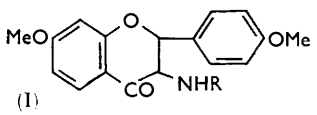
986. *Potential Bronchodilators in the Flavonoid Series.*

By DAVID KIDD.

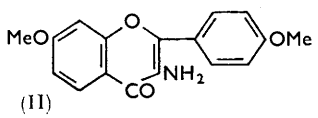
3-Amino-4′,7-dimethoxy-flavanone and -flavone have been synthesised. Many variations in the position of substituents known to give enhanced bronchodilator activity to the flavone molecule have been introduced. 7-Amino-4′-methoxyflavone and two new phenolic chloroflavones have been prepared. Some isoflavone derivatives have also been studied.

KHELLIN has long been known to be effective as a coronary dilating agent [1] and its worth in the allied pharmacological field of bronchodilation [2] was recently demonstrated. Simpler chromones [3] and flavones [4] have more recently been investigated and the former effect especially has been the subject of much comment.[5] A series of 4-hydroxyquinolines, regarded in their tautomeric form as chromone analogues,[6] also had some spasmolytic effect.

The most interesting of the new flavonoids prepared in the present work were 3-amino-4′,7-dimethoxyflavone (I; R = H) and the corresponding flavone (II) since a resemblance to ephedrine or ψ-ephedrine is detectable. Reduction of 3-hydroxyimino-4′,7-dimethoxyflavanone [7] (III) with stannous chloride did not afford 3-amino-4′,7-dimethoxyflavanone (I; R = H) as might be expected from earlier results,[8] but gave instead 3-amino-4′,7-dimethoxyflavanone (II) in accordance with the work of Wheeler *et al.*[9] The weak



(I)



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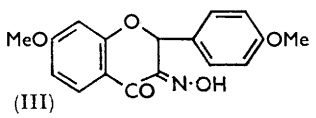
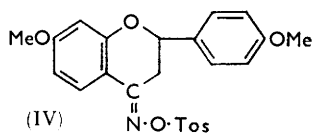


(III)

basicity of the product (it gives a hydrochloride that is easily dissociated in water), its stability to reducing agents, and its ultraviolet and infrared spectra support this conclusion. It therefore seems probable that reduction of compound (III) gives an unstable intermediate flavanone (I; R = OH) having a hydroxyamino-group [10] in the *cis*-position to the 2-hydrogen atom. Elimination of water would then be facilitated and subsequent rearrangement would give the stable 3-aminoflavone structure.

A Neber rearrangement [11] of the oxime toluene-*p*-sulphonate (IV), however, gave the 3-aminoflavanone (I; R = H). This compound gave a stable hydrochloride; its



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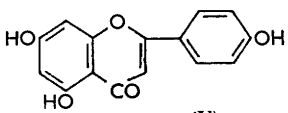

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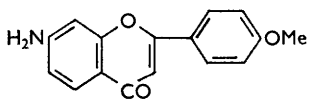

(VI)

N-acetyl derivative was reduced with sodium borohydride, and its spectra differed from those of the 3-aminoflavone (II), in agreement with both Kasahara [8] and Wheeler *et al.*[9]

[1] Anrep, Barsoum, Kenawy, and Miarahy, *Brit. Heart J.*, 1946, **8**, 171.
[2] Anrep, Barsoum, and Kenawy, *J. Pharm. Pharmacol.*, 1949, **1**, 164.
[3] Wiley, *J. Amer. Chem. Soc.*, 1952, **74**, 4329; Jongebruer, *Arch. int. Pharmacodyn.*, 1952, **90**, 384.
[4] Hava and Janku, *Arch. int. Pharmacodyn.*, 1958, **117**, 23.
[5] Da Re, Colleoni, and Setnikar, *Farmaco* (*Pavia*), *Ed. Sci.*, 1958, **13**, 561; Da Re, B.P. 803,372, 824,547; *Ann. Chim.* (*Italy*), 1959, **49**, 1632; U.S.P. 2,921,070; Ritter and Kunsch, G.P. 952,899.
[6] Šorm and Novotný, *Chem. Listy*, 1955, **49**, 901.
[7] Juppen and Kostanecki, *Ber.*, 1904, **37**, 4162.
[8] Oyamada and Fukawa, *J. Chem. Soc. Japan*, 1943, **64**, 1163; Kasahara, *ibid.*, 1959, **80**, 416; Shimizu and Nakazawa, *J. Pharm. Soc. Japan*, 1953, **73**, 522.
[9] Bognar, O'Brien, Philbin, Ushioda, and Wheeler, *Chem. and Ind.*, 1960, 1186.
[10] Chang and Hartung, *J. Amer. Chem. Soc.*, 1953, **75**, 89.
[11] Neber and Friedolsheim, *Annalen*, 1926, **449**, 109; Hatch and Cram, *J. Amer. Chem. Soc.*, 1953, **75**, 38.

