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ANTHOCYANIDINS AND RELATED COMPOUNDS—XVII

REACTIONS OF FLAVYLIUM SALTS AND 2-HYDROXYCHALCONES WITH HYDROXYLAMINE AND HYDRAZINE

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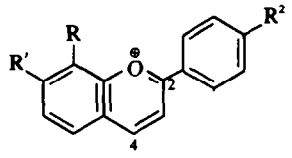
Abstract—Flavylium salts and 2-hydroxychalcones (1-phenyl-3-(2-hydroxyphenyl)-2-propen-1-ones) react with hydroxylamine in pyridine to form 2,5-dihydroisoxazoles. These undergo thermal and acid-catalyzed rearrangements to isomeric 4,5-dihydroisoxazoles and chalcone oximes, respectively. With hydrazine, flavylium salts yield phenolic 4,5-dihydro-3,5-diphenyl-1H-pyrazoles. Since these readily condense with acetone to form cyclic acetonides, the hydrazination reaction involves initial nucleophilic attack at position 2 of the flavylium nucleus.

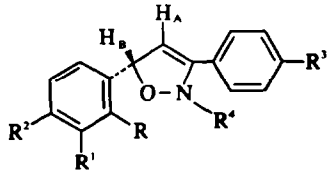
The reactions of 2,4,6-trisubstituted pyrylium salts with hydroxylamine and hydrazine have recently been well documented.[1,2] However, the condensation reactions of flavylium salts and related 4-phenyl-benzopyrylium compounds with these reagents have not been investigated since an early report[3] that, with the exception of 8,4'-dimethoxyflavylium chloride **1a** and 7-hydroxy-4-phenylflavylium chloride, they yield amorphous or resinous products of uncertain constitution. As a result of this ambiguity, "carbonyl" reagents have rarely been used in the characterization and structural elucidation of natural anhydro bases derived from flavylium salts.

In this early work[3] it was observed that **1a** reacts with hydroxylamine in pyridine to give a *colorless*, crystalline compound (m.p. 148°), which was assumed to be a chalcone oxime, while 7-hydroxy-4-phenylflavylium chloride gave a crystalline product of an unknown but different structural type, containing about twice the nitrogen content expected from an equimolecular reaction. Since chalcone oximes should be yellow, the identities of crystalline oximation and hydrazination products formed from **1a** and a variety of related flavylium salts and phenolic chalcones have now been re-examined.

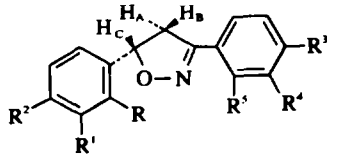
When **1a** was warmed briefly with hydroxylamine in pyridine, it gave good yields of a colorless (λ_{max} 290 nm) crystalline product (m.p. 174°), now assigned the 2,5-dihydroisoxazole structure **2a**. In accord with this structure, the product forms diacetyl and dimethyl derivatives and gives an immediate intense blue color with Gibbs reagent.[4] When heated briefly above its m.p., it rearranges to a lower melting, colorless isomer **3a** (m.p. 148°, λ_{max} 278 nm), apparently identical with the product earlier obtained by prolonged heating of **1a** with hydroxylamine in pyridine. This lower melting isomer forms only a monoacetyl derivative. In agreement with the 4,5-dihydroisoxazole structure, **3b**, the NMR spectrum of the acatate closely coincides with that of 4,5-dihydro-3,5-diphenyl-isoxazole,[5] i.e. the H_A, H_B and H_C protons of the dihydroisoxazole ring appear as well-defined double doublets at δ3·22, 3·65 and 5·73, respectively, with J_{AB} = 17·0 Hz, J_{AC} = 8·0 Hz, J_{BC} = 11·0 Hz.



