SYNTHETIC EXPERIMENTS IN THE BENZO-PYRONE SERIES

Part LXV. Synthesis of α-Methyl Karanjin and Related Compounds

BY S. S. CHIBBER, A. K. GANGULI, S. K. MUKERJEE AND T. R. SESHADRI, F.A.SC.

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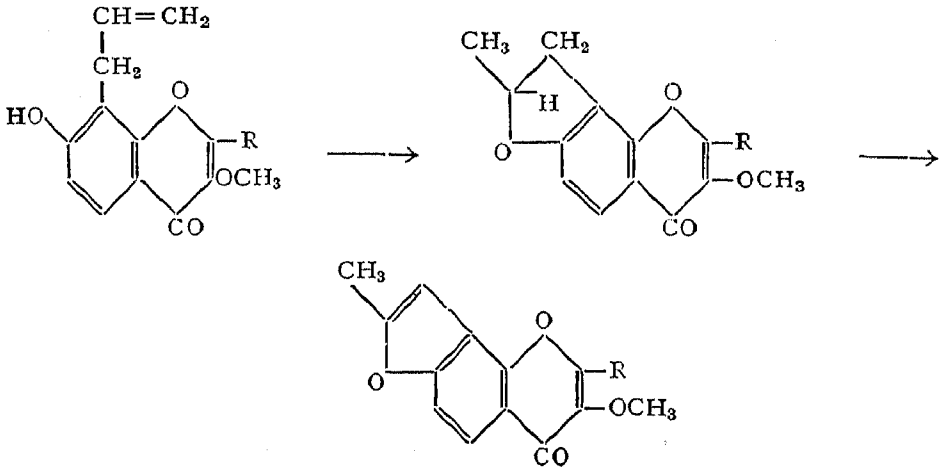
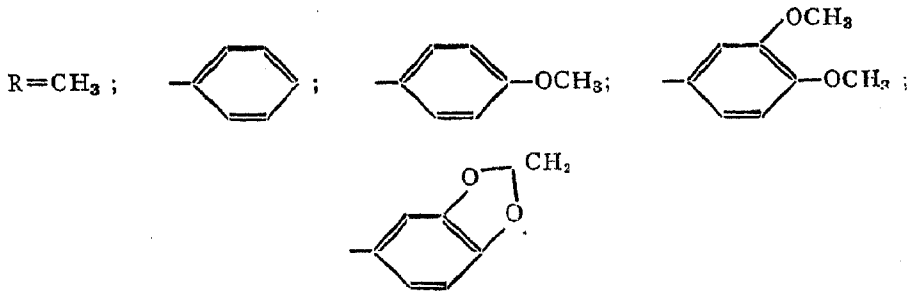
IN earlier work[1-4] on the synthesis of furanochromones in which the furan ring was built on an existing chromone, flavone or isoflavone system, it was noticed that, when there was no substitution in the furan ring, the yield of the final product was very poor, mainly due to large losses in the last stage of decarboxylation. On the other hand if a methyl group was present in the β-position, comparatively good yields were obtained.[4] It could be expected that the substituents may affect also the physiological properties of the furano compounds concerned. Rotenone, a powerful insecticide, has substitution in the α-position of the furan ring. In order to study the potency of compounds with methyl substituents in the α-position, α-methyl karanjin and its analogues have now been prepared.

The method adopted has already been mentioned in a previous publication.[5] 3-Methoxy-7-hydroxy flavone and its derivatives with substituents in the side phenyl nucleus have been allylated and subjected to Claisen migration. Addition of hydrogen bromide to the allylic double bond and subsequent elimination of it with pyridine effected the dihydro-furan ring closure. The final stage of dehydrogenations was brought about by N-bromo-succinimide.





The yields of the dihydrofuran derivatives were uniformly good in all the cases. Particular mention should be made of the use of N-bromo-succinimide as a dehydrogenating agent in this series of compounds. The difficulties reported by Pavanaram and Row[6] in the preparation of certain linear furanoflavones were not experienced. Pyridine was adequate for dehydrobromination and no demethylation took place. The bromination proceeded with increasing slowness as the bulk of the substituent in the 2-position was increased and this is markedly exhibited by experiments carried out with closely related 2-methyl chromones. The study of the chromones is given at the end of the paper.

