The Reaction of Aldehydes and Ammonium Acetate with some Acetonyl and Phenacyl Derivatives: A Correction

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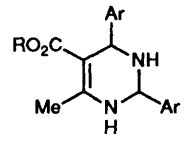
The products formed from the reaction of aromatic aldehydes and ammonium acetate with pentane-2,4-dione are 5-acetyl-2,4-diaryl-6-methyl-1,2,3,4-tetrahydropyrimidines; when 1-phenyl-2-phenylsulfonylethan-1-one is used instead of pentane-2,4-dione, 3-aryl-3-arylmethyleneamino-1-phenyl-2-phenylsulfonylpropan-1-ones are formed. There is no evidence of oxazine formation.

The reaction of aromatic aldehydes with β-keto esters and ammonia (or, alternatively, with β-aminocrotonates) affords 1,2,3,4-tetrahydropyrimidines **1**[1,2] which, under mild conditions, undergo fission and rearrangement.[3] We now report that, not surprisingly, the reaction of benzaldehyde with pentane-2,4-dione and ammonium acetate affords the 1,2,3,4-tetrahydropyrimidine derivative **2a**. The formulation **2a** is confirmed by microanalysis (carbon, hydrogen and nitrogen) and by ^{1}H and ^{13}C NMR spectroscopy.



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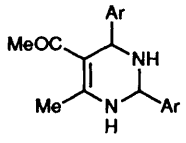

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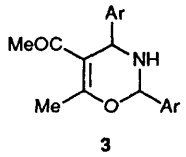


3

a Ar = Ph
b Ar = *o*-$C_6H_4NO_2$
c Ar = *m*-$C_6H_4NO_2$
d Ar = *p*-$C_6H_4NO_2$

It has recently been reported that the reaction of benzaldehyde with pentane-2,4-dione and ammonium acetate under similar conditions affords the unusual 3,4-dihydro-2*H*-1,3-oxazine derivative **3a** as sole product.[4] We have attempted to repeat this preparation, duplicating the conditions described, but the only product obtained is the 1,2,3,4-tetrahydropyrimidine derivative **2a**; the formation of an oxazine product **3a** cannot be confirmed.

Consideration of the physical, analytical and spectral data suggests that the compound formulated as the oxazine **3a** is identical with the tetrahydropyrimidine **2a**. The melting point of the compound formulated as the oxazine **3a** is slightly lower than that of the tetrahydropyrimidine **2a** (see Table 1). The results of carbon and hydrogen analysis are, of course, very similar, but, significantly, nitrogen analysis was not performed on the compound formulated as the oxazine **3a**.

The positions of the signals in the ^{13}C NMR spectrum recorded for the compound formulated as the oxazine **3a** are virtually identical with those of the tetrahydropyrimidine **2a** (*cf.* Table 2). The positions of the signals in the ^{1}H NMR spectra are also virtually superimposable. It is significant, however, that in the case of the tetrahydropyrimidine **2a** the NH signals (exchangeable with D_2O) are detected at δ 3.05 and 7.36 with the 10 aryl protons occurring as a multiplet at δ 7.33–7.20. The ^{1}H NMR spectrum of the compound formulated as the oxazine derivative **3a** was interpreted as having only one NH signal, at δ 3.11, all the signals at δ 7.44–7.21 being attributed to aryl protons.

Formation of tetrahydropyrimidine products rather than 3,4-dihydro-2*H*-1,3-oxazine derivatives is confirmed when *o*- and *m*-nitrobenzaldehydes are used instead of benzaldehyde. The microanalytical data of the products (carbon, hydrogen and nitrogen) accord with the tetrahydropyrimidine formulation, as do the NMR spectra. In the case of each compound, two distinct NH signals (exchangeable with D_2O) are present in the ^{1}H spectra.

The patterns of the ^{13}C NMR spectra for the compounds formulated as **3b** and **3c** are identical with those of the tetrahydropyrimidines **2b** and **2c**, but each signal, as reported, occurs consistently 4.2 ppm downfield. (The ^{1}H signals also display a downfield shift.) We can only suggest that this consistent discrepancy may be due to an incorrect setting of the NMR machine.

