

Reactivity of 3-Alkyl-4-arylazomethylene-3,4-dihydro-1,2,3-benzotriazines in Protic Solvents: 1,4-Addition Reactions and Dimroth Rearrangement
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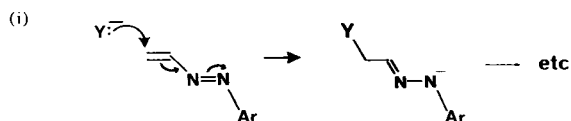
3-Alkyl-4-arylazomethylene-3,4-dihydro-1,2,3-benzotriazines **5a** and **5b** undergo facile 1,4-addition of methanol or ethanol to afford stable crystalline hydrazones, **6** and **8** which have been characterised by spectroscopic analysis. In particular, the nmr spectrum of **8** shows novel features due to the diastereotopic nature of the CH₂ protons in the two *O*-ethyl groups. Compound **5b** shows a property unique to the compounds in this series; refluxing this arylazomethylenetriazine in ethanol affords a rearranged product, characterised as the 1-aryl-2-cinnolinylhydrazone (**9**). The formation of **9** is rationalised as a ring opening-ring closure process analogous to the Dimroth rearrangement. The cinnoline **9** displays some novel chemistry arising from the facility of the arylhydrazino substituent to react with acid to give a fragmentation product, 3-methylindazole (**7**).

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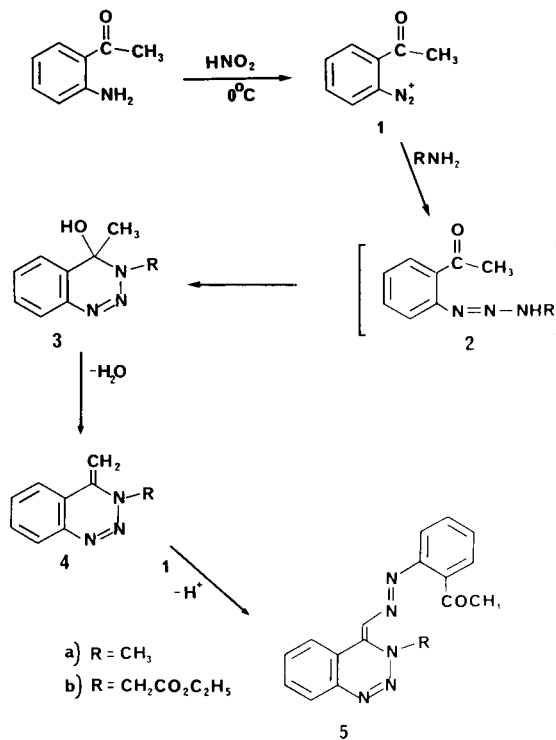
Triazenes of the type ArN=N-NHR, known commonly as "Monoalkyltriazenes", are obtained conventionally by the diazonium coupling reaction with a primary alkylamine [1]. Such triazenes are usually colourless or of only pallid (off-white or pale yellow) colour. However, the coupling reaction of the diazonium salt **1**, derived from *o*-aminoacetophenone, with alkylamines affords triazenes, formally with structure **2**, which display unusually intense colouration from bright yellow to deep red. In a previous report [2], it was shown that the *o*-acylphenyltriazenes **2** undergo facile cyclization to the novel 4-hydroxy-3,4-dihydrobenzo-1,2,3-triazines ("triazinols"), e.g. **3**, which in turn undergo dehydration to give the 4-methylene-1,2,3-benzotriazines **4** [3]. These heterocycles are bright yellow in colour.

Further study has revealed that, under appropriate reaction conditions, the diazonium coupling reaction of **1** with an alkylamine, RNH₂, affords bright red products, which have been characterised as the arylazomethylenetriazines **5** [4]. These products may be formalised as the result of diazonium coupling to the exocyclic vinylic carbon atom of **4**; this behaviour confirms the anticipated enamine character of molecules of type **4**.

