δ: 7.33 (1H, d, J=15.0, C-α-H), 7.77 (1H, d, J=15.0, C-β-H).

ii) Condensation between XXVII and XVIII in a manner similar to that described above and purification of the product by column chromatography using benzene, followed by recrystallization from hexane–$(CH_3)_2CO$, gave yellow needles (XXXb) (yield, 67%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (C≡CH). NMR ($CDCl_3$) δ: 7.45 (1H, d, J=16.5, C-α-H), 7.90 (1H, d, J=16.5, C-β-H).

iii) Similar condensation between XXVIII and XVIII and purification of the product by column chromatography using hexane-$(CH_3)_2CO$ (5:1) gave a faintly yellow oily product (XXXc) (yield, 31%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (C≡CH). NMR (CCl_4) δ: 7.41 (1H, d, J=16.0, C-α-H), 7.91 (1H, d, J=16.0, C-β-H).

iv) Similar condensation between IX and XXIX and purification of the product by column chromatography using hexane–$(CH_3)_2CO$ (10:1) gave a yellow viscous product (XXXd) (yield, 55%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (C≡CH). NMR (CCl_4) δ: 7.33 (1H, d, J=15.0, C-α-H), 7.68 (1H, d, J=15.0, C-β-H).

v) Similar condensation between X and XXIX and purification of the product by column chromatography using hexane–$(CH_3)_2CO$ (10:1) followed by recrystallization from hexane–$(CH_3)_2CO$ gave light yellow plates (XXXe) (yield, 47%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (C≡CH). NMR ($CDCl_3$) δ: 7.45 (1H, d, J=15.0, C-α-H), 7.74 (1H, d, J=15.0, C-β-H).

Catalytic Hydrogenation of XXXa—e to give XXXIa—e——i) XXXa (1.17 g) in benzene (30 ml) was hydrogenated over Lindlar catalyst (200 mg); 156 ml of H_2 was absorbed during 1 hr. After removal of the catalyst, benzene was evaporated off to afford 1.13 g of a yellow crystalline product (XXXIa). IR $\nu_{max}^{liq.}$ cm^{-1}: no 3300 (C≡CH).

ii) Similarly, catalytic hydrogenation of XXXb, c, d, e gave XXXIb, c, d, e, respectively.

Claisen Rearrangement of XXXIa—e to give 1—5——i) XXXIa (1.10 g) in diethylaniline (30 ml) was agitated for 7 hr at 130° under an N_2 atmosphere. Diethylaniline was evaporated off and the residue was column-chromatographed using hexane–$(CH_3)_2CO$ (8:1) to give 900 mg of 2′,4,4′-trihydroxy-3,3′-bis(3-methyl-2-butenyl)chalcone (**1**) as a yellow oil. NMR ($CDCl_3$) δ: 1.79 (12H, s, $CH_3\times4$), 3.36, 3.50 (each 2H, each d, each J=7.5, Ar–CH_2– $\times2$), 5.30 (2H, t, J=7.5, –CH_2–C<u>H</u>= $\times2$), 5.58, 6.13 (each 1H, each s, C-4,4′-OH), 6.38 (1H, d, J=9.0, C-5′-H), 6.80 (1H, d, J=9.0, C-5-H), 7.35 (1H, br, s, C-2-H), 7.40, 7.67 (each 1H, each d, each J=9.0, C-6,6′-H), 13.82 (1H, s, C-2′-OH). Physical and other analytical data are recorded in Table I.