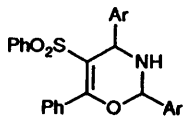
In our experience, the best yields of tetrahydropyrimidines **2** are obtained when the reaction is carried out at room temperature. Even the mild heating conditions indicated[4] tend to reduce the yield. The rather surprising claim that *p*-nitrobenzaldehyde fails to react in the same way as *o*- and *m*-nitrobenzaldehydes is not confirmed when the reaction is carried out at room temperature, the appropriate 1,2,3,4-tetrahydropyrimidine **2d** being readily obtained.

Apart from the products formed using pentane-2,4-dione, it has also been claimed[4] that when 1-phenyl-2-phenylsulfonylethan-1-one is used in the reactions, instead of pentane-2,4-dione, the 3,4-dihydro-2*H*-1,3-oxazine derivatives **5** are obtained. Once again, we find no evidence of oxazine formation; in fact, the products formed are the uncyclised 3-aryl-3-arylmethyleneamino-1-phenyl-2-phenylsulfonylpropan-1-ones **4**.

Compounds formulated as the oxazines **5** are isomeric with the propanone derivatives **4** and, accordingly, the formulation **5** cannot be rejected on the basis of analytical data. The only NMR spectral evidence proffered for any of the compounds formulated as **5** is the ^{1}H NMR spectrum in deuteriochloroform of the phenyl derivative **5a**, the signals for which are reported as δ 8.13–7.19 (m, 20 ArH), 5.80 (1 H, d), 5.36 (1 H, d) and 4.75 (1 H, br, NH). For the propanone derivative **4a**, the signals in the downfield area are correctly interpreted as δ 8.12 (s, 1 H, CH=) and 7.89–7.17 (m, 20 H, ArH). The two aliphatic CH signals are strongly coupled (J 9.8 Hz) and, of course, addition of D_2O fails to alter this coupling; there is no NH signal. The formulation **4a** is confirmed by the ^{13}C NMR spectrum, in which the methylene (CH=) carbon signal occurs at δ 163.3.

Further confirmation of the structures **4** is obtained when *o*- and *m*-nitrobenzaldehydes are used instead of benzaldehyde, the nitrophenyl derivatives **4b** and **4c** being formed, respectively. Optimal yields of the propan-1-one derivatives **4** are obtained at room temperature or with very brief heating.

4



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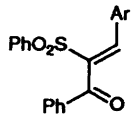

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a Ar = Ph
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c Ar = *m*-$C_6H_4NO_2$
d Ar = *p*-$C_6H_4NO_2$

Table 1 Comparison of melting point data

Compound	M.p. (°C)	Previous formulation	M.p. (°C)
2a	180–182	**3a**	173
2b	188–190	**3b**	190
2c	188–190	**3c**	183
2d	174–176		
4a	167–168	**5a**	160
4b (isomer A)	150–154	**5b**	132
4b (isomer B)	159–160		
4c	167–169	**5c**	153

Table 2 Comparison of NMR signals of compound **2a** and the compound previously formulated **3a**

Compound **2a**: $\delta_C(C^2HCl_3)$ 195.1, 153.1, 143.6, 139.5, 129.1, 128.9, 128.7, 128.4, 127.3, 126.6, 104.5, 64.3, 57.0, 28.7 and 22.8; compound **3a**: $\delta_C(C^2HCl_3)$ 195.0, 153.2, 143.8, 139.7, 129.7–125.8, 104.8, 64.4, 57.2, 28.6, 22.6.

Compound **2a**: $\delta_H([^2H_6]$-DMSO) 7.36, 7.33–7.20, 4.96, 4.53, 3.05, 2.36, 1.88; compound **3a**: $\delta_H([^2H_6]$DMSO) 7.44–7.21, 4.96, 4.47, 3.11, 2.36, 1.88.

The only by-products obtained from this reaction are small amounts of the prop-2-en-3-one derivatives **6**;[5,6] prolonged refluxing of the reaction solutions affords these prop-2-enones **6** as the sole product. We cannot claim to have repeated exactly the experimental conditions described in the literature for the preparation of the compounds formulated as **5**, since neither the use nor the quantity of ammonium acetate has been specified.

There are two (racemic) diastereoisomers corresponding to structure **4**. The phenyl derivative **4a**, however, consists exclusively of one of these. In the case of the *m*-nitrophenyl derivative **4c**, only one is isolated, although spectral examination of the reaction residues indicates the presence of traces of a second, which is not isolable. In the case of the *o*-nitrophenyl derivative **4b**, the presence of two isomers is clearly established. These have identical behaviour on TLC, but are isolable by fractional crystallisation. The only notable spectral difference between them is the position of the methylene (CH=) signal in the ^1H NMR spectrum which occurs at δ 8.97 and at 8.70 respectively in isomer A and B.

