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Some Basic Derivatives of 3-Methylflavone-8-carboxylic Acid

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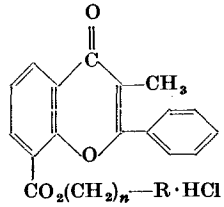
The basic esters of carboxylic acids form a large group of substances with various pharmacological properties, e.g. local anaesthetic, spasmolytic, nicotinolytic and tranquilizing.[1,2,3] As the type of biological action seems to be determined very often by the esterifying acid,[4,5] a study was undertaken to examine the pharmacological properties of basic esters of new types of acids.

Previously some chromone and flavone carboxylic acids[6,7] had been tested; the investigation has now been extended to 3-methylflavone-8-carboxylic acid, which forms the subject of this paper.

The pharmacological screening showed that one of the derivatives of the series, i.e. the piperidinoethyl ester (Rec 7–0040) (Table I), possesses a very marked papaverine-like muscle-relaxing activity. The detailed pharmacological properties will be described elsewhere.[8] Particularly interesting is the observation that the product does not seem to affect normal tone or movements of intestine but it inhibits specifically spasms provoked by various agents. Rec 7–0040 also has analgesic and local anaesthetic activity which could perhaps be of therapeutical importance in cases where the spastic condition is sustained by pain stimuli.

The synthesis of 3-methylflavone-8-carboxylic acid, the key intermediate in this work, can be effected by the introduction of the carboxyl group into the flavone nucleus either before or after the formation of the γ-pyrone ring. In the former case 2-hydroxy-3-carboxypropiophenone is the starting material. For the preparation of this compound, we considered the simplest and

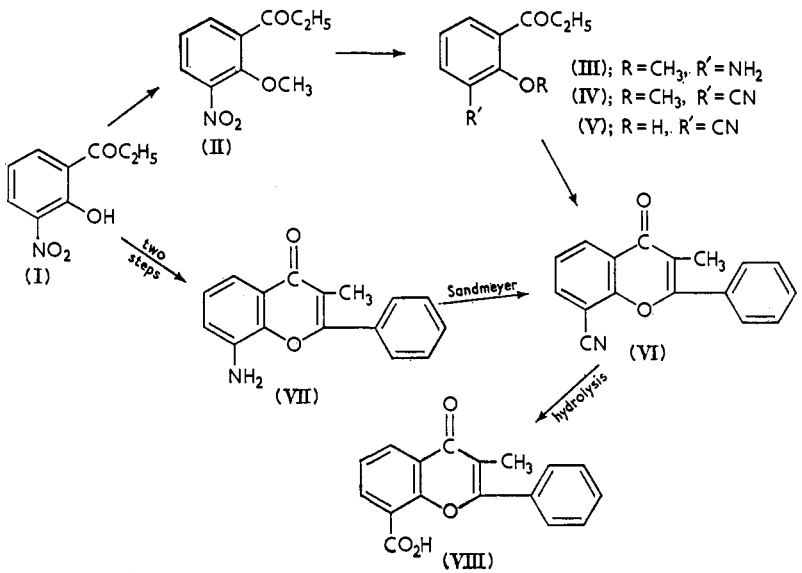
Table I. Basic esters of 3-methylflavone-8-carboxylic acid



