455. *Properties and Orientation of Some Derivatives of 3-Acylchromones.*

By Wilson Baker and V. S. Butt.

3-Acylchromones are produced by acylation of either *o*-hydroxyacetophenones or *o*-hydroxy-1 : 3-diketones of the type (IV). In the general case the product may possess either of the alternative structures (VI) or (VII), and there has hitherto been no satisfactory method for distinguishing between such isomerides, as the only procedure, that of degradative hydrolysis to an unacylated chromone, here reviewed, is usually ambiguous. A method for distinguishing between these isomerides has now been found in their reaction with benzylamine, which splits off the 3-acyl group as an acylbenzylamine and reacts with the rest of the molecule to give a yellow, fluorescent derivative of the type (XI).

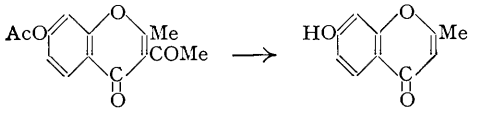
The reaction between 3-acylchromones and phenylhydrazine has been shown to yield 4-acyl-1-phenyl-5-*o*-hydroxyphenyl-3-alkylpyrazoles of the type (XXI).

The reaction of *o*-hydroxyacetophenones, or their substituted derivatives, with the anhydride and the sodium salt of an aliphatic or aromatic carboxylic acid has been widely used for the preparation of chromones, including many flavones and flavonols. In certain cases where an acid of the type $CH_2R{\cdot}CO_2H$ is used coumarins have also been obtained, and whether a chromone or coumarin or a mixture of both is produced depends on the structures of the acid and of the ketone used and on the reaction conditions employed (see, for example, Sethna and Shah, *Chem. Reviews*, 1945, **36**, 8).

A 3-acylchromone is another type of product which may be formed in this reaction; this was first established by von Kostanecki *et al.* (*Ber.*, 1901, **34**, 102, 2946) in the case of 7-acetoxy-3-acetyl-2-methylchromone (I) prepared from resacetophenone, acetic anhydride, and sodium acetate.

Other cases of the similar formation of 3-acylchromones have since been recorded, and it was shown by Baker (*J.*, 1933, 1383) that the production of these compounds is a general feature of the reaction, but that owing to the fact that the whole reaction product was usually subjected to

vigorous alkaline hydrolysis the 3-acyl group was lost and a chromone unsubstituted in position 3, for example (II), was isolated.



(I.) (II). (III.)

(V.) (IV.) (VI.) (VII.)

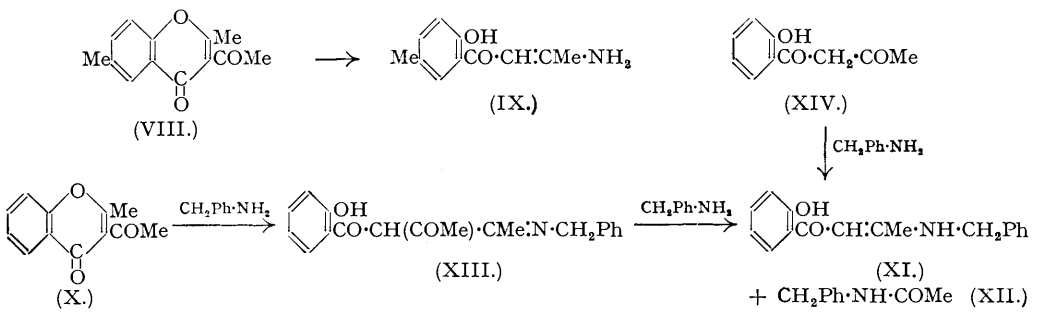
3-Acylchromones can also be similarly prepared from 1 : 3-diketones of the type (IV), and it was first established by Baker (*loc. cit.*; see also Mahal and Venkataraman, *Current Science*, 1933, **2**, 214) that these diketones were formed in the reaction under discussion by intramolecular migration of the acyl group R·CO from the phenolic oxygen atom in the *o*-acyloxyacetophenone (V). It was also shown that the same chromone was produced both from 2-propionoacetyl-4-methylphenol, acetic anhydride, and sodium acetate, and from 2-acetoacetyl-4-methylphenol, propionic anhydride, and sodium propionate, so that the reaction clearly involves the formation of an intermediate triacylmethane of the type (III). In the more general case of 3-acylchromones prepared from preformed 1 : 3-diketones of the type (IV) and the anhydride and sodium salt of an acid R''·CO_2H (Müller, *J.*, 1915, **107**, 872; Wittig, Bangert, and Richter, *Annalen*, 1925, **446**, 155; Algar, McCarthy, and Dick, *Proc. Roy. Irish Acad.*, 1933, **41**, 155; Baker, *loc. cit.*) the product might therefore possess either of the isomeric structures (VI) or (VII).

Hydrolytic evidence hitherto employed to establish the structure of these 3-acylchromones has been criticised (Baker, *loc. cit.*) on the grounds that the nature of the product will depend on whether the 3-acyl group is removed by direct hydrolysis, or whether the heterocyclic ring is first opened to give a triacylmethane of the type (III), which then loses one acyl group by hydrolysis and subsequently undergoes ring-closure.

The main object of the present investigation has been to devise methods which could be used to distinguish between isomeric 3-acylchromones of the types (VI) and (VII), without recourse to alkaline hydrolysis. This is also a problem of interest in connection with the structure of buddleoflavonol, a yellow colouring matter occurring as a glycoside in *Buddleia variabilis*, Hemsl., which according to Yü (*Bull. Soc. Chim. biol.*, 1933, **15**, 482) is 5 : 7-dihydroxy-4'-methoxy-3-acetylflavone, but which might on the available evidence be the isomeric 5 : 7-dihydroxy-3-anisoyl-2-methylchromone.

Reaction of 3-Acylchromones with Amines or Ammonia.

The reaction between 3-acylchromones and alcoholic ammonia was investigated by Schneider and Kunau (*Ber.*, 1921, **54**, 2304), Schneider and Bode (*Ber.*, 1923, **56**, 1042), Wittig (*Ber.*, 1925, **58**, 19), and Wittig and Blumenthal (*Ber.*, 1927, **60**, 1085). Wittig and Blumenthal showed that with 3-acetyl-2 : 6-dimethylchromone (VIII) loss of an acetyl group and addition of ammonia occurred to give 2-β-aminocrotonyl-4-methylphenol (IX), which was also produced by the



(VIII.) (IX.) (XIV.)