The results obtained by testing 6 selected compounds as fish poisons are presented in Table I.

TABLE I

Toxicity of α-methyl karanjin and related compounds

(6 Fish were employed in each test)

	Compound	P.P.M. (Concentration)	Turning time
1.	α-Methyl karanjin	8	38
		19	14
2.	α-Methyl-4′-methoxy karanjin ..	15	30
3.	α-Methyl-3′ : 4′-Dimethoxy karanjin ..	32	No effect
4.	α-Methyl-3′ : 4′-methylenedioxy karanjin (α-Methyl pongapin)..	25	18
		37	10
5.	Dihydro derivative of (1)	8	15
		17	5
6.	Dihydro derivative of (2)	17	5
		21	4

The following broad conclusions seem to be justified. The dihydro compounds are definitely more toxic than the corresponding furan derivatives and substitution in the α-position of the furan seems to diminish toxicity. It was earlier reported[7] that 12 p.p.m. of karanjin yields a turning time of 5·5 minutes; the α-methyl compound in a concentration of 18·9 p.p.m. gives a turning time of 14 minutes.

Experimental

3-*Methoxy-7-hydroxy-8-(β-bromopropyl)-flavone.*—An ice-cold suspension of 3-methoxy-7-hydroxy-8-allyl flavone[8] (2 g.) in dioxan (250 c.c.) containing a little anhydrous ferric chloride was saturated with dry hydrogen bromide gas, kept for 24 hours at room temperature and then poured into ice-water. The solid (2·9 g.) that separated, crystallised from chloroform as colourless needles, m.p. 219–20° (Found: C, 58·6; H, 4·2; $C_{19}H_{17}O_4Br$ requires C, 58·6; H, 4·8%).

3-*Methoxy-α-methyl dihydrofurano-(2′: 3′: 7: 8)-flavone.*—The above bromoflavone (2 g.) smoothly cyclised when heated with pyridine (5 c.c.) for 1 hour. The product was purified by percolating a benzene solution of it through a column of alumina (30 g.). The percolate together with benzene washings furnished the dihydrofurano flavone (0·7 g.) which came out of alcohol as colourless needles, m.p. 142–43° (Found: C, 74·0; H, 4·7; $C_{19}H_{15}O_4$ requires C, 74·0; H, 5·2%).

3-*Methoxy-α-methyl furano-(2′: 3′: 7: 8)-flavone* (*α-methyl karanjin*).—A solution of the dihydrofuranoflavone (0·5 g.) and benzoyl peroxide (trace) in dry carbon tetrachloride (25 c.c.) was refluxed for 20 minutes with N-bromosuccinimide (0·3 g.). The cooled mixure was filtered from the precipitated succinimide and the filtrate evaporated to dryness. The yellow residue was dissolved in pyridine (6 c.c.), kept at 100° for 20 minutes and then poured into dilute acid when the furanoflavone (0·4 g.) separated as an oil which solidified on cooling and stirring. It crystallised from dilute alcohol as colourless rectangular plates, m.p. 121–22° (Found: C, 73·9; H, 5·1; $C_{19}H_{14}O_4$ requires C, 74·5; H, 4·6%).

3 : 4′-*Dimethoxy-7-allyloxy flavone.*—Obtained by the allylation of 3 : 4′-dimethoxy-7-hydroxy flavone,[9] this allyl ether came out as colourless rectangular prisms from dilute acetone, m.p. 102–3° (Found: C, 71·5; H, 5·1; $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3%).

3 : 4′-*Dimethoxy-7-hydroxy-8-allyl flavone.*—Claisen migration of the allyl ether (2 g.) at 200° for 2·5 hrs. under reduced pressure and working up in the usual manner yielded the hydroxy allyl flavone (1·3 g.) as colourless

needles from acetone. It melted at 238–9° and gave a sparingly soluble sodium salt with sodium hydroxide solution (Found: C, 71·0; H, 5·6; $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3%).