Code	R	n	Formula	m.p. °C [a, b]	Calcd. N	Calcd. Cl	Found N	Found Cl	LD_{50} mg/kg (i.p.)	ED_{50} [c] µg/ml
Rec 1–0269	$N(CH_3)_2$	2	$C_{21}H_{22}ClNO_4$	177–178	3·61	9·14	3·58	9·11	315	20
Rec 1–0270	$N(C_2H_5)_2$	2	$C_{23}H_{26}ClNO_4$	163–164	3·37	8·53	3·33	8·42	600	20
Rec 7–0249	$N(C_3H_7)_2$	2	$C_{25}H_{30}ClNO_4$	212–215	3·15	7·99	3·10	7·95	500	3
Rec 1–0469	$N(i\text{—}C_3H_7)_2$	2	$C_{25}H_{30}ClNO_4$	190–192	3·15	7·99	3·08	7·97	1500	7
Rec 7–0040	$N{=}C_5H_{10}$	2	$C_{24}H_{26}ClNO_4$	232–234	3·27	8·14	3·15	8·20	350	2·5
Rec 7–0037	$N{=}C_4H_8O$	2	$C_{23}H_{24}ClNO_5$	233–234	3·25	8·25	3·00	8·18	600	18
Rec 7–0248	$N(CH_3)_2$	3	$C_{22}H_{24}ClNO_4$	207–210	3·48	8·82	3·32	8·81	160	3·5
Rec 1–0473	$N(C_2H_5)_2$	3	$C_{24}H_{28}ClNO_4$	187–189	3·25	8·25	3·25	8·21	200	3
Papaverine									240	5

[a] M.ps. are not corrected. [b] Crystallizing solvent was alcohol/ether. [c] Concentrations at which maximal spastic contractions, provoked on the guinea-pig small intestine by 50 µg/ml of $BaCl_2$, were inhibited by 50% [cf. R. Magnus, *Arch. Anat. Physiol., Lpz.*, **102**, 123 (1904)]. An isolated strip of small intestine was immersed in oxygenated Tyrode solution at 37° and the substance was added to the perfusion liquid. After one minute, 50 µg/ml of $BaCl_2$ were added. This normally provokes a submaximal contraction. Inhibitions of these contractions, expressed as percentage values, were plotted and the ED_{50}'s were determined graphically.

most straightforward methods, i.e. the introduction of a propionyl group into the salicylic acid molecule or of a carboxyl group into *o*-hydroxypropiophenone. In neither case however did we obtain the desired compound. Indeed, Fries rearrangement applied to ethyl 2-propionoxybenzoate and Friedel–Crafts synthesis with methyl salicylate gave rise to 5-acyl derivatives;[9,10] in fact, the entering acyl radical is directed to the 3-position only if the 5-position is already occupied. This was proved,



e.g., with methyl 5-methylsalicylate. Further, the Marassè modification of the Kolbe–Schmitt synthesis[11] for the direct introduction of a carboxyl group in phenolic compounds, already successfully applied to *p*-hydroxypropiophenone,[12] when tried on the *ortho* isomer led, unexpectedly, to 3-methyl-4-hydroxycoumarin.*

In view of the difficulties encountered in preparing 2-hydroxy-3-carboxypropiophenone, we decided to introduce the carboxyl group in a potential form, i.e. as a cyano group. Starting from 2-hydroxy-3-nitropropiophenone (I)[14] with a series of easily

* A patent is pending for this new and simple method for preparing 4-hydroxycoumarins.[13]

foreseeable reactions, we arrived at 2-hydroxy-3-cyanopropiophenone (V), which thus became the fundamental intermediate in the synthesis. For carrying out some steps of the synthesis easily, it was found convenient to mask the phenolic hydroxyl group as the methyl ether. The preparation of a benzyl ether, though more advantageous, is inadvisable because in the reduction of 2-benzyloxy-3-nitropropiophenone with iron and a little hydrochloric acid, the product was debenzylated, thus depriving the procedure of its protective purpose.

Acylation of 2-hydroxy-3-cyanopropiophenone (V) with benzoyl chloride and sodium benzoate, according to the Kostanecki–Robinson procedure, gives rise to 3-methyl-8-cyanoflavone (VI), hydrolysis of which yields the desired 8-carboxylic acid (VIII). One gets the same result by applying the Sandmeyer reaction to 3-methyl-8-aminoflavone (VII), which we have already described.[15]

The basic esters are prepared via 3-methylflavone-8-carbonyl chloride; they are listed, together with the main physico-chemical and pharmacological data, in Table I.

