Some Reactions of 3,6-Disubstituted-s-Tetrazines; A New Synthesis of the 1,2,4-Triazine Ring System.

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The synthesis of variously substituted pyridazines by 1,4-cycloaddition of cyclic enol ethers, esters, and some electron-rich acetylenes is described. Extension of the scheme to include some imino-ethers as dienophiles resulted in the synthesis of 1,2,4-triazine derivatives.

The synthesis of dihydropyridazines by the 1,4-cycloaddition of olefins to *s*-tetrazines has been reported (1-3) and may be regarded as an "inverse" Diels-Alder type of reaction where the dienophile is preferably electron-rich and the diene electron deficient. Sauer *et al.*, (4) have extended the range of dienophiles to include some acylic enol ethers and esters and found that the initial dihydropyridazine adducts could not be isolated, but aromatised spontaneously by loss of the ether or ester residues, (see Scheme).

We envisaged that adducts retaining the elements of the original ether, ester or amine might be formed by reaction of *s*-tetrazines with cyclic enol ethers, esters and electron rich acetylenes such as yne-amines. Furthermore, the use of imino ethers as dienophiles was investigated as a novel route to the 1,2,4-triazine ring system.

The reaction of 3,6-diphenyltetrazine (5) with dioxene (6) in boiling toluene gave a colourless crystalline product in good yield. Differentiation of this between the bicyclic dihydropyridazine (IIIa) and its isomer (IIIb) in favour of the latter, was based on the following evidence.

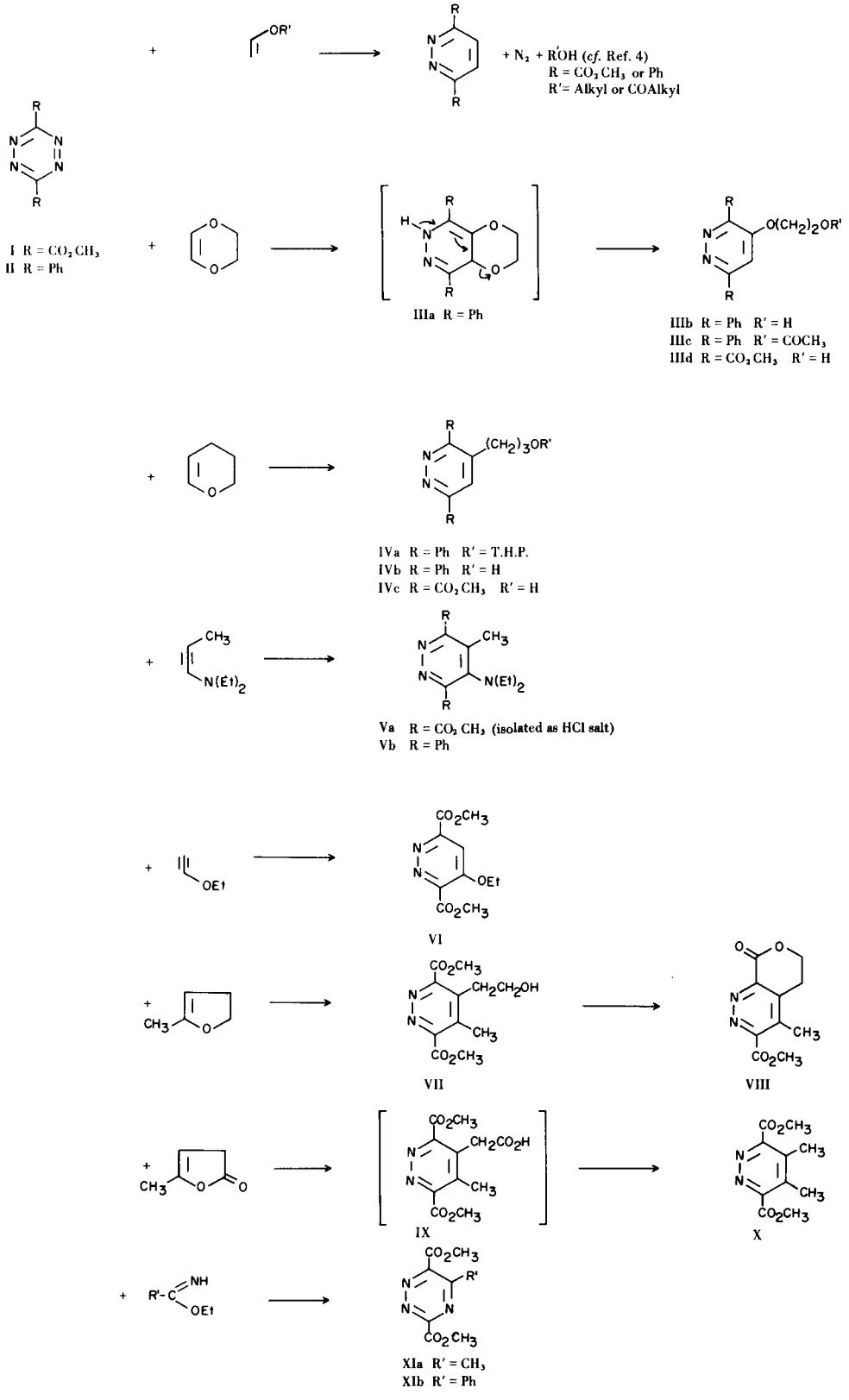
The NMR spectrum in deuterated dimethylsulphoxide contained a low field singlet peak due to the aromatic pyridazine proton and a triplet peak, J = 5Hz, which was exchangable with deuterium oxide and indicative of a hydroxyl proton coupling to neighboring methylene protons (7). Acetylation gave a crystalline product (IIIc), the infrared spectrum of which showed a strong band at 1730 cm^{-1} for acetoxy absorption, but lacked a band characteristic of an *N*-acetyl group near 1680 cm^{-1}. Any isomerisation during acetylation was discounted since base hydrolysis of IIIc gave back the original condensation product.