3: 4'-*Dimethoxy-7-hydroxy-8-(β-bromopropyl)-flavone.*—Crystallised from chloroform as colourless rectangular plates, m.p. 212–13° (Found: C, 57·6; H, 4·8; $C_{20}H_{19}O_5Br$ requires C, 57·3; H, 4·5%).

3: 4'-*Dimethoxy-α-methyl dihydrofurano-(2': 3–7: 8)-flavone.*—Cyclisation of the bromoflavone (1·7 g.) and purification of the pale yellow product as in a previous case gave the dihydro furanoflavone (0·6 g.). It came out of alcohol as colourless prisms, m.p. 147–48° (Found: C, 71·1; H, 5·2; $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3%).

3: 4'-*Dimethoxy-α-methyl furano-(2': 3'-7: 8)-flavone.*—Dehydrogenation of the above with N-bromosuccinimide in the usual manner yielded the furanoflavone in 60% yield. It formed colourless needles from alcohol, m.p. 159–60° (Found: C, 71·2; H, 4·7; $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%).

3: 3': 4'-*Trimethoxy-7-allyloxy flavone.*—Obtained by the allylation of 3: 3': 4'-trimethoxy-7-hydroxy flavone,[10] the allyl ether crystallised from a mixture of chloroform and alcohol as colourless silky needles, m.p. 152–53° (Found: C, 68·7; H, 5·7; $C_{21}H_{20}O_6$ requires C, 68·5; H, 5·4%).

3:3': 4'-*Trimethoxy-7-hydroxy-8-allyl flavone.*—It formed colourless plates from alcohol, m.p. 228–30° (Found: C, 68·5; H, 5·4; $C_{21}H_{20}O_6$ requires C, 68·5, H, 5·4%).

3: 3': 4'-*Trimethoxy-7-hydroxy-8-(β-bromopropyl)-flavone.*—It crystallised from ethyl acetate as colourless needles, m.p. 202–04°, yield 90% (Found: C, 56·1; H, 4·9; $C_{21}H_{21}O_6Br$ requires C, 56·1; H, 4·7%).

3: 3': 4'-*Trimethoxy-α-methyl dihydrofurano-(2': 3': 7: 8)-flavone.*—Obtained by the cyclisation of the bromoflavone and purified in the manner mentioned already, the dihydrofurano-flavone came out of alcohol as colourless long rectangular plates, m.p. 144–45° (Found: C, 68·1; H, 5·7; $C_{21}H_{20}O_6$ requires C, 68·5; H, 5·4%).

3: 3': 4'-*Trimethoxy-α-methyl furano-(2': 3'-7: 8)-flavone.*—The reaction between the dihydro compound (0·5 g.) and N-bromosuccinimide (·25 g.) under the usual conditions was slow and appeared to be complete after 2·5 hours. Subsequent dehydro-bromination with hot pyridine (2 c.c.) yielded the furano-flavone (0·3 g.) which formed pale yellow needles from alcohol, m.p. 152–53° (Found: C, 68·8; H, 5·1; $C_{21}H_{18}O_6$ requires C, 68·9; H, 4·9%).

3-*Methoxy*-7-*allyloxy*-3′ : 4′-*methylenedioxy flavone*.—Allylation of 3-methoxy-7-hydroxy-3′ : 4′-methylenedioxy flavone[11] (4·5 g.) yielded the allyl ether which formed colourless plates from alcohol, m.p. 128–29° (Found: C, 67·8; H, 4·5; $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%).

3-*Methoxy*-7-*hydroxy*-8-*allyl*-3 : 4′-*methylenedioxy flavone*.—This hydroxy allyl flavone (0·8 g.), obtained by the Claisen migration of the allyl ether (1·2 g.), crystallised from alcohol as colourless needles, m.p. 271–73° (Found: C, 68·0; H, 4·3; $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%).

3-*Methoxy*-3′ : 4′-*methylenedioxy*-7-*hydroxy*-8-(*β-bromopropyl*) *flavone*.—Obtained from the hydroxy allyl flavone (1·2 g.) this bromoflavone (1 g.) formed pale yellow prisms from a mixture of chloroform and methanol, m.p. 218–19° (Found: C, 55·2; H, 3·8; $C_{20}H_{17}O_6Br$ requires C, 55·4; H, 3·9%).

