The Enamine Route to 2-Morpholinoisoflav-3-ene

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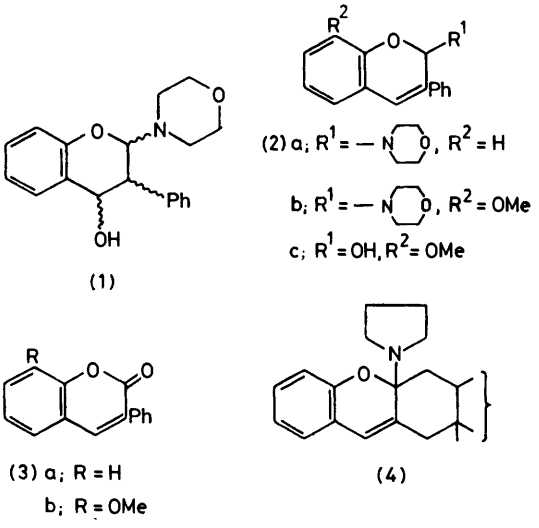
In contrast to earlier reports, the condensation of *N*-styrylmorpholine with salicylaldehyde or with 3-methoxysalicylaldehyde gives 2-morpholinoisoflav-3-ene derivatives. 2-Morpholinoisoflav-3-ene can be hydrogenolysed in a useful synthesis of isoflavan; with acids it gives in high yield a remarkably stable di(isoflavenyl) ether (6); with triphenylmethyl perchlorate it gives isoflavylium perchlorate.

A similar condensation with *N*-(cyclohexenyl)morpholine behaves differently, giving alcohols that are oxidised to chromone (or tetrahydroxanthone) derivatives, in accord with previous reports.

WHEN we attempted to prepare isoflavone in the manner described by Paquette and Stucki,[1] a heated mixture of *N*-styrylmorpholine and salicylaldehyde in benzene gave a thick oil which had been formulated as the alcohol (1) by the previous authors but which we found to be stable to chromium(VI) oxide in pyridine. Since this product did not appear to contain a secondary benzylic alcohol function we chromatographed it on basic alumina and obtained 2-morpholinoisoflav-3-ene (2a) in >55% yield. Its u.v. spectrum [$\lambda_{max.}$ (EtOH) 289 and 329 nm] indicated that the compound is a derivative of *E*-stilbene, because isoflav-2-enes lack an absorption maximum above 300 nm.[2] In accord with this assumption, the ^{1}H n.m.r. spectrum shows two one-proton singlets at δ 7.04 (4-H) and 5.74 (2-H), and the mass spectrum exhibits a molecular-ion peak at *m/z* 293 and a base peak at *m/z* 207 corresponding to the 3-phenyl-1-benzopyrilium ion. The isoflav-3-ene derivative (2a) could be oxidised with chromium(VI) oxide only under forcing conditions in acetic acid and the products included 3-phenylcoumarin (3a), m.p. 139 °C but no isoflavone, m.p. 131 °C. A similar synthesis beginning with 3-methoxysalicylaldehyde supplied 8-methoxy-2-morpholinoisoflav-3-ene (2b) (*ca.* 46%) as a gum, along with the crystalline alcohol (2c) (*ca.* 12%); oxidation of the latter compound with the Sarett's reagent (CrO_3–py) afforded 8-methoxy-3-phenylcoumarin (3b) and not 8-methoxyisoflavone as previously reported.[1]

