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NEW REACTIONS OF 1,3,5- TRIALKYL-HEXAHYDRO-1,3,5-TRIAZINES. PART 1. THE FORMATION OF 3,7-DIAZABICYCLO[3,3,1] NONA-2,6-DIONES AND HEXAHYDROPYRIMIDINES USING ACTIVATED ACETATES

GEOFFREY DARNBROUGH, PHILIP KNOWLES*,
SEAN P. O'CONNOR, AND FRANCIS J. TIERNEY.

The Research Laboratories, May & Baker Ltd.,
Dagenham, Essex. RM10 7XS.

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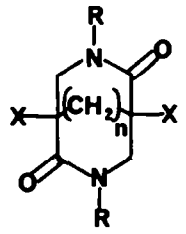
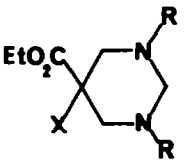
Abstract - The activated acetates (4, a-c) react with 1,3,5-trialkyl hexahydro-1,3,5-triazines (5, a-c) to form, depending on the conditions, 1,5-disubstituted-3,7-dialkyl-3,7-diazabicyclo [3,3,1] nona-2,6-diones (1, b-i) or 5,5- disubstituted -1,3-dialkyl hexahydropyrimidines. In the case of the reaction of ethyl benzoylacetate (4d) with 1,3,5-trimethyl-hexahydro-1,3,5-triazine (5a) an alternative pathway produces the tetrahydropyridine(8).

We have previously reported[1] that the reaction between 1,3,5 - trimethyl- hexahydro-1,3,5- triazine (5a) and tetraethyl 1,1,2,2- ethane tetracarboxylate (3d) leads to the di-lactam (1a). In an attempt to extend this reaction, we have now demonstrated that the reaction of tetraethyl 1,1,3,3- propane tetracarboxylate (3b) with (5a) gives the expected 3,7-diazabicyclo[3,3,1]nona-2,6-dione (1e). However, previous workers have shown that the formation of (3 a,b) [2,3] is achieved by the reaction of the corresponding α- substituted acetic esters (4a, b) with formaldehyde and a catalytic amount of a secondary or tertiary amine. Thus, it was argued that the hexahydrotriazines (5) (acting as a source of formaldehyde) and the esters (4a-d) should form compounds of type (1) directly. Contrary to this argument, there is evidence that in protic media, compounds containing methylene groups activated by suitable electron withdrawing groups i.e. C=O, NO_2[4] react with formaldehyde and primary amines (effectively a source of the hexahydrotriazines) to give hexahydropyrimidines, although reaction with activated esters to form compounds of type (2) had not been attempted. We have found that both compounds of type (1) and type (2) can be formed under varying conditions in most cases.

The hexahydropyrimidines (2) are formed preferentially in benzene solution at 80° using equivalent amounts of activated ester (4, a-d), the triazine (5, a-c) and trifluoroacetic acid. The 3,7- diazabicyclo[3,3,1]nona-2,6-diones (1) are obtained from the esters (4, a-c), the triazines (5, a-c) and trifluoroacetic acid in a molar ratio of 2 : 1: 1, at or around 100° without solvent. The reactivity of ethyl cyanoacetate is such, however, that even in benzene solution with 0.1 equivalents of trifluoroacetic acid, or at a slower rate without trifluoroacetic acid, the 3,7-diazabicyclo[3,3,1]nona-2,6-diones (1, b-c) are produced in good yield. The formation of compounds of type (1) and type (2) by the latter methods becomes more difficult as the size of the substituents R and X increases and (1 g) can only be obtained by the reaction of (3b) and (5c).

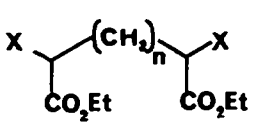
In a more detailed study of the reaction of diethyl malonate (4b) with 1,3,5- trimethyl-hexahydro-1,3,5- triazine (5a) it was observed that the omission of the trifluoracetic acid in the reaction medium to form the hexahydropyrimidine (2b) led to no products being formed. With either 0.1 or 1 equivalent of trifluoracetic acid, (2b) is formed exclusively in good yield (compare the reactions of ethyl cyanoacetate - see experimental).

