Novel Products of 1,4-Addition of Alcohols to 5-Ethenyl-3,4-dihydro-4-isopropylidene-2,2-dimethyl-2*H*-pyrrole

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Reactions of 5-ethenyl-3,4-dihydro-4-isopropylidene-2,2-dimethyl-2*H*-pyrrole (**2**) with a variety of alcohols led to formation of the 1,4-addition products (**4**) rather than the 2-alkoxypyrrolidine derivatives [*e.g.* (**7**)]. On distillation the adducts (**4**) suffered thermal rearrangement to the 5-(2-alkoxyethyl)-3,4-dihydro-2*H*-pyrroles (**5**).

Heteroatom dienes have been used sparingly in organic synthesis.[1] Perhaps the most useful application involved *N*-acyl-1-azadienes such as (**1a**)[1,2] or dialkylamino-1-azadienes,[1,3] which have been used as enophiles in cycloaddition reactions. Cyclic 1-azadienes such as 5-ethenyl-3,4-dihydro-2*H*-pyrrole are virtually unknown, however, as are their synthetic applications. The preparation and reactions of these compounds appeared to be a fruitful area for study, but only one 5-ethenyl-3,4-dihydro-2*H*-pyrrole derivative was known, *viz.* 5-ethenyl-3,4-dihydro-4-isopropylidene-2,2-dimethyl-2*H*-pyrrole (**2**), prepared by reaction of 2,5-dimethylhexane-2,5-diol with acrylonitrile in concentrated sulphuric acid.[4] We have explored synthetic routes to 5-ethenyl-3,4-dihydro-2*H*-pyrrole derivatives in the belief that they would operate as Michael donors with electron-deficient alkenes. The initial Michael addition would generate an enolate-iminium salt intermediate, and subsequent vinylogous addition of the enolate to the iminum salt would complete the cycloaddition process. The 5-ethenyl-3,4-dihydro-2*H*-pyrroles have remained elusive, however, prompting us to examine the reactivity of the dienes (**1**). The neopentyl-like environment of the imine nitrogen of structure (**2**) suggested that it should be a rather poor Michael donor. However, refluxing (**2**) with acrylonitrile or ethyl acrylate, in methanol, gave, after distillation, 3,4-dihydro-4-isopropylidene-5-(2-methoxyethyl)-2,2-dimethyl-2*H*-pyrrole (**5a**), in 84% and 85% yield, respectively. Further study revealed that the initial product of the reaction, before distillation, was the enamine (**4a**), and it was obvious that compound (**2**) had reacted with the methanol solvent rather than with the alkene. We were curious about the scope of this reaction and subsequently treated (**2**) with ethanol, propan-1-ol, butan-1-ol, and propan-2-ol, at reflux. The adducts (**5b**—**e**) were obtained readily, on distillation of the products. Methanol was the most reactive of the alcohols examined.

The formation of products such as (**4**) and (**5**) was curious since previous work had shown that acyclic 1-azadienes, without conjugating groups, did not react with alcohol solvents.[5] This contrasted with 1-azadienes possessing conjugating groups, which reacted with protic solvents such as methanol by a 1,2-addition process.[1-3,6] Fowler has shown that *N*-acyl-1-azadienes such as (**1a**) react with methanol to give the 2-methoxy derivatives, *e.g.* (**6a**).[2] Likewise, the imine (**1b**) reacts with benzenethiol to give (**6b**).[6] In no case was a 1,4-addition product such as (**4**) reported; thus the reaction we have observed with (**2**) appears unique. It is possible that the reaction proceeds *via* a 'normal' 1,2-addition of methanol of (**2**), forming the species (**7**) as an intermediate. This would be analogous to the reactions observed with (**1**), but would require that (**7**) suffer a 1,3-sigmatropic shift, or an ionic rearrangement, to generate (**5**). Such sigmatropic or ionic shifts in the acyclic systems have not been reported, and appeared to be difficult in this system.

We present here evidence in support of the contention that the dihydro-2*H*-pyrrole (**2**), in contrast to 1-azadienes such as (**1**), reacts with alcohols by a direct 1,4-addition process to form the enamine (**4**), as the initial product. Thermal rearrangement of (**4**) to (**5**) occurs on distillation. We have shown that this reaction follows pseudo-first-order kinetics, consistent with a direct 1,4-addition, and that the acidity of the alcohols plays a role in the addition process.