For the flavanone obtained by Neber rearrangement Kasahara has assigned the equatorial conformation to the 3-amino-group. Since the 2-*p*-methoxyphenyl substituent in the dihydropyran ring is known to take up an equatorial conformation [12] it is to be expected that greater molecular stability would result if the 3-amino-group had this conformation also.[13]

Although the bronchodilator effect of apigenin (V) is not marked, the fact that it is of long duration [4] led us to prepare and screen a number of analogous compounds. Derivatives of 4',7-,[14] 4',8-,[15] and 4',5-dihydroxyflavone [14] and of 4'-hydroxy-[16] and 4',7-dihydroxy-flavonol [14] are contained in Table 1. In Table 2 are listed derivatives of the isoflavone, daidzein (4',7-dihydroxyisoflavone) [17] and of some intermediates from its synthesis. Table 3 shows the derivatives of liquiritigenin (4',7-dihydroxyflavanone)[18] studied.

The general synthesis described by Bapat and Venkataraman [19] was used to prepare 7-amino-4'-methoxyflavone (VI) from 2-hydroxy-4-nitroacetophenone. This amine was, however, so weakly basic that it did not give a hydrochloride. The same method applied to 2-hydroxy-5-nitroacetophenone failed at the initial stage and no diketone was obtained. Simpson and Gardner's methods [14] for the synthesis of hydroxyflavones have been applied to 4-chloro-2-hydroxyacetophenone, yielding 7-chloro-4'-hydroxyflavone, and demethylation of 7-chloro-3-hydroxy-4'-methoxyflavone [20] by aluminium chloride gave 7-chloro-3,4'-dihydroxyflavone.

Biological screening showed the most active members of the series to be 4',7-di-(2-morpholinoethoxy)flavone dihydrobromide trihydrate, 7-chloro-4'-(2-piperidinoethoxy)-flavone hydrobromide and 2-ethoxycarbonyl-4'-methoxy-7-(2-piperidinoethoxy)isoflavone hydrogen fumarate. Whilst the bronchodilator activities generally are much higher than that of apigenin, they are still somewhat lower than that of khellin.

Experimental

Ultraviolet spectra (log ε are given below in parentheses) were measured with a Unicam spectrophotometer for methanol solutions, and infrared spectra with a Perkin-Elmer Infracord spectrophotometer for potassium bromide discs.

3-*Hydroxyimino-4',7-dimethoxyflavanone* (III).—To a cold solution of 4',7-dimethoxyflavanone (25·6 g.) and pentyl nitrite (76·8 g.) in ether (1·6 l.) was added concentrated hydrochloric acid (19·2 ml.) in portions, with shaking, during 2 hr. The mixture was kept overnight at 0°. 2% Sodium hydroxide solution (1·0 l.) was added and the aqueous layer separated after stirring (30 min.). Acidification of the aqueous layer with acetic acid gave 3-hydroxyimino-4',7-dimethoxyflavanone as buff crystals (17·11 g.). Washing with hot benzene (100 ml.) greatly improved the quality of the product and gave material (14·2 g., 50%) of m. p. 144—148°. Crystallisation from benzene or nitromethane–benzene gave a product of m. p. 156—157° (decomp.) (lit.,[7] 170°) (Found: C, 65·1; H, 4·6; N, 4·4. Calc. for $C_{17}H_{14}NO_5$: C, 65·4; H, 4·5; N, 4·5%), $\nu_{max.}$ 3200 (OH), 1680 (C=O), 1610 (C=N), and 925 cm.$^{-1}$ (N–OH).