This paper reports a further study of the chemistry of the arylazomethylenetriazines **5**, which in our hands have shown a susceptibility to reaction or decomposition in protic solvents. We reasoned that the reactivity of molecules of type **5** could be due to the activation of the exocyclic carbon-carbon double bond to nucleophilic attack by the arylazo substituent. Such activation has been observed in similar compounds with a variety of nucleophiles leading to 1,4-addition reactions of the type following (i) [5]:

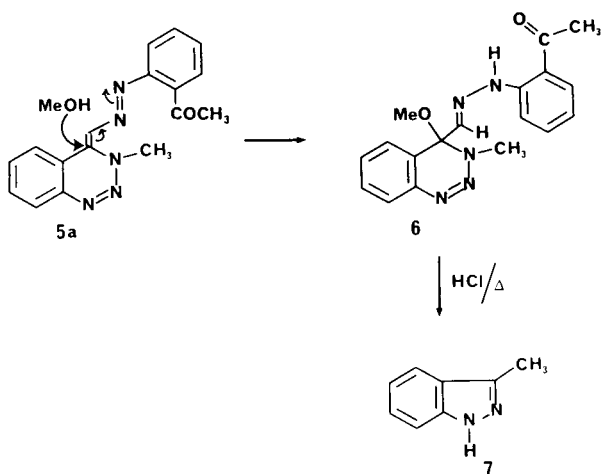


Thus, 1,4-addition of methanol to the exocyclic carbon-carbon double bond of the 3-methylazomethylene triazine **5a** occurs readily at 60° and affords a crystalline yellow solid, identified as the 4-methoxy-1,2,3-benzotriazinyl-formaldehyde hydrazone **6**. The hydrazone is formally the



product of 1,4-addition of methanol to the azomethylene group of **5a**.

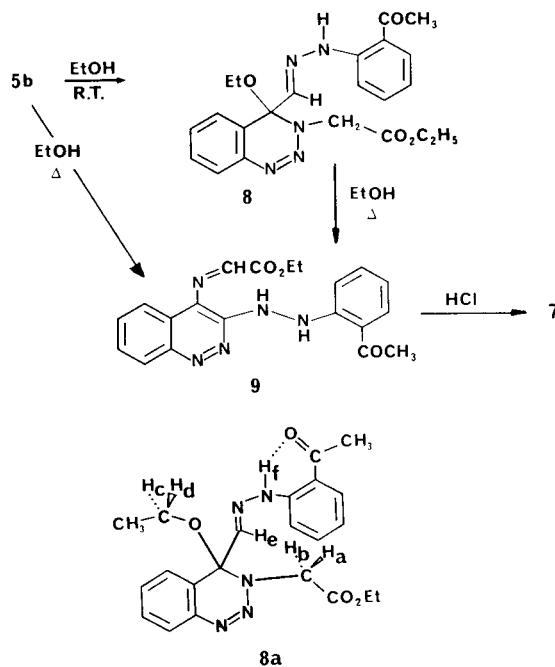
The structure of **6** follows from elemental analysis, ir and ^1H and ^{13}C nmr spectroscopy. The ^1H nmr spectrum of **6** shows the acetyl-Me and N-Me groups in addition to the new O-Me group at 3.58 ppm. The vinylic proton at the α -exocyclic carbon atom shows only a slight upfield shift from 7.74 ppm in **5a** to 7.51 ppm in **6**, whereas the C-4 carbon of the triazine ring shows a marked shift from 117.7 in **5a** to 84.5 in **6**. This large shift is consistent with the change of hybridisation from sp^2 in **5a** to sp^3 in **6**. A signal at δ 201.7 confirms the presence of the acetyl-carbonyl group. The ir spectrum of **6** has an NH band at 3210 cm^{-1} and a carbonyl absorption band at 1645 cm^{-1} , which is characteristic of an aromatic acyl-group *ortho* to a NH group [6]. The break in the conjugation resulting from addition of the methoxy group at C-4 is reflected in the shift in the uv/visible maxima of **6**. The conversion of **5a** into the hydrazone **6** results in loss of the red colouration and a shift in absorption maximum from 430 to 369 nm.



An analogous hydrazone **8** precipitated as a yellow crystalline solid when the azomethylene compound **5b** was heated for a short time in ethanol. The ^{13}C nmr spectrum of **8** shows characteristic peaks for two CH_2 groups at 51.1 and 61.3 ppm and two CH_3 groups at 14.0 and 14.7 ppm respectively for the *O*-ethyl groups, a quaternary C-4 carbon at 84.0 ppm, an acetyl methyl carbon at 27.9 ppm, a N- CH_2 carbon at 58.7 ppm, an ester carbonyl carbon at 169.0 ppm and an acetyl carbonyl carbon at 201.4 ppm, together with the requisite number of aromatic carbon atoms.