In an analogous manner, reaction of excess 2,3-dihydropyran with II in boiling toluene for two days gave the pyridazine derivative (IVa). When equimolar quantities of reactants were used, the purple colour due to the presence of 3,6-diphenyltetrazine was still evident after three weeks reaction time. The only product which could be isolated was the tetrahydropyranyl (THP) ether (IVa), thus indicating that the rate of reaction of the intermediate alcohol (IVb) with 2,3-dihydropyran was much faster than the addition of the enol ether to II.

The reaction of I (4) with dioxene and 2,3-dihydropyran proceeded smoothly in dioxane to yield the pyridazine derivatives (IIId and IVc) in good yield. Both compounds exhibited low field singlet peaks in their NMR spectra, characteristic of aromatic pyridazine protons, and also typical aromatic C-H stretching frequencies in their infrared spectra between 3060-3070 cm^{-1}. Additional proof of the monocyclic, rather than the isomeric bicyclic, nature of IVc was obtained by acetylation. The infrared spectrum of the product contained a strong band at 1735 cm^{-1} due to the carbomethoxy and acetoxy absorptions but no band characteristic of an *N*-acetyl group near 1680 cm^{-1}.

The above type of reaction has been extended to include five membered ring enol ethers. Addition of 5-methyl-2,3-dihydrofuran to a solution of I in dioxane led to an exothermic reaction and the production of VII. The NMR spectrum in deuterated dimethylsulphoxide included a singlet peak at τ 7.4 due to the aromatic CH_3 protons and a broad peak at τ 5.3, exchangable with deuterium oxide, due to the hydroxyl proton. Unfortunately, this was not clearly resolvable into a triplet. As expected, VII was readily converted by mild acid treatment into the lactone (VIII) in a virtually quantitative yield. The infrared spectrum included strong bands at 1745 and 1725 cm^{-1} due to the carbomethoxy and δ lactone absorptions, respectively.