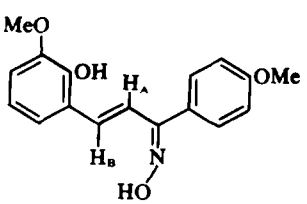
1a: R = R^2 = OMe; R^1 = H
b: R = Me; R^1 = OH; R^2 = H
c: R = Me; R^1 = OH; R^2 = OMe
d: R^2 = OMe; R = R^1 = H
e: R^1 = R^2 = OMe; R = H



2a: R = OH; R^1 = R^3 = OMe; R^2 = R^4 = H
b: R = OCOMe; R^1 = R^3 = OMe; R^4 = COMe; R^2 = H
c: R = R^1 = R^3 = OMe; R^4 = Me; R^2 = H
d: R = R^2 = OCOMe; R^1 = Me; R^4 = COMe; R^3 = H
e: R = R^2 = OCOMe; R^1 = Me; R^3 = OMe; R^4 = COMe



3a: R = OH; R^1 = R^3 = OMe; R^2 = R^4 = R^5 = H
b: R = OCOMe; R^1 = R^3 = OMe; R^2 = R^4 = R^5 = H
c: R^2 = R^4 = OMe; R^5 = OH; R = R^1 = R^3 = H



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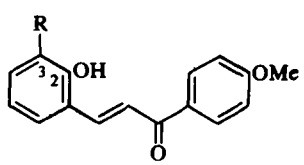
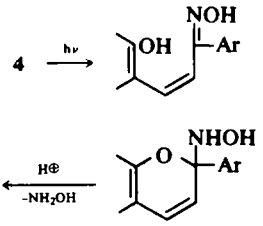


5a: R = OMe
b: R = H

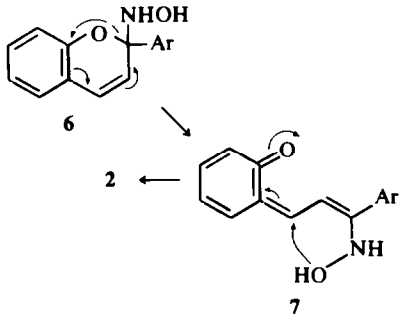
In acid solutions the oximation product **2a** rearranges to a third, brightly yellow, crystalline isomer, m.p. 160°. The UV spectrum of this isomer (λ_{max} 330 nm) is closely similar to that of *trans*-2-hydroxy-3,4'-dimethoxychalcone **5a**, while the NMR spectrum of its monoacetyl derivative shows doublets (J = 18·0 Hz) at δ6·32 and δ7·68 (*trans* ethylenic protons) and a 1H singlet at δ8·05 (=NOH). Since the yellow isomer rapidly recyclizes to the colorless **2a** in the presence of pyridine, these data establish that it is a chalcone oxime with the probable configuration indicated in **4**. It is noteworthy that, although the chalcone oxime **4** is stable in dilute alcoholic acid solutions in the dark, in sunlight it rapidly loses hydroxylamine and recyclizes to the flavylium salt **1a**.

This photochemical reaction presumably involves initial photoisomerization of **4** to the *cis* chalcone oxime, cyclization, and subsequent acid-catalyzed elimination of hydroxylamine. This sequence is similar to that previously noted[6] in the photochemical cyclization of the parent *trans* chalcone:

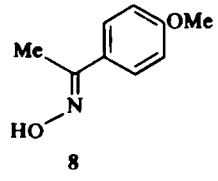


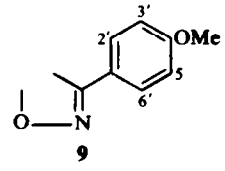
The NMR spectra of the oximation product **2a** and its diacetyl derivative are complicated by the multiplicity of overlapping signals from aromatic protons, although the diacetyl derivative does show doublets (J = 16·0 Hz) at δ6·88 and δ7·46, which would be expected for the H_B and H_A protons, respectively, in structure **2b**. Unequivocal spectral evidence for the 2,5-dihydroisoxazole ring structure was provided, however, by crystalline oximation products formed from flavylium salts more suitably substituted in the aromatic rings, viz. **1b** and **1c**. The product (an oil) from **1b** gave a crystalline triacetyl derivative whose NMR spectrum was in unambiguous accord with the 2,5-dihydroisoxazole structure **2d**, i.e. the three acetyl and the Me groups appeared as 3H singlets at δ1·96, 2·13, 2·30, 2·32, the H_A and H_B protons of the dihydroisoxazole ring as doublets (J = 16·0 Hz) at δ7·50 and δ6·74, respectively, the H_5 and H_6 aromatic protons as ortho-coupled doublets (J = 8·0 Hz) at δ7·02 and δ7·58, and the phenyl ring protons as a multiplet at δ7·47.