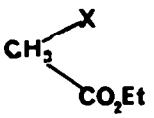


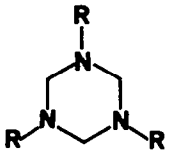


1. a) X = CO_2Et, R = CH_3, n = 0
   b) X = CN, R = CH_3, n = 1
   c) X = CN, R = C_2H_5, n = 1
   d) X = CN, R = CH_2Ph, n = 1
   e) X = CO_2Et, R = CH_3, n = 1
   f) X = CO_2Et, R = C_2H_5, n = 1
   g) X = CO_2Et, R = CH_2Ph, n = 1
   h) X = SO_2Ph-4-CH_3, R = CH_3, n = 1
   i) X = SO_2Ph-4-CH_3, R = C_2H_5, n = 1

2. a) X = CN, R = CH_3
   b) X = CO_2Et, R = CH_3
   c) X = CO_2Et, R = C_2H_5
   d) X = CO_2Et, R = CH_2Ph
   e) X = SO_2Ph-4-CH_3, R = CH_3
   f) X = SO_2Ph-4-CH_3, R = C_2H_5
   g) X = PhCO, R = CH_3







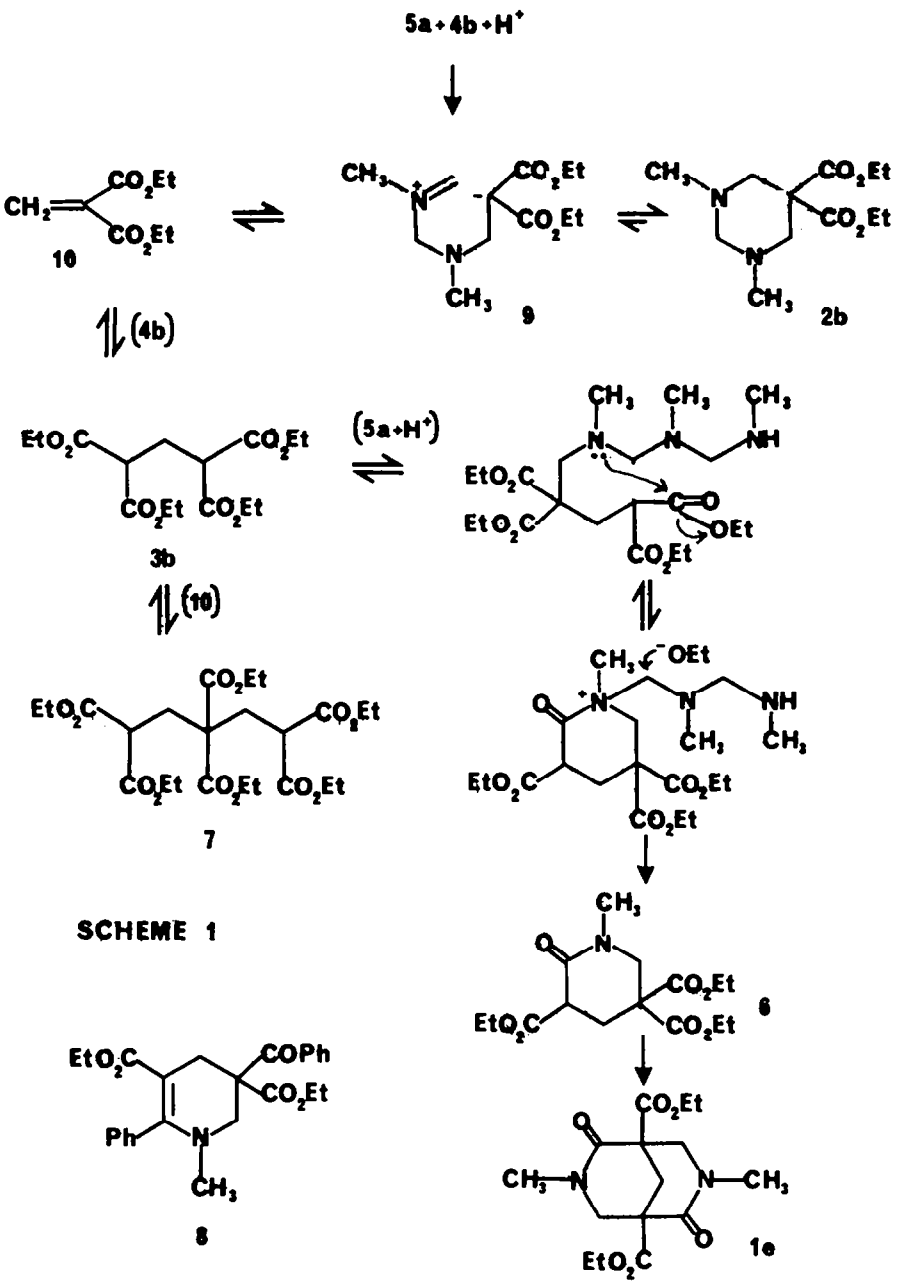
3. a) X = CN n = 1
   b) X = CO_2Et, n = 1
   c) X = PhCO, n = 1
   d) X = CO_2Et, n = 0

4. a) X = CN
   b) X = CO_2Et
   c) X = -SO_2Ph-4-CH.
   d) X = PhCO

5. a) R = CH_3
   b) R = C_2H_5
   c) R = CH_2-Ph

Analysis of the products of the reaction of (4b, 2eq), (5a, 1eq) and trifluoracetic acid (1eq.) carried out, without solvent, at 100° (20 h) showed the formation of the 3,7-diazabicyclo[3,3,1]nona-2,6-dione (1e), the piperidone (6), the hexahydropyrimidine (2b), the hexa-ester (7) and polymeric material. T.L.C. examination (Merck Kieselgel-ethyl acetate) of samples taken after 30 min during the course of this experiment indicated an initial formation of the hexahydropyrimidine (2b).