(X.) (XIII.) (XI.) + $CH_2Ph·NH·COMe$ (XII.)

action of alcoholic ammonia on 2-acetoacetyl-4-methylphenol or on 2 : 6-dimethylchromone. It was suggested that this compound was produced by fission of the acetyl group in (VIII)

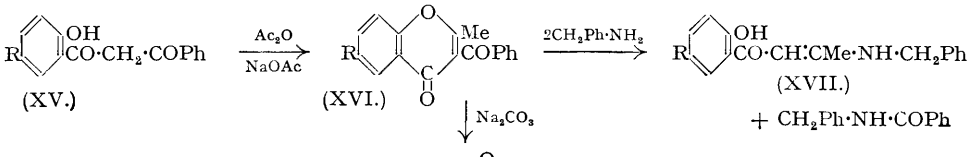
followed by hydrolytic opening of the chromone ring and reaction of ammonia with the resulting 1 : 3-diketone.

In the present investigation benzylamine has been used in place of ammonia, and it has been shown that the method serves to distinguish between isomeric 3-acylchromones of the types (VI) and (VII). Benzylamine was chosen as being a powerful primary base which readily reacts with 3-acylchromones to give easily isolated products; a secondary base such as diethylamine and weaker bases, for example, *p*-toluidine do not attack 3-acylchromones even under vigorous conditions.

3-Acetyl-2-methylchromone (X) in either anhydrous alcohol or benzene reacts rapidly with two molecules of benzylamine at room temperature to give a yellow solution from which both 2-β-*benzylaminocrotonylphenol* (XI) and acetobenzylamide (XII) may be isolated in very high yield. The fact that this reaction proceeds rapidly under anhydrous conditions shows that the hydrolytic mechanism proposed by Wittig and Blumenthal is probably incorrect, and certainly cannot apply to the reactions now recorded. We regard the reaction as initiated by the attack of the anionoid benzylamine on the carbon atom in position 2 which is strongly cationoid owing to conjugation with the two carbonyl groups, and the resulting product, in which benzylamine is added to the double bond between carbon atoms 2 and 3, would then be expected to rearrange to the more stable open-chain Schiff's base (XIII) (for work on the addition of amines to αβ-unsaturated carbonyl compounds see Tambor and Wildi, *Ber.*, 1898, **31**, 349; Ruhemann, *J.*, 1903, **83**, 1371; 1904, **85**, 1451; Ruhemann and Watson, *J.*, 1904, **85**, 456, 1170). This Schiff's base (XIII), in which carbon atom 2 of the chromone nucleus with its attached methyl group is labelled by the benzylimino-group, would be expected to behave like a triacylmethane since the >C=N– group is analogous to a carbonyl group. Claisen showed that triacylmethanes readily lose an acyl group as an acid amide when reacted upon with a base (*Annalen*, 1893, **277**, 204; 1896, **291**, 99), and the further reaction of (XIII) with benzylamine would, therefore, be expected to yield the observed products, namely 2-β-benzylaminocrotonylphenol (XI) and acetobenzylamide (XII). Loss of the 3-acetyl group as acetobenzylamide cannot precede the opening of the heterocyclic ring, because 2-methylchromone is attacked by benzylamine to give (XI) much more slowly than is the 3-acyl derivative. Compound (XI) is also very readily prepared from 2-acetoacetylphenol (XIV) and benzylamine. It may be noted that reaction of a secondary amine with a 3-acylchromone could not give rise to a Schiff's base of the type (XIII), thus accounting for the failure of the reaction in these cases.

Reaction with benzylamine, therefore, serves to distinguish between the isomerides of the general types (VI) and (VII), the former giving *o*-HO·C_6H_4·CO·CH:CR'·NH·CH_2Ph and the amide CH_2Ph·NH·COR'', and the latter giving *o*-HO·C_6H_4·CO·CH:CR''·NH·CH_2Ph and the amide CH_2Ph·NH·COR'. Several other cases of the reaction have been carried out, including some with 3-acylchromones having different groups R' and R'', the structures of which have not hitherto been established.

7-Methoxy-3-acetyl-2-methylchromone reacts with benzylamine to give *5-methoxy-2-β-benzylaminocrotonylphenol* and acetobenzylamide. Müller (*J.*, 1915, **107**, 872) prepared *o*-hydroxydibenzoylmethane (XV; R = H) by the partial hydrolysis of flavone, and by heating this compound with acetic anhydride and anhydrous sodium acetate obtained an " acetyl derivative " (actually an anhydroacetyl derivative) for which no structure was proposed and which might be either 3-benzoyl-2-methylchromone (XVI; R = H) or 3-acetylflavone (see Baker, *loc. cit.*). Since, however, it reacts with benzylamine to give 2-β-benzylaminocrotonylphenol (XVII; R = H) and benzobenzylamide it must be *3-benzoyl-2-methylchromone* (XVI; R = H).



A similar case is provided by the compound prepared by Wittig and Blumenthal (*Ber.*, 1927, **60**, 1085) by heating the *O*-benzoyl derivative of 2-β-aminocrotonyl-4-methylphenol; this was

regarded as 3-acetyl-6-methylflavone because it could be hydrolysed to 6-methylflavone. The compound, however, reacts with benzylamine to give 2-β-*benzylaminocrotonyl-4-methylphenol* (XVII; R = Me), and must, therefore, be 3-*benzoyl*-2 : 6-*dimethylchromone* (XVI; R = Me), a conclusion which brings to light an interesting migration of the benzoyl group from oxygen to carbon when the *O*-benzoyl derivative of 2-β-aminocrotonyl-4-methylphenol is heated. The benzylamino-compound (XVII; R = Me) was also prepared from benzylamine and 2-acetoactyl-4-methylphenol.

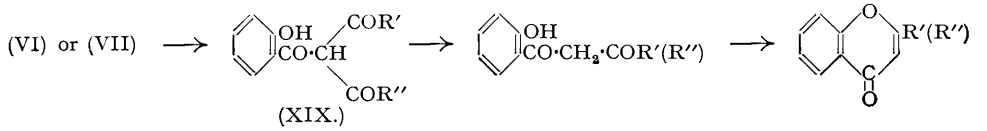
3-Propionyl-2 : 6-dimethylchromone reacted with benzylamine to give (XVII; R = Me) with loss of the propionyl group, thus definitely establishing the structure of this chromone which had been previously suggested on the basis of its hydrolysis to 2 : 6-dimethylchromone (Wittig, Bangert, and Richter, *loc. cit.*; see, however, Baker, *loc. cit.*, and below). The preparation of this chromone is mentioned on p. 2143.