Similarly, Claisen rearrangement was carried out to obtain **2**—**5** as follows; their physical and analytical data are recorded in Table I.

ii) Claisen rearrangement of XXXIb and purification of the product by column chromatography using benzene, followed by recrystallization from hexane–$(CH_3)_2CO$, gave 2′,4′-dihydroxy-3′-(3-methyl-2-butenyl)-4-(3-methyl-2-butenyloxy)chalcone (**2**) as yellow needles (yield, 55%).

iii) Claisen rearrangement of XXXIc and purification of the product by column chromatography using benzene, followed by recrystallization from hexane–$(CH_3)_2CO$, gave 4′-hydroxy-3′-(3-methyl-2-butenyl)-4-(3-methyl-2-butenyloxy)chalcone (**3**) as yellow scales (yield, 55%).

iv) Claisen rearrangement of XXXId and purification of the product by recrystallization from hexane–$(CH_3)_2CO$ gave 2′,4-dihydroxy-3-(3-methyl-2-butenyl)-4′-(3-methyl-2-butenyloxy)chalcone (**4**) as yellow needles (yield, 56%). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH). NMR ($CDCl_3$) δ: 1.78, 1.81 (12H, each s, $CH_3\times4$), 3.37

(2H, d, J=7.0, $C\underline{H}_2CH$=), 4.55 (2H, d, J=7.0, $OC\underline{H}_2CH$=), 5.20—5.60 (2H, m, CH=C$\langle$ ×2), 13.75 (1H, s, C-2′-OH).

v) Claisen rearrangement of XXXIe and purification of the product by recrystallization from hexane–$(CH_3)_2CO$ gave 4-hydroxy-3-(3-methyl-2-butenyl)-4′-(3-methyl-2-butenyloxy)chalcone (**5**) as yellow needles (yield, 56%). NMR ($CDCl_3$) δ: 1.78 (12H, s, CH_3×4). 3.37 (2H, d, J=7.0, $C\underline{H}_2CH$=), 4.57 (2H, d, J=7.0, $OC\underline{H}_2CH$=), 5.80 (1H, s, C-4-OH).

Methoxymethoxyl Derivatives (XXXIII and XXXIV)——i) To a solution of VIII (3.54 g) in abs. benzene (150 ml), NaOEt (Na 480 mg: EtOH 40 ml) and XXXII (1.50 g) were added, then the same amounts of NaOEt and XXXII were added again with stirring, and the mixture was agitated for 3 hr at RT. Conventional work-up[17] gave a residue, which was column-chromatographed using benzene to give 3.6 g of a colorless oily product (XXXIII). bp 161° (2 Torr). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO). NMR (CCl_4) δ: 2.42 (3H, s, $COCH_3$), 3.41 (3H, s, $OCH_2OC\underline{H}_3$), 5.17 (3H, s, $OC\underline{H}_2OCH_3$ and –CH=).

ii) A similar reaction of XVII with XXXII followed by purification by column chromatography using benzene gave a colorless oily product (XXXIV) (yield, 75%). bp 133—134° (1.4 Torr). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (CHO). NMR (CCl_4) δ: 5.10—5.35 (3H, m, $OC\underline{H}_2OCH_3$ and –CH=).

Condensation between XXXIII and XXXIV to give XXXV——Condensation of XXXIII and XXXIV in a manner similar to that described for the formation of chalcone (**2**) and purification of the product by column chromatography using hexane–$(CH_3)_2CO$ (9: 1) gave a light yellow viscous product (XXXV) (yield, 71%). NMR (CCl_4) δ: 7.25—7.80 (8H, aromatic H×6 and C-α, β-H).

Demethoxymethylation of XXXV to give 6——To a solution of XXXV (439 mg) dissolved in MeOH (30 ml), conc. HCl (0.06 ml) was added, and the solution was agitated for 6 hr at 60°. Conventional work-up[17] gave a residue, which was column-chromatographed using hexane–$(CH_3)_2CO$ (3: 1) to give 259 mg of 4,4′-dihydroxy-3,3′-bis(3-methyl-2-butenyl)chalcone (**6**) as a yellow viscous liquid. NMR ($(CD_3)_2CO$) δ: 8.78, 9.07 (each 1H, each s, C-4,4′-OH). Physical and other analytical data are recorded in Table I.