Synthesis of 5-*Acetyl*-6-*methyl*-2,4-*diphenyl*-1,2,3,4-*tetrahydropyrimidine* **2a**.—A mixture of benzaldehyde (10.6 g, 0.1 mol), pentane-2,4-dione (5.0 g, 0.05 mol) and ammonium acetate (7.7 g, 0.1 mol) in ethanol (25 cm^3) was stirred at room temperature for 5 h. The colourless product which separated from solution was then filtered off, being essentially pure. Following recrystallisation, it was identified as 5-*acetyl*-6-*methyl*-2,4-*diphenyl*-1,2,3,4-*tetrahydropyrimidine* **2a** (5.2 g, 37%), crystals, m.p. 180–182 °C (methanol) (Found: C, 78.35; H, 6.9; N, 9.6. $C_{19}H_{20}N_2O$ requires C, 78.05; H, 6.90; N, 9.58%); ν_{max}(Nujol)/cm^{-1} 3299 (NH), 3237 (NH) and 1608 (C=O); δ_H(300 MHz, $[^2H_6]$-DMSO, Me_4Si) 7.36 (s, 1 exchangeable H, 1-NH), 7.33–7.20 (m, 10 H, ArH), 4.96 (s, 1 H, 2-H), 4.53 (s, 1 H, 4-H), 3.05 (br s, 1 exchangeable H, 3-NH), 2.36 (s, 3 H, acetyl CH_3) and 1.87 (s, 3 H, CH_3); δ_C(300 MHz, C^2HCl_3, Me_4Si), 195.1 (C=O), 153.1 (C-6), 143.6, 139.5 (two C-1′), 129.1, 128.9 × 2, 128.7 × 2, 128.4 × 2, 127.3, 126.3 × 2 (10 ArC), 104.5 (C-5), 64.3 (C-2), 57.0 (C-4), 28.7 (acetyl CH_3) and 22.8 (CH_3).

Repetition of the above preparation, using less (3.85 g, 0.05 mol) ammonium acetate, afforded the same product **2** in reduced yield (2.9 g, 20%). When the preparation was repeated again using less (3.85 g, 0.05 mol) ammonium acetate and heating the solution under reflux for 13 min (*i.e.* until an orange colour developed), the yield was reduced to 0.1 g (< 1%).

Synthesis of 5-*Acetyl*-6-*methyl*-2,4-*bis*(2-*nitrophenyl*)-1,2,3,4-*tetrahydropyrimidine* **2b**.—A mixture of 2-nitrobenzaldehyde (3.02 g, 20 mmol), pentane-2,4-dione (1.0 g, 10 mmol) and ammonium acetate (1.54 g, 20 mmol) when stirred at room temperature for 5 h, afforded the title compound **2b** as yellow crystals, m.p. 188–190 °C (methanol) (1.5 g, 39%) (Found: C, 59.7; H, 4.7; N, 14.7. $C_{19}H_{18}N_4O_5$ requires C, 59.68; H, 4.74; N, 14.65%); ν_{max}(Nujol)/cm^{-1} 3310 (NH), 3258 (NH) and 1609 (C=O); δ_H(300 MHz, $[^2H_6]$-DMSO, Me_4Si) 7.81 (d, 1 exchangeable H, *J* 4, 1-NH), 7.51–6.74 (m, 8 H, ArH), 5.90 (dd, 1 H, *J* 6.5, 4.0, 2-H), 5.71 (d, 1 H, *J* 6.5, 4-H), 3.89 (t, 1 exchangeable H, *J* 6.5, 3-NH), 2.51 (s, 3 H, acetyl CH_3) and 1.89 (s, 3 H, CH_3); δ_C(300 MHz, $[^2H_6]$-DMSO, Me_4Si) 192.2 (C=O), 153.2 (C-6), 149.0 and 148.0 (2 C-2′) 137.5 and 135.3 (2 C-1′), 131.5, 130.9, 129.8, 128.9, 128.2, 126.9, 124.1, 124.0 (ArC), 103.0 (C-5), 60.9 (C-2), 48.6 (C-4), 29.1 (acetyl CH_3) and 21.6 (CH_3).