Experimental

With regard to the preparation of the basic esters, we shall report in full only the preparation of dimethylaminoethyl 3-methylflavone-8-carboxylate hydrochloride, identical procedures being used for the others. The essential data are given in Table I.*

2-Methoxy-3-nitropropiophenone (*II*). A mixture of 2-hydroxy-3-nitropropiophenone (19·5 g),[14] anhydrous acetone (250 ml) anhydrous potassium carbonate (28 g), and methyl sulphate (12·5 g) was refluxed on a steam bath for 8–10 h, cooled, filtered and the solid washed with hot acetone. Removal of the solvent left an oil which was distilled fractionally, collecting the fraction boiling at 160–165°/10 mm. The yield of yellow oil (10·5 g) had $D^{20} = 1 \cdot 2136$; $n_D^{20} = 1 \cdot 5379$.

Anal. Calcd. for $C_{10}H_{11}NO_4$: N, 6·69. Found: N, 6·51. U.V. maximum: mμ 231; $\epsilon \times 10^{-3}$: 12·3.

* All the products described in the present paper are the subject of Swiss Patent Application Nos. 25282–25283.

2-Methoxy-3-aminopropiophenone hydrochloride (*III*). A solution of 2-methoxy-3-nitropropiophenone (10 g) in 95 per cent ethanol (100 ml) containing 3 ml of concentrated HCl, was reduced under reflux with iron powder (20 g), added in stages in the course of one hour. The mixture was decolorized and filtered hot. The filtrate was acidified with alcoholic hydrochloric acid and evaporated under vacuum on a steam bath. The crude product on crystallizing from alcohol–ether gave a faintly pink product (6·5 g), m.p. 154–155° (d.).

Anal. Calcd. for $C_{10}H_{14}ClNO_2$: Cl, 16·44; N, 6·49. Found: Cl, 16·32; N, 6·59. U.V. maxima: mμ 230, 325; $\epsilon \times 10^{-3}$: 19·9, 2·11.

2-Methoxy-3-cyanopropiophenone (*IV*). A solution of 2-methoxy-3-aminopropiophenone hydrochloride (10 g) in a mixture of concentrated hydrochloric acid (10 ml) and water (150 ml), was diazotized by addition at 0–5° of sodium nitrite (3·3 g) in water (20 ml). The solution of the diazonium salt was added with stirring to a solution of cuprous cyanide (prepared from 12·5 g of $CuSO_4.5H_2O$ and 14·7 g of NaCN in 150 ml of water), at 60–70°. When the addition was complete and the evolution of nitrogen ceased, the mixture was cooled and filtered. The crude product was washed with water and dried. On crystallizing from 50 per cent ethanol, a pale yellow solid (6 g) was obtained, m.p. 87–88°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: N, 7·40. Found: N, 7·25. U.V. maxima: mμ 295; $\epsilon \times 10^{-3}$: 2·28.

2-Hydroxy-3-cyanopropiophenone (*V*). A mixture of 2-methoxy-3-cyanopropiophenone (3 g) and $AlCl_3$ (3 g) in benzene (50 ml) was refluxed for two hours. Removal of the solvent left a solid which was decomposed with ice-cold water and HCl. The crude product was filtered, washed with water and dried. On crystallizing from 95 per cent ethanol, a yellow crystalline solid (2 g) was obtained, m.p. 82–85°.

Anal. Calcd. for $C_{10}H_9NO_2$: N, 8·00. Found: N, 8·08. U.V. maxima: mμ 330; $\epsilon \times 10^{-3}$: 6·16.

3-Methyl-8-cyanoflavone (*VI*). A mixture of 2-hydroxy-3-cyanopropiophenone (15 g), benzoyl chloride (30 g) and sodium benzoate (20 g) was heated in an oil bath at 180–190° for 7–8 h. After cooling, the resulting product was triturated in a mortar with four portions of 100 ml of 10 per cent sodium hydroxide solution, filtering each time through a filter plate, then washing

with water until the alkaline reaction disappeared. The crude product on crystallizing from 95 per cent ethanol gave a crystalline solid (7 g), m.p. 160–162°.