Reaction of XXXVI with Allyl Bromide (XXXVII) to give 14——XXXVII (2 g) was added dropwise to a mixture of XXXVI (0.5 g), anhyd. K_2CO_3 (2 g) and $(CH_3)_2CO$ (20 ml), and the mixture was agitated for 5 hr at RT. The similar procedures described for the formation of chalcone (**2**) were carried out, and recrystallization from $(CH_3)_2CO$–MeOH gave 0.48 g of 4,4′-diallyloxychalcone (**14**) as light yellow needles. Physical and analytical data are recorded in Table I.

Reaction of Ethyl Bromoacetate (XXXIX) with Acetophenones and Benzaldehydes to give XL—XLIV and XLV, XLVI——i) A mixture of IX (10.2 g) and KOH (3.3 g) in $(CH_3)_2CO$ (100 ml) was agitated for 0.5 hr at RT, then XXXIX (8.0 g) was added dropwise. The mixture was agitated for 3 hr at RT and filtered. $(CH_3)_2CO$ was evaporated off and the residue was recrystallized from petroleum ether to give 8.8 g of colorless needles (XL), mp 63—64°. *Anal.* Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.67; H, 7.18. IR ν_{max}^{KBr} cm^{-1}: 1757 (COO), 1654 (CO). NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.0, $COOCH_2C\underline{H}_3$), 1.77, 1.81 (each 3H, each s, CH_3×2), 2.69 (3H, s, $COCH_3$), 4.28 (2H, q, J=7.0, $COOC\underline{H}_2CH_3$), 4.54 (2H, t, J=7.5, $OC\underline{H}_2CH$=), 4.68 (2H, s, $OC\underline{H}_2COOC_2H_5$), 5.47 (1H, t, J=7.5, $OCH_2C\underline{H}$=), 6.34 (1H, d, J=1.5, C-3-H), 6.57 (1H, dd, J=9.0, 1.5, C-5-H), 7.84 (1H, d, C-6-H).

Similarly, XLI-XLIII were obtained as follows.

ii) A similar reaction of XXXVIII with XXXIX and purification of the product by recrystallization from petroleum ether gave colorless needles (XLI) (yield, 81%). mp 33—35°.

iii) A similar reaction of II with XXXIX and purification of the product by column chromatography using hexane–$(CH_3)_2CO$ (10: 1) afforded a light yellow oily product (XLII) (yield, 77%). MS m/e: 222 (M^+ for $C_{12}H_{14}O_4$). NMR (CCl_4) δ: 4.48 (2H, s, OCH_2COO).

iv) A similar reaction of I with XXXIX and purification of the product by recrystallization from petroleum ether gave colorless needles (XLIII) (yield, 85%). mp 60—61°.

v) A solution of XII (4 g) in DMF (30 ml) was added dropwise to a solution of NaH (0.4 g) in DMF (10 ml), and the solution was agitated for 0.5 hr at RT. A solution of XXXIX (3.6 g) in DMF (10 ml) was added dropwise to this solution and the mixture was agitated for 2 hr at RT. Removal of DMF left a residue, which was column-chromatographed using $(CH_3)_2CO$–hexane to give a light yellow oily product (XLIV) (yield, 65%). MS m/e: 374 (M^+ for $C_{22}H_{30}O_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (COO), 1635 (CO). NMR (CCl_4) δ: 1.30 (3H, t, J=7.0, $CH_2C\underline{H}_3$), 4.25 (2H, q, J=7.0, $C\underline{H}_2CH_3$), 4.65 (2H, s, $OC\underline{H}_2COOC_2H_5$).