Two derivatives of a 7-acyloxychromone which have been examined react differently with benzylamine. 7-Acetoxy-3-acetyl-2-methylchromone reacts in cold benzene solution to give merely 7-hydroxy-3-acetyl-2-methylchromone, thus showing that the 7-hydroxy-group stabilises the heterocyclic ring (see section Hydrolysis of 3-Acylchromones, below), and confirming that in the cases of the chromones previously discussed the loss of the 3-acyl substituent occurs after the opening of the ring. In the case of 7-benzoyloxy-3-benzoylflavone reaction at room temperature with benzylamine in benzene gave an uncrystallisable mixture

The unsaturated benzylamine derivatives, as (XI) and (XVII) described above, are represented as " enamines " rather than " ketimines," since the former conjugated structure is more consistent with their bright yellow-green colour, and with the fact that they exhibit vivid yellow-green fluorescences in ultra-violet light. The benzyl group is not essential for colour or fluorescence; 2-β-*methylaminocrotonylphenol*, prepared from 2-acetoacetylphenol and 2-β-aminocrotonyl-4-methylphenol (Wittig and Blumenthal, *loc. cit.*), also exhibits these characteristics.

Hydrolysis of 3-Acylchromones.

Chromones and flavones have frequently been prepared by the partial hydrolysis of their 3-acyl derivatives [see, for example, the preparation of the chromone (II) from the 3-acetylchromone (I)], and it has been generally assumed that the reaction involves direct hydrolytic fission of the 3-acyl group. On this assumption Wittig, Bangert, and Richter (*loc. cit.*) have allotted structures to chromones of the type (VI) and (VII) where R′ and R″ represent different groups, but it was pointed out by Baker (*loc. cit.*) that this evidence of structure is inconclusive in any case where the reaction may involve ring opening to give the triacylmethane (XIX), because the particular acyl group lost and the structure of the final product would depend solely on the nature of the groups R′ and R″ and not on their position in the original chromone.



(XIX.)

Direct evidence of the formation of triacylmethanes during hydrolysis of certain 3-acylchromones (orientation determined by reaction with benzylamine) has now been obtained. 3-Benzoyl-2-methylchromone (XVI; R = H) undergoes hydrolysis with aqueous-alcoholic sodium carbonate to give flavone (XVIII; R = H) and not 2-methylchromone which would have been produced by direct loss of the 3-benzoyl group. A similar case is provided by the hydrolysis (Wittig and Blumenthal, *loc. cit.*) of 3-benzoyl-2 : 6-dimethylchromone (XVI; R = Me) which yields 6-methylflavone (XVIII; R = Me). That the chromone ring should first open and then close under the same reaction conditions receives a natural explanation as follows. The ready opening of the ring is initiated by attack of hydroxyl ions at carbon atom 2, which is rendered strongly cationoid by the two carbonyl groups (cf. the rapid reaction of benzylamine with 3-acylchromones), and the resulting triacylmethane (XIX) is then hydrolysed to a 2-acetoacylphenol which does, in fact, undergo ring closure in presence of sodium carbonate to give a chromone. The latter point has been established by cyclising *o*-hydroxydibenzoylmethane to flavone under the influence of boiling sodium carbonate solution; it may be mentioned that cyclisation also occurs in boiling 50% alcohol. It is probable that an equilibrium between flavone and diketone is set up in solution, the proportion of diketone increasing with the alkalinity of the solution. As is well known, the action of caustic alkalis brings about further degradation of the 1 : 3-diketone, frequently in both possible ways.

The direction of hydrolysis of the intermediate triacylmethanes can be predicted from the work of Claisen (*Annalen*, 1893, **277**, 192), who showed that such compounds containing two aroyl groups and one aliphatic acid residue are hydrolysed with loss of the aliphatic group. The direction of hydrolysis is less certain when the chromone can yield a triacylmethane containing two different aliphatic residues, and the reaction is further complicated in these cases by the possibility that the aliphatic 3-acyl group of the chromone may undergo direct hydrolytic fission. Thus the hydrolysis of 3-propionyl-2 : 6-dimethylchromone with aqueous-alcoholic sodium carbonate (Wittig, Bangert, and Richter, *loc. cit.*; Baker, *loc. cit.*) gave a poor yield of 2 : 6-dimethylchromone as the sole neutral product, and the absence of 6-methyl-2-ethylchromone strongly suggests that two simultaneous reactions are occurring, (*a*) direct fission of the 3-propionyl group to give the relatively stable 2 : 6-dimethylchromone, and (*b*) ring opening to the triketone which breaks down to the two diketones by partial loss of both acetyl and propionyl groups, and subsequent further hydrolytic degradation of the two diketones rather than ring closure. Relevant observations are that 2-acetoacetyl-4-methylphenol is not cyclised under the above reaction conditions, and that 3-propionyl-2 : 6-dimethylchromone is hydrolysed by strong aqueous potassium hydroxide to give a mixture of volatile ketones in which methyl ethyl ketone has been identified as its 2 : 4-dinitrophenylhydrazone, m. p. 110°.

In these cases hydrolysis experiments are clearly insufficient to establish with certainty the structure of the parent chromone.

Hydrolysis of hydroxylated 3-acylchromones. 7-Hydroxy- and 5 : 7-dihydroxy-chromones and -flavones are very resistant towards alkaline hydrolysis, and this is probably due to the presence of neutralised systems between the hydroxyl groups and the carbonyl group in position 4, so that the latter cannot cause marked cationoid activity at carbon atom 2. This suggestion is supported by the fact that whilst flavone and 2-ethylchromone form 2 : 4-dinitrophenylhydrazones (Adkins and Mozingo, *J. Amer. Chem. Soc.*, 1938, **60**, 669), 7-hydroxyflavone does not react under the same conditions. With such hydroxylated chromones possessing an aliphatic 3-acyl group it therefore seems probable that when boiled with aqueous-alcoholic sodium carbonate, direct loss of the 3-acyl group occurs without opening of the pyrone ring, so that the structure of the chromone may be deduced from the nature of the products of hydrolysis (for examples see Kostanecki and Rozycki, *Ber.*, 1901, **34**, 102; Nagai, *Ber.*, 1892, **25**, 1284; Limaye and Kelkar, *Rasayanam*, 1936, **1**, 24; Gulati, Seth, and Venkataraman, *J.*, 1934, 1765).