Crystalline 2-hydroxy-3,4'-dimethoxychalcone **5a** reacts with hydroxylamine and pyridine under the same conditions as **1a** to give high yields of the identical dihydroisoxazole **2a**. It is possible, therefore, that the formation of 2,5-dihydroisoxazoles from flavylium salts may involve initial hydrolysis of the salt[7] by traces of water to the 2-hydroxychalcone, formation of the chalcone oxime, and ring closure to the dihydroisoxazole. This route, however, is improbable in view of our observation that 3-methylflavylium salts (3-methyl-4'-hydroxyflavylium chloride and 3-methyl-4',8-dimethoxyflavylium perchlorate), which are known *not* to form 2-hydroxychalcones on hydrolysis,† readily yield crystalline 2,5-dihydroisoxazoles with hydroxylamine in pyridine. Thus, 2,5-dihydroisoxazole formation probably involves direct nucleophilic attack by hydroxylamine on the pyrylium ring leading to intermediates of types **6** and **7**:



It should be noted that flavylium salts may undergo nucleophilic attack at *either* position 2 (as in hydrolysis[7] reactions) or position 4 (as in reduction reactions[8,9] or in condensations with polyphenols[8] and active methylene compounds[10,11]). In the present work it has been established that hydroxylamine (and hydrazine) attack occurs at position 2. Thus, reaction at position 2 of **1a** should give, as previously indicated, the 2,5-dihydroisoxazole **2a** and, after rearrangement, the 4,5-dihydroisoxazole **3a**. If attack occurred at position 4, however, the 4,5-dihydroisoxazole formed by subsequent rearrangement would be the isomer **3c**. That the 4,5-dihydroisoxazole is **3a**, and not the possible isomer **3c**, is indicated by comparison of the chemical shifts of the 2'(6') and 3'(5') protons of the *p*-methoxyphenyl ring of the 4,5-dihydroisoxazole with the corresponding aromatic protons of the model *p*-methoxyacetophenone oxime **8**. In **8** these protons appear as 2H doublets (J = 9·0 Hz) at δ7·58 and δ6·87, respectively. In the 4,5-dihydroisoxazole the 2'(6') and 3'(5') protons show virtually identical chemical shifts, viz. δ7·60 and δ6·88 (2H doublets, J = 9·0 Hz), and thus confirm the presence of the partial structure **9**.

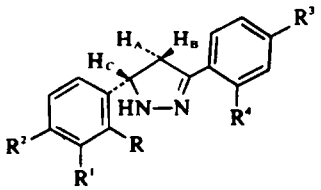




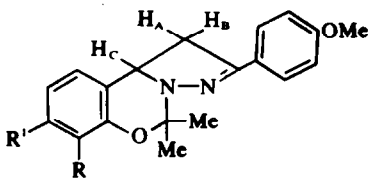
In contrast to 2,5-dihydroisoxazole formation with hydroxylamine, hydrazine reacts with the flavylium salts **1a**, **1d** and **1e** or their corresponding 2-hydroxy-chalcones to give crystalline 4,5-hydro-1H-pyrazoles **10a**, **b**, **c**, respectively. Although these products form oily diacetyl derivatives, they readily yield crystalline mono N-acetyl compounds on brief treatment with acetic anhydride and pyridine. The NMR spectra of the hydrazination products and their N-acetyl derivatives establish unequivocally the 4,5-dihydro-1H-pyrazole ring structures, e.g. for **10b** the H_A, H_B and H_C protons appear as double doublets at δ3·06, δ3·39 and 4·88, respectively, with J_{AB} = 17·0 Hz, J_{AC} = 14·0 Hz and J_{BC} = 10·0 Hz.

The phenolic 1H-pyrazole derivatives **10a**, **b** and **c**

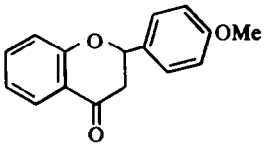
†Hydrolysis of 3-methylflavylium salts yields colorless carbinol bases *without* fission of the heterocyclic ring. The oximation products of these flavylium salts, unlike **1a** which gives the chalcone oxime **4**, rapidly yield the original flavylium salt on treatment with acids.