The following were similarly prepared. 5-*Acetyl*-6-*methyl*-2,4-*bis*(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyrimidine* **2c** as yellow crystals, m.p. 188–190 °C (methanol) (56%) (Found: C, 59.5; H, 4.7; N, 14.7. $C_{19}H_{18}N_4O_5$ requires C, 59.68; H, 4.74; N, 14.65%); ν_{max}(Nujol)/cm^{-1} 3330 (NH), 3230 (NH) and 1625w (C=O); δ_H(300 MHz, $[^2H_6]$-DMSO, Me_4Si) 8.03 (d, 1 exchangeable H, *J* 4, 1-NH), 7.74–7.13 (m, 8 H, ArH), 5.42 (dd, 1 H, *J* 4, 6, 2-H), 5.08 (d, 1 H, *J* 6, 4-H), 3.96 (t, 1 exchangeable H, *J* 6, 3-NH), 2.53 (s, 3 H, CH_3) and 1.92 (s, 3 H, CH_3); δ_C(300 MHz, $[^2H_6]$-DMSO, Me_4Si) 192.1 (C=O), 153.1 (C-6), 146.7 × 2, 146.6 and 144.1 (two C-3′ and two C-1′), 135.0, 133.3, 128.7, 128.4, 122.7, 121.7, 121.2, 120.3 (ArC), 104.1 (C-5), 64.1 (C-2), 53.1 (C-4), 29.4 (acetyl CH_3) and 21.8 (CH_3).

5-*Acetyl*-6-*methyl*-2,4-*bis*(4-*nitrophenyl*)-1,2,3,4-*tetrahydropyrimidine* **2b** as yellow crystals, m.p. 174–176 °C (methanol) (53%) (Found: C, 59.6; H, 4.8; N, 14.6. $C_{19}H_{18}N_4O_5$ requires C, 59.68; H, 4.74; N, 14.65%); ν_{max}(Nujol)/cm^{-1} 3326 (NH), 3240 (NH) and 1612 (C=O); δ_H(80 MHz, $[^2H_6]$-DMSO, Me_4Si) 7.95 (d, 1 exchangeable H, 1-NH), 7.84–7.07 (m, 8 H, ArH), 5.40 (br s, 1 H, 2-H), 5.07 (s, 1 H, 4-H), 3.91 (br s, 1 exchangeable H, 3-NH), 2.50 (s, 3 H, CH_3) and 1.90 (s, 3 H, CH_3).

Synthesis of 3-*Benzylideneamino*-1,3-*diphenyl*-2-*phenylsulfonylpropan*-1-*one* **4a**.—Benzaldehyde (2.12 g, 20 mmol) and ammonium acetate (0.77 g, 10 mmol) were added to a solution of 1-phenyl-2-phenylsulfonylethan-1-one (2.60 g, 10 mmol) in ethanol (40 cm^3) which had been heated on a water-bath to dissolve. The mixture was stirred without further heating, when a product began to crystallise quickly. Stirring was continued for 5 h, after which the product was filtered off and recrystallised to give the *title compound* **4a** as colourless crystals (3.39 g, 75%), m.p. 167–168 °C (methanol) (Found: C, 74.2, H, 5.1; N, 2.9. $C_{28}H_{23}NSO_3$ requires C, 74.15; H, 5.11; N, 3.09%); ν_{max}(Nujol)/cm^{-1} 1681 (C=O) and 1639 (CH=N); δ_H(300 MHz,

$CDCl_3$, Me_4Si) 8.12 (s, 1 H, CH=), 7.89–7.17 (m, 20 H, ArH), 5.95 (d, 1 H, *J* 10, 3-H) and 5.34 (d, 1 H, *J* 10, 2-H); δ_C(300 MHz, $CDCl_3$, Me_4Si) 192.8 (C=O), 163.3 (CH=), 139.3, 138.4 × 2, 135.5 (C-1[1] × 4), 133.4 × 3, 131.0 × 2, 128.8 × 3, 128.6 × 3, 128.5 × 3, 128.4 × 3, 128.3 × 3 (ArC), 74.6 (C-3) and 74.0 (C-2).

A report of this preparation in which the reaction mixture was heated under reflux for 1 h gave the same product **4a** in 38% yield, together with 1,3-diphenyl-2-phenylsulfonyl-2-propen-1-one **6a**, m.p. and lit.[5] 132 °C (33%). A report reaction in which the mixture was heated under reflux for 8 h gave the propen-1-one **6a** as the sole product (62%).