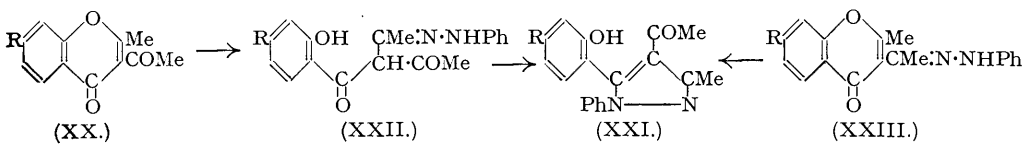
When, however, the 3-acyl substituent is an aroyl group, the hydroxylated derivatives are usually only attacked by alcoholic potassium hydroxide and, under these conditions, it is probable that the pyrone ring opens at least to a certain extent, so that the final product obtained after acidification may not be directly related to the original molecule. Moreover, the intermediate 1 : 3-diketone cannot cyclise under the strongly alkaline conditions of the hydrolysis, and will usually undergo considerable further breakdown to an acid and a monoketone, thus accounting for the low yields of flavones frequently obtained by the Allan–Robinson process. An example of a compound of this type is *7-acetoxy-3-benzoyl-2-methylchromone*, prepared by the acetylation of ω : 4-dibenzoylresacetophenone. When hydrolysed with hydrochloric acid or with aqueous-alcoholic sodium carbonate it yields *7-hydroxy-3-benzoyl-2-methylchromone*; with alcoholic potassium hydroxide it gives in poor yield 7-hydroxy-2-methylchromone and *2 : 4-dihydroxydibenzoylmethane*. The structure assigned to the 3-acylchromone is based on (1) the stability of the 3-acyl group towards sodium carbonate, which suggests a benzoyl, rather than an acetyl group; (2) the production of 7-hydroxy-2-methylchromone, probably by direct hydrolytic fission of the benzoyl group, since if a triacylmethane were first produced by opening of the pyrone ring the acetyl and not the benzoyl group would be lost by hydrolysis, so that if subsequent ring closure occurred the product would be 7-hydroxyflavone; (3) analogy with the structure of 3-benzoyl-2-methylchromone which is prepared by a precisely similar reaction.

Reaction between 3-Acylchromones and Phenylhydrazine.

Tahara (*Ber.*, 1892, **25**, 1292) has described the reaction between phenylhydrazine and 7-methoxy-3-acetyl-2-methylchromone (XX; R = MeO) and the hydrolysis of the compound produced, but his results were interpreted on the basis of an erroneous naphthalene structure for the chromone (the correct formula was established by Kostanecki *et al.*, *Ber.*, 1901, **34**, 102, 2946), and no later investigation has been made. Without evidence, however, the primary product is formulated in the 4th Edition of Beilstein's "Handbuch der organischen Chemie," 1934, **18**, 108, as the simple phenylhydrazone of the carbonyl group in position 4.

Reinvestigation of the reaction between phenylhydrazine and some 3-acylchromones has been made.

3-Acetyl-2-methylchromone (XX; R = H) reacted with phenylhydrazine in alcoholic solution giving not a simple phenylhydrazone but a phenolic isomeride stable to alkalis. The compound is proved to be 4-*acetyl*-1-*phenyl*-5-o-*hydroxyphenyl*-3-*methylpyrazole* (XXI; R = H) as follows. It exhibited normal phenolic properties, and gave a *methyl ether* by treatment with methyl sulphate and alkali. The presence of a *C*-acetyl group was established by a positive iodoform reaction, and by the formation of a 2 : 4-*dinitrophenylhydrazone* and a piperonylidene derivative. After reduction with sodium and alcohol it gave a purple colour with sulphuric acid and ferric chloride (Knorr pyrazoline reaction; *Ber.*, 1893, **26**, 101; 1909, **42**, 4411).



In the formation of the pyrazole, the initial reaction is probably not between the phenylhydrazine and the 4-carbonyl group of the chromone (XX; R = H) which would lead to an isomeride of (XXI; R = H) having the phenyl group attached to the other nitrogen atom, because the 4-carbonyl group of the simple chromones is generally inert towards the usual ketonic reagents (see, for example, Simonis, *Samm. Chem. Vort.*, 1917, **24**, 438), although a few oximes (Wittig and Bangert, *Ber.*, 1925, **58**, 2627, 2636) and 2 : 4-dinitrophenylhydrazones (Adkins and Mozingo, *loc. cit.*) have been prepared, while the more likely condensation of phenylhydrazine with the 3-acetyl group would appear to be excluded by the fact that this phenylhydrazone (preparation described below) is very stable. The most probable first step, therefore, appears to be attack by the phenylhydrazine at carbon atom 2 (cf. the benzylamine reaction) to give a phenylhydrazone (XXII; R = H) of the open chain triacylmethane.

In acetic acid solution 3-acetyl-2-methylchromone (XX; R = H) gave a simple non-phenolic phenylhydrazone which, for the reasons given above, is assumed to be 2-*methyl*-3-(1-*phenylhydrazonoethyl*)*chromone* (XXIII; R = H). By treatment with alcoholic potassium hydroxide, or better, aqueous alcoholic sodium carbonate, this phenylhydrazone underwent an isomeric change giving the same pyrazole (XXI; R = H) as had been previously prepared by the action of phenylhydrazine upon (XX; R = H) in alcoholic solution.

7-Methoxy-3-acetyl-2-methylchromone (XX; R = MeO) did not react smoothly with phenylhydrazine in alcoholic solution, but in acetic acid it gave a product agreeing in its properties with that prepared by Tahara under the same conditions. This compound, for the reasons given above, is regarded as 7-methoxy-2-methyl-3-(1-phenylhydrazonoethyl)chromone (XXIII; R = MeO). Treatment with alcoholic potassium hydroxide gave a product agreeing in most of its properties with the substance similarly prepared by Tahara, but this worker concluded, on the grounds of a nitrogen analysis only, that an acetyl group was lost during the course of the reaction. We now find that, as in the case of the phenylhydrazone (XXIII; R = H), the treatment with potassium hydroxide gives a phenolic isomeride which is now formulated as 4-acetyl-1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole (XXI; R = MeO). The compound was characterised by the preparation of a 2 : 4-*dinitrophenylhydrazone*, an *acetyl* derivative, and a *monomethyl ether*.