This information suggests that the kinetically favoured product (2b) is in equilibrium with a postulated intermediate (9) which in the presence of sufficient diethyl malonate is slowly converted by way of an elimination reaction and a series of equilibria to the piperidone (6) (see scheme 1). Most of piperidone (6) is then converted by a similar mechanism to the stable bicyclic compound (1e). The hexaester (7) is a product of the reaction of (3b) presumably with its precursor (10) and has been isolated in previous preparations of (3b)[2]. Some evidence of this mechanism is given by the fact that reaction of (2b) with diethyl malonate (4b) gives rise to a similar distribution of products.



SCHEME 1

The reaction of the benzoyl esters (4d) and (5a) in benzene solution was anomalous in that a complex mixture resulted. Two compounds were isolated: the expected, but somewhat unstable hexahydropyrimidine (2g) and the enamine (8). The formation of the latter can be explained if the Mannich base produced from the postulated intermediate (3c) prefers to form an enamine rather than a lactam.

Compounds (1, b–i) are chiral, with a C_2 axis of symmetry. Evidence for this chirality can be shown from their P.M.R. spectra in all cases except those of (1b) and (1h). In the spectra of (1d, g), as well as the AB system produced by the constitutionally heterotopic ring protons adjacent to nitrogen, a further AB system is observed due to the diastereotopic benzylic protons. This is indicated in the spectra of (1e, f, i) by the occurrence of an ABX_3 system attributable to the N- ethyl groups. Further evidence of chirality is shown in the spectra of (1e, g) where the ester groups appear, also as an ABX_3 system. This is not evident in the case of (1f).

EXPERIMENTAL

M.p's were uncorrected. I.r spectra were determined on a Pye Unicam SP3-200 spectrometer, ^1H n.m.r. spectra and ^{13}C n.m.r. spectra were determined on Varian CFT 20 and Varian XL200 spectrometers and low-resolution mass spectra on a V.G. Micromass-126 spectrometer.

General procedure for the formation of the hexahydropyrimidines (2a,b,c,e,f,) - The ester (4, 20 mmol.) the triazine (5, 20 mmol) and trifluoro-acetic acid (2.28 g, 20 mmol) in dry benzene (30 ml) were heated with stirring under reflux for 4 h. The cooled reaction mixture was extracted with aqueous 2M hydrochloric acid (40 ml, 10 ml). The aqueous extract was neutralised with sodium bicarbonate and mixed with diethyl ether (50 ml). With cooling (5-10°) and stirring, aqueous 50% sodium hydroxide (10 ml) was added and after 2 min. the organic layer was separated, washed with saturated brine (3x10 ml) and dried (K_2CO_3). Removal of the solvent gave the crude hexahydropyrimidines which were purified as indicated.

5,5-Diethoxycarbonyl-1,3-dimethyl-hexahydro pyrimidine (2b) (70%), b.p. 97-99°/0.3 mmHg was prepared from (4b) and (5a)[5] (Found : C, 55.8; H, 8.7; N, 11.0, M^+, 258; $C_{12}H_{22}N_2O_4$ requires C, 55.79; H, 8.59; N, 10.85%; M^+,258); ν_{max} (liq. film) 1735(s) (C=O) cm^{-1}, δ_H ($CDCl_3$) 1.23 (6H, t, J=7Hz, CH_3), 2.24 (6H, s, NCH_3), 2.86 (4H, s, NCH_2), 2.96 (2H, s, N-CH_2-N), 4.20 (4H, q, J=9Hz, OCH_2); δ_C ($CDCl_3$) 13.97(CH_3), 42.73(NCH_3), 54.21(C), 57.20(NCH_2), 61.43(OCH_2), 78.62 (NCH_2N), 168.89 (C=O).
This product was produced in identical yield when the amount of trifluoroacetic acid was reduced 10-fold. When no acid was present no reaction occurred.

5,5-Diethoxycarbonyl-1,3-diethyl-hexahydropyrimidine (2c) (63%) b.p. 108-112°/0.5 mmHg was prepared from (4b) and (5b)[5]. (Found C; 58.4; H, 9.5; N, 9.8; M^+ 286; $C_{14}H_{26}N_2O_4$ requires C, 58.72; H, 9.15; N, 9.78%, M^+, 286): ν_{max} (liquid film) 1730s(C=O)cm^{-1}; δ_H ($CDCl_3$) 1.1 (6H, t, J=8Hz, CH_3), 1.25(6H, t, J,=8Hz, CH_3), 2.42(4H, q, J=8Hz, NCH_2), 2.95(4H, s, ring NCH_2) 3.1(2H, s, NCH_2N), 4.2(4H, q, J_1=8Hz, OCH_2) : δ_C($CDCl_3$) 12.13(CH_3) 13.98(CH_3), 48.9(NCH_2), 54.08(C), 55.06(NCH_2), 61.33(OCH_2) 75.93(NCH_2N), 169.06(C=O).