The ^1H nmr spectrum of **8** is more complex than that of **6** and shows the effect of the new chiral centre at C-4 of the triazine ring on the signals from the diastereotopic protons of the N- CH_2 group (see structure **8a**), which appear as an AB-system at δ 4.52-4.74 with J_{AB} 17 Hz. The proton signals of the ester O-Et group give the expected

triplet (δ 1.21) and quartet (δ 4.16). The signals of the ether O-Et group are much more interesting and informative; the methylene protons are split into two double quartets at δ 2.97 and 3.24. Decoupling of the CH_3 protons at δ 1.1 causes the collapse of the pattern for the methylene protons to an AB quartet and decoupling either of the double quartets causes the methyl signal to collapse to a pair of unequal singlets. These observations are consistent with the diastereotopic character of the methylene protons H_C and H_D , parallel to the diastereotopicity of protons H_A and H_B .



The facility of reaction of the azomethylenetriazines **5a** and **5b** with alcohols is not shared with the simple 4-methylenetriazines **4**, which appear to be impervious to alcohols. Thus, the arylazo-group does exert an activating effect on the exocyclic-ene group in molecules of type **5**. Whereas the arylazomethylenetriazines **5** are bright red in colour, the hydrazones **6** are yellow in colour; however, the hydrazones have been observed to revert back to the red precursors slowly in the solid state and quite quickly in chloroform solution presumably by acid catalysis. Examination of deuteriochloroform solutions of **6** by nmr over time showed the reappearance of the signals of **5a**.

The uv spectra of the azomethylenetriazines **5a** and **5b** show significant changes when solutions of these compounds in acetonitrile are acidified. Thus, the strong band at 420 nm in the spectrum of **5b** in acetonitrile shifts to 489 nm, and becomes more intense, when a little hydrochloric acid is added to the solution. The species responsible for the 489 nm band is unstable; the initial deep red colour of the hydrochloric acid/acetonitrile solution fades slowly to pink and then to colourless. An analogous shift in

the spectrum of **5a** from 430 to 477 nm is observed when hydrochloric acid is added to an ethanolic solution.

The azomethylenetriazine **5b** shows one very significant property not shared by **5a** or by the simple methylenetriazines **4a** and **4b**. When **5b**, or the ethoxyhydrazone **8**, is refluxed in ethanol for *ca.* 1 hour, a different deeply red-coloured product is obtained with a much higher melting point (235°). This deep-red compound also has a molecular ion at *m/e* 377 and is evidently an isomer of **5b** (confirmed by elemental analysis). The ir spectrum of the isomer shows that the ketone and ester carbonyl groups are intact (1640 and 1730 cm^{-1} respectively); new bands appear in the ir in the NH region at 3180 and 3300 cm^{-1} . The ^1H nmr spectrum confirms the presence of the acetyl-Me and ester-Et groups, but surprisingly the signal for the protons of the N-CH₂ group of **5b** have completely disappeared, and the associated carbon signal has shifted to the aromatic region of the ^{13}C spectrum.

Analysis of the spectroscopic properties of this red product lead to the structure **9**, a diarylhydrazine derivative which may exist in equilibrium with the tautomeric forms **9a**, a hydrazone, and **10**, a 3-arylazocinnoline. The absence of N-CH₂ signals in the nmr spectrum of this red product indicate that any amounts of the tautomers **9a** and **10** must be small. However, the deep red colouration of this material may derive from small amounts of one of the tautomers in equilibrium with the major species **9**, which would not be expected to display such colour. The red colour may be associated with the azo-form **10**; there are examples reported of yellow hydrazones reverting to red azo-tautomers in some carbohydrate derivatives [8]. Al-