The different reactions occurring between phenylhydrazine and 3-acylchromones in alcoholic and acetic acid solution find a parallel in the work of Auwers and Mauss (*Ber.*, 1926, **59**, 611) on the reaction between phenylhydrazine and ethyl benzylideneacetoacetate, which in alcohol gave an addition product at the olefinic bond, but which in acetic acid reacted to give the phenylhydrazone.

A few other pyrazole derivatives have been prepared during the course of this work. Interaction of phenylhydrazine with 2-acetoacetylphenol and with 5-methoxy-2-acetoacetylphenol gave 1-*phenyl*-5-o-*hydroxyphenyl*-3-*methylpyrazole* and 1-*phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazole* respectively. In these cases the location of the phenyl group at position 1 rather than position 2 is assumed by analogy with the structure of the pyrazole prepared by the action of phenylhydrazine upon benzoylacetone which has been proved to be 1 : 5-diphenyl-3-methylpyrazole (see Knorr, *Ber.*, 1887, **20**, 1096; Knorr and Duden, *ibid.*, 1893, **26**, 111; Auwers and Mauss, *loc. cit.*; Drumm, *Proc. Roy. Irish Acad.*, 1931, **40**, 106). Like the 4-acylpyrazoles previously described these pyrazoles give no ferric chloride reaction, but are soluble in dilute sodium hydroxide.

Reaction of phenylhydrazine with 2-hydroxy-4-methoxystyryl methyl ketone in alcohol gave directly what is probably 1-*phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazoline* (cf. direct preparation of similar pyrazolines by Auwers and Voss, *Ber.*, 1909, **42**, 4411) since it give the Knorr pyrazoline test. The location of the phenyl group rests upon the likely assumption that the phenylhydrazine first reacts with the ketonic carbonyl group, rather than the olefinic bond.

7-*Methoxy*-2-*methyl*-4-*thionchromone* was prepared from 7-methoxy-2-methylchromone by the action of phosphorus pentasulphide. It reacted with alcoholic phenylhydrazine in presence of a trace of alkali to give 1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole, identical with that previously prepared from phenylhydrazine and 5-methoxy-2-acetoacetylphenol. This observation is in contrast with those of Simonis and Rosenberg (*Ber.*, 1914, **47**, 1232) who have described the preparation of a number of phenylhydrazones of chromones by the reaction between phenylhydrazine and 4-thionchromones.

Experimental.

3-*Acetyl*-2-*methylchromone* (X).—2-Acetoacetylphenol (XIV) was prepared in 60% yield from *o*-hydroxyacetophenone (50 g.) (Wittig, Bangert, and Richter, *loc. cit.*; cf. preparation of 2-propionoacetyl-4-methylphenol, Baker, *loc. cit.*) and obtained as colourless needles from light petroleum (b. p. 60—80°), m. p. 101° (lit. m. p. 90·5—91·5°) (Found: C, 67·2; H, 5·4. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·6%); this compound was then converted into 3-acetyl-2-methylchromone, m. p. 89°, by treatment with acetic anhydride and anhydrous sodium acetate. The 2 : 4-*dinitrophenylhydrazone* of 3-acetyl-2-methylchromone, prepared by the use of Brady's reagent (*J.*, 1931, 757), separated from acetic acid as orange-yellow needles, m. p. 252° (Found: C, 57·3; H, 3·9. $C_{18}H_{14}O_6N_4$ requires C, 56·6; H, 3·7%).

2-β-*Benzylaminocrotonylphenol* (XI).—(a) *From* 2-*acetoacetylphenol*. To the diketone (0·5 g.) in alcohol (10 c.c.) was added benzylamine (0·3 g.), and after 1 hour the yellow solution when disturbed began to deposit crystals. After 24 hours the yellow-green needles (0·45 g.) of 2-β-*benzylaminocrotonylphenol* (XI) were collected; these had m. p. 124° both before and after crystallisation from alcohol (Found: C, 76·4; H, 6·4; N, 5·2. $C_{17}H_{17}O_2N$ requires C, 75·9; H, 6·3; N, 5·4%). The compound is insoluble in aqueous sodium hydroxide, gives an intense greenish-brown coloration with alcoholic ferric chloride, and shows a vivid yellow-green fluorescence in ultra-violet light. The compound is sparingly soluble in alcohol but readily soluble in benzene, and is dimorphous. It separates from light petroleum (b. p. 60—80°) or usually from alcohol in the form of long needles, but may also separate, sometines simultaneously, in the form of thick, almost rectangular tablets, both forms appearing to melt at the same temperature. The tablet form is frequently obtained by slow crystallisation from alcohol.

(b) *From* 3-*acetyl*-2-*methylchromone* (X). Benzylamine (2·2 g., 2 mols.) was added to the chromone (2 g., 1 mol.) dissolved in benzene (10 c.c.), and the bright yellow solution was left at room temperature for 24 hours and the solvent then removed under diminished pressure on the water-bath. The yellow, crystalline solid was crushed, shaken for 10 minutes with warm water (30 c.c.), filtered, washed with warm water and dried, giving 2-β-benzylaminocrotonylphenol (XI) as a bright yellow powder (2·5 g.; theory requires 2·7 g.), m. p. 122—123°. Crystallisation from ethyl alcohol readily gave the pure compound, m. p. 124° (2·4 g.). The aqueous filtrate and washings were evaporated to dryness giving directly acetobenzylamide (1·5 g.; theory requires 1·5 g.), m. p. 53—55°; recrystallisation from carbon tetrachloride–light petroleum (b. p. 60—80°) gave the pure compound, m. p. and mixed m. p. with an authentic specimen 62°.

When a similar reaction was carried out in alcohol (40 c.c.) the yellow solution began to deposit crystals of (XI) after 3 hours; these could be collected in the pure state, but the yield was somewhat less than that obtained in benzene solution.