3-*Methoxy*-3′ : 4′-*methylenedioxy*-α-*methyl dihydrofurano*-(2′ : 3′-7 : 8)-*flavone*.—The above bromoflavone (0·9 g.) cyclised smoothly with pyridine and the product (0·6 g.) came out of alcohol as colourless prisms melting at 145–46° (Found: C, 68·5; H, 4·7; $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%).

3-*Methoxy*-3′ : 4′-*methylenedioxy*-α-*methyl furano*-(2′ : 3′-7 : 8)-*flavone* (α-*methyl pongapin*).—The dihydrofurano-flavone (0·5 g.) was dehydrogenated in the usual manner by the N-bromosuccinimide-pyridine method. The furano-flavone (0·2 g.) formed colourless plates from alcohol and melted at 190-91° (Found: C, 68·1; H, 3·8; $C_{20}H_{14}O_6$ requires C, 68·6; H, 4·0%).

2-*Methyl*-3-*methoxy*-7-*hydroxy*-8-(*β-bromopropyl*)-*chromone*.—Formed from 2-methyl-3-methoxy-7-hydroxy-8-allyl chromone[8] (2·3 g.) by the usual method, this bromochromone (3 g.) crystallised from ethyl acetate as colourless rectangular tablets, m.p. 210–11° (Found: C, 51·5; H, 4·5; $C_{14}H_{15}O_4Br$ requires C, 51·4; H, 4·6%).

α: 2-*Dimethyl*-3-*methoxy-dihydrofurano*-(2′ : 3′-7 : 8)-*chromone*.—Obtained by the cyclisation of the above bromo compound, the dihydrofurano-chromone came out of alcohol as colourless plates melting at 151–52° (Found: C, 68·0; H, 5·6; $C_{14}H_{14}O_4$ requires C, 68·4; H, 5·7%).

α: 2-*Dimethyl*-3-*methoxy furano*-(2′ : 3′-7 : 8)-*chromone*.—Dehydrogenation of the dihydro compound (6 mt.) yielded the furano-chromone, which formed colourless needles melting at 151–52°, from alcohol. Its yellow solution in concentrated sulphuric acid changed to deep crimson on warming (Found: C, 68·4; H, 4·6; $C_{14}H_{12}O_4$ requires C, 68·9; H, 4·9%).

2-*Methyl*-5-*hydroxy*-7-*allyloxy chromone*.—Partial allylation of 2-methyl-5: 7-dihydroxy chromone[12] during 5 hours yielded this allyl ether. It crystallised from alcohol as colourless prisms melting at 111–12° and gave a violet

ferric reaction (Found: C, 67·3; H, 4·7; $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%).

2-Methyl-5 : 7-dihydroxy-8-allyl chromone—was obtained as pale yellow plates from dilute alcohol and melted at 190–91° (Found: C, 67·2; H, 5·4; $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%).

2-Methyl-5 : 7-dihydroxy-8-(β-bromopropyl)-chromone.—Prepared in the usual manner, this bromo derivative came out of ethyl acetate as colourless needles melting at 199–200° (Found: C, 49·3; H, 4·3; $C_{13}H_{13}O_4Br$ requires C, 49·8; H, 4·2%).

α-2-Dimethyl-5-hydroxy-dihydrofurano-(2′ : 3′-7 : 8)-chromone.—Cyclisation of the bromo derivative yielded the dihydrofurano-chromone which formed colourless plates melting at 156–57° from alcohol and gave a violet ferric reaction (Found: C, 66·7; H, 5·1; $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). The acetate crystallised from alcohol as rectangular prisms melting at 170–71°.

SUMMARY

A number of α-methyl-furano-flavones and their dihydro derivatives have been prepared using 7-hydroxy-8-allyl flavone derivatives. Ring closure is effected with anhydrous hydrogen bromide followed by pyridine and dehydrogenation with N-bromosuccinimide. 2-Methyl cromone derivatives have also been made. Tests with fish of select compounds indicate that dihydrofurano compounds are better poisons and an α-methyl group reduces toxicity in the furano compounds.

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