5-Ethoxycarbonyl-5-(4-methylphenylsulphonyl)-1,3-dimethyl-hexahydro-pyrimidine(2e)(69.5%) m.p. 89-90° (100-120° petrol) was prepared from (4c)[6] and (5a)[5]. (Found : C, 56.5; H, 7.2; N, 8.2; S, 9.4; M^+, 340. $C_{16}H_{24}N_2O_4S$ requires C, 56.44; N, 7.11; N, 8.23; S, 9.42%; M^+,340); ν_{max} (KBr disc) 1742(s)(C=O)cm^{-1}; δ_H($CDCl_3$) 1.20(3H, t, J=7Hz), 2.25(6H, s, NCH_3), 2.4(3H, s, aromatic CH_3), 2.4 and 3.45 (2H, AB system, J_{AB}=11 Hz), 2.55 and 3.45 (2H, AB system, $J_{(AB)'}$=11 Hz), 4.1 (2H, q, J=7Hz, OCH_2), 7.3 (2H, d, J_a=8 Hz, aromatic H), 7.65(2H, d, J_a=8Hz, aromatic H).

5-Ethoxycarbonyl-5-(4-methylphenylsulphonyl)-1,3 diethyl- hexahydropyrimidine(2f) (35%) m.p. 72-75° (60/80° petroleum ether) was prepared from (4c)[6] and (5b)[5]. (Found C 58.3; H, 7.7; N, 7.5; M^+, 368; $C_{18}H_{28}N_2O_4S$ requires C, 58.66; H, 7.60; N, 7.66%; M^+, 368); ν_{max} (KBr disc) 1730s (C=O)cm^{-1}. δ_H($CDCl_3$) 1.04(6H, t, J=7Hz, CH_3), 1.18 (3H, t, J,=7Hz, CH_3), 2.26 - 2.60 (4H, m, NCH_2), 2.46 (3H, s, aromatic CH_3), 2.6 and 3.64 (4H, AB system, J_{AB}=10 Hz, ring NCH_2), 2.64 and 3.64 (2H, AB system, $J_{(AB)'}$=8 Hz, NCH_2N), 4.14 (2H, q, J=7Hz, OCH_2), 7.35 (2H, d, J=8 Hz aromatic H), 7.66 (2H, d, J_a=8 Hz, aromatic H). δ_C ($CDCl_3$) 12.14(CH_3), 13.65(CH_2), 21.72(CH_3), 48.91(NCH_2), 52.54(NCH_2), 62.31(OCH_2), 70.45(C), 74.92(NCH_2N), 129.55, 129.92, 133.09, 145.55 (aromatic C), 166.47(C=O).

5-Cyano-5-ethoxycarbonyl-1,3-dimethyl-hexahydro pyrimidine (2a)(66%) b.p. 76° (bath temp)/0.3 mmHg was prepared from (4a) and (5a) [5]. (Found : C, 56.6; H, 8.3; N, 20.0; M^+, 211; $C_{10}H_{17}N_3O_4$ requires C, 56.80; H, 8.10; N, 19.89%; M^+, 211); ν_{max} (liquid film) 1745(s) (C=O), 2245(w)(C≡N) cm^{-1}. δ_H($CDCl_3$) 1.32(3H, t, J=7 Hz, CH_3), 2.38 (6H, s, NCH_3), 2.53 and 3.18 (4H, AB system, J_{AB}=11 Hz, NCH_2), 2.64 and 3.54 (2H, AB system, $J_{(AB)'}$=10 Hz, NCH_2N), 4.28 (2H, q, J=7Hz, OCH_2); δ_C($CDCl_3$) 13.88(CH_3), 42.41(NCH_3), 43.38(C), 58.20(CH_2N), 62.89(OCH_2), 77.70(NCH_2N), 118.60(C≡N), 165.89(C=O). A modification of the work-up procedure consisted of washing the reaction mixture with aqueous saturated sodium carbonate solution (50 ml), drying the organic layer (K_2CO_3) and removing the solvent under reduced pressure.