(c) *From* 2-*methylchromone*. A mixture of the chromone (0·5 g.) and benzylamine (0·35 g.) in alcohol (5 c.c.) reacted slowly at room temperature depositing crystals after 2 days. The golden-yellow plates (0·6 g.) of (XI) which had separated after 9 days had m. p. and mixed m. p. 124°. Recrystallisation from alcohol under normal conditions gave the usual needle form, reconverted into the plate form by very slow crystallisation. The same reaction mixture when heated under reflux for 3 hours and then cooled gave (XI) (0·35 g.).

(d) *From* 3-*benzoyl*-2-*methylchromone* (XVI; R = H) *o*-Hydroxydibenzoylmethane, prepared by molecular rearrangement of *o*-benzoyloxyacetophenone (Baker, *loc. cit.*) was converted into 3-benzoyl-2-methylchromone (Müller, *loc. cit.*). The chromone (0·2 g.), alcohol (3 c.c.), and benzylamine (0·2 g.) were heated under reflux for 3 hours, yielding yellow-green needles of 2-β-benzylaminocrotonylphenol, m. p. and mixed m. p. 123—124°. Evaporation of the mother-liquors and crystallisation of the residue from light petroleum (b. p. 60—80°) gave benzobenzylamide, m. p. and mixed m. p. with a genuine specimen (Dermer and King, *J. Org. Chem.*, 1943, **8**, 169) 106—107°.

7-*Methoxy*-2-*methylchromone and* 7-*Methoxy*-3-*acetyl*-2-*methylchromone*.—Paeonol (2-hydroxy-4-methoxyacetophenone) was converted into 5-methoxy-2-acetoacetylphenol (cf. previous preparation) which formed fine needles, m. p. 71—72° from benzene–light petroleum (b. p. 40—60°; 2 : 1) (Nagai, *loc. cit.*, gives m. p. 68°) (Found: C, 63·4; H, 5·8. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·8%), and thence by solution in hot 10% hydrochloric acid into 7-methoxy-2-methylchromone, m. p. 115° (Found: C, 69·6; H, 5·4. Calc. for $C_{11}H_{10}O_3$: C, 69·5; H, 5·3%). Treatment of the diketone with acetic anhydride and anhydrous sodium acetate at 160—180° for 3 minutes gave 7-methoxy-3-acetyl-2-methylchromone as colourless needles, m. p. 162° (from alcohol), which became yellow on exposure to light (Found: C, 67·4; H, 5·3. Calc. for $C_{13}H_{12}O_4$: C, 67·2; H, 5·2%); the 2 : 4-*dinitrophenylhydrazone* separated from glacial acetic acid as orange plates, m. p. 262° (decomp.) (Found: C, 56·0; H, 3·4. $C_{19}H_{16}O_7N_4$ requires C, 55·3; H, 3·9%).

5-*Methoxy*-2-β-*benzylaminocrotonylphenol*.—7-Methoxy-3-acetyl-2-methylchromone (1 g.), anhydrous

alcohol (20 c.c.), and benzylamine (0·9 g.) were heated under reflux for 7 hours, and after cooling the crystalline material (1·1 g.) was collected and recrystallised from ethyl alcohol. The 5-*methoxy*-2-β-*benzylaminocrotonylphenol* formed very pale yellow-green needles, m. p. 136° (Found : C, 72·4; H, 6·5; N, 5·0. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%). The crystals become yellow on prolonged exposure to light, show a blue-green fluorescence in ultra-violet light, and give an intense dull olive-green coloration with alcoholic ferric chloride. The mother-liquors from the reaction mixture yielded acetobenzylamide as needles from light petroleum (b. p. 60—80°), m. p. and mixed m. p. 62—63°.

2-β-*Benzylaminocrotonyl*-4-*methylphenol* (XVII; R = Me).—(a) *From* 2-*acetoacetyl*-4-*methylphenol*. 2-Acetoacetyl-4-methylphenol (1 g.), alcohol (10 c.c.), and benzylamine (0·5 g.) were heated under reflux for 7 hours, giving 2-β-*benzylaminocrotonyl*-4-*methylphenol* (0·75 g.) as yellow-green, diamond-shaped plates from alcohol, m. p. 123° (Found : C, 77·0; H, 6·6; N, 5·0. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8; N, 5·0%). The substance shows a bright yellow-green fluorescence in ultra-violet light, and gives a dark olive-green coloration with alcoholic ferric chloride.

(b) *From* 3-*benzoyl*-2 : 6-*dimethylchromone*. The chromone (0·28 g.), alcohol (4 c.c.), and benzylamine (0·21 g.) were heated under reflux for 1 hour, and from the resulting solution was isolated 2-β-benzylaminocrotonyl-4-methylphenol (0·075 g.), m. p. 122—123°.

(c) *From* 3-*propionyl*-2 : 6-*dimethylchromone*. The chromone (0·2 g.), alcohol (5 c.c.), and benzylamine (0·2 g.) were heated under reflux for 3 hours and yielded the characteristic plates of 2-β-benzylaminocrotonyl-4-methylphenol, m. p. and mixed m. p. 122—123°.

2-β-*Methylaminocrotonylphenol*.—To a solution of 2-acetoacetylphenol (0·5 g.) in alcohol (5 c.c.) was added a 30% solution of methylamine (0·3 c.c.), and the crystals (0·13 g.) which began to separate after 24 hours were collected after 3 days, and crystallised from light petroleum (b. p. 60—80°). 2-β-*Methylaminocrotonylphenol* formed yellow-green, thick needles, m. p. 101° (Found : C, 68·7; H, 6·9; N, 7·9. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). It exhibits a bright green fluorescence in ultra-violet light.

Hydrolysis of 3-*Benzoyl*-2-*methylchromone* (XVI; R = H).—The chromone (0·1 g.) in alcohol (5 c.c.) was heated under reflux for ½ hour with 2N-sodium carbonate (5 c.c.), water added, kept at 0°, and the crystalline product (0·03 g.) collected. After crystallisation from light petroleum (b. p. 60—80°) it formed needles, m. p. and mixed m. p. with an authentic specimen of flavone 98°.

Ring Closure of o-*Hydroxydibenzoylmethane*.—(*a*) The diketone (0·1 g.) in alcohol (5 c.c.) was heated under reflux for ½ hour with 2N-sodium carbonate (5 c.c.), diluted, and kept at 0°. The colourless needles (0·04 g.) after crystallisation from light petroleum (b. p. 60—80°) melted at 97·5°, either alone or when mixed with flavone. (*b*) A similar experiment using water in place of the 2N-sodium carbonate, and heating the solution under reflux for 18 hours, gave unchanged diketone (0·03 g.) and flavone (0·05 g.).