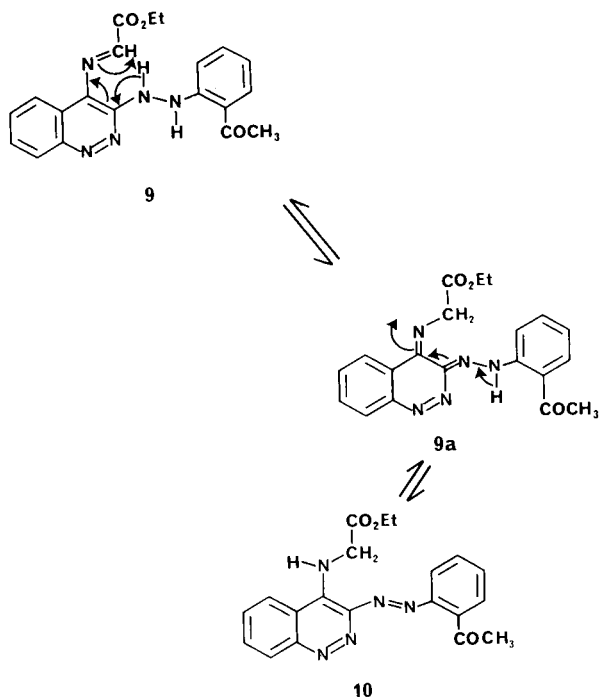
ternatively, the red colour may be associated with the autoxidation product of the hydrazone-form **9a**; it has been known for some time [9] that the colouration of phenylhydrazones is due to the presence of small amounts of intensely absorbing arylazoalkane hydroperoxides.

The nmr analysis to support structure **9** is as follows:

The ^{13}C nmr spectrum shows two carbonyl carbon atoms at 162.1 ppm for the α,β -unsaturated ester and 201.8 ppm for the aryl ketone. The aromatic region shows the required number of singlet, quaternary carbon atoms and of double doublets for the tertiary carbon atoms. There is one signal in the aromatic region showing only a doublet splitting at δ 140.1 corresponding to $^1J_{\text{CH}}$ and this is assigned to the imino carbon atom adjacent to the ester carbonyl group. This is corroborated by the observation that the signal of this carbon collapses to a singlet when the proton signal at δ 7.86 is irradiated; this observation also permitted assignment of the δ 7.86 signal to the vinylic proton. One of the singlets in the aromatic region at δ 173.5 is assigned to the carbon at C-3 of the cinnoline ring; the effect of the adjacent nitrogen atoms is clearly evident in the low-field signal of this aromatic carbon.

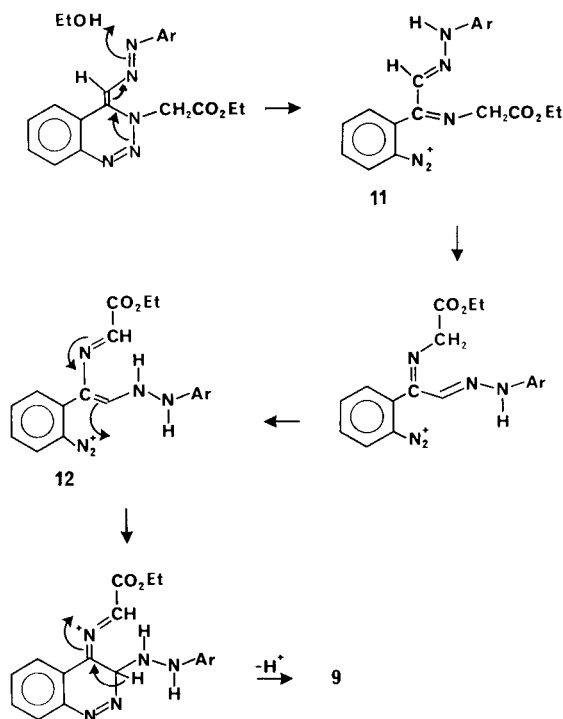
A significant feature of the ^1H nmr spectrum of **9** is the absence of the N-CH₂ signal. There are three one-proton singlets at δ 6.45, 7.86 and 12.53 ppm. As mentioned previously, the δ 7.86 signal is assigned to the vinylic CH, leaving the other signals assigned to the NH groups of the hydrazine. The large difference in chemical shift of the NH protons could be due to intramolecular hydrogen bonding of the NH group *ortho* to the acetyl group, which could also explain the absence of any exchange of this NH proton in the presence of deuterium oxide. The reluctance of the other NH proton in **9** to exchange may be related to the tautomerism between **9** and **9a**. Although **9a** is not detectable by nmr, the interaction of the NH proton with the vinylic carbon could be sufficient to hinder exchange. The ir spectrum of **9** supports the assigned structure, with carbonyl absorption at 1730 cm^{-1} (ester) and 1642 cm^{-1} (aryl ketone with NH in *ortho* position) and NH absorption bands at 3180 and 3280 cm^{-1} .