1,5-Dicyano-3,7-dimethyl-3,7-diazabicyclo[3,3,1] nona-2,6-dione(1b) : A mixture of ethyl cyanoacetate (4a) (2.26 g, 20 mmol) 1,3,5-trimethyl hexahydrotriazine(5a)[5] and trifluoroacetic acid (230 mg, 2 mmol) in dry benzene (30 ml) was heated under reflux for 3 h. The precipitated solid was filtered off and recrystallised from 2-ethoxyethanol to give the 3,7-diazabicyclo[3,3,1]nona-2,6-dione (1.8 g, 77.6%), m.p. 288-291°. (Found : C, 56.7 : H, 5.3, N, 24.0, M^+; 232, $C_{11}H_{12}N_4O_2$ requires C, 56.9; H, 5.2; N, 24.1%; M^+, 232). ν_{max} (KBr disc) 1675s(C=O), 2250 m(C≡N) cm^{-1}; δ_H(CD_3SOCD_3), 2.88(6H, s, NCH_3), 3.15(2H, s, CH_2), 3.6 and 3.96 (4H, AB system, J_{AB}=11 Hz, NCH_2); δ_C (CD_3SOCD_3) 31.98(CH_2), 34.36(NCH_3), 40.28(C), 54.81(NCH_2), 117.10(C≡N), 161.71(C=O).

1,5-Dicyano-3,7-diethyl-3,7-diazabicyclo[3,3,1] nona-2,6-dione (1c) (73.5%), m.p. 213-215° (ethanol) was prepared similarly from (4a) and (5b)[7]. Precipitation of the crude product was assisted by addition of an equal volume of (60-80°) petroleum ether to the reaction mixture. (Found : C, 60.3; H, 6.33; N, 21.8; M^+, 260. $C_{13}H_{16}N_4O_2$ requires C, 59.98; H, 6.20; N, 21.53%, M^+, 260). ν_{max} (KBr disc) 1658s (C=O), 2250(C≡N) cm^{-1}; δ_H (CD_3SOCD_3) 0.96(6H, t, J=9 Hz,CH_3) 3.17(2H, s, CH_2), 3.1 and 3.5 (4H, ABX_3 system, J_{AB}=16 Hz, J=9 Hz, NCH_2), 3.62 and 3.96 (4H, AB system, $J_{(AB)'}$=16 Hz, ring NCH_2); δ_C (CD_3SOCD_3) 11.24(CH_3), 31.98 (CH_2), 40.36(C), 41.59(NCH_2), 53.07(NCH_2), 117.14(C≡N), 161.16(C=O).

A General procedure for the formation of the 3,7-diaza bicyclo[3,3,1] nona-2,6-diones(1, d-f, h-i): A mixture of the ester (4) (40 mmol), the triazine (5) (20 mmol) and trifluoroacetic acid (2.28 g) was heated at 100° for 24 h. The work up procedure is given for each individual compound.

3,7-Dibenzyl-1,5-dicyano-3,7-diazabicyclo[3,3,1] nona-2,6-dione(1d): This was prepared from (4a) and (5c)[7]. The reaction mixture was triturated with ether and the resultant crystals were recrystallised from ethanol to give the 3,7-diazabicyclo[3,3,1]nona-2,6-dione (42%), m.p 211-213° (Found C, 71.6; H, 5.36; N, 14.6; M^+, 384. $C_{23}H_{20}N_4O_2$ requires C, 71.86; H, 5.24; N, 14.57%; M^+, 384); ν_{max} (KBr disc) 2260 (C≡N), 1660s (C=O) cm^{-1}; $\delta_H(CDCl_3)$ 2.92(2H, s, CH_2), 3.68 and 3.80 (4H, AB system, J_{AB}=15 Hz, ring CH_2), 4.45 and 4.72 (4H, AB system, $J_{(AB)}$=16 Hz, benzyl CH_2), 7.3(10 H, m, aromatic H); $\delta_C(CDCl_3)$ 34.37(CH_2), 40,89(C), 51.19(NCH_2), 54.03(NCH_2), 115.81(C≡N), 128.43, 128.54, 128.75, 129.17, 134.19 (aromatic H), 161.80(C=O).

1,5-Diethoxycarbonyl-3,7-dimethyl-3,7-diazabicyclo[3,3,1] nona-2,6-dione (1e): This was prepared from (4b) and (5a)[5]. After the reaction, any volatile material was removed by heating at 80°/10 mmHg to give a viscous oil (7.5 g). Chromatography (M.P.L.C., Merck Kieselgel (40-63 μm), ethyl acetate/hexane 1:1 then ethyl acetate) and recrystallistion from cyclohexane gave the 3,7-diazabicyclo[3,3,1]nona-2,6-dione (3.68 g, 56%) m.p. 103-104° (Found : C, 55.0, H, 6.78; N, 8.7; M^+, 326; $C_{15}H_{22}N_2O_6$; requires C, 55.20; H, 6.80; N, 8.59%; M^+, 326); ν_{max} (KBr disc) 1742s(C=O), 1665s(C=O) cm^{-1}; $\delta_H(CDCl_3)$ 1.25(6H, t, J=7 Hz), 2.67(2H, s, CH_2), 3.0(6H, s, CH_3), 3.66 and 3.88(4H, AB system, J_{AB}=14 Hz, CH_2N), 4.24(4H, ABX_3 system, $J_{(AB)}$'= 14.5 Hz, J=7 Hz); $\delta_H(CDCl_3)$ 13.92(CH_3), 33,47(CH_2), 33.84(NCH_3), 49.66(C), 55.08(NCH_2), 62.07(OCH_2), 166.38(C=O), 168.80(C=O). In this experiment, the minor products previously eluted with ethyl acetate/hexane 1:1 were also investigated.
In order of elution:-