7-*Acetoxy*-3-*benzoyl*-2-*methylchromone*.—ω : 4-Dibenzoylresacetophenone (Baker, *loc. cit.*) (5 g.), acetic anhydride (5 c.c.), and anhydrous sodium acetate (5 g.) were heated under reflux for ½ hour, poured into water, and extracted with ether, the ethereal solution was washed with excess of 2N-sodium carbonate, and dried, and the solvent evaporated. The residue was crystallised from light petroleum (b. p. 80—100°) giving colourless needles (1·7 g.) of 7-*acetoxy*-3-*benzoyl*-2-*methylchromone*, m. p. 132° (Found : C, 70·4; H, 4·4. $C_{19}H_{14}O_5$ requires C, 70·8; H, 4·4%). The 2 : 4-*dinitrophenylhydrazone* separated from aqueous dioxan as orange needles, m. p. 295—197° (decomp.) (Found : C, 60·0; H, 3·7. $C_{25}H_{18}O_8N_4$ requires C, 59·8; H, 3·6%).

Hydrolysis of 7-*Acetoxy*-3-*benzoyl*-2-*methylchromone*.—(*a*) Heating with concentrated hydrochloric acid for 5 minutes, or with aqueous-alcoholic sodium carbonate for ½ hour, gave 7-*hydroxy*-3-*benzoyl*-2-*methylchromone* as needles, m. p. 243°, from alcohol (Found : C, 72·9; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%). (*b*) Hydrolysis of the chromone (0·5 g.) in alcohol (20 c.c.) with potassium hydroxide (0·5 g.) in water (0·5 c.c.) for 20 minutes, dilution, and saturation with carbon dioxide gave a yellow solid which was extracted with light petroleum (b. p. 60—80°) in a Soxhlet apparatus for 6 hours, yielding 2 : 4-*dihydroxydibenzoylmethane* (0·06 g.) as pale yellow needles, m. p. 162°, from benzene (Found : C, 70·3; H, 4·6. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%). The petroleum-insoluble material was crystallised several times from dilute alcohol (charcoal) and proved to be 7-hydroxy-2-methylchromone, m. p. 249°. (*c*) Air was aspirated through solutions of the chromone (0·1 g.) in 20% aqueous potassium hydroxide at 100° and 2 : 4-dinitrophenylhydrazine in hydrochloric acid and the orange 2 : 4-dinitrophenylhydrazone of acetone (0·003 g.), m. p. 123°, was obtained during 2½ hours.

2 : 4-*Dinitrophenylhydrazones*.—3-*Propionyl*-2 : 6-*dimethylchromone* 2 : 4-*dinitrophenylhydrazone* separated from ethyl alcohol in yellow needles, m. p. 215° (decomp.) (Found : C, 58·0; H, 4·3. $C_{20}H_{18}O_6N_4$ requires C, 58·5; H, 4·4%). The 2 : 4-*dinitrophenylhydrazone* of 7-acetoxy-3-acetyl-2-methylchromone (Kostanecki and Rozycki, *Ber.*, 1901, **34**, 102) crystallised from alcohol–ethyl acetate (2 : 1) in pale yellow needles, m. p. 172° (Found : C, 54·4; H, 3·8. $C_{20}H_{16}O_8N_4$ requires C, 54·5; H, 3·6%).

Action of Phenylhydrazine on 3-*Acetyl*-2-*methylchromone in Alcohol*.—To 3-acetyl-2-methylchromone (XX; R = H) (10 g.), dissolved in warm alcohol (50 c.c.), was added phenylhydrazine (5 g.) and after 15 minutes the mixture was allowed to cool. The crystalline precipitate (7 g.) was collected, washed, and crystallised from pyridine–alcohol (1 : 4), giving 4-*acetyl*-1-*phenyl*-5-o-*hydroxyphenyl*-3-*methylpyrazole* (XXI; R = H) as colourless, compact bi-pyramids, m. p. 237° (decomp.) (Found : C, 74·1; H, 5·6; N, 9·6. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). It gives no ferric chloride reaction, but is soluble in cold sodium hydroxide solution, from which it may be recovered even after boiling for several hours. By treatment with 2N-sodium hydroxide and iodine–potassium iodide solution at 60° it gave iodoform, m. p. 119°; with piperonal (1 mol.) in aqueous-alcoholic sodium hydroxide it gave a piperonylidene derivative, m. p. 186—187°, and, after reduction with sodium and alcohol, it showed the Knorr pyrazoline reaction. The 2 : 4-*dinitrophenylhydrazone* formed dark red needles from acetic acid, m. p. 225° (Found : C, 61·5; H, 4·2; N, 18·3. $C_{24}H_{20}O_5N_6$ requires C, 61·0; H, 4·2; N, 17·8%). By shaking the pyrazole (1 g.) for 2 hours at room temperature with sodium hydroxide (3 g.) in water (10 c.c.) and methyl sulphate (0·75 g.) the *methyl ether* (0·3 g.) separated; by crystallisation from alcohol this formed thick needles, m. p. 133° (Found : C, 74·2; H, 5·9; N, 9·4. $C_{19}H_{18}O_2N_2$ requires C, 74·5; H, 5·9; N, 9·2%).

Action of Phenylhydrazine on 3-Acetyl-2-methylchromone in Acetic Acid.—Phenylhydrazine (5 g.) was added to 3-acetyl-2-methylchromone (XX; R = H) (10 g.) in glacial acetic acid (30 c.c.). The crystals 2·5 g.) which separated were collected after 24 hours and crystallised from acetic acid (charcoal) and then from dioxan, being obtained as rhombic tablets, m. p. 194—195° (Found: C, 74·0; H, 5·6; N, 9·4. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). *2-Methyl-3-(1-phenylhydrazonoethyl)chromone* (XXIII; R = H) shows no phenolic properties.