vi) A mixture of XIII (12.2 g) and anhyd. K_2CO_3 (20 g) in $(CH_3)_2CO$ (120 ml) was agitated for 1 hr at RT. XXXIX (17.4 g) was added dropwise to this solution, and the mixture was agitated for 6 hr at RT and filtered. $(CH_3)_2CO$ was evaporated off, and the residue was distilled *in vacuo* to give 13.8 g of a colorless oily product (XLV), bp 152—155° (1.3 Torr). MS m/e: 208 (M^+ for $C_{11}H_{12}O_4$). NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.0, $CH_2C\underline{H}_3$), 4.21 (2H, q, J=7.0, $OCH_2COOC\underline{H}_2CH_3$), 4.66 (2H, s, OCH_2COO), 9.83 (1H, s, CHO).

vii) XIV and XXXIX were reacted as described for the formation of XL above, and the product was purified by recrystallization from hexane–benzene to give colorless needles (XLVI) (yield, 83%). MS m/e: 208 (M^+ for $C_{11}H_{12}O_4$). NMR (CCl_4) δ: 1.23 (3H, t, J=7.0, $COOCH_2C\underline{H}_3$), 4.23 (2H, q, J=7.0, $OCH_2COOC\underline{H}_2CH_3$), 4.57 (2H, s, OCH_2COO), 10.29 (1H, s, CHO).

Condensation between Acetophenones and Benzaldehydes, with Hydrolysis, to give Chalcones (15—30)——As described for the formation of chalcone (**2**), condensation was carried out to obtain chalcone (**15—30**) as

follows.

i) Condensation of XL and XVIII, followed by purification of the product by recrystallization from EtOH, gave 2′-carboxymethoxy-4,4′-bis(3-methyl-2-butenyloxy)chalcone (**15**) as light yellow needles (yield, 74%). IR ν_{max}^{KBr} cm^{-1}: 1743 (COOH). NMR ($CDCl_3$) δ: 1.76 (12H, s, $CH_3\times4$), 4.55 (4H, d, $J=7.5$, $OC\underline{H}_2CH=\times2$), 4.73 (2H, s, $OC\underline{H}_2COOH$), 5.47 (2H, t, $J=7.5$, $OCH_2C\underline{H}=\times2$), 6.50 (1H, d, $J=2.2$, C-3′-H), 6.61 (1H, dd, $J=9.0$, $J=2.2$, C-5′-H), 6.88 (2H, d, $J=9.0$, C-3,5-H), 7.50 (2H, d, $J=9.0$, C-2,6-H), 7.64 (1H, d, $J=9.0$, C-6′-H), 11.83 (1H, s, COOH). Physical and other analytical data are recorded in Table I.

Physical and analytical data for the following chalcones (**16**—**30**) are also recorded in Table I.

ii) Similar condensation of XL and XX and purification of the product by recrystallization from MeOH gave 2′-carboxymethoxy-3,4′-bis(3-methyl-2-butenyloxy)chalcone (**16**) as light yellow needles (yield, 27%).

iii) Similar condensation of XL and XIX and purification of the product by recrystallization from benzene-hexane gave 2′-carboxymethoxy-2,4′-bis(3-methyl-2-butenyloxy)chalcone (**17**) as yellowish-white needles (yield, 75%).

iv) Similar condensation of XL and XIV and purification of the product by recrystallization from benzene-hexane gave 2′-carboxymethoxy-2-hydroxy-4′-(3-methyl-2-butenyloxy)chalcone (**18**) as yellow needles (yield, 18%).

v) Similar condensation of XL and XLVII and purification of the product by recrystallization from benzene-hexane gave 2′-carboxymethoxy-4′-(3-methyl-2-butenyloxy)chalcone (**19**) as yellow needles (yield, 58%).

vi) Similar condensation of IX and XLVI and purification of the product by recrystallization from MeOH gave 2-carboxymethoxy-2′-hydroxy-4′-(3-methyl-2-butenyloxy)chalcone (**20**) as yellow needles (yield, 67%).

vii) Similar condensation of X and XLV and purification of the product by recrystallization from MeOH–DMF gave 4-carboxymethoxy-4′-(3-methyl-2-butenyloxy)chalcone (**21**) as colorless needles (yield 51%).