Hexaethyl pentane-1,1,3,3,5,5-hexacarboxylate(7) (0.4 g, 6%), m.p. 49-50° (lit. mp 53-54°[8]) (Found: C, 54.7; H, 7.3. Calc for $C_{23}H_{36}O_{12}$: C, 54.75; H, 7.19%); ν_{max}(KBr disc) 1730s(C=O), 1750s(C=O); $\delta_H(CDCl_3)$ 1.27(18H, t, $J=J_1$=8 Hz, CH_3), 2.5(4H, d, J_2=6 Hz, CH_2), 3.5(2H, t, J_2=6 Hz, CH), 4.05(4H, q, J=8 Hz, OCH_2), 4.15(8H, q, J_1=8 Hz, OCH_2).

1-Methyl-3,5,5-tri(ethoxycarbonyl)piperidin-2-one(6) (0.93 g, 14%), b.p. 230° (bath temp)/0.1 mmHg (Found: C, 54.3; H, 7.13; N, 4.13; M^+, 329. $C_{15}H_{23}NO_7$ requires C; 54.7; H, 7.04; N, 4.25%; M^+, 329); ν_{max} (liquid film) 1740b(O-C=O), 1660sb(N-C=O)cm^{-1}; $\delta_H(CDCl_3)$ 1.3(9H, m, CH_3's unresolved), 2.52, 2.78 and 3.5(3H, ABX system, J_{AB}=14 Hz, J_{AX}=11 Hz, J_{BX}=7 Hz, ring CH_2 and CH), 3.0(3H, s, NCH_3), 3.8(2H, AB system, $J_{(AB)}$'=14 Hz, NCH_2), 4.22(6H, m, OCH_2's unresolved); $\delta_C(CDCl_3)$ 13.98(CH_3), 14.05(CH_3), 30.24(CH_2), 35.19(CH), 46.52(NCH_3), 52.52(NCH_2), 52.89(C) 61.65(OCH_2), 62.40(OCH_2), 165.3H(C=O), 168.62(C=O), 170.03(C=O).
Thin layer chromatography (Merck kieselgel, ethyl acetate/triethylamine 9:1, R = 0.43) showed the presence of (2b) in the reaction mixture by comparison with an authentic sample. (2b) was difficult to remove from the column used above and was contaminated with polymeric material.

By substituting the following reactants in the above reaction there was obtained a similar distribution of the same products : - 5,5-diethoxycarbonyl-1,3-dimethyl hexahydropyrimidine (2b, 20 mmol) diethyl malonate (4b, 20 mmol) and trifluoroacetic acid (2 mmol).

1,5-Diethoxycarbonyl-3,7-diethyl-3,7-diazabicyclo[3,3,1] nona-2,6-dione(1f):- This was prepared from (4b) and (5b)[5]. The reaction mixture was dissolved in ethyl acetate (100 ml) and the resultant solution was washed with aqueous 2N hydrochloric acid (2x50 ml) saturated brine (20 ml) and dried (Na_2SO_4). Removal of the solvent gave an oil which was subjected to M.P.L.C. [75 mm column, Merck Kieselgel(40-63 μm particles), ethyl acetate] to give the 3,7-diazabicyclo[3,3,1]nona-2,6-dione, (1.84 g., 26%), m.p. 94-96°. (Found: C, 57.7; H, 7.5; N, 8.0; M^+, 354. $C_{17}H_{26}N_2O_6$ requires C, 57.61; H, 7.40; N, 7.90%; M^+, 354); ν_{max} (KBr disc) 1735s(C=O), 1645s(C=O) cm^{-1}; $\delta_H(CDCl_3)$ 1.12(6H, t, J=7 Hz), 1.30(6H, t, J_1=7 Hz), (2H, 2.68 s, CH_2), 3.24 and 3.64(4H, ABX_3 system, J_{AB}=14 Hz, J=7 Hz, NCH_2), 3.71 and 3.84 (4H, AB system, $J_{(AB)}$'=11 Hz, ring NCH_2), 4.26(4H, q, J_1=7 Hz); $\delta_C(CDCl_3)$ 11.64(CH_3), 14.02(CH_3), 33.74(CH_2), 42.26(NCH_2), 50.01(C), 53.03(NCH_2), 61.99(OCH_2), 165.92(C=O), 169.05(C=O).