Similarly prepared (*i.e.* without heating after mixing of the reactants) was 3-(3-*nitrobenzylideneamino*)-1-(3-*nitrophenyl*)-3-*phenyl*-2-*phenylsulfonylpropan*-1-*one* **4c**. The crude product separated from the reaction solution partly in crystalline form but mainly as a heavy oil which was not removed from the reaction mixture until it had gradually solidified (2–3 days). On recrystallisation, it was obtained as colourless crystals, m.p. 167–169 °C (methanol) (89%) (Found: C, 61.8; H, 3.9; N, 7.6. $C_{28}H_{21}N_3O_7S$ requires C, 61.87; H, 3.89; N, 7.73%); ν_{max}(Nujol)/cm^{-1} 1681 (C=O) and 1646 (CH=N); δ_H(80 MHz, $CDCl_3$, Me_4Si) 8.60 (s, 1 H, CH=), 8.48–7.32 (m, 18 H, ArH), 6.00 (d, 1 H, *J* 10, 3-H) and 5.66 (d, 1 H, *J* 10, 2-H).

3-(2-*Nitrobenzylideneamino*)-1-(2-*nitrophenyl*)-3-*phenyl*-2-*phenylsulfonylpropan*-1-*one*. This was similarly prepared (*i.e.* without heating after the reactants were mixed). When the crude reaction product was filtered off and examined, three constituents were present: 3-(2-nitrophenyl)-1-phenyl-2-phenylsulfonylprop-2-en-1-one[6] **6b** (Found: C, 64.3; H, 3.9; N, 3.5. Calc. for $C_{21}H_{15}NO_5S$: C, 64.11; H, 3.84; N, 3.56%) was easily separated from the mixture by recrystallisation from methanol, since it was very soluble and separated much more slowly from solution than the other two constituents. The latter displayed identical behaviour on TLC, but were separated by repeated recrystallisation, one (isomer A) being less soluble than the other (isomer B), and crystallising more rapidly. *Isomer A* was colourless crystals, m.p. 150–154 °C (methanol) (43%) (Found: C, 61.8; H, 4.0; N, 7.5. $C_{28}H_{21}N_3O_7S$ requires C, 61.87; H, 3.89; N, 7.73%); ν_{max}(Nujol)/cm^{-1} 1670 (C=O) and 1633 (CH=N); δ_H(300 MHz, $CDCl_3$, Me_4Si) 8.97 (s, 1 H, CH=), 8.03–7.22 (m, 18 H, ArH), 6.35 (d, 1 H, *J* 10, 3-H) and 5.95 (d, 1 H, *J* 10, 2-H); δ_C(300 MHz, $CDCl_3$, Me_4Si) 191.3 (C=O), 161.2 (CH=), 149.7, 148.9 (C-2′ × 2), 138.2, 136.8, 133.4, 131.8 (C-1′ × 4), 134.0, 133.9, 133.4, 132.3, 131.4, 130.9, 130.1, 129.3 × 2, 129.2, 129.0, 128.8 × 2, 128.6 × 3, 124.3, 124.2 (ArC), 74.0 (C-3) and 66.7 (C-2). *Isomer B* was colourless crystals, m.p. 159–160 °C (methanol) (17%) (Found: C, 62.2; H, 4.0; N, 7.5. $C_{28}H_{21}N_3O_7S$ requires C, 61.87; H, 3.89; N, 7.73%); ν_{max}(Nujol)/cm^{-1} 1680 (C=O) and 1637 (CH=N) cm^{-1}; δ_H(300 MHz, $CDCl_3$, Me_4Si) 8.70 (s, 1 H, CH=), 7.89–7.26 (m, 18 H, ArH), 6.47 (d, 1 H, *J* 10, 3-H) and 5.96 (d, 1 H, *J* 10, 2-H); δ_C(300 MHz, $CDCl_3$, Me_4Si) 191.5 (C=O), 161.5 (CH=), 150.0, 148.7 (C-2′ × 2), 138.4, 137.6, 131.3, 130.0 (C-1′ × 4), 133.9, 133.7, 133.3, 132.5, 132.3, 131.2, 129.7, 129.4, 128.8 × 4, 128.6 × 2, 128.5 × 2, 124.8, 124.1 (ArC), 72.7 (C-3) and 69.6 (C-2).

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