3-*Amino-4',7-dimethoxyflavone* (II).—To the preceding compound (14·0 g.) in glacial acetic acid (375 ml.) was added a solution of anhydrous stannous chloride (31·0 g.) in concentrated hydrochloric acid (62·0 ml.). The mixture was shaken and overnight deposited a yellow crystalline complex which was filtered off, washed with a little acetic acid and decomposed by stirring it for an hour with 10% aqueous sodium hydroxide (300 ml.). The amine was extracted with chloroform (500 ml.), and the organic layer separated, washed with water (3 × 100 ml.), dried (Na_2SO_4), and evaporated. The residue gave 3-*amino-4',7-dimethoxyflavone*, yellow blades (from ethanol, 175 ml.) (8·6 g., 64%), m. p. 145—147° (Found: C, 69·0; H, 5·1; N, 4·7.

[12] Kulkarni and Joshi, *J. Indian Chem. Soc.*, 1957, **34**, 218.
[13] Mahesh and Seshadri, *Proc. Indian Acad. Sci.*, 1958, **47**, *A*, 184.
[14] Simpson and Gardner, *J.*, 1952, 4638; Tambor, *Ber.*, 1916, **49**, 1709.
[15] Baker, Flemons, and Winter, *J.*, 1949, 1562.
[16] Gowan, Hayden, and Wheeler, *J.*, 1955, 862.
[17] Baker, Chadderton, Harborne, and Ollis, *J.*, 1953, 1855.
[18] Nadkarni and Wheeler, *J.*, 1938, 1320.
[19] Bapat and Venkataraman, *Proc. Indian Acad. Sci.*, 1955, **42**, 336.
[20] Chen and Chang, *J.*, 1958, 148.

$C_{17}H_{15}NO_4$ requires C, 68·7; H, 5·1; N, 4·7%), $\lambda_{max.}$ 263 (4·32), 316 (4·08), and 363 mμ (4·19), $\nu_{max.}$ 3400, 3300 (NH) and 1637 cm.$^{-1}$ (C=O) [*acetyl derivative* (from ethanol), blades, m. p. 235—236° (Found: C, 67·1; H, 5·2; N, 4·2. $C_{19}H_{17}NO_5$ requires C, 67·2; H, 5·1; N, 4·1%), $\nu_{max.}$ 3300 (NH), 1690 (C=O), 1610 and 1600 cm.$^{-1}$ (CO–NH)]. The hydrochloride was prepared by adding a slight excess of hydrogen chloride in isopropyl ether to a solution of the base in chloroform. Crystallised from ethanol–dry ether, it had m. p. 205—208° (decomp.). In water it dissociated to the parent base.

*4′,7-Dimethoxyflavanone Oxime Toluene-*p*-sulphonate* (IV).—4′,7-Dimethoxyflavanone oxime[7] (20·8 g.) was dissolved in dry pyridine (80 ml.) and toluene-*p*-sulphonyl chloride (18·6 g.) was added in portions with stirring in 0·5 hr. After 2 hr. the mixture was poured into water and the white oxime ester filtered off, washed with water, dried at 60°, and crystallised from methanol. It (27·8 g., 92%) had m. p. 134—137°.