SCHEME


+ N2 + R'OH (cf. Ref. 4)
R = CO2CH3 or Ph
R'= Alkyl or COAlkyl
I R = CO2CH3
II R = Ph
IIIa R = Ph
IIIb R = Ph R' = H
IIIc R = Ph R' = COCH3
IIId R = CO2CH3 R' = H
IVa R = Ph R' = T.H.P.
IVb R = Ph R' = H
IVc R = CO2CH3 R' = H
Va R = CO2CH3 (isolated as HCl salt)
Vb R = Ph
VI
VII
VIII
IX
X
XIa R' = CH3
XIb R' = Ph

The above results indicate that 1,4-cycloadditions of cyclic enol ethers to *s*-tetrazines occur readily and that the intermediate bicyclic dihydropyridazine adducts isomerise by ring cleavage under the reaction conditions to produce pyridazine derivatives with hydroxyalkyl or alkoxyalkyl substituents.

By analogy with cyclic enol ethers the reaction of I with α-angelica lactone was expected to lead to the carboxylic acid (IX). In fact the reaction gave a mixture of products from which only 3,6-dicarbomethoxy-4,5-dimethylpyridazine (X) could be isolated, (18% yield). The NMR spectrum contained two singlet peaks of equal intensity, τ 5.9 and 7.5, due to the resonances of the carbomethoxy and aromatic methyl protons respectively, and a mass spectrometric molecular weight determination was in agreement with the above structure. Presumably the intermediate (IX), being both a vinylogue of a β-carbomethoxy carboxylic acid and an α-pyridylacetic acid, suffered decarboxylation under the reaction conditions (8).

In contrast to acyclic enamines and enol ethers, the reaction of *s*-tetrazines with acetylenic amines and ethers has resulted in a further method of synthesis of pyridazine derivatives with retention of the amine or ether residues. On mixing equimolar amounts of I and 1-diethylamino-prop-1-yne in dioxane, an immediate exothermic reaction occurred with concomitant evolution of nitrogen and decolourisation of the red tetrazine solution. The initial oily condensation product was readily converted into a crystalline hydrochloride (Va). The presence of both ester and protonated tertiary amine groups was evident from bands in the infrared spectrum at 1740 and 2460 cm^{-1}, and peaks at τ 5.99, 6.01, and 6.6, 8.75, and -4.3 in the NMR spectrum. The related free base (Vb) was obtained upon brief treatment of II with the above yne-amine in refluxing toluene. Of the electron rich compounds investigated, the yne-amines easily showed the most dienophile-like character in the 1,4-cycloaddition reactions with *s*-tetrazines.

Ethoxyacetylene readily underwent a reaction with I to produce the expected 3,6-dicarbomethoxy-4-ethoxypyridazine (VI), which proved identical with the product isolated from the reaction of I with ketene diethylacetal (4).

The electron rich dienophiles described above all led to pyridazine derivatives by the addition of the elements of C=C to the *s*-tetrazine molecule. In an attempt to extend the sequence to include the C=N moiety, thus producing some 1,2,4-triazine derivatives, the reactions of some imino ethers were studied. Although there is no report in the literature of these acting as dienophiles (9) we found that I readily reacted with ethylacetimidate in dioxane at 60°. Chromatography of the crude reaction product over silica gel gave the triazine derivative (XIa) in 13% yield. The visible spectrum of this compound showed a low intensity n-π^* absorption at 355 nm characteristic of the 1,2,4-triazine ring system (10) and the NMR spectrum showed two singlet peaks, τ 5.9, 5.87, and a singlet peak τ 7.1 as expected for the carbomethoxy and aromatic CH_3 protons. In a similar way reaction of I and ethylbenzimidate gave 5-phenyl-3,6-dicarbomethoxy-1,2,4-triazine (XIb) in 27% yield, but both of the above imino ethers failed to react with II under a variety of conditions.

EXPERIMENTAL (11)

3,6-Diphenyl-4-(2′-hydroxyethoxy)pyridazine (IIIb).