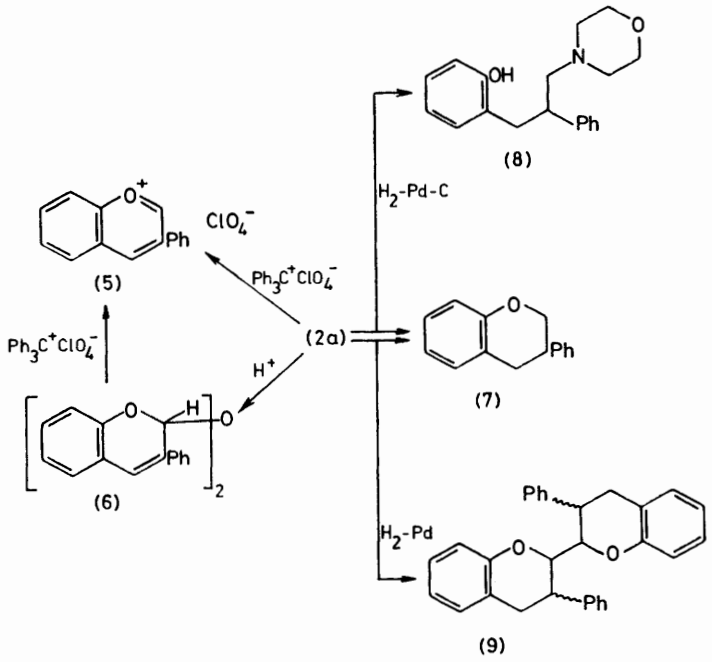
On the other hand, similar condensations with 1-morpholinocyclohexene lead to the formation of tetrahydroxanthones exactly as described previously;[1] *e.g.* reaction with 3-methoxysalicylaldehyde and 2-hydroxy-1-naphthalenecarbaldehyde in anhydrous benzene at room temperature overnight or under refluxing conditions (3—4 h) resulted in the formation of oily alcohols which were oxidisable by Sarett's reagent to 5-methoxy-1,2,3,4-tetrahydroxanthone and 8,9,10,11-tetrahydro-12*H*-benzo[*a*]xanthen-12-one, respectively, in good yield.[1] It seems likely that in the styrylmorpholine reactions similar alcohols are formed but suffer ready dehydration because this extends the conjugation between the two rings. Steroidal enamines are said to react with salicylaldehyde to give mainly dehydrated products[3] such as compound (4), but in this work the reaction times were unusually long (3 days).

Since isoflav-3-enes are well known oestrogens,[4-6] and since we failed to find in the literature[2,7-10] any previous example of a 2-aminoisoflavene derivative, we made a preliminary investigation of the chemistry of the isoflavene (2a). Compound (2a) with triphenylmethyl perchlorate in acetic acid gave (quantitatively) crystalline



isoflavylium perchlorate (5).[11] Surprisingly, this salt could not be obtained by treating the isoflavene (2a) with perchloric acid; the symmetrical, oxy-2,2′-di-isoflav-3-ene (6), m.p. 242—243 °C, was the exclusive (and nearly quantitative) product and it was also obtained on treatment of compound (2a) with phosphoric acid and even with silica gel. Another compound reported to have structure (6) was recently prepared by a different route[12] and was reported as having m.p. 210 °C; the discrepancy might indicate a difference in diastereoisomers. So great a stability to acids is perhaps surprising in bisacetals; whilst there is good precedent for acid stability of the cyclic part of bisacetals such as sapogenins[13] and aflatoxins,[14] there is none that we know of for the acyclic part. The bisacetal (2a) is almost insoluble in most solvents, especially those containing water, and we attribute the seeming lack of reactivity to the imbalance produced by this factor on the salt-forming equilibria.

Hydrogenation of the isoflavene (2a) in methanol (10% Pd–C) overnight gave only hydrogenolysis products,[15] mainly isoflavan[8] (7) which was identified by its ^{1}H n.m.r. spectrum.[16] This process provides a convenient synthesis of isoflavan. The other product was the ring-opened compound (8), a semi-solid mass whose i.r. spectrum indicated the presence of a hydroxy-group modified by hydrogen-bonding to nitrogen ($\nu_{max.}$ *ca.* 3 000 cm^{-1}). The ^{1}H n.m.r. spectrum of compound (8) was clarified by decoupling experiments and confirmed the structure. Hydrogenation of the isoflavene (2a) over an unsupported palladium catalyst was examined in acetic acid (containing HCl). Isoflavan (7) was obtained in poor yield along with what appeared to be a mixture of stereoisomers corresponding to structure (9). One component could be crystallised from methanol in a fairly pure state and was assigned structure (9) on the basis of ^{1}H n.m.r. and mass spectral results, although its stereochemistry remains unknown.



EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus and are uncorrected. The ^{1}H n.m.r. spectra were recorded on a Perkin-Elmer R34 spectrometer operating at 220 MHz with tetramethylsilane as internal standard. U.v. and i.r. spectra were measured on Pye Unicam SP8-100 and Perkin-Elmer 125 spectrometers, respectively, and mass spectra on an AEI MS12 spectrometer by the direct-inlet technique. Light petroleum refers to the fraction of boiling range 40—60 °C and ether refers to diethyl ether. Benzene was redistilled after drying over sodium wire and solutions in organic solvents were dried with anhydrous magnesium sulphate.

2-Morpholinoisoflav-3-ene (2a).—A mixture of *N*-styrylmorpholine[17] (2.84 g) and salicylaldehyde (1.83 g) was refluxed in benzene (8 ml) under nitrogen for 2.5—3 h; removal of benzene afforded a yellowish red gum (A) (4.2 g) which, on column chromatography on basic alumina with ether–light petroleum (1 : 10) as eluant, afforded the product (2.4 g, 55%) which crystallised from hexane giving 2-*morpholinoisoflav*-2-*ene* (2a) as rectangular rods, m.p. 105—106 °C; $\lambda_{max.}$ (EtOH) 289 (ε 16 200) and 329 nm (11 900); $\nu_{max.}$ (KBr) 1 620, 1 592, 1 562, 1 482, 1 450, 1 107, 1 034, 888, and 760 cm^{-1}; δ ($CDCl_3$) 7.67—6.96 (9 H, m, ArH), 7.04 (1 H, s, 4-H), 5.74 (1 H, s, 2-H), 3.56 (4 H, m, CH_2OCH_2), 3.04 (2 H, m, NCH_2), and 2.61 (2 H, m, NCH_2); *m/z* 293 (M^+) and 207 (M − 86, 100) (Found: C, 77.45; H, 6.35; N, 4.80. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.52; N, 4.77%).

Attempted Oxidations with Chromium(VI) *Oxide.*—(*a*) *In pyridine.* Following literature procedure,[1] we oxidised a sample of the yellowish red gum [(A), see above] (1.37 g) with a stirred suspension of chromium(VI) oxide complex [CrO_3 (2.96 g) in pyridine (17.5 ml)]. The mixture was stirred with cooling (ice-bath) for another 2.5 h, kept overnight at room temperature, then poured into ice–water and the dark brown slurry repeatedly extracted with ether. The combined extracts were washed with water, dried, filtered, and concentrated. Pyridine was removed from the residue by passing a solution in ether–hexane (1 : 1) through a small column of alumina and the product then crystallised as thin, rectangular rods, m.p. 104—105 °C (hexane), identical (i.r., n.m.r., m.s.) with 2-morpholinoisoflav-3-ene (2a), recovery 85%.

(b) *In acetic acid.* A solution of the isoflavene (2a) (50 mg) in acetic acid (5 ml) was gradually added, over a period of 2—3 h, to a mixture of chromium(VI) oxide in 80% acetic acid, maintaining the temperature in the range 10—15 °C, and with constant stirring. The mixture was kept for 3 d then worked up by pouring it into ice-cold water and extracting the product into ether. Isolated in the usual way, the product was purified by passage through a silica gel column

with ether-petroleum (1 : 9, v/v) as eluant, to give 3-phenylcoumarin (3a) (10%), m.p. 139 °C (lit.,[18] 140 °C); $\nu_{max.}$ (Nujol) 1 715 cm^{-1}; δ ($CDCl_3$) 7.80 (1 H, s, 4-H); the major component (70%) was the ether (6).

Oxy-2,2'-di-isoflav-3-ene (6).—The isoflavene (2a) on maceration with polyphosphoric acid developed a yellowish green fluorescence and upon addition of water gave *oxy-2,2'-di-isoflav-3-ene* (6) as transparent needles (>98%), m.p. 242—243 °C (ether); $\lambda_{max.}$ (CH_2Cl_2) 287 and 315sh nm; $\nu_{max.}$ (KBr) 1 624, 1 595, 1 567, 1 484, 1 452, 947, 907, and 755 cm^{-1}; δ ($CDCl_3$) 7.38—7.02 (20 H, m, ArH + 4- and 4'-H) and 6.75 (2 H, s, 2- and 2'-H); *m/z* 430 (M^+), 213, and 207 (100%) (Found: C, 83.90; H, 5.40. $C_{30}H_{22}O_3$ requires C, 83.70; H, 5.15%). The ether (6) was also obtained by treatment of the isoflavene (2a) with perchloric acid, hydrochloric acid, phosphoric acid, or silica gel.