viii) Similar condensation of X and XLVI and purification of the product by column chromatography using $CHCl_3$, followed by recrystallization from $CHCl_3$, gave 2-carboxymethoxy-4′-(3-methyl-2-butenyloxy)-chalcone (**22**) as light yellow needles (yield, 49%).

ix) Similar condensation of XLI and XXI and purification of the product by column chromatography using $CHCl_3$, followed by recrystallization from benzene, gave 2′-carboxymethoxy-2,4-bis(3-methyl-2-butenyloxy)chalcone (**23**) as light yellow needles (yield, 47%).

x) Similar condensation of XLI and XVIII and purification of the product by column chromatography using $CHCl_3$, followed by recrystallization from benzene, gave 2′-carboxymethoxy-4-(3-methyl-2-butenyloxy)-chalcone (**24**) as yellow needles (yield, 31%).

xi) Similar condensation of XLI and XIX and purification of the product by column chromatography using $CHCl_3$, followed by recrystallization from hexane–$(CH_3)_2CO$, gave 2′-carboxymethoxy-2-(3-methyl-2-butenyloxy)chalcone (**25**) as white needles (yield, 57%).

xii) Similar condensation of XLII and XXI and purification of the product by column chromatography using $CHCl_3$, followed by recrystallization from $(CH_3)_2CO$–hexane, gave 4′-carboxymethoxy-2,4-bis(3-methyl-2-butenyloxy)chalcone (**26**) as yellow needles (yield, 22%).

xiii) Similar condensation of XLIII and XVIII and purification of the product by column chromatography using $CHCl_3$ gave 4′-carboxymethoxy-2′-hydroxy-4-(3-methyl-2-butenyloxy)chalcone (**27**) as yellow needles (yield, 32%).

xiv) Similar condensation of XLIII and XIX and purification of the product by recrystallization from EtOH gave 4′-carboxymethoxy-2′-hydroxy-2-(3-methyl-2-butenyloxy)chalcone (**28**) as yellow needles (yield, 33%).

xv) Similar condensation of XLII and XIX and purification of the product by column chromatography using $CHCl_3$, followed by recrystallization from isopropyl alcohol, gave 4′-carboxymethoxy-2-(3-methyl-2-butenyloxy)chalcone (**29**) as yellow needles (yield, 24%).

xvi) Similar condensation of XLIV and XXII and purification of the product by recrystallization from MeOH gave 2′-carboxymethoxy-4,4′-digeranyloxychalcone (**30**) as light yellow needles (yield, 60%).

Bioassay

Male Wistar strain rats weighing 180—220 g were used. Animals were deprived of food for 48 hr before the experiments, but were allowed free access to water. Samples were suspended in 0.4% (w/v) sodium carboxymethylcellulose solution and 0.2 ml/100 g of the suspension was given *i.p.*

$$\text{Inhibitory ratio (\%)} = \frac{\text{ulcer index (control)} - \text{ulcer index (sample)}}{\text{ulcer index (control)}} \times 100$$

Shay's Pylorus-ligated Rats[4]——Under ether anesthesia, the animals were laparotomied and the pylorus was ligated. Samples were given immediately after the pylorus ligation. The animals were sacrificed 18 hr after the pylorus ligation by means of an overdose of ether, then the stomach was excised, and lesions developing in the forestomach were grossly examined. The sum of the areas (mm^2) of lesions for each rats was determined and used as the ulcer index.

Water-immersed and Restraint Stress Rats[5]——After administering the samples, the animals were placed in a stress cage and immersed in a water bath (23°) for 7 hr to the xiphoid level. At the end of the stress, the animals were sacrificed by means of a blow on the head, then the stomach was excited, inflated with 1% Formalin solution, and placed in 1% Formalin solution for 5 min. The stomach was then cut open along the greater curvature and examined grossly for lesions in the glandular portion. The ulcer index was calculated as the sum of the lengths of the lesions in the stomach.