To a solution containing 4 g. of 3,6-diphenyltetrazine and a trace of hydroquinone in 60 ml. of dry toluene was added 9 g. of dioxene. The solution was heated under reflux for two weeks when a T.L.C. examination on silica gel using a mixture of benzene-ethyl acetate (2:8) as the developing agents indicated the absence of starting tetrazine. Upon allowing the reaction mixture to cool, colourless crystals of 3,6-diphenyl-4-(2′-hydroxyethoxy)-pyridazine separated which were removed by filtration, washed with a small amount of toluene, and dried. Yield 4.3 g. (78%), m.p. 154-155°; U.V. λ max 237 (ε, 21,200), 273 nm (ε, 24,000); infrared cm^{-1} included major bands at, 3260, 3060, 1590, 1448, 1080, 1070, 695, (potassium bromide disc); NMR spectrum (dimethylsulfoxide-d_6) showed two multiplets centred at τ 1.9 and 2.5 (10H), phenyl protons, a singlet τ 2.7 (1H), pyridazine proton, a triplet τ 4.9 (1H, J = 5 Hz) exchangeable with deuterium oxide, $-CH_2OH$ proton, a triplet τ 5.5 (2H, J = 5 Hz), $-OCH_2CH_2-OH$ protons, and a multiplet τ 6.1 (2H), $-OCH_2CH_2OH$ protons.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 74.0; H, 5.5; N, 9.6. Found: C, 73.8; H, 5.8; N, 9.5.

3,6-Diphenyl-4-(2′-acetoxyethoxy)pyridazine (IIIc).

A solution containing 1 g. of IIIb, 4 ml. of pyridine and 8 ml. of acetic anhydride was heated at 90° for 3 hours. Removal of the solvents *in vacuo* and trituration of the resultant oil with ether gave 3,6-diphenyl-4-(2′-acetoxyethoxy)pyridazine as a colourless crystalline solid. Yield 800 mg. (70%), m.p. 116-118°; infrared cm^{-1} included major bands at 3060, 1730, 1270, 1215, 770, 698 (potassium bromide disc); NMR spectrum (deuteriochloroform) showed two multiplets centred at τ 1.9 and 2.5 (10H), phenyl protons, a singlet τ 2.7 (1H), pyridazine proton, an A_2B_2 spin multiplet between τ 5.3 and 5.7 (4H), $-CH_2-$ protons, and a singlet τ 7.9 (3H), $-OCOCH_3$ protons.

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.8; H, 5.4; N, 8.4. Found: C, 71.6; H, 5.8; N, 8.6.

Hydrolysis of IIIc.

A solution containing 200 mg. of IIIc in 10 ml. of ethanol and 5 ml. of 5 *N* sodium hydroxide was heated under reflux for 3 hours. After cooling and dilution with 50 ml. of water the resultant white precipitate was extracted into 50 ml. of chloroform. Evaporation of the organic layer *in vacuo* and trituration of the residue with 2-propanol gave 100 mg. of crystalline material, m.p. 148-151°. Recrystallization from benzene gave 54 mg. of pure hydrolysis product, m.p. 154-155°, which was indistinguishable

from IIIb by T.L.C., I.R., U.V., NMR, and a mixed m.p. determination.

3,6-Diphenyl-4[3-(2-pyranyloxy)propyl]pyridazine (IVa).

To a solution containing 5 g. of 3,6-diphenyltetrazine and a trace of hydroquinone in 75 ml. of dry toluene was added 15 ml. of 2,3-dihydropyran. The mixture was heated under reflux for 48 hours and evaporated *in vacuo* to give 6.8 g. of a straw coloured oil which crystallized on standing. Recrystallization from ether gave pure 3,6-diphenyl-4[3-(2-pyranyloxy)propyl]pyridazine. Yield 5.5 g. (71%), m.p. 104°; U.V. λ max 262 nm (ε, 24,000); infrared cm^{-1} included major bands at 3260, 2920, 1585, 1390, 1070, 1030, 1015, 695 (potassium bromide disc); NMR spectrum (deuteriochloroform) showed two multiplets centred at τ 1.8 and 2.8 (10H), phenyl protons, three multiplets centred at τ 6.5, 7.1, and 8.2 (14H), $-CH_2-$ protons, a singlet τ 2.2 (1H) pyridazine proton, and a singlet τ 5.5 (1H), methine proton of tetrahydropyranyl residue.

Anal. Calcd. for $C_{24}H_{26}N_2O_2$: C, 77.0; H, 7.0; N, 7.5; *M*, 374. Found: C, 77.4; H, 6.9; N, 7.5; *M*, (mass spec.) 374.