Results and Discussion

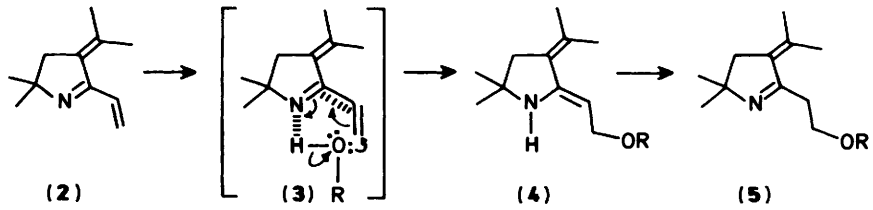
Dissolution of the dihydro-2*H*-pyrrole (**2**) in [$^2H_4$]methanol, at 35 °C, clearly showed loss of the vinyl signal at δ 5.40—7.05 and the appearance of a methylene signal at δ 3.68, typical of an enamine.[7] A plot of [(**2**)] *vs.* time is shown in the Figure; the reaction follows pseudo-first-order kinetics.[8] The plot of ln [(**2**)] *vs.* time was linear over three half-lives ($t_{\frac{1}{2}} = 8.28 \times 10^4$ s^{-1}), with rate 8.38×10^{-6} dm^3 mol^{-1} s^{-1}, at 25 °C. At 60 °C the reaction was also first-order with $t_{\frac{1}{2}}$ 3.178×10^4 s^{-1} and rate 2.18×10^{-5} dm^3 mol^{-1} s^{-1}. Compound (**4**) was the only observed product, suggesting that the conversion into (**5**) requires the more vigorous thermal conditions found during distillation.

The pseudo-first-order behaviour is pertinent to the question of 1,2- *vs.* 1,4-addition. We did not observe a ^{1}H n.m.r. signal corresponding to (**7**), or any other intermediate. If the concentration of (**7**) was too small for detection by n.m.r, a very fast conversion of (**7**) into (**4**) would be required. The 'normal' 1,2-addition of alcohols to 1-azadienes (**1**) gives (**6**)[1-3] as the isolated product. One possible rearrangement pathway would be a 1,3-alkoxy shift. No such sigmatropic rearrangement has been reported with derivatives of (**6**). A 1,3-sigmatropic rearrangement of (**7**) to (**4**) would probably proceed as a concerted, antarafacial migration under thermal conditions,[9] a process which should be difficult at the reaction temperatures utilized. A stepwise, ionic process could also produce this isomerization since the cation involved would be highly delocalized. We have not observed any ^{1}H n.m.r. signal to support either mechanistic rationale, however, and there is no evidence that an ionic rearrangement would be too fast for observation of (**7**) by ^{1}H n.m.r. It is, therefore, reasonable to assume that if (**7**) were an intermediate, it would be observed by ^{1}H n.m.r., and its absence lends credence to the idea of a direct 1,4-addition of the alcohol to (**2**).

We envision a transition state such as (**3**), in which interaction of the basic imine nitrogen and the acidic proton of the alcohol leads to transfer of the alcohol oxygen to the end of the con-

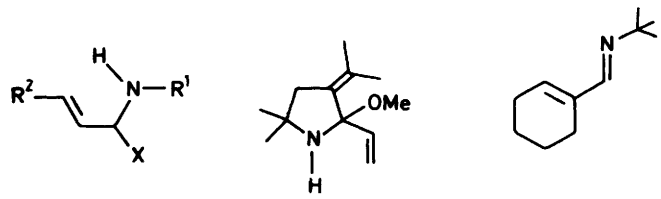
(1)

a; R^1 = Ac, R^2 = H
b; R^1 = R^2 = Ph



(2) (3) R (4) (5)

a; R = Me b; R = Et c; R = Pr d; R = Bu e; R = Pr^i



(6) (7) (8)

a; R^1 = Ac, R^2 = H, X = OMe
b; R^1 = R^2 = Ph, X = SPh

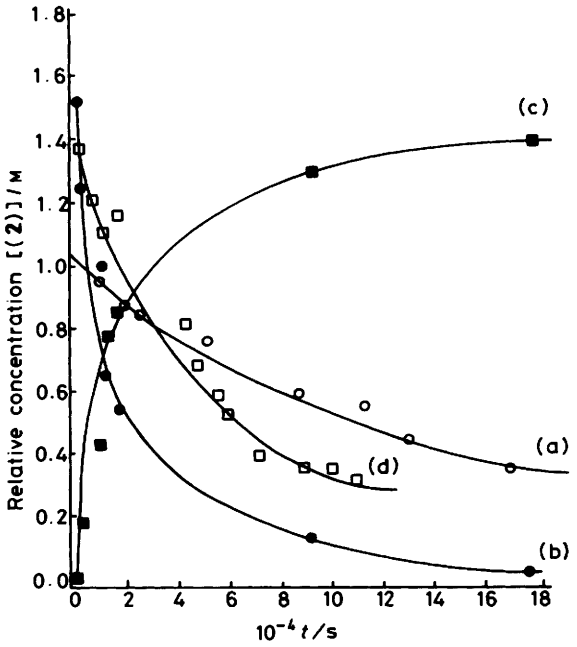


Figure. Plot of concentration of (**2**) *vs.* time for reaction of (**2**) (a) with methanol at 25 °C; (b) with [$^2H_4$]methanol at 60 °C and (c) the resultant formation of (**4**); and (d) reaction with [$^2H_8$]propan-2-ol at 60 °C