10a: R = OH; R¹ = R³ = OMe; R² = R⁴ = H
b: R = OH; R³ = OMe; R¹ = R² = R⁴ = H
c: R = OH; R² = R³ = OMe; R¹ = R⁴ = H
d: R⁴ = OH; R² = OMe; R = R¹ = R³ = H
e: R⁴ = OH; R² = R³ = OMe; R = R¹ = H



11a: R = OMe; R¹ = H
b: R = R¹ = H
c: R¹ = OMe; R = H



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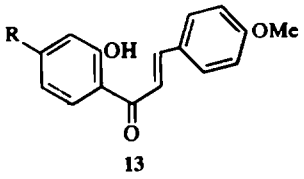

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condense with acetone with remarkable ease. On warming their solutions in this solvent, they yield quantitatively the colorless, crystalline acetonides **11a, b** and **c**, respectively. In accord with these structural assignments, the acetone condensation products do not give immediate blue colors with Gibbs reagent and they do not react with acetic anhydride (absence of free OH and NH groups). Their NMR spectra, e.g. of **11b**, show the presence of the gem-dimethyl groups as 3H singlets at δ1·58 and δ1·99, and the H_A, H_B and H_C protons as double doublets at δ3·20, δ3·46 and δ5·08, respectively; J_{AB} = 16·0 Hz, J_{AC} = 2·0 Hz, J_{BC} = 8·0 Hz.

The facile reaction of phenolic 4,5-dihydro-1H-pyrazoles of type **10a, b** and **c** with acetone is clearly due to the favorable location of the phenolic OH relative to the NH group of the heterocyclic ring. The formation of these acetone derivatives provides good chemical evidence that, as in the case of oximation, initial attack of hydrazine occurs at position 2 of the flavylium nucleus. As expected, isomeric phenolic 4,5-dihydro-1H-pyrazoles of type **10d** and **10e**, which are formed by hydrazination of 4'-methoxyflavanone **12** or 2'-hydroxychalcones of type **13**, do not react with acetone under these conditions.

EXPERIMENTAL

3 - (4 - Methoxyphenyl) - 5 - (2 - hydroxy - 3 - methoxyphenyl) - 2,5-dihydroisoxazole (**2a**)

(a) A soln of **1a**;[6] (2·0 g) and hydroxylamine hydrochloride (1 g) in pyridine (15·0 ml) was heated on a steam bath for 2 hr. The oily product, obtained on adding excess of water, crystallized from MeOH to yield **2a** as colorless needles, m.p. 173–174° (0·90 g). (Found: C, 68·2; H, 5·68. Calc. for $C_{17}H_{17}O_4N$: C, 68·2; H, 5·73). With ethanolic ferric chloride, it gave an intense red-brown color; λ_{max}^{EtOH} 290 (4·50), 236 (4·00), 225 (4·06) nm (log ϵ).

2a was acetylated by heating it for 5 min with Ac_2O containing two drops of pyridine. The *diacetyl derivative* **2b** separated from MeOH as colorless prisms, m.p. 127–128°. (Found: C, 65·9; H, 5·43. Calc. for $C_{21}H_{21}O_6N$: C, 65·8; H, 5·52), λ_{max}^{EtOH} 295, 240 nm.

The oximation product **2a** (0·20 g) was heated under reflux with Me_2SO_4 (1·0 ml), K_2CO_3 (3·0 g) and acetone (10·0 ml) for 1·5 hr. The mixture was concentrated and diluted with water. The oily product crystallized from MeOH to give the *dimethyl* derivative **2c** (0·12 g; m.p. 122°). (Found: C, 69·7; H, 6·39; N, 4·15. Calc. for $C_{19}H_{21}O_4N$: C, 69·7; H, 6·47; N, 4·28), 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ3·71; 6H, s, δ3·83; 3H, s, δ4·02; 9H, m, δ6·80–δ7·62.

(b) Compound **6a** (10·0 g), heated with hydroxylamine hydrochloride (5·0 g) and pyridine (60 ml) as described above, gave **4a**, m.p. and m.m.p. 173–4° (8·2 g). This product formed a diacetyl derivative, m.p. and m.m.p. with the above diacetyl compound, 127–8°.

3 - (4 - Methoxyphenyl) - 5 - (2 - hydroxy - 3 - methoxyphenyl) - 4,5 - dihydroizoxazole **3a**.