The Dimroth-type rearrangement of **5b** \rightarrow **9** in refluxing ethanol is similar to a previously reported isomerisation of the methylenetriazine **4a** to 4-methylaminocinnoline [4]. However, the rearrangement of **4a** required strongly acidic conditions compared to the relative ease of isomerisation of **5b** \rightarrow **9**, which appears to be a unique property of this triazine **5b**. The simple methylenetriazines **4a** and **4b** were recovered quantitatively unchanged after refluxing for two hours in ethanol, whereas the 3-methyl-4-arylazomethylenetriazine **5a** decomposed under these conditions, but yielded only an intractable tar which showed more than twelve spots on a thin layer chromatogram. The reactivity of **5b** in this rearrangement sug-



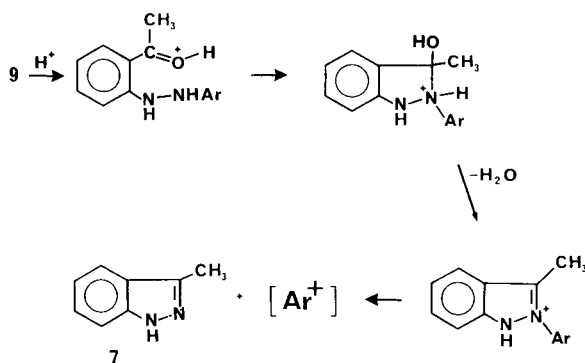
gests that the combined electron-withdrawing effect of the ethoxycarbonylmethyl group at N-3 and the azomethylene group at C-4 promotes the cleavage of the N₂-N₃ bond of the triazine ring (see Scheme I). Protonation of the azo-nitrogen by solvent also encourages the ring opening step to give the diazonium intermediate **11**. Bond rotation and a 1,5-prototropic shift gives the isomeric diazonium cation **12**, which then undergoes ring reclosure and loss of a proton to give the observed hydrazone **9**.

Scheme I



One other piece of evidence for the diarylhydrazone structure of **9** arises from its chemistry. When a solution of the red hydrazone **9** in chloroform is treated with concentrated hydrochloric acid for 1 hour, the red colour disappears and a complex mixture is formed. Chromatography of this mixture afforded only one stable, identifiable sub-

Scheme II



stance, which has been characterised as 3-methylindazole (**7**). The formation of this indazole is strong evidence for the presence of an *ortho*-acetyl phenylhydrazone moiety in the red compound **9**, and a likely mechanism for the formation of **7** is shown in Scheme II. 3-Methylindazole (**7**) is also found as a product from hydrochloric acid treatment of the hydrazone **6**.

EXPERIMENTAL

Melting points were obtained on a Koffler hot-stage apparatus and are uncorrected. Infra-red spectra were recorded with nujol mulls on a Perkin Elmer 299 grating spectrophotometer. The nmr spectra were obtained with Varian EM360 (60 MHz) or CFT20 (80 MHz) and Nicolet 360NB (360 MHz) spectrometers and mass spectra were recorded with a Dupont CEC-104 medium resolution spectrometer. The uv/visible spectra were recorded on a Cary 219 (Varian) spectrophotometer.

4-(2-Acetylphenylazo)methylene-3,4-dihydro-1,2,3-benzotriazines **5a** and **5b**.

The azomethylenetriazines **5a** and **5b** were prepared by coupling the diazonium salt from 2-aminoacetophenone with the appropriate amine, under the reaction conditions described previously [4].

Compound **5a** had λ_{\max} (acetonitrile): 193 (ϵ 3.37 \times 10⁴), 231 (ϵ 2.93 \times 10⁴), 268 (9.2 \times 10³), 304 sh (5.3 \times 10³) and 430 (ϵ 2.8 \times 10⁴) nm.

Compound **5b** had λ_{\max} (acetonitrile): 193 (ϵ 2.67 \times 10⁴), 236 (ϵ 2.20 \times 10⁴) and 420 (ϵ 2.78 \times 10⁴) nm.