jugated chain, in the six-centre process shown. This sequence is consistent with the hydrogen-bonding phenomenon of amines and alcohols and the nucleophilic nature of the alcoholic oxygen, and would generate the conjugated product (**4**) directly. This is also consistent with our observation of a slow process following pseudo-first-order kinetics with no observed intermediate. If this premise is correct, there should be a correlation between the acidity of the alcohol and the relative reactivity with (**2**). Indeed, methanol was the most reactive of the alcohols examined. When [$^2H_8$]propan-2-ol, for example, was stirred with the dihydro-2*H*-pyrrole (**2**), neat at 35 °C, very little reaction was observed over 14 days. Reaction occurred at a rate of 1.46 × 10^{-6} dm^3 mol^{-1} s^{-1} when the mixture was heated to 60 °C, with $t_{\frac{1}{2}}$ 4.74 × 10^5 s^{-1}. The kinetic plots of (**2**) with [$^2H_4$]methanol and [$^2H_8$]propan-2-ol, at 60 °C, can be compared in the Figure, indicating that both reactions show pseudo-first-order kinetics. Propan-2-ol is known to be less acidic than methanol by about 2 pK_a units,[10] and the observed kinetics offer some corroboration for the relevance of the acidity of the alcohols in the 1,4-addition to (**2**). The kinetics of the reaction with water would be pertinent to this argument; such information would facilitate a study of the dependence of the rate on pH, but was unavailable because of the insolubility of (**2**) in D_2O. Admixture of the azadiene and water with a co-solvent such as ether, tetrahydrofuran, or acetone improved the solubility but the reaction was too slow, even at elevated temperatures, for useful kinetic data to be obtained.

There is no spectral, kinetic, or product evidence for the presence of a 1,2-adduct such as (**7**); nor for an intermediate resulting from a sigmatropic shift or an ionic rearrangement of (**7**) to (**4**). The rearrangement to (**5**) must be thermal in nature since (**4**) is the only observed product at ambient temperatures. The conjugating effect of the isopropylidene group in 1-azadienes may assist addition of the alcohol. In (**1**), a con-

jugating π-system was present in all cases where 1,2-addition of alcohols was observed: an acyl carbonyl group in (**1a**) and a phenyl group in (**1b**). This is supported by the observation that 1-azadienes such as (**8**) are isolated from methanolic solvents without formation of 1,2- or 1,4-addition products.[5] It remains to be explained, however, why (**2**) suffers 1,4-addition rather than the 1,2-addition observed with (**1**). The presence of the methyl on the isopropylidene group in (**2**) would be expected to encumber sterically the approach of the alcohol to C-2, especially if the alcohol were associated with the imino nitrogen *via* hydrogen bonding. The geminal methyl groups at C-5 would also exacerbate the steric encumbrance. Such steric effects would retard the 1,2-addition, allowing the observed 1,4-addition to proceed.

A second, perhaps more important, effect of the isopropylidene group is the influence of the isopropylidene methyl groups on the conformation of the vinyl group of (**1**). The methyl groups probably force the 5-ethenyl-3,4-dihydro-2*H*-pyrrole moiety of (**1**) into the s-*cis* conformation shown, rather than the usual s-*trans* conformation. The s-*cis* conformation is more amenable to 1,4-type addition and may be the dominant factor in the 'anomalous' reactivity of (**1**).

Clearly, the 1,4-addition of alcohols with (**2**) is a unique observation in the chemistry of 1-azadienes. Although the hoped for Michael addition of (**2**) was precluded, the reaction we have observed offers insights into anomalous pathways which are possible in 1-azadienes possessing unusual steric or conjugating effects.