2a (1·0 g) was heated in an open tube to 190°, cooled and the oily product crystallized from MeOH, **3a** separated as colorless plates, m.p. 148° (0·60 g). (Found: C, 68·3; H, 5·67. Calc. for $C_{17}H_{17}O_4N$: C, 68·2; H, 5·73), λ_{max} 278 (4·11) nm (log ϵ). **3a** gives an intense blue color with Gibbs reagent, 100 MHz NMR spectrum in $CDCl_3$: 1H, dd, δ3·25, J = 17·0, 8·0 Hz; 1H, dd, δ3·77, J = 17·0, 11·0 Hz; 3H, s, δ3·81; 3H, s, δ3·87; 1H (OH), s, δ5·88; 1H, dd, δ5·94, J = 11·0, 8·0 Hz; 7H, m, δ6·78–δ7·65.

Warmed with Ac_2O and pyridine **3a** formed a monoacetate. Crystallized from MeOH, the *acetate* **3b** separated as colorless needles, m.p. 108°. (Found: C, 66·8; H, 5·56; N, 4·07. Calc. for $C_{19}H_{19}O_5N$: C, 66·8; H, 5·61; N, 4·10%).

2-Hydroxy-3,4'-dimethoxychalcone oxime **4**

A soln of **2a** (1·0 g) in EtOH (8·0 ml) containing conc HCl (0·5 ml) was heated to boiling and slowly diluted with 10% HClaq (20·0 ml). On cooling *in the dark*, the chalcone oxime **4** crystallized as yellow needles, m.p. 160° (0·86 g) $\lambda_{max}^{EtOH-0.5\%}$ 330 (4·30), 226 (3·99) nm (log ϵ). Without further purification **4** (0·20 g) was acetylated by suspending it in Ac_2O (1·0 ml) containing 2 drops of conc. H_2SO_4. After 2 min water was added and the yellow solid was collected. Recrystallization from MeOH gave a *monoacetyl derivative* of **4** as pale yellow prisms, m.p. 145–146° (0·12 g). (Found: C, 67·1; H, 5·58; N, 4·04. Calc. for $C_{19}H_{19}O_5N$: C, 66·9; H, 5·61; N, 4·10%), 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ2·36; 3H, s, δ3·61; 3H, s, δ3·76; 1H, d, δ6·32, J = 18·0 Hz; 5H, m, δ6·60–δ7·15; 2H, d, δ7·46, J = 9·0 Hz; 1H, d, δ7·68, J = 18·0 Hz; 1H, s, δ8·05 (OH).

2 - Acetyl - 3 - phenyl - 5 - (2,4 - diacetoxy - 3 - methylphenyl) - 2,5 - dihydroisoxazole **2d**

Compound **1b**[12] (2·0 g) warmed with hydroxylamine hydrochloride (2·0 g) and pyridine (10 ml) for 1 hr gave an oil on adding water. The oil was acetylated by treatment with Ac_2O (5 ml) and pyridine (0·5 ml). The product crystallized from MeOH to give **2d** as colorless needles, m.p. 90° (0·95 g). (Found: C, 66·5; H, 5·35; N, 3·38. Calc. for $C_{22}H_{21}O_6N$: C, 66·8; H, 5·35; N, 3·54%).

Oximation of **1c** and acetylation of the product as above gave *2 - acetyl - 3 - (4 - methoxyphenyl) - 5 - (2,4 - diacetoxy - 3 - methylphenyl) - 2,5 - dihydroisoxazole* **2e** as colorless needles, m.p. 118–9°. (Found: C, 65·0; H, 5·43; N, 3·16. Calc. for $C_{23}H_{23}O_7N$: C, 64·9; H, 5·45; N, 3·29%), 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ1·96; 3H, s, δ2·18; 3H, s, δ2·27; 3H, s, δ2·32; 3H, s, δ3·83; 1H, d, δ6·77, J = 17·0 Hz; 2H, d, δ6·93, J = 9·0 Hz;

1H, d, δ7·01, J = 9·0 Ha; 1H, d, δ7·41, J = 17·0 Hz; 2H, d, δ7·48, J = 9·0 Hz; 1H, d, δ7·56, J = 9·0 Hz.