3-Methyl-4-methoxy-3,4-dihydro-1,2,3-benzotriazin-4-ylformaldehyde 2'-acetylphenylhydrazone (**6**).

The azomethylenetriazine **5a** (100 mg) was dissolved in methanol (10 ml) and stirred at 60° for 0.5 hour. Evaporation of the red solution afforded the hydrazone **6**, 115 mg (100%). The product was recrystallised from methanol/ether to give light yellow needles, mp 133-135°; ir (carbon disulfide): ν_{\max} 3210, 3080, 3000, 2940, 2830 and 1645 cm⁻¹; uv (methanol): λ_{\max} 210 (ϵ 1.78 \times 10⁴), 226 (ϵ 2.16 \times 10⁴), 252 (ϵ 1.16 \times 10⁴), 295 (ϵ 1.44 \times 10⁴) and 369 (ϵ 8.10 \times 10³) nm; uv (methanol + hydrogen chloride): λ_{\max} 216, 245, 280 (sh) and 477 nm; ¹H nmr (deuteriochloroform): δ 2.60 (s, acetyl Me), 2.90 (s, N-Me), 3.58 (s, O-Me), 6.80 (t, arom), 7.33-7.43 (m, arom), 7.50 (t, arom), 7.51 (s, vinylic CH), 7.64 (d, arom), 7.74 (d, arom) and 11.9 (s, NH); ¹³C nmr (deuteriochloroform): 28.0 (acetyl Me), 37.5 (N-Me), 49.9 (O-Me), 84.5 (C-4 of triazine), 114.0, 117.4, 118.0, 125.5, 126.2, 128.1, 129.8, 130.1, 131.6, 135.1, 138.1, 141.2, 146.9 and 201.7 (C=O) ppm.

Anal. Calcd. for C₁₈H₁₉N₅O₂: C, 64.10; H, 5.70; N, 20.80. Found: C, 64.07; H, 5.87; N, 20.74.

3-Ethoxycarbonylmethyl-4-ethoxy-3,4-dihydro-1,2,3-benzotriazin-4-ylformaldehyde 2'-Acetylphenylhydrazone (**8**).

The crude azomethylenetriazine **5b** (1.0 g) was recrystallized quickly from absolute ethanol. The first crop of crystals were red needles (0.35 g), which had mp 124-127° and were identified by ir and nmr spectra as the pure azomethylenetriazine **5b** described above. The ethanolic filtrate was concentrated to afford a second crop of yellow crystals. Further recrystallisation of the yellow product from ethanol afforded the hydrazone **8**, 0.11 g, mp 121-122° (yellow needles); ir: ν_{\max} 3200, 1735 and 1640 cm⁻¹; uv (acetonitrile): λ_{\max} 192 (ϵ 2.65 \times 10⁴), 226 (ϵ 2.42 \times 10⁴), 252 (ϵ 1.18 \times 10⁴),

296 (ϵ 1.64×10^4) and 367 (ϵ 9.0×10^3) nm; uv (methanol + hydrogen chloride): λ max 192 and 488 (ϵ 2.54×10^4) nm; ^1H nmr (deuteriochloroform): δ 1.11 (3H, t, $J = 7.0$ Hz), 1.21 (3H, t, $J = 7.1$ Hz), 2.59 (3H, s), 2.97 (dq, $J = 7.0$ and 1.9 Hz) and 3.24 (dq, $J = 7.0$ and 1.9 Hz) (2H), 4.16 (2H, q, $J = 7.1$ Hz), 4.52-4.74 (2H, AB $J_{AB} = 17.2$ Hz), 6.80 (1H, t, $J = 7.9$ Hz), 7.36-7.56 (6H, m), 7.69 (1H, d, $J = 7.8$ Hz), 7.73 (1H, d, $J = 7.5$ Hz) and 11.88 (1H, s); ^{13}C nmr (deuteriochloroform): 14.0 (q, CH_3 of ethyl) and 14.7 (q, CH_3 of ethyl), 27.9 (q, acetyl CH_3), 51.1 (t, CH_2 of ethyl), 58.7 (t, N- CH_2), 61.3 (t, CH_2 of ethyl), 84.0 (s, C-4 of triazine), 114.0 (d), 117.0 (s), 118.0 (d), 118.6 (s), 126.1 (d), 130.0 (d), 131.5 (d), 134.9 (d), 137.5 (s), 140.1 (d), 141.0 (d), 146.8 (s), 169.0 (s, ester C=O), 201.4 (s, ketone C=O).

