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THE SYNTHESIS OF 3-VINYLINDOLES AND 11H-5-CYANOBENZO[a]CARBAZOLE

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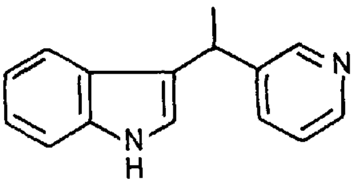
Abstract - The synthesis of 3-vinylindoles through Wadsworth Emmons reactions with 3-formyl and 3-acylindoles is described. Although 3-formylindoles react directly with phosphonate derivatives, 3-acylindoles need prior activation by N-sulphonation. 11H-5-Cyanobenzo[a]carbazole has been prepared by the oxidative cycloaddition of E-3-(indol-3'-yl) propenonitrile and benzyne.

3-[1-(3-Ethylpyridyl)]indoles (1) are essential intermediates in our synthesis of 6H-pyrido-[4, 3-b]carbazoles (2) and we have already described several ways of preparing them.[1] Unfortunately the most direct route - reactions between indolyl magnesium bromide and 3-(1-chloroethyl)pyridines - is unproductive and, although the 3-acylation of indoles with nicotinoyl chloride affords the corresponding indolylpyridylmethanones (3, R=H) in good yield so far we have been unable to effect an efficient interconversion of the two types of products by reactions with "one carbon" reagents. The primary reason for these failures is that the methanones are vinylogous amides, rather than ketones, and exhibit carbonyl bands at ~1600 cm^{-1} in their infra-red spectra. On conversion to the N-phenylsulphonyl



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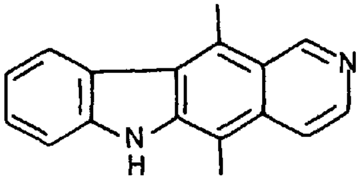

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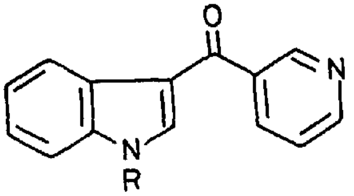

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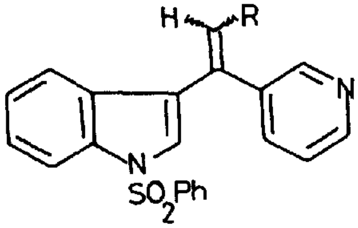

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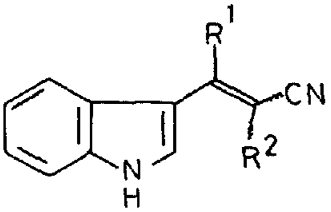
derivatives (3, R=SO$_2$Ph), however, these bands are shifted to $\sim$1640 cm^{-1}, and we expected that the products should now show enhanced ketone character. Disappointingly the N-substituent is sensitive to base treatment and reactions with methyl lithium, dimethylsulphonium methylide and Wittig reagents all caused extensive cleavage of the N-sulphonyl group and led to complex mixtures. Success was achieved with triethylphosphonoacetate and diethylphosphonoacetonitrile under Wadsworth Emmons conditions affording the 3-vinylindoles (4, R=CO$_2$Et) and (4', R=CN) respectively as mixtures of isomers. Here the increased reactivity of the reagents compared to, say, triphenylmethylphosphonium iodide ensured that no excess base remained after formation of the ylides to bring about N-deprotection. Attempts to introduce a single atom by using, for example, methyl bis-(dimethylamino)phosphonate were unsuccessful, but we hoped to be able to reduce, hydrolyse and decarboxylate the two products already in hand to 3-[1-(3-ethylpyridyl)]indole. The implementation of these steps proved to be difficult and unproductive even when compared to the yield obtained by the direct alkylation of indolyl magnesium bromide. Nevertheless these 3-vinylindoles are unique and they may well have value in the synthesis of pyrido-[4,3-b]carbazoles bearing a two carbon unit attached to position 11.