Isoflavylium Perchlorate (5).—To a solution of the isoflavene (2a) in acetic acid (4 ml) was added triphenylmethyl perchlorate (equimolar amount) in small portions and the mixture was warmed on an oil-bath (110—130 °C) for 5—10 min and then cooled. Work-up gave the product as yellowish brown needles (*ca.* 100%), m.p. 140—141°C (CH_3CO_2H); $\nu_{max.}$ (KBr) 1 616, 1 579, 1 492, [1 147, 1 105, 1 085 (ClO_4^- ion)], 767, and 622 cm^{-1}; δ ($CDCl_3$–CF_3CO_2H) 9.83 (1 H, d, *J* 2 Hz, 2-H), 9.7 (1 H, d, *J* 2 Hz, 4-H), and 8.46—7.56 (9 H, m, ArH). The ether (6) also gave the perchlorate (5) in quantitative yield under similar conditions.

Hydrogenation of the Isoflavene (2a).—(a) *With Pd–charcoal.* The isoflavene (2a) (0.293 g) was dissolved in methanol (50 ml) and hydrogenated overnight using 10% Pd–charcoal (0.058 g). The catalyst was filtered off and the methanol was removed under reduced pressure yielding a gummy residue which was separated into two components by column chromatography over silica gel. Elution with hexane gave the faster moving compound as a gum (70%); crystallisation from methanol afforded isoflavan (7) as stout needles, m.p. 53—54 °C (lit.,[19] 55 °C); $\nu_{max.}$ (film) 1 580, 1 488, 1 450, 1 235, 1 220, 754, and 698 cm^{-1}; δ ($CDCl_3$) 7.36—7.16 (5 H, m, 3-Ph), 7.09—6.80 (4 H, m, ArH), 4.39—4.32 (1 H, q, *J* 10.5, *J* 3.5 Hz, 2-H), 4.03 (1 H, t, *J* 10.5 Hz, 2-H), 3.3—3.15 (1 H, m, 3-H), and 3.06—3.0br (2 H, m, 4-H_2); *m/z* 210 (M^+) and 119 (100).

The slower moving compound was obtained by eluting with ethyl acetate–methanol (10 : 1); work-up gave the *morpholinophenol* (8) as a semi-solid mass (25%); $\nu_{max.}$ (KBr) 3 150—2 800br, 1 600, 1 574, 1 480, 1 447, 1 250, 1 110, 1 000, 866, 770, and 758 cm^{-1}; δ ($CDCl_3$) 9.4br (1 H, s, Ar-OH, exchanged with D_2O), 7.25—6.34 (9 H, m, ArH), 3.85 (4 H, m, CH_2OCH_2), 3.35 (1 H, m, CH_2CHPh), 3.18 (1 H, dd, *J* 4.5 Hz, ArC*H*H), 2.76 (4 H, m, $CHCH_2N$ + NCH_2), 2.50br [CH, m (sharpens at 50 °C), NCH_2], and 2.35 (1 H, dd, *J* 4.5 Hz, $ArCH_2$). Assignments were confirmed by double irradiation of the multiplets at δ 3.85, 3.35, and 2.50 (Found: M^+, 297.172 05. $C_{19}H_{23}NO_2$ requires *M*, 297.172 87).