Anal. Calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}_3$: C, 62.40; H, 5.95; N, 16.54. Found: C, 62.83; H, 6.08; N, 16.60.

1-(4-Ethoxycarbonylformylideneaminocinnolin-3-yl)-2-(2'-acetylphenyl)hydrazine (**9**).

(a) The crude azomethylenetriazine **5b** (1.0 g) was dissolved in absolute ethanol (25 ml) and the solution refluxed for 0.75 hour. The deep red solution was cooled and filtered to afford a mass of dark red crystals (0.71 g), mp 235-236°; this product was identical with that prepared in (b).

(b) The hydrazone **8** (50 mg) was dissolved in absolute ethanol and the solution refluxed for 1.0 hour. Cooling the deep red solution afforded the cinnoline **9**, 11.6 mg (21%), mp 235-236° (red prisms); ms: m/e 377 (M^+), 359, 345, 304, 286, 278, 277, 263, 156, 155, 143, 131; ir: ν max 3280, 3180, 1730 and 1642 cm^{-1} ; uv (acetonitrile): λ max 192 (ϵ 3.85×10^4), 210 (ϵ 2.98×10^4), 255 (ϵ 1.67×10^4) and 398 (ϵ 2.5×10^4) nm; uv (acetonitrile + hydrogen chloride): λ max 192 (ϵ 2.9×10^5) and 500 (unstable) nm; ^1H nmr (deuteriochloroform): 1.37 (3H, t, $J = 7.1$ Hz, CH_3 -C), 2.65 (3H, s, acetyl Me), 4.36 (2H, q, $J = 7.1$ Hz, O- CH_2), 6.45 (NH), 6.72 (d), 6.94 (t), 7.18 (t), 7.37 (t), 7.42 (d), 7.48 (t), 7.56 (d), 7.82 (d), 7.86 (1H, s, CH) and 12.53 (1H, s, NH); ^{13}C nmr (deuteriochloroform): 14.1 (q, $J = 127$ Hz, CH_3 -C), 28.0 (q, $J = 128$ Hz, acetyl CH_3), 62.2 (t, $J = 148$ Hz, O- CH_2), 114.5 (dd, $J = 162$ and 6.2 Hz, arom), 118.3 (s), 119.8 (dd, $J = 164$ and 8.0 Hz), 120.7 (dd $J =$

164 and 8.0 Hz), 124.2 (dd, $J = 164$ and 7.7 Hz), 128.1 (s), 131.6 (dd, $J = 158$ and 7.8 Hz), 131.8 (dd, $J = 164.5$ and 8.5 Hz), 132.5 (dd, $J = 163$ and 8.5 Hz), 135.0 (dd, $J = 160$ and 8.5 Hz), 140.1 (d, $J = 167.4$ Hz), 145.5 (s), 151.2 (s), 154.1 (s), 162.1 (s, C=O, ester), 173.5 (s, C-3 of cinnoline) and 201.8 (s, C=O, ketone) ppm.

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_5\text{O}_3$: C, 63.65; H, 5.07; N, 18.56. Found: C, 63.70; H, 4.92; N, 18.33.

3-Methylindazole (7).

The cinnoline **9** (85 mg) was dissolved in chloroform (5 ml) and the solution treated with 50% aqueous hydrochloric acid (1.0 ml). After stirring for 1 hour, the mixture was washed with water and the dried chloroform layer evaporated to give an oily residue. Column chromatography of this residue on silica gel gave in an early fraction the 3-methylindazole (28 mg), mp 113° (lit [7] 113°); ir (carbon disulfide): ν max 3480 (NH) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.61 (3H, s, C-methyl), 7.15 (1H, t, arom), 7.38 (1H, t, arom), 7.43 (1H, d, arom), 7.68 (1H, d, arom) and 10.1 (1H, broad s, NH); ^{13}C nmr (deuteriochloroform): 11.9 (CH_3), 109.5, 120.1, 122.6, 126.6, 140.9, 143.4, 159.5, M^+ 132 ($\text{C}_8\text{H}_8\text{N}_2$).

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