Experimental

The ^{1}H n.m.r. spectra were recorded at 200 MHz and the ^{13}C spectra at 50.1 MHz with an IBM WP200-SY spectrometer (standard tetramethylsilane). The mass spectra were recorded with an AEI MS-902 spectrometer. The 5-ethenyl-3,4-dihydro-4-isopropylidene-2,2-dimethyl-2*H*-pyrrole (**2**) was prepared by the method of Meyers, from reaction of 2,5-dimethylhexane-2,5-diol and acrylonitrile in concentrated sulphuric acid.[4] The methanol, ethanol, propan-1-ol, butan-1-ol, propan-2-ol, [$^2H_4$]methanol, D_2O, [$^2H_8$]propan-2-ol, acrylonitrile, and 2,5-dimethylhexane-2,5-diol were obtained from Aldrich Chemical Co.

General Procedure for the Preparation of the Adducts (**5**).—A solution of the ethenyldihydropyrrole (**2**) (1.00 g, 6.13 mmol) in the appropriate alcohol (25 ml) was refluxed for 4—6 h, then cooled. The alcohol was removed *in vacuo*, and the residual oil distilled at reduced pressure to give the adduct (**5**). If the oil was isolated directly, without distillation, the product was the enamine (**4**).

(a) *With methanol.* Refluxing the solution for 4 h gave, after distillation, 3,4-*dihydro*-4-*isopropylidene*-5-(2-*methoxyethyl*)-2,2-*dimethyl*-2H-*pyrrole* (**5a**) (0.730 g, 3.74 mmol, 61%), b.p. (0.2 mmHg) 60—62 °C; $\delta_H(CDCl_3)$ 1.18 (s, 6 H), 1.78 (s, 3 H), 1.98 (s, 3 H), 2.35 (s, 2 H), 2.88 (t, 2 H), 3.59 (s, 3 H), and 3.79 (t, 2 H); $\delta_C(CDCl_3)$ 21.14 (q), 25.16 (q), 29.62 (q), 44.71 (t), 45.03 (t), 66.42 (s), 68.70 (q), 72.79 (t), 129.89 (s), 136.60 (s), and 170.19 (s); *m/z* 195 (20%), 180 (100), 148 (92), 133 (36), 95 (39), 73 (41), and 41 (81); $\nu_{max.}$ (neat, KBr) 3 584, 3 184, 3 130, 3 106, 3 030, 1 761, 1 700, 1 621, 1 581, 1 470, 1 432, 1 395, 1 220, 1 158, and 1 028 cm^{-1} (Found: M^+, 195.1614. $C_{12}H_{21}NO$ requires *M*, 195.1624).

Similar reaction at 35 °C, for 12 h, gave the enamine (**4a**) (0.536 g, 2.75 mmol, 45%).

(b) *With* [$^2H_4$]*methanol.* Reaction with [$^2H_4$]methanol at 60 °C, for 50 h, gave N-*deuterio*-4-*isopropylidene*-2,2-*dimethyl*-5-(2-*trideuteriomethoxyethylidene*)*pyrrolidine* (**4a**), $\delta_H(CDCl_3)$ 1.21 (s, 6 H), 1.84 (s, 3 H), 2.04 (s 3 H), 2.44 (s, 2 H), 3.65 (s,* 2 H), and 4.69 (s,* 1 H); $\delta_C(CDCl_3)$ 20.14 (q), 24.42 (q), 28.48 (q), 44.25 (t), 49.01 (m, CD_3), 64.58 (s), 68.18 (t), 132.25 (s), 135.64 (s), 161.98 (d), and 166.80 (s); $\nu_{max.}$ (neat, KBr) 3 436, 2 710, 2 681, 2 617, 2 500, 2 250 (N–D), 2 170 (C–D), 1 529, 1 600, 1 391, 1 371, 1 340, 1 160, and 1 005 cm^{-1} (Found: M^+, 199.1874. $C_{12}H_{17}D_4NO$ requires *M*, 199.1875).

(c) *With ethanol.* Refluxing the solution for 5 h gave, after distillation, the 5-(2-*ethoxyethyl*) *derivative* (**5b**) (0.87 g, 3.92 mmol, 64%), b.p. (0.4 mmHg) 68—70 °C; $\delta_H(CDCl_3)$ 0.83 (t, 3 H, *J* 7.0 Hz), 1.19 (s, 6 H), 1.80 (s, 3 H), 1.94 (s, 3 H), 2.40 (s, 2 H), 2.77 (t, 2 H, *J* 8.1 Hz), 3.35 (t, 2 H, *J* 8.1 Hz), and 3.67 (t, 2 H, *J* 6.8 Hz); *m/z* 180 (21%), 163 (38), 148 (100), 136 (70), 133 (49), 95 (81), 67 (54), and 41 (73) (Found: M^+, 209.1779. $C_{13}H_{23}NO$ requires *M*, 209.1781).