3-Amino-4′,7-dimethoxyflavanone (I; R = H).—A cold solution from potassium (1·95 g.) in dry ethanol (75 ml.) was added to a solution of the preceding product (18·8 g.) in benzene (100 ml.) at 10°. The mixture was shaken for 5½ hr. at ~10°. After removal of potassium toluene-*p*-sulphonate by filtration, the filtrate was concentrated. A further small amount of potassium salt separated and was removed. This filtrate was acidified with 12% hydrochloric acid and evaporated until 3-amino-4′,7-dimethoxyflavanone hydrochloride separated as a yellow-brown solid (8·1 g., 65%) that, crystallised from methanol–ether (charcoal), had m. p. 226—228° (decomp.). The *base* was obtained by neutralisation with aqueous sodium acetate solution and crystallisation from methanol as pale yellow plates, m. p. 149—150° (Found: C, 68·3; H, 5·8; N, 4·6. $C_{17}H_{17}NO_4$ requires C, 68·2; H, 5·8; N, 4·7%), $\lambda_{max.}$ 274 (4·22) and 312 mμ (3·87), $\nu_{max.}$ 3400, 3300 (NH) and 1695 cm.$^{-1}$ (C=O). The *acetyl derivative* was obtained as white needles (from ethanol), m. p. 223—225° (Found: C, 67·2; H, 5·5; N, 4·2. $C_{19}H_{19}NO_5$ requires C, 66·9; H, 5·6; N, 4·1%), $\nu_{max.}$ 3300 (NH), 1690 (C=O), 1625, and 1610 cm.$^{-1}$ (CO–NH).

3-Acetamido-4′,7-dimethoxyflavan-4-ol.—To a warm solution of 3-acetamido-4′,7-dimethoxyflavanone (0·55 g.) in methanol (50 ml.) and dioxan (15 ml.) was added sodium borohydride (0·15 g.) with shaking. After 1 hr. the methanol was removed and water (200 ml.) added. The white *flavanol* that separated was collected, washed with water, and dried at 100° (yield 0·46 g., 82%). Crystallisation from methanol gave blades, m. p. 198—201° (Found: C, 66·5; H, 6·3; N, 3·8. $C_{19}H_{21}NO_5$ requires C, 66·4; H, 6·2; N, 4·0%), $\nu_{max.}$ 3400 (NH), 1630 and 1620 (CO–NH), 1290, 1260, and 1030 cm.$^{-1}$ (CH·OH).

Various.—For the *derivatives* recorded in Tables 1—3, the preparative methods were similar to those described for the phenolic chloroflavones.

TABLE 1.

Substituted flavones.

A = ·O·CH_2·CO_2·Et. B = ·O·CH_2·CH_2·NMe_2. P = ·O·CH_2·CH_2·N<[CH_2·CH_2]$_2$>CH_2. M = ·O·CH_2·CH_2·N<[CH_2·CH_2]$_2$>O.

Subst.	Yield (%)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N	HBr salt (m. p.)
3-A, 4′-A, 7-OMe	96	101°	63·1	5·2		$C_{24}H_{24}O_9$	63·2	5·3		
3-A, 4′-OMe, 7-OMe...	76	129	64·9	5·3		$C_{21}H_{20}O_7$	65·3	5·2		
3-P, 4′-OMe, 7-OMe...	30	—	59·0	5·5	2·9	$C_{24}H_{28}BrNO_5$	58·8	5·7	2·9	186° *
3-M, 4′-OMe	75	122	57·3	5·6	2·9	$C_{22}H_{24}BrNO_5$	57·3	5·7	3·0	199 †
3-A, 4′-OMe	62	82	68·2	5·3		$C_{20}H_{18}O_6$	68·0	5·1		
3-A, 4′-OMe, 7-Cl ...	57	124	60·9	4·6		$C_{20}H_{17}ClO_6$	61·7	4·4		
4′-A, 5-A	50	189	65·0	4·9		$C_{23}H_{22}O_8$	64·8	5·2		
4′-A, 5-OMe	66	136	68·2	4·9		$C_{20}H_{18}O_6$	68·0	5·1		
4′-A, 7-A	96	114	64·6	5·5		$C_{23}H_{22}O_8$	64·8	5·3		
4′-A, 7-OMe	93	118	67·8	5·1		$C_{20}H_{18}O_6$	67·8	5·1		
4′-B, 7-OMe	33	138	71·1	6·1	4·3	$C_{20}H_{21}NO_4$	70·8	6·2	4·1	237
4′-OMe, 5-A	45	133	68·3	5·2		$C_{20}H_{18}O_6$	68·0	5·1		
4′-OMe, 8-A	90	160	67·8	5·1		$C_{20}H_{18}O_6$	67·8	5·1		
4′-OMe, 8-P	61	148	58·8	6·0	3·3	$C_{23}H_{26}BrNO_4$	60·0	5·7	3·0	263 ‡
4′-P, 7-OMe	64	110	72·7	6·8	3·6	$C_{23}H_{25}NO_4$	72·6	6·9	3·7	249
4′-M, 7-OMe	38	124	68·6	6·4	3·8	$C_{23}H_{23}NO_5$	69·1	6·1	3·7	264
4′-M, 7-M	41	—	47·2	6·0	3·7	$C_{27}H_{34}Br_2N_2O_6$	46·5	5·8	4·0	125 §