Oximation under similar conditions of 4'-hydroxyflavylium chloride[13] and acetylation of the product gave 2 - *acetyl* - 3 - (4 - *acetoxyphenyl*) - 5 - (2 - *acetoxyphenyl*) - 2,5 - *dihydroisoxazole*, colorless prisms *ex* THF-MeOH, m.p. 157–8°. (Found: C, 66·2; H, 4·98; N, 3·71. Calc. for $C_{21}H_{19}O_6N$: C, 66·1; H, 5·02; N, 3·67%). 3 - Methyl - 4' - hydroxyflavylium chloride[14] gave 3 - (4 - *hydroxyphenyl*) - 4 - *methyl* - 5 - (2 - *hydroxyphenyl*) - 2,5 - *dihydroisoxazole*, colorless prisms *ex* benzene, m.p. 120°. (Found: C, 71·4; H, 5·60. Calc. for $C_{16}H_{15}O_3N$: C, 71·4; H, 5·61%); *triacetyl derivative*, colorless prisms *ex* MeOH, m.p. 92–3°. (Found: C, 67·1; H, 5·32. Calc. for $C_{22}H_{21}O_6N$: C, 66·8; H, 5·35%). 3 - Methyl-4',8 - dimethoxy - flavylium perchlorate[8] gave 3 - (4 - *methoxyphenyl*) - 4 - *methyl* - 5 - (2 - *hydroxy* - 3 - *methoxyphenyl*)-2,5 - *dihydroisoxazole*, colorless prisms *ex* THF-MeOH, m.p. 172°. (Found: C, 68·9; H, 6·00. Calc. for $C_{18}H_{19}O_4N$: C, 69·0; H, 6·11%); *diacetyl derivative*, colorless prisms *ex* ether-Skelly solve F, m.p. 122–3°. (Found: C, 66·6; H, 5·93; N, 3·41. Calc. for $C_{22}H_{23}O_6N$: C, 66·5; H, 5·83; N, 3·52%).

3 - (4 - *Methoxyphenyl*) - 5 - (2 - *hydroxyphenyl*) - 4,5 - *dihydro* - 1H - *pyrazole*, **10b**

(a) Compound **1d**[13] (2·0 g), hydrazine hydrate soln (64%; 3·0 ml), and pyridine (10·0 ml) were heated on a steam bath for 1 hr. The solid obtained on adding water crystallized from MeOH to give **10b** as colorless, glistening prisms, m.p. 159–160° (0·85 g).

(b) Compound **5b**[16] (2·0 g) treated with hydrazine as in (a) gave **10b**, m.p. and m.m.p. 159–160° (2·0 g). (Found: C, 71·8; H, 5·89; N, 10·1. Calc. for $C_{16}H_{16}O_2N_2$: C, 71·6; H, 6·01; N, 10·44%). **10b** gives a blue color with Gibbs reagent and an olive green color with alcoholic $FeCl_3$.

A suspension of **10b** (0·5 g) in Ac_2O (5·0 ml) was treated with 2 drops of pyridine at room temp. After 2 min, water was added and the solid product crystallized from THF-MeOH. The N-*acetyl derivative* of **10b** was obtained as colorless needles, m.p. 226–7° (0·35 g). (Found: C, 69·6; H, 5·77. Calc. for $C_{18}H_{18}O_3N_2$: C, 69·7; H, 5·85%), 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ2·37; 2H, m, δ3·50–δ3·70; 3H, s, δ3·88; 1H, dd, δ5·83, J = 10·0, 4·5 Hz; 5H, m, δ6·72–δ7·24; 2H, d, δ7·80; J = 9·0 Hz.

10b (1·0 g) was dissolved in boiling acetone (15·0 ml). MeOH (50 ml) was added and the soln was concentrated to 10·0 ml and cooled. The solid product was recrystallized from acetone-methanol to give **11b** as colorless, glistening needles, m.p. 130° (0·90 g). (Found: C, 74·1; H, 6·53. Calc. for $C_{19}H_{20}O_2N_2$: C, 74·0; H, 6·54%).