3,7-Dimethyl-1,5-di-(4-methylphenylsulphonyl)-3,7-diazabicyclo[3,3,1]nona-2,6-dione(1h):- This was prepared from (4c)[6] and (5a)[5]. The reaction mixture was digested in hot ethanol (300 ml). On cooling the preciptitated solid was recrystallised from chloroform/ethanol(x2) to give the 3,7-diazabicyclo[3,3,1]nona-2,6-dione (3.0 g, 30.5%), mp. 324-329°(decomp) (Found: C, 56.0; H, 5.29; N, 5.62; S, 13.0; M^+- not observed, 433(17%); $C_{23}H_{26}N_2O_6S_2$ requires C, 56.31; H, 5.34; N, 5.71; S, 13.07%; M^+, 490); ν_{max} (KBr disc) 1655s (C=O) cm^{-1}; $\delta_H(CDCl_3)$ 2.42 (6H, s, Ar-CH_3) 2.80(6H, s, NCH_3), 3.02(2H, s, CH_2), 3.32 and 3.85(4H, AB system, J_{AB}=11 Hz, NCH_2), 7.35(4H, d, J=8 Hz, aromatic H), 7.85(4H, d, J=8 Hz, aromatic H).

3,7-Diethyl-1,5-di-(4-methylphenylsulphonyl)-3,7-diazabicyclo[3,3,1]nona-2,6-dione(1i):- This was prepared from (4c)[6] and (5b)[5]. The reaction mixture was boiled with ethanol (50 ml). On cooling the precipitated solid (2.0 g) was subjected to M.P.L.C. (Column diameter - 5 cm, Merck Kieselgel (40-63 μm particles), 1:9 Ethyl acetate/dichloromethane]. Recrystallisation of the requisite fractions from chloroform/ethanol gave the 3,7-diazabicyclo[3,3,1]nona-2,6-dione (17.7%) m.p 274-276° (Found C, 57.9; H, 5.75; N, 5.33; M^+, 518. $C_{25}H_{30}N_2O_6S_2$ requires C, 57.89; H, 5.84; N, 5.40%; M^+, 518); $\delta_H(CDCl_3)$ 0.92(6H, t, J=7 Hz, CH_3), 2.48(6H, s, CH_3), 3.04(2H, s, CH_2), 3.18 and 3.27 (4H, ABX_3 system, J_{AB}=14Hz, J=7 Hz, NCH_2), 3.46 and 3.86 (4H, AB system, $J_{(AB)}$=15 Hz, ring CH_2), 7.30(4H, d, J_e = 8 Hz aromatic H), 7.86(4H, d, J_e = 8 Hz, aromatic H); $\delta_C(CDCl_3)$ 11.38(CH_3), 21.76(CH_3), 29.00(C), 42.73(CH_2), 52.23(CH_2N), 66.00(CH_2N), 129.60, 131.22, 133.17, 145.95 (aromatic C), 163.27(C=O).

1,3-Dibenzyl-5,5-diethoxycarbonyl-hexahydropyrimidine (2d):- A mixture of 1,3,5-tribenzyl-hexahydro-1,3,5-triazine (5c)[7] (3.6 g, 10 mmol), diethyl malonate, (4b) (3.2 g, 20 mmol) and trifluoroacetic acid (114 mg) was heated at 100° for 24 h. Any volatile material was removed under reduced pressure (90°/10 mm) and the residual oil was subjected to M.P.L.C. [Merck Kieselgel (40-63 μm particles), ethyl acetate/hexane, 1:1] to give the hexahydropyrimidine (2.1 g, 51%) as a colourless non-distillable oil. (Found C, 69.6; H, 7.5; N, 6.54; M^+ 410 $C_{24}H_{30}N_2O_4$ requires C, 70.22; H, 7.37; N, 6.82%; M^+, 410); ν_{max} (KBr) 1730s (C=O)cm^{-1}; $\delta_H(CDCl_3)$ 1.24(6H, t, J=7 Hz), 3.0(4H, s, CH_2N), 3.2(2H, s, NCH_2N), 3.55(4H, s, benzyl CH_2) 4.15(4H, q, J=7 Hz, OCH_2), 7.3(10 H, m, aromatic H).

1,5-Diethoxycarbonyl-3,7-dimethyl-3,7-diazabicyclo [3,3,1]nona-2,6-dione (1a) from (3b):- A mixture of tetramethyl 1,1,3,3-propane tetracarboxylate (3b)[3] (13.28 g, 40 mmol), 1,3,5 trimethyl hexahydro-1,3,5-triazine (5a)[5] (5.16 g, 40 mmol) and trifluoroacetic acid (0.46 g, 4 mmol) was heated at 100° for 24 h. Any volatile material was removed under reduced pressure (80°, 10 mmHg) and the residue was triturated with cyclohexane to give a waxy solid. Recrystallisation from cyclohexane gave the 3,7-diazabicyclo[3,3,1]nona-2,6-dione (9.5 g, 73%). The m.p., IR, ^1H n.m.r. were identical to the compound (1e) described previously.