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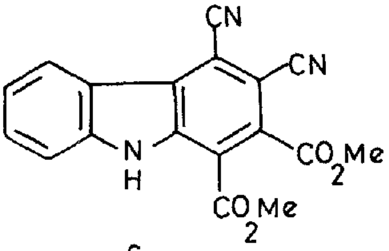
In principle other 3-vinylindoles may serve as the starting materials for a wide range of other heterocycles through cycloaddition reactions with either dienes or dienophiles. Noland *et al.*,[2] for example, have already shown that the vinylindole (5, R^1=R^2=CN) reacts with dimethyl acetylenedicarboxylate to give the carbazole (6) in moderate yield. It occurred to us that we might obtain other 3-vinylindoles through Wadsworth Emmons reactions with 3-formylindoles, but in practice since these compounds are much more reactive than the methanones (3, R=H) it proved unnecessary to N-sulphonylate them prior to reactions with phosphonate derivatives. Thus the 3-vinylindole (5, R^1=H; R^2=H) was prepared simply by reacting the ylide of diethylphosphonoacetonitrile with 3-formylindole. As in the reactions with the methanones the products were a mixture of E- and Z-isomers (10:1) which in this case were then separated by column chromatography into the individual isomers.

One point of interest in this synthesis was that instead of the usual Vilsmeier Haack route to 3-formylindole, we used the approach of Bergman *et al.*,[3] whereby indole is treated with imidazole and acetic anhydride and the product 3-imidazolin-2-ylindole (7) is then hydrolysed. This indirect procedure is very convenient and high yielding ($\sim$80%), but we were surprised to note that the ^{1}H n.m.r. spectrum of the imidazolinylindole (7) showed eight singlet peaks in the "methyl region" with an overall integration equivalent to six protons. When the spectrum (in d^6 DMSO) was re-run at 150° only a 6H singlet (δ 1.95 ppm) was observed and we conclude that this result reflects not only the presence of rotamers associated with each amide unit, but also restricted rotation about the bond joining the two heterocyclic units, one of which also contains a chiral centre.



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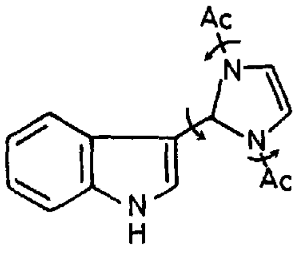
Despite Noland's results with what is a more sterically crowded substrate we were unable to combine the E-isomer (5, R^1=R^2=H) with dienophiles such as dimethyl acetylenedicarboxylate, tetracyanoethene or maleic anhydride. Either the reactions failed completely or else afforded complex mixtures. Cycloadditions with 1,3-dipolarophiles, e.g. benzonitrile oxide were also unsuccessful, however, when reacted with an excess of benzyne the benzo[a]carbazole (9) was formed in $\sim$15% yield. The structure of this product was unexpected since we anticipated that, in line with Noland's experience cited above, hydrogen



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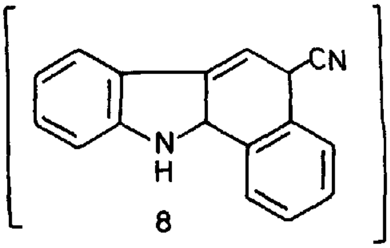

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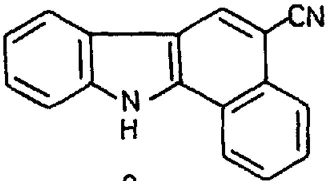

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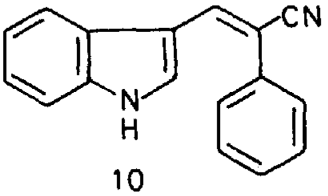

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cyanide would be eliminated from the initial adduct (8) rather than hydrogen.

We are certain, however, of the constitution of our product since it has been made previously[4] by the oxidative photocyclisation of the indolystyrene (10). Thus it appears that benzyne is an efficient oxidant for the intial adduct, but attempts to reduce the molar ratio of the aryne and the vinylindole to ∿1:1 simply reduce the yield of the carbazole without providing any other products.

EXPERIMENTAL

All UV spectra were recorded in 95% ethanol solution and IR spectra as mulls in Nujol.