3 - (4 - *Methoxyphenyl*) - 5 - (2 - *hydroxy* - 3 - *methoxyphenyl*) - 4,5 - *dihydro* - 1H - *pyrazole* **10a**

5a (2·0 g) treated with hydrazine in pyridine as described above gave **10a**, slightly yellow needles *ex* THF-benzene, m.p. 133–134° (1·73 g). (Found: C, 68·6; H, 6·07. Calc. for $C_{17}H_{18}O_3N_2$: C, 68·4; H, 6·08%), 100 MHz NMR spectrum in $CDCl_3$: 1H, dd, δ3·05, J = 16·0, 11·0 Hz; 1H, dd, δ3·45, J = 16·0, 10·0 Hz; 3H, s, δ3·84; 3H, s, δ3·89; 1H, dd, δ5·09; J = 11·0, 10·0 Hz; 6H, m, δ6·76–δ7·00; 2H, d, δ7·66, J = 9·0 Hz.

10a (3·0 g), suspended in Ac_2O (20 ml) and pyridine (2·0 ml) for 2 min, formed the N-*acetyl derivative* (3·3 g), which crystallized from THF as colorless, glistening needles, m.p. 222°. (Found: C, 67·1; H, 5·91. Calc. for $C_{19}H_{20}O_4N_2$: C, 67·0; H, 5·92%). With Gibbs reagent, the mono-acetyl compound gives an immediate, intense blue color (free OH), 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ2·43; 1H, dd, δ3·26, J = 17·0, 5·0 Hz; 1H, dd, δ3·74, J = 17·0, 11·0 Hz; 6H, s, δ3·88; 1H, dd, δ5·86, J = 11·0, 5·0 Hz; 5H, m, δ6·58–δ7·32; 2H, d, δ7·76, J = 9·0 Hz.

10a (3·0 g), dissolved in boiling acetone, diluted with MeOH and concentrated, gave **11a** as colorless glistening needles, m.p. 177–178° (2·85 g). (Found: C, 71·0; H, 6·59; N, 8·31. Calc. for $C_{20}H_{22}O_3N_2$: C, 71·0; H, 6·55; N, 8·28%); 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ1·60; 3H, s, δ2·06; 1H, dd, δ3·18, J = 16·0, 2·5 Hz; 1H, dd, δ3·45, J = 16·0, 9·0 Hz; 3H, s, δ3·74; 3H, s, δ3·77; 1H, dd, δ5·08, J = 9·0, 2·5 Hz; 5H, m, δ6·54–δ6·94; 2H, d, δ7·58, J = 9·0 Hz.

3 - (4 - *Methoxyphenyl*) - 5 - (2 - *hydroxy* - 4 - *methoxyphenyl*) - 4,5 - *dihydro* - 1H - *pyrazole* **10c**

Compound **1e**[17] (m.p. 270°) with hydrazine gave **10c**, cream-colored plates *ex* THF–MeOH, m.p. 183°, meas. mass = 298. 1329; calc. for $C_{17}H_{18}O_3N_2$ = 298. 1318; N-*acetyl derivative*, m.p. 186–187° *ex* acetone-methanol; meas. mass = 340. 1430; calc. for $C_{19}H_{20}O_4N_2$ = 340, 1424; 100 MHz NMR spectrum in $CDCl_3$; 3H, s, δ2·39; 1H, dd, δ3·40, J = 17·0, 4·0 Hz; 1H, dd, δ3·69, J = 17·0, 11·0 Hz; 3H, s, δ3·73; 3H, s, δ3·88; 1H, dd, δ5·75, J = 11·0, 4·0 Hz; 2H, m, δ6·30–δ6·50; 1H, d, δ6·95, J = 9·0 Hz; 2H, d, δ6·97, J = 9·0 Hz; 2H, d, δ7·78, J = 9·0 Hz. Treated with acetone, **10c** gave **11c**, colorless needles *ex* acetone-methanol, m.p. 108–109°; mass spectral analysis shows loss of 2H, meas. mass = 324. 1432; calc. for $C_{19}H_{20}O_3N_2$ = 324. 1474; 100 MHz NMR spectrum in $CDCL_3$: 3H, s, δ1·60; 3H, s, δ2·00; 1H, dd, δ3·19, J = 16·0, 2·0 Hz; 1H, dd, δ3·46, J = 16·0, 8·0 Hz; 3H, s, δ3·72; 3H, s, δ3·79; 1H, dd, δ5·06, J = 8·0, 2·0 Hz; 1H, d, δ6·27, J = 3·0 Hz; 1H, dd, δ6·49, J = 9·0, 3·0 Hz; 2H, d, δ6·83, J = 9·0 Hz; 1H, d, δ6·92, J = 9·0 Hz; 2H, d, δ7·58, J = 9·0 Hz.