3,7-Dibenzyl-1,5-diethoxycarbonyl-3,7-diazabicyclo[3,3,1]nona-2,6-dione (1g), m.p. 137-139° (67%) (hexane) was prepared similarly from (3b) and (5c)[6]. The crude product was subjected to chromatography [M.P.L.C., Merck Kieselgel 60 (40-63 μm particle size), ethyl acetate/hexane, 1:1]. (Found: C, 67.46; H, 6.29; N, 5.79, M^+ 478: $C_{27}H_{30}N_2O_6$ requires : C, 67.77; H, 6.32; N, 5.85%; M^+, 478); ν_{max} (KBr disc) 1745s(O-C=O), 1660s (N-C=O)cm^{-1}; $\delta_H(CDCl_3)$ 1.28(6H, t, J=7 Hz, CH_3), 2.66(2H, s, CH_2), 3.68 and 3.78 (4H, AB system, J_{AB}=12 Hz, ring CH_2) 4.22 (4H, ABX_3 system, $J_{(AB)}$=14.5 Hz, J=7 Hz, OCH_2), 4.28 and 4.86 (4H, AB system, $J_{(AB)}$ =15 Hz, benzylic CH_2); $\delta_C(CDCl_3)$ 13.91(CH_3), 33.67(CH_2), 50.02(C), 50.74(NCH_2), 53.14(NCH_2), 62.09(OCH_2), 127,80, 127.84, 128.77, 135.76 (aromatic C), 166.58(C=O), 168.81(C=O).

The reaction of ethyl benzoylacetate (4d) with (5a)[5]:- A mixture of ethyl benzoylacetate (4d) (19.2 g, 100 mmol) trimethyl hexahydro-1,3,5-triazine(5a) (12.9 g, 100 mmol) and trifluoroacetic acid (1.14 g, 10 mmol) in benzene (150 ml) was heated under reflux for 24 h. The cooled reaction mixture was extracted with aqueous 2M hydrochloric acid (75 ml x 2). The benzene layer was washed with water (3x20 ml) and dried (Na_2SO_4). Removal of the solvent under reduced pressure and trituration with petroleum (b.p. 40-60°) gave a white solid. This was recrystallised from diethyl ether/petroleum (b.p. 40-60°) to give 5-benzoyl-3,5-diethoxycarbonyl-1-methyl-2-phenyl-1,4,5,6-tetrahydropyridine(8) (4.6 g, 22%), m.p. 79-80° (Found: C, 71.4; H, 6.40; N, 3.20; M^+, 421. $C_{25}H_{27}NO_3$ requires C; 71.24; H, 6.46; N, 3.32%; M^+, 421), ν_{max} (KBr disc) 1741s (O-C=O), 1680s(C=C-C=O), 1660s(C=O) cm^{-1}; $\delta_H(CDCl_3)$ 0.75(3H, t, J=7 Hz, CH_3), 1.15(3H, t, J_1=7 Hz), 2.54(3H, s, NCH_3), 3.06 and 3.30(2H, AB system, J_{AB}=16 Hz, ring CH_2), 3.74(4H, m, ring NCH_2 + OCH_2), 4.21(2H, q, J_1=7 Hz, OCH_2),7.0-7.6 (8H, m, aromatic H), 7.9(2H, m, aromatic H).

The aqueous acidic layer was cooled to 5°-10° and diethyl ether (100 ml) was added. 50% w/v aqueous sodium hydroxide was then added until the mixture was strongly alkaline (pH13). After stirring for 2 min, the organic layer was separated, washed with water (3x15 ml) and dried (K_2CO_3). Removal of the solvent under reduced pressure gave a brown oil (9.0 g). Chromatography [Merck Kieselgel 60 (particle size 63-200 μm)], Ethyl acetate 95%/Triethylamine 5%] gave a clear oil (3.1 g). Crystallisation (x2) from diethyl ether/petroleum (bp. 40-60°) gave 5-Benzoyl-5-ethoxycarbonyl-1,3-dimethyl-hexahydropyrimidine (2g) (1.0 g, 3.5%) m.p. 60-64° (Found: C; 66.1; H, 7.7; N, 9.3; $C_{16}H_{20}N_2O_3$ requires C, 66.18; H, 7.64; N, 9.65%). ν_{max} (KBr disc) 1742s(O-C=O) 1690s(C=O)cm^{-1}; $\delta_H(CDCl_3)$ 1.15(3H, t, J=7 Hz), 2.2(6H, s, NCH_3), 3.0(6H, m, ring CH_2), 4.15(2H, q, J=7 Hz, OCH_2), 7.35(3H, m, aromatic H), 7.8(2H, m, aromatic H).

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