(b) *With unsupported Pd catalyst.* To a yellowish, turbid solution of 2-morpholinoisoflav-3-ene (2a) (1.17 g) in acetic acid (80 ml) containing a few drops of hydrochloric acid was added unsupported $PdCl_2$ catalyst (0.2 g) and the solution was shaken overnight under hydrogen. The solid which formed was filtered off from the resulting suspension, washed with water, and dried. The solid (0.5 g) melted over the range 210—290 °C and had *m/z* 419 (M^+), 209, and 208. The mother liquor was neutralised with aqueous sodium hydrogen carbonate and the organic products were extracted with ether. The extracts were dried and evaporated to dryness to afford a gum which, on fractional crystallisation from methanol, afforded two substances. One was identified as the isoflavan (7), obtained as long, thick needles, m.p. 53—54 °C and the other, believed to have the bisisoflavan structure (9), melted in the range 135—155 °C (methanol); $\nu_{max.}$ (KBr) 1 605, 1 578, 1 484, 1 447, 1 235, 1 217, 1 054, 748, and 698 cm^{-1}; δ ($CDCl_3$) 7.16—6.64 (*ca.* 18 H, m, ArH), 4.23br (2 H, s, (2- and 2'-H), 3.34 (2 H, m, 3- and 3'-H), and 3.05 (4 H, d, *J* 7 Hz, 4- and 4'-H_2); irradiation of the multiplet at δ 3.34 sharpened the singlet at δ 4.23 and the doublet at δ 3.05 collapsed into a singlet (Found: M^+, 418.192 00. $C_{30}H_{26}O_2$ requires *M*, 418.193 27); *m/z* 418 (M^+), 312, 321, 222, 209 (96), 208, 207, and 91 (100). This substance did not fluoresce in mineral acids [*cf.* the isoflavene (2a)].

8-Methoxy-2-morpholinoisoflav-3-ene (2b) *and 2-Hydroxy-8-methoxyisoflav-3-ene* (2c).—A mixture of *N*-styrylmorpholine (3.78 g) and 3-methoxysalicylaldehyde (3.04 g) was refluxed in benzene (10 ml) under nitrogen for 2 h. The resulting reddish yellow oil, which resolved on silica gel from ether–petroleum (1 : 4, v/v) into two components, was chromatographed on basic alumina with ether–hexane (1 : 10) as eluant whence the faster moving compound *8-methoxy-2-morpholinoisoflav-3-ene* (2b) was obtained as a gum (45.6%); $\nu_{max.}$ (film) 1 630, 1 595, 1 578, 1 480, 1 263, 1 115, 1 040, 994, 780, and 736 cm^{-1}; δ ($CDCl_3$) 7.68—6.80 (8 H, m, ArH), 7.06 (1 H, s, 4-H), 5.83 (1 H, s, 2-H), 3.9 (3 H, s, OCH_3), 3.61 (4 H, m, CH_2OCH_2), 3.10 (2 H, m, NCH_2), and 2.63 (2 H, m, NCH_2) (Found: M^+, 323.151 87. $C_{20}H_{21}NO_3$ requires *M*, 323.152 13); *m/z* 323 (M^+) and 237 (*M* − 86, 100%).

Subsequent elution with ethyl acetate as eluant afforded *2-hydroxy-8-methoxyisoflav-3-ene* (2c) (11.5%), as needles, m.p. 138—139 °C (hexane–ether); $\lambda_{max.}$ (EtOH) 292 nm (ε 23 585); $\nu_{max.}$ (KBr) 3 420, 1 580, 1 492, 1 270, 1 225, 1 105, 1 065, 997, and 776 cm^{-1}; δ ($CDCl_3$) 7.6—6.82 (8 H, m, ArH), 7.0 (1 H, s, 4-H), 6.4 (1 H, s, 2-H), 3.87 (3 H, s, OCH_3), and 3.7br (1 H, OH, exchanged with D_2O) (Found: M^+, 254.094 74. $C_{16}H_{14}O_3$ requires *M*, 254.094 29); *m/z* 254 (M^+), 237 (*M* − 17, 100), 225, 210, and 165. Oxidation with CrO_3-pyridine complex gave 8-methoxy-3-phenylcoumarin (3b) as thick needles, m.p. 155—157 °C (lit.,[20] 156 °C); $\nu_{max.}$ (KBr) 1 710 cm^{-1}; δ ($CDCl_3$) 7.76 (1 H, s, 4-H); *m/z* 252 (M^+, 100) and 224 (*M* − 28).

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