When a solution containing 1.07 g. (0.05 mole) of 3,6-diphenyltetrazine and 0.45 g. (0.05 mole) of 2,3-dihydropyran in 15 ml. of toluene was heated under reflux for three weeks the only compounds isolated were IVa (*ca.* 25% yield) and unreacted 3,6-diphenyltetrazine.

3,6-Dicarbomethoxy-4-(2′-hydroxyethoxy)pyridazine (IIId).

To a solution containing 4 g. of 3,6-dicarbomethoxytetrazine in 80 ml. of dry dioxane was added 2.4 g. of dioxene at room temperature. The mixture was stirred and the temperature was increased to 60° when effervescence of nitrogen commenced. After 0.5 hour at this temperature the solution was a light straw colour and the evolution of nitrogen ceased. Removal of the solvent *in vacuo* gave an oil which crystallized from 2-propanol to give 3,6-dicarbomethoxy-4-(2′-hydroxyethoxy)pyridazine. Yield 4.1 g. (80%), m.p. 109°; λ max 275 nm (ε, 3070); infrared cm^{-1} included major bands at 3280, 3070, 2950, 1740, 1580, 1440, 1360, 1270, 1150, 1080, 1020, 820 (potassium bromide disc); NMR spectrum (dimethylsulfoxide-d_6) showed a singlet τ 1.9 (1H), pyridazine proton, a triplet τ 5.0 (1H, J = 5Hz) exchangeable with deuterium oxide, $-CH_2OH$ proton, a triplet τ 5.5 (2H, J = 6Hz)-CH_2CH_2OH protons, a singlet τ 5.9 (6H), $-CO_2CH_3$ protons, and a multiplet τ 6.1 (2H), $-CH_2CH_2OH$ protons.

Anal. Calcd. for $C_{10}H_{12}N_2O_6$: C, 46.9; H, 4.7; N, 10.9. Found: C, 46.6; H, 4.7; N, 11.0.

3,6-Dicarbomethoxy-4-(3′-hydroxypropyl)pyridazine (IVc).

To a stirred solution containing 2 g. of 3,6-dicarbomethoxytetrazine in 50 ml. of dry dioxane was added 1.2 g. of 2,3-dihydropyran. An exothermic reaction commenced immediately with concomitant evolution of nitrogen and after 2 hours the solution was almost colourless. After standing overnight at room temperature the solvent was removed to give 3 g. of an oil which on trituration with ether gave 3,6-dicarbomethoxy-4-(3′-hydroxypropyl)pyridazine as a colourless crystalline solid. Yield 2.1 g. (80%), m.p. 72-74°; infrared cm^{-1} included major bands at 3400, 3060, 2950, 1740, 1730, 1440, 1270, 1190, 1140, 950, 820 (potassium bromide disc); NMR spectrum (dimethylsulfoxide-d_6) showed a singlet τ 1.7 (1H), pyridazine proton, a broad singlet τ 5.5 (1H) exchangeable with deuterium oxide, $-CH_2OH$ proton, a singlet τ 5.9 (6H), $-CO_2CH_3$ protons, a triplet τ 6.5 (2H, J = 7Hz), $-CH_2CH_2OH$ protons, a triplet τ 7.0 (2H, J = 7Hz)-$ArCH_2CH_2$ protons, and a multiplet centred at τ 8.2 (2H), $-CH_2CH_2CH_2$ protons.

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 52.0; H, 5.6; N, 11.0. Found: C, 52.1; H, 5.9; N, 11.1.

3,6-Dicarbomethoxy-4-(3′-acetoxypropyl)pyridazine.