3 - (2 - *Hydroxyphenyl*) - 5 - (4 - *methoxyphenyl*) - 4,5 - *dihydro* - 1H - *pyrazole* **10d**

Compound **13a**[18] (2·0 g) heated with hydrazine and pyridine as above gave **10d**, colorless plates *ex* MeOH, m.p. 103–4°. **12**, treated with hydrazine and pyridine under the same conditions also gave **10d**. (Found: C, 71·8; H, 5·88. Calc. for $C_{16}H_{16}O_2N_2$: C, 71·6; H, 6·01%); 100 MHz NMR spectrum in $CDCl_3$: 1H, dd, δ3·04; J = 16·5, 9·0 Hz; 1H, s, δ3·45; 1H, dd, δ3·48, J = 16·5, 10·5 Hz; 3H, s, δ3·78; 1H, dd, δ4·79, J = 10·5, 9·0 Hz; 9H, m, δ6·76–δ7·22. With both Gibbs reagent and alcoholic ferric chloride **10d** gives deep blue colors.

10d (0·30 g), heated with Ac_2O (1·0 ml) and pyridine (1·0 ml) on a steam-bath for 5 min, formed the 0,N - *diacetyl derivative*, colorless prisms *ex* MeOH, m.p. 138°. (Found: C, 68·2; H, 5·69; N, 7·94. Calc. for $C_{20}H_{20}O_4N_2$: C, 68·2; H, 5·72; N, 7·95%), 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ2·28; 3H, s, δ2·34; 1H, dd, δ3·12, J = 17·0, 5·0 Hz; 3H, s, δ3·74; 1H, dd, δ3·76, J = 17·0, 11·0 Hz; 1H, dd, δ5·45, J = 11·0, 5·0 Hz; 2H, d, δ6·83, J = 9·0 Hz; 6H, m, δ7·00–δ7·66.

3 - (2 - *Hydroxy* - 4 - *methoxyphenyl*) - (4 - *methoxyphenyl*) - 4,5 - *dihydro* - 1H - *pyrazole* **10e**

With hydrazine and pyridine as above, **13b** (m.p.110°) (5·0 g) gave **10e** (4·5 g), colorless needles *ex* THF–MeOH, m.p. 156–157°; 100 MHz NMR spectrum in $CDCl_3$: 1H, dd, δ3·03, J = 17·0, 9·0 Hz; 1H, dd, δ3·47, J = 17·0, 11·0 Hz; 6H, s, δ3·80; 1H, dd, δ4·79, J = 11·0, 9·0 Hz; 8H, m, δ6·35–δ7·34. **10e** gave deep blue colors with both Gibbs reagent and alcoholic $FeCl_3$.

Acetylation of **10e** by adding one drop of pyridine to its suspension in Ac_2O at room temp formed the N-*acetyl derivative*, which crystallized from acetone–MeOH as colorless needles, m.p. 174°. (Found: C, 67·2; H, 5·82. Calc. for $C_{19}H_{20}O_4N_2$: C, 67·0; H, 5·92%), 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ2·34; 1H, dd, δ3·21, J = 17·0, 5·0 Hz; 3H, s, δ3·77; 1H, dd, δ3·79, J = 17·0, 12·0 Hz; 3H, s, δ3·83; 1H, dd, δ5·48, J = 12·0, 5·0 Hz; 8H, m, δ6·40–δ7·21. Heating **10e** with Ac_2O and pyridine for 10 min give an oily product. Crystallization from MeOH gave the 0,N-diacetyl derivative as colorless needles, m.p. 93°. (Found: C, 66·0; H, 5·70, N, 7·37. Calc. for $C_{21}H_{22}O_4N_2$: C, 66·0; H, 5·80; N, 7·33%), 100 MHz NMR spectrum in $CDCl_3$: 3H, s, δ2·30; 3H, s, δ2·33; 1H, dd, δ3·07, J = 17·0, 5·0 Hz; 1H, dd, δ3·71, J = 17·0, 12·0 Hz; 3H, s, δ3·75; 3H, s, δ3·82; 1H, dd, δ5·48, J = 12·0, 5·0 Hz; 5H, m, δ6·60–δ7·20; 2H, d, δ7·50, J = 9·0 Hz.

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