* Found: Br, 16·0. Required: Br, 16·3%. † Found: Br, 17·6. Required: Br, 17·3. ‡ Found: Br, 17·0. Required: Br, 17·4%. § Found: Br, 23·6. $C_{27}H_{34}Br_2N_2O_2,3H_2O$ requires Br, 23·0%.

TABLE 2.

Substituted isoflavones.

A = ·O·CH_2·CO_2Et. B = ·CO_2Et. P = ·O·CH_2·CH_2·N<[CH_2·CH_2]$_2$>CH_2.

Subst.	Yield (%)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N	HBr salt (m. p.)
2-B, 4'-OMe, 7-A	80	110°	65·1	5·1		$C_{23}H_{22}O_8$	64·8	5·2		
2-B, 4'-OMe, 7-P	30	142	68·9	6·6	3·3	$C_{26}H_{29}NO_6$	69·2	6·5	3·1	177 *
4'-A, 7-A	77	108	65·0	5·3		$C_{23}H_{22}O_8$	64·8	5·2		
4'-OMe, 7-A	67	146	67·7	5·3		$C_{20}H_{18}O_6$	67·9	5·1		
4'-OMe, 7-P	82	—	59·4	5·9	3·2	$C_{23}H_{26}BrNO_4$	60·0	5·7	3·0	208 †
4'-P, 7-P	40	157	73·5	7·6	5·8	$C_{29}H_{36}N_2O_4$	73·1	7·6	5·9	300

* Acid fumarate. † Found: Br, 18·0. Required: Br, 17·4%.

TABLE 3.

Substituted flavanones.

A = ·O·CH_2·CO_2Et. M = ·O·CH_2·CH_2·N<[CH_2·CH_2]$_2$>O.

Subst.	Yield (%)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N	HBr salt (m. p.)
4'-A, 7-A	50	89°	64·5	5·7		$C_{23}H_{24}O_8$	64·5	5·7		
4'-M, 7-M	50	—	49·1	5·9	4·2	$C_{27}H_{36}Br_2N_2O_6$	50·3	5·7	4·4	257 *

* Found: Br, 24·4. Required: Br, 24·9%.

4'-Benzyloxy-4-chloro-2-hydroxychalcone.—To a cold solution of 4-chloro-2-hydroxyacetophenone (20 g.) and 4-benzyloxybenzaldehyde (36·0 g.) in ethanol (400 ml.) aqueous sodium hydroxide (40 g. in 80 ml.) was slowly added, with shaking and cooling. After being kept overnight the precipitate was filtered off and washed with ether. An aqueous slurry (250 ml.) of this salt was acidified with acetic acid. The *chalcone* was collected, dried at 100°, and crystallised from chloroform–alcohol as yellow needles (33·2 g., 77·5%), m. p. 143—145° (Found: C, 72·8; H, 4·9; Cl, 9·6. $C_{22}H_{17}ClO_3$ requires C, 72·4; H, 4·7; Cl, 9·7%).