3-(1'-Benzenesulphonylindol-3'-ylformyl)-pyridine (3, R=SO_2Ph). A solution of 3-(indol-3-ylformyl)pyridine (5g)[5] in dry dimethylsulphoxide (20cm^3) was added to a stirred solution of dimsyl sodium [sodium hydride (2.25g) in dry dimethylsulphoxide (10cm^3)] protected by an atmosphere of nitrogen. After 1h, benzene sulphonyl chloride (8.6g) was introduced and after another period of 1h, the mixture was poured onto crushed ice. The colourless solid which formed was filtered off and recrystallised from ethanol to give prisms of the title compound (5.3g, 65%), m.p. 110°. ν_{max} 1637 cm^{-1}, δ(d^6 DMSO) 9.15 (1H,s,H-2), 8.90 (1H,m,H-7'), 8.5 (1H,s,H-2'), 8.40-8.18 (4H,m), 8.08 (1H,m,H-4), 7.80-7.52 (5H,m), 7.51-7.45 (1H,dd,J_a=J_b=4Hz,H-5). [Found: C, 66.1; H, 4.0; N, 7.8. $C_{20}H_{14}N_2O_3S$ requires C, 66.3; H, 3.9; N, 7.7%].

3-(1'-Benzenesulphonyl-5'-methoxyindol-3'-ylformyl) pyridine. This compound, m.p. 155-156°, was similarly prepared, δ(d^6 DMSO) 9.10 (1H,s,H-2), 8.91 (1H,m,H-7'), 8.42 (1H,s,H-2'), 8.44-7.60 (9H,m), 7.15, 7.06 (1H,dd,J_a=8Hz,J_b=2Hz,H-6'), 3.85 (3H,s,CH_3O). [Found: C, 64.1; H, 4.0; N, 7.2. $C_{21}H_{16}N_2O_4S$ requires C, 64.2; H, 4.1; N, 7.1%].

Ethyl-3-(1"-benzenesulphonylindole-3"-yl)-3-(3'-pyridyl)propenoate (4, R=CO_2Et). Triethylphosphonoacetate (3.7g) was added dropwise to a cooled and well stirred suspension of sodium hydride (0.8g) in dry tetrahydrofuran (25cm^3) protected by a nitrogen atmosphere. When no further gas was evolved, 3-(1'-benzenesulphonyl indol-3'-ylformyl)pyridine (5g) in tetrahydrofuran (50cm^3) was introduced into the reaction mixture which was then left stirring overnight. When the mixture was poured onto ice a solid was formed and this, on crystallisation from methanol, afforded the title compound as a single isomer (4.9g, 80%), m.p. 123°, (although TLC analyses of the crude reaction product initially indicated two components of similar physical properties to be present, the minor component was not isolated). λ_{max} (ε) nm., 216 (40,390), 256 (19,980), 308 (18,430), ν_{max} cm^{-1}, 1710, δ($CDCl_3$) 8.65 (1H,bd,J=6Hz H-6'), 8.5 (1H,bs,H-2'), 8.01-7.22 (12H,m), 6.56 (1H,s,H-2), 4.05 (2H,q,J=8Hz,CH_2CH_3), 1.1 (3H,t,J=8Hz,CH_2CH_3). [Found: C, 68.45; H, 4.1; N, 11.1. $C_{22}H_{15}N_3O_2S$ requires C, 68.6; H,3.9; N,10.9%].

3-(1"-Benzenesulphonylindol-3"-yl)-3-(3'-pyridyl)propenonitrile (4, R=CN). The previous experiment was repeated using diethylphosphonoacetonitrile (5.9g) instead of triethylphosphonoacetate. Again only one isomer was isolated, although TLC analyses indicated two to be present in the crude product (9.3g, 86%), m.p. 156°, λ_{max} (ε)nm., 217 (23,050), 256 (12,420), 315 (11,890), ν_{max} cm^{-1}, 2200, δ(d^6 DMSO) 8.8 (2H,m,H-2',H-6'), 8.21-7.22 (12H,m), 6.6 (1H,s,H-2). [Found: C, 66.5; H, 4.8; N, 6.7. $C_{24}H_{20}N_2O_4S$ requires C, 66.7; H, 4.7; N, 6.5%].