(d) *With propan-1-ol.* Refluxing the solution for 5 h gave, after distillation, the 5-(2-*propoxyethyl*) *derivative* (**5c**) (0.57 g, 2.55 mmol, 42%), b.p. (0.4 mmHg) 86—88 °C; $\delta_H(CDCl_3)$ 0.95 (t, 3 H), 1.19 (s, 6 H), 1.26—1.31 (m, 2 H), 1.76 (s, 3 H), 2.34 (s, 2 H), 2.80 (t, 2 H), and 3.25—3.96 (m, 4 H); *m/z* 180 (54%), 148 (71), 136 (74), 95 (69), 66 (49), 55 (39), and 41 (100) (Found: M^+, 233.1925. $C_{14}H_{25}NO$ requires *M*, 223.1938).

(e) *With butan-1-ol.* Refluxing the solution for 6 h gave, after distillation, the 5-(2-*butoxyethyl*) *derivative* (**5d**) (0.475 g, 2.00 mmol, 33%), b.p. (0.2 mmHg) 96—98 °C; $\delta_H(CDCl_3)$ 0.83 (t, 3 H), 0.96—1.56 (m, 10 H), 1.91 (s, 3 H), 2.35 (s, 2 H), 2.73 (t, 2 H), and 3.47 (t, 2 H); *m/z* 180 (28%), 148 (53), 136 (19), 95 (31), 56 (100), and 41 (94) (Found: M^+, 237.2090. $C_{15}H_{27}NO$ requires *M*, 237.2094).

(f) *With propan-2-ol.* Refluxing the solution for 6 h gave, after distillation, the 5-(2-*isopropoxyethyl*) *derivative* (**5e**) (0.350 g, 1.57 mmol, 26%), b.p. (0.2 mmHg) 70—73 °C; $\delta_H(CDCl_3)$ 1.10 (d, 6 H), 1.25 (s, 6 H), 1.75 (s, 3 H), 1.96 (s, 3 H), 2.38 (s, 2 H), 2.78 (t, 2 H), and 3.45—4.10 (m, 3 H); $\delta_C(CDCl_3)$ 20.98 (q), 22.24 (q), 25.20 (q), 29.65 (q), 35.16 (t), 45.26 (t), 66.16 (s), 67.19 (t), 71.47 (d), 130.10 (s), 137.08 (s), and 167.33 (s); *m/z* 180 (100%), 148 (96), 136 (39), 133 (42), 95 (48), 66 (38), and 41 (93) (Found: M^+, 223.1935. $C_{14}H_{25}NO$ requires *M*, 237.1938).

(g) *With* [$^2H_8$]*propan-2-ol.* Reaction with [$^2H_8$]propan-2-ol at 60 °C, for 50 h, gave *N*-deuterio-4-isopropylidene-5-(heptadeuterioisopropoxyethylidene)-2,2-dimethylpyrrolidine (**4e**): $\delta_H(CDCl_3)$ 1.21 (s, 6 H), 1.81 (s, 3 H), 2.03 (s, 3 H), 2.39 (s, 2 H), 3.68 (s, 2 H), and 5.17 (s, 1 H); $\delta_C(CDCl_3)$ 21.20 (q), 21.96 (q), 24.20 (q), 29.82 (m), 36.74 (t), 45.79 [m, $CD(CD_3)_2$], 62.91 (s), 68.22 (t), 131.53 (s), 137.36 (s), 163.50 (d), and 168.81 (s).

Reactions of the 5-*Ethenyl*-3,4-*dihydro*-2H-*pyrrole* (**2**) *with* [$^2H_4$]*Methanol and* [$^2H_8$]*Propan*-2-*ol.*—A mixture of compound (**2**) (0.122 g, 0.75 mmol) in the alcohol (0.50 ml) was added to an n.m.r. tube containing a small amount of tetramethylsilane; dimethylformamide (0.04 g, 0.53 mmol) was added as an internal standard. The signals at δ 3.68 and 5.40—7.05 were observed, at intervals, until the reaction was deemed complete. Integration of these signals (normalized to the standard signal at δ 8.10) gave the ratio of the products used for the kinetic plots. The n.m.r. tubes were maintained at 35 °C or 60 °C in an oil-bath. The kinetic data obtained are presented in the Figure.

* These two signals appeared as singlets; only slight broadening was observed at 200 MHz. Intramolecular dipole effects between the N–H and *O*-methyl groups may hold the methylene protons at an angle which, by the Karplus equation, would give a small coupling constant. This is essentially an anomeric-type effect which is known to reduce the coupling constant.

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