4'-Benzyloxy-7-chloroflavone.—A solution of 4'-benzyloxy-4-chloro-2-hydroxychalcone (33·2 g.) in pentyl alcohol (1475 ml.) was boiled under reflux with selenium dioxide (33·2 g.) for 17 hr., then filtered hot through kieselguhr, and, on cooling, deposited *4'-benzyloxy-7-chloroflavone* as pale yellow plates (28·2 g., 85%), m. p. 203—205° (Found: C, 72·5; H, 4·3; Cl, 10·4. $C_{22}H_{15}ClO_3$ requires C, 72·4; H, 4·2; Cl, 9·7%).

7-Chloro-4'-hydroxyflavone.—4'-Benzyloxy-7-chloroflavone (25·0 g.) was warmed on the water-bath with concentrated hydrochloric acid (125 ml.) and glacial acetic acid (170 ml.) for 1 hr., then cooled, and the precipitated 7-chloro-4'-hydroxyflavone hydrochloride was filtered off, washed with water, and dried at 60° (17·8 g., 83·5%; m. p. 295—297° with loss of hydrogen chloride). *7-Chloro-4'-hydroxyflavone* (13·5 g.), recrystallised from pyridine–ethanol, had m. p. 298—299° (Found: C, 66·1; H, 3·5; Cl, 13·3. $C_{15}H_9ClO_3$ requires C, 66·1; H, 3·4; Cl, 13·0%).

Ethyl 7-Chloroflavon-4'-yloxyacetate.—7-Chloro-4'-hydroxyflavone (5·0 g.), ethyl bromoacetate (3·1 g.), and anhydrous potassium carbonate (2·0 g.) were boiled in acetone (50 ml.) for 1 hr. The acetone was then removed and water (200 ml.) was added. The solid was filtered off and crystallised from alcohol, to give slightly pink plates of *ethyl 7-chloroflavon-4'-yloxyacetate* (5·7 g., 85·5%), m. p. 174—176° (Found: C, 69·0; H, 6·0; Cl, 9·9. $C_{22}H_{22}ClNO_3$ requires C, 68·8; H, 5·8; Cl, 9·8%).

7-Chloro-4'-(2-piperidinoethoxy)flavone.—Sodium (0·23 g., 0·01 g.-atom) was dissolved in dry ethanol (250 ml.), and 7-chloro-4'-hydroxyflavone (2·5 g., 0·009 mole) and 2-piperidinoethyl chloride (from 3·0 g. of hydrochloride) in ethanol were added. After boiling under reflux for 1 hr., the mixture was filtered and concentrated to ~70 ml. *7-Chloro-4'-(2-piperidinoethoxy)flavone* separated and was filtered off, dried at 100°, and crystallised from ethanol. It (2·5 g., 71%) had m. p. 165—168° (Found: C, 69·1; H, 6·0; Cl, 9·9; N, 3·6. $C_{22}H_{22}ClNO_3$ requires C, 68·9; H, 5·8; Cl, 9·8; N, 3·7%). The *hydrobromide* crystallised in light-yellow blades (from water), m. p. 271—272° (Found: C, 57·2; H, 5·1; N, 3·1. $C_{22}H_{23}BrClNO_3$ requires C, 57·8; H, 5·0; N, 3·0%).

7-Chloro-3,4′-dihydroxyflavone.—7-Chloro-3-hydroxy-4′-methoxyflavone [20] (11·6 g.) and powdered aluminium chloride (34·8 g.) in dry benzene were heated on the water-bath for 2 hr., then cooled and treated with ice and hydrochloric acid. The *product* was filtered off, washed with water, and crystallised from ethanol (charcoal); it (9·2 g., 87%) had m. p. 256—258° (Found: C, 62·1; H, 3·0; Cl, 12·2. $C_{15}H_9ClO_4$ requires C, 62·4; H, 3·1; Cl, 12·3%).

7-Chloro-3,4′-di(ethoxycarbonylmethyl)flavone.—Reaction of the chlorodihydroxyflavone with ethyl bromoacetate gave the *diester* as white needles, m. p. 130—132° (Found: C, 60·0; H, 4·5; Cl, 7·7. $C_{23}H_{21}ClO_8$ requires C, 60·1; H, 4·6; Cl, 7·7%).

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