3-(Indol-3'-yl)propenonitrile (5, R^1=R^2=H) Diethylphosphonoacetonitrile (12g) was added over a 2h period to a well stirred suspension of sodium hydride (1.62g) in tetrahydrofuran (60cm^3) maintained at 0-5° under a nitrogen atmosphere. Further portions (total 50cm^3) of tetrahydrofuran were added during the course of the reaction to prevent solidification. 3-Formylindole (8.18g) in the same solvent 100cm^3) was then introduced and the stirring continued overnight. Then the contents of the reaction flask were poured onto ice and the mixture extracted with dichloromethane (3 x 250cm^3). After drying, the combined solvent layers were evaporated to yield a pale yellow solid which was flash chromatographed on silica eluting with petrol (40-60°) and ethyl acetate (3:2). Single spot fractions (TLC silica petrol 40-60°-ethylacetate, 3:2) R_F 0.38 were combined and evaporated to give *E*-3-(indol-3-yl)propenonitrile as a pale yellow solid (6.96g, 73.4%), m.p. 135-137° (lit., 147-148°[6] or 140-147°[7]), *m/e* (%) 168 (M^+ 100), 167 (16), 141 (11), 140 (17), 114 (10). $\lambda_{max}(\varepsilon)$ nm., 221 (12,721), 271 (8,075), 323 (16,026), ν_{max} 3300 (NH), 2215 (CN), 1610 (C=C), δ($CDCl_3$:d^6 DMSO, 10:1) 11.16 (1H,bs,N*H*), 7.78-7.17 (6H,m), 5.73 (1H,d,*J*=17Hz, H-2). [Found: C, 78.5; H, 5.0; N, 16.6. Calculated for $C_{11}H_8N_2$: C, 78.55; H, 4.8; N, 16.7%].

Single spot fractions R_F 0.60 were also combined and evaporated to give the *Z*-isomer (0.70g, 7.4%), m.p. 124-125°, *m/e* (%), 168 (M^+ 100), 167 (15), 141 (19), 140 (29), 114 (15). λ_{max} (ε) nm., 218 (17,930), 223 (17,930), 337 (9,903), ν_{max} cm^{-1}, 3300 (NH), 2210 (CN), 1595 (C=C), δ($CDCl_3$:d^6 DMSO, 10:1) 11.56 (1H,bs,NH), 8.28 (1H,bd,H-2'; irrad. at 11.56 reduces this signal to a broad singlet), 7.75-7.15 (5H,m), 5.19 (1H,d,*J*=12Hz,H-2). [Found: C, 78.6; H, 4.75; N, 17.0. $C_{11}H_8N_2$ requires C, 78.55; H, 4.8; N, 16.7%].

11H-5-Cyanobenzo[a]carbazole (9). *Benzene diazonium-2-carboxylate hydrochloride* (0.74g) as a suspension in acetonitrile (10cm^3) was added in portions to *E*-3-(indol-3'-yl)propenonitrile (1.0g) in 1,2-epoxypropane (0.55cm^3) and acetonitrile (3cm^3) under reflux and protected under an atmosphere of nitrogen. After 2h, the solvents were removed and the oily product partitioned between chloroform (20cm^3) and aqueous sodium carbonate (2N,20cm^3). The organic phase was collected, dried and evaporated to yield a dark brown solid (760mg) which was chromatographed on silica using diethylether-ethylacetate mixtures of increasing polarity as eluants. Some unreacted nitrile was obtained together with a component R_F 0.61 (silica petrol 40-60°-ethylacetate, 3:2) which gradually crystallised as amber prisms of the title compound (0.21g, 15%), m.p. 295-300° (sublimes) (sealed tube m.p. ∿ 320-325°, lit.,[4] 331°), *m/e* (%) 242.0843 (18), calculated for $C_{17}H_{10}N_2$ 242.0844, 168 (100), 140 (35), 139 (24), λ_{max} nm., 231, 245, 260.5, 284, 301, 334 342.5, 353, ν_{max} cm^{-1}, 3290 (NH), 2230 (CN), δ($CDCl_3$:d^6 DMSO, 5:1) 11.29 (1H,bs,NH exchanged by D_2O), 8.79 (2H,bs), 8.35-7.10 (7H,m). [Found: C, 84.3; H, 4.2; N, 11.4. Calculated for $C_{17}H_{10}N_2$: C, 84.3; H, 4.2; N, 11.6%].

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