Anal. Calcd. for $C_{17}H_{11}NO_2$: N, 5·36. Found: N, 5·34. U.V. maxima: mμ 241, 289, 321; $\epsilon \times 10^{-3}$: 15·00, 11·34, 11·90.

3-Methylflavone-8-carboxylic acid (VIII). (*a*) A mixture of 3-methyl-8-cyanoflavone (3 g) and 70 per cent sulphuric acid (10 ml) was refluxed for 1–2 h. The reaction mixture was then poured into ice-water and the precipitated solid was filtered. Crystallization of the solid from 50 per cent ethanol gave a white crystalline product (1·5 g), m.p. 230–231°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 71·58; H, 6·01. Found: C, 71·50; H, 5·95.

The *ethyl ester* was obtained from the acid by boiling in ethanolic sulphuric acid solution, crystals from ligroin, m.p. 97–99°.

(*b*) 3-Methyl-8-aminoflavone[15] (40 g) was added portionwise with stirring to a mixture of concentrated hydrochloric acid (75 ml) and water (40 ml). Stirring was continued for ½ h and then a solution of sodium nitrite (12·3 g) in water (25 ml) was added at 0–5° over a ½-h period. The solution of the diazonium salt was filtered and added to a solution of cuprous cyanide (prepared from 45 g of sodium cyanide and 45 g of $CuSO_4.5H_2O$ in 500 ml of water), at 90°. The resulting mixture was kept at 90° for 1 h, then cooled, filtered and the solid washed thoroughly with water. The crude nitrile was hydrolysed directly by boiling under reflux with 60 per cent sulphuric acid (600 ml), the reaction mixture was poured into ice-water and the 3-methylflavone-8-carboxylic acid was isolated by filtration. The crude product so obtained was purified by double precipitation (yield of acid, 15 g). Crystallization from 50 per cent ethanol or a large volume of methanol gave a colourless solid, m.p. 229–230°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 71·58; H, 6·01. Found: C, 71·35; H, 5·90. U.V. maxima: mμ 244, 292; $\epsilon \times 10^{-3}$: 17·8, 13·6.

3-Methylflavone-8-carbonyl chloride. A mixture of 3-methylflavone-8-carboxylic acid (12 g), thionyl chloride (10 g) and anhydrous benzene (200 ml) was boiled under reflux for two hours. At the end of this time a clear, orange coloured solution was obtained. Removal of the solvent and of the excess of thionyl

chloride left a solid which was sufficiently pure for subsequent use. It can be crystallized from ligroin to give pale yellow crystals, m.p. 155–156°.

Anal. Calcd. for $C_{17}H_{11}ClO_3$: Cl, 11·87. Found: Cl, 11·82.

Dimethylaminoethyl 3-methylflavone-8-carboxylate hydrochloride. A solution of 3-methylflavone-8-carbonyl chloride (11 g) in anhydrous benzene (150 ml) was added, at room temperature, to dimethylaminoethanol (3·3 g). The resulting solution was boiled under reflux for 2–3 h, cooled, filtered and the solid washed with hot benzene. The crude product (12 g) on crystallizing from ethanol ether gave a white solid, m.p. 177–178°.

Anal. Calcd. for $C_{21}H_{22}ClNO_4$: Cl, 9·14; N, 3·61. Found: Cl, 9·11; N, 3·58.

Summary. Basic esters of 3-methylflavone-8-carboxylic acid with a papaverine-like muscle-relaxing action are described. A detailed account for the synthesis of this acid is given. It is effected by two methods: (1) acylation of 2-hydroxy-3-cyanopropiophenone according to the Kostanecki–Robinson procedure; (2) from 3-methyl-8-aminoflavone by a Sandmeyer reaction.

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