A solution containing 400 mg. of IVc, 2 ml. of pyridine and 5 ml. of acetic anhydride was heated at 90° for 3 hours. Removal of the solvents *in vacuo* gave an oil which was extracted into 20 ml. of dichloromethane, washed with aqueous bicarbonate, water, and dried (magnesium sulfate). Evaporation of the dichloromethane gave 3,6-dicarbomethoxy-4-(3′-acetoxypropyl)pyridazine as a colourless oil. Yield 310 mg. (70%). A T.L.C. examination of this on silica gel using a mixture of benzene-ethyl acetate (2:8) as the developing agent showed the presence of only one compound, R_f 0.75. In the above system the alcohol (IVc) had an R_f of 0.40; infrared cm^{-1} included major bands at 2960, 1735, 1440, 1140 (chloroform); NMR spectrum (deuteriochloroform) showed a singlet τ 1.9 (1H), pyridazine proton, a singlet τ 5.9 (6H), $-CO_2CH_3$ protons partially superimposed onto a triplet τ 5.8 (2H, J = 7Hz), $-CH_2CH_2OCOCH_3$ protons, a triplet τ 6.9 (2H, J = 7Hz), $-ArCH_2CH_2-$ protons, and a singlet τ 7.95 (3H), $-OCOCH_3$ protons partially superimposed onto a multiplet centred at τ 7.9 (2H), $-CH_2CH_2CH_2-$ protons. Mass spectra calcd. for $C_{13}H_{10}N_2O_6$., *M*, 296.1008; Found: *M*, 296.1008.

3,6-Dicarbomethoxy-4-methyl-5-diethylaminopyridazine hydrochloride (Va).

To a solution containing 4 g. of 3,6-dicarbomethoxytetrazine in 75 ml. of dry dioxane at room temperature was slowly added a solution of 3 g. of 1-diethylaminoprop-1-yne in 25 ml. of dioxane. An immediate exothermic reaction occurred and after 2 hours the solvent was removed *in vacuo* to give 65 g. of a yellow oil. This was dissolved in 100 ml. of dry ether and ethereal hydrogen chloride was added dropwise until precipitation of the hydrochloride was complete. Crystallization from 2-propanol-ether gave pure 3,6-dicarbomethoxy-4-methyl-5-diethylaminopyridazine hydrochloride. Yield, 5.4 g. (73%), m.p. 98-101° dec; infrared cm^{-1} showed major bands at 2980, 2460, 1900, 1745, 1560, 1520, 1470, 1300, 1230, 1140, 1070 (potassium bromide disc); NMR spectrum (deuteriochloroform) showed a broad singlet τ -4.3 (1H) exchangeable with deuterium oxide, NH proton, two singlets τ 6.0, 6.1 (each 3H), $-CO_2CH_3$ protons, a singlet τ 7.55 (3H), aromatic-CH_3 protons, and a quartet τ 6.6 (4H, J = 7Hz) and a triplet τ 8.75 (6H, J = 7Hz), diethylamino protons.

Anal. Calcd. for $C_{13}H_{20}ClN_3O_4$: C, 49.1; H, 6.3; N, 13.2. Found: C, 49.6; H, 6.5; N, 13.2.

3,6-Diphenyl-4-methyl-5-diethylaminopyridazine (Vb).

To a solution containing 5 g. of 3,6-diphenyltetrazine in 60 ml. of dry toluene was added 4 g. of 1-diethylaminoprop-1-yne. After heating under reflux for 15 minutes evolution of nitrogen ceased and the solution became light yellow. Removal of the solvent *in vacuo* gave an oil which solidified on trituration with ether. Crystallization from 2-propanol gave 3,6-diphenyl-4-methyl-5-diethylaminopyridazine as colourless needles. Yield 4.8 g. (65%), m.p. 120-121°; infrared cm^{-1} included major bands at 2980, 2855, 1520, 1420, 1380, 1270, 1070, 1015, 770, 700, (potassium bromide disc); NMR spectrum (deuteriochloroform) showed a multiplet centred at τ 2.4 (10H), phenyl protons, a singlet τ 7.8 (3H), aromatic $-CH_3$ protons and a quartet τ 7.1 (4H, J = 7Hz) and a triplet τ 9.0 (6H, J = 7Hz), diethylamino protons.

Anal. Calcd. for $C_{21}H_{23}N_3$: C, 79.5; H, 7.3; N, 13.2. Found: C, 79.7; H, 7.4; N, 13.4.

3,6-Dicarbomethoxy-4-ethoxypyridazine. (VI).

To a solution containing 1 g. of 3,6-dicarbomethoxytetrazine in 15 ml. of dry dioxane was added 0.4 g. of ethoxyacetylene in 5 ml. of dry dioxane. The solution was kept at 45° for 3 hours and finally heated under reflux for 30 minutes. Removal of the solvent gave a light orange oil which crystallized on standing. Recrystallization from 2-propanol-petroleum ether (b.p. 40-60°) gave 3,6-dicarbomethoxy-4-ethoxypyridazine. Yield 700 mg. (63%), m.p. 72-75° (lit. m.p. (4a) 74-76°).