Treatment of 2-Methyl-3-(1-phenylhydrazonoethyl)chromone with Alkali.—The phenylhydrazone (XXIII; R = H) (1·5 g.) was heated under reflux with (*a*) alcohol (60 c.c.) and 2N-sodium carbonate (60 c.c.) for 6 hours, or (*b*) alcohol (15 c.c.) and potassium hydroxide (1·5 g.) in water (15 c.c.) for 1 hour, the solutions then evaporated, water added, and, in the second case, acidified. The precipitates (*ca.* 1·1 g.) were crystallised several times from alcohol (charcoal) giving the pyrazole (XXI; R = H), m. p. 243° (decomp.) (Found: C, 73·5; H, 5·6; N, 9·4. Calc. for $C_{18}H_{16}O_2N_2$: C, 74·0; H, 5·5; N, 9·6%). Complete identity with the previous specimen, which, owing to decomposition, is not satisfactorily established by mixed melting-point, was proved by mixed melting-point determinations of the related 2 : 4-dinitrophenylhydrazones and the methyl ethers.

Action of Phenylhydrazine on 7-Methoxy-3-acetyl-2-methylchromone.—Phenylhydrazine (1·5 g.) was added to a solution of 7-methoxy-3-acetyl-2-methylchromone (XX; R = MeO) (2·4 g.) in glacial acetic acid (50 c.c.) with cooling. Crystals soon separated and were later collected (1·7 g.) and recrystallised from acetic acid, giving colourless, prismatic needles of 7-methoxy-2-methyl-3-(1-phenylhydrazonoethyl)-chromone (XXIII; R = MeO), m. p. 210° (lit. 213°) (Found: C, 70·5; H, 5·7; N, 8·6. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·8; H, 5·6; N, 8·7%), showing no phenolic properties.

4-Acetyl-1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole (XXI; R = MeO).—The phenylhydrazone (XXIII; R = MeO) (1 g.) in alcohol (20 c.c.) was heated under reflux with potassium hydroxide (1 g.) in water (5 c.c.) for 2 hours. The solution was concentrated, water was added, and the solution acidified, precipitating a solid (0·9 g.) which was crystallised from dilute alcohol (charcoal) and then from chloroform–light petroleum (b. p. 60—80°), giving *4-acetyl-1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole* (XXI; R = MeO) as fine colourless needles, m. p. 206° (decomp.) (Found: C, 70·8; H, 5·6; N, 9·2. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%). This pyrazole gives no ferric chloride reaction when pure, but the crude material gave a red colour as described by Tahara. It is soluble in cold aqueous sodium hydroxide, and after reduction with sodium and alcohol gives the Knorr reaction for pyrazolines. The 2 : 4-*dinitrophenylhydrazone* forms fine, orange needles, m. p. 183°, from benzene (Found: C, 59·5; H, 3·8; N, 16·7. $C_{25}H_{22}O_6N_6$ requires C, 59·8; H, 4·4; N, 16·7%). The *acetyl* derivative (acetic anhydride and pyridine for 1½ hours at 100°, followed by addition of water) separated from alcohol in rectangular plates, m. p. 194° (Found: C, 68·6; H, 5·5; N, 7·6. $C_{21}H_{20}O_4N_2$ requires C, 69·2; H, 5·5; N, 7·7%). The methyl ether, prepared as in the case of the pyrazole (XXI; R = H), separated from dilute alcohol in colourless, prismatic needles, m. p. 150° (lit. 150°) (Found: C, 70·8; H, 5·7; N, 9·0. Calc. for $C_{20}H_{20}O_3N_2$: C, 71·4; H, 5·9; N, 8·3%).

1-Phenyl-5-o-hydroxyphenyl-3-methylpyrazole.—Phenylhydrazine (1 g.), 2-acetoacetylphenol (1·5 g.), and alcohol (20 c.c.) were heated under reflux for 1 hour, most of the alcohol was distilled off, and water added. The precipitated material crystallised from dilute alcohol in colourless needles, m. p. 190—191° (Found: C, 76·8; H, 6·0; N, 10·1. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%). *1-Phenyl-5-o-hydroxyphenyl-3-methylpyrazole* is soluble in dilute sodium hydroxide but gives no coloration with alcoholic ferric chloride.

1-Phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole.—This was prepared from 5-methoxy-2-acetoacetylphenol (1 g.) as in the previous case. The *1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole* (1·9 g.) crystallised from the cooled reaction mixture and separated from alcohol in opaque prisms, m. p. 155° (Found, in material dried at 110° in a vacuum over phosphoric anhydride: C, 72·2; H, 5·7; N, 10·5. $C_{17}H_{16}O_2N_2$ requires C, 72·9; H, 5·7; N, 10·0%). Its properties were similar to those of the previous pyrazole.

1-Phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazoline.—A mixture of 2-hydroxy-4-methoxystyryl methyl ketone (2 g.; McGookin and Sinclair, *J.*, 1926, 1580), alcohol (30 c.c.), water (50 c.c.), and phenylhydrazine (1 g.) was boiled and allowed to cool slowly. The oily product was washed and crystallised from methyl alcohol and then from dilute methyl alcohol (charcoal), giving *1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazoline* as square plates, m. p. 149° (Found: C, 72·1; H, 6·4. $C_{17}H_{18}O_2N_2$ requires C, 72·3; H, 6·4%). It is soluble in dilute sodium hydroxide and gives a deep red ferric chloride reaction which rapidly changes to yellow-green. Its colourless solution in concentrated sulphuric acid becomes deep purple on addition of ferric chloride.

7-Methoxy-2-methyl-4-thionchromone.—7-Methoxy-2-methylchromone (9 g.) and phosphorus pentasulphide (9 g.) were heated at 120—130° for ½ hour, and the product was repeatedly extracted with boiling benzene (8 times with 100 c.c.), and the extracts united, treated with charcoal, filtered, and distilled. The residue (2 g.) separated from alcohol in pale orange-red needles, m. p. 146° (Found: C, 63·7; H, 4·5; S, 15·7. $C_{11}H_{10}O_2S$ requires C, 64·1; H, 4·9; S, 15·5%). This *7-methoxy-2-methyl-4-thionchromone* (0·2 g.) was heated under reflux in alcohol (8 c.c.) with phenylhydrazine (0·15 g.) and 2N-sodium hydroxide (2 drops) for 1½ hours, cooled, and a few drops of concentrated hydrochloric acid added. The crystals which separated at 0° were collected, washed with water, and the crystalline residue (0·01 g.) was recrystallised from alcohol, giving crystals which became opaque on drying, and had m. p. and mixed m. p. with a specimen of 1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole 152—153°.

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