3,6-Dicarbomethoxy-4-methyl-5-(2′-hydroxyethyl)pyridazine (VII).

To a solution containing 5 g. of 3,6-dicarbomethoxytetrazine in 80 ml. of dry dioxane was added a solution of 2.4 g. of 5-methyl-2,3-dihydrofuran in 24 ml. of dioxane at room temperature. After the initial exothermic reaction had ceased the mixture was heated at 85° for 2.5 hours. Removal of the solvent *in vacuo* gave an oil which solidified on trituration with ether. Pure 3,6-dicarbomethoxy-4-methyl-5-(2′-hydroxyethyl)pyridazine was obtained by crystallization from methanol-ether. Yield 4.9 g. (77%), m.p. 105-107°; infrared cm^{-1} included major bands at 3400, 2950, 1740, 1450, 1370, 1260, 1160, 1065, 1045, 950, 820 (potassium bromide disc); NMR spectrum (dimethylsulfoxide-d_6) showed a broad singlet τ 5.3 (1H) exchangeable with deuterium oxide, OH proton, a singlet τ 6.0 (6H), $-CO_2CH_3$ protons, a triplet τ 6.3 (2H, J = 6 Hz), $-ArCH_2CH_2-$ protons, a triplet τ 6.9 (2H, J = 6Hz), $-CH_2CH_2OH$ protons, and a singlet τ 7.5 (3H), aromatic $-CH_3$ protons.

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 52.0; H, 5.6; N, 11.0; Found: C, 52.2; H, 5.6; N, 11.2.

8-Oxo-4-methyl-3-carbomethoxy-5,6-dihydropyrano[3,4-*c*]pyridazine (VIII).

A solution of 200 mg. of VII in 15 ml. of dry methanol was saturated with hydrogen chloride gas and heated under reflux for 15 minutes. The solvent was removed *in vacuo* and the resultant oil crystallized from 2-propanol to give 8-oxo-4-methyl-3-carbomethoxy-5,6-dihydropyrano[3,4-*c*]pyridazine as colourless needles. Yield 170 mg. (96%) m.p. 161-163°; infrared cm^{-1} included major bands at 2950, 1745, 1725, 1450, 1400, 1290, 1270, 1150, 1070, 1050, 950, 805 (potassium bromide disc); NMR spectrum (pyridine-d_5) showed a triplet τ 5.35 (2H, J = 6Hz), $-COOCH_2CH_2-$ protons, a singlet τ 6.0 (3H), $-CO_2CH_3$ protons, a triplet τ 6.9 (2H, J = 6Hz), $-ArCH_2CH_2$ protons, and a singlet τ 7.6 (3H), aromatic $-CH_3$ protons.

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.1; H, 4.5; N, 12.6. Found: C, 54.1; H, 4.7; N, 12.6.

3,6-Dicarbomethoxy-4,5-dimethylpyridazine (X).

To a solution containing 1 g. of 3,6-dicarbomethoxytetrazine in 15 ml. of dioxane was added a solution of 0.6 g. of α-angelica lactone in 5 ml. of dioxane. The mixture was heated at 60-70° for 4 hours and the solvents were removed *in vacuo* to give 1.5 g. of a yellow oil. Trituration with 2-propanol gave 400 mg. of a crystalline product, m.p. 85-90°. Recrystallization from 2-propanol (with charcoal) gave colourless needles of 3,6-dicarbomethoxy-4,5-dimethylpyridazine. Yield 200 mg. (18%), m.p. 101-102°; infrared cm^{-1} included major bands at 2950, 1740, 1440, 1260, 1070, 820 (potassium bromide disc); NMR spectrum (deuteriochloroform) showed a singlet τ 5.9 (6H), $-CO_2CH_3$ protons, and a singlet τ 7.5 (6H), aromatic-CH_3 protons.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.4; N, 12.5; *M*, 224. Found: C, 53.6; H, 5.0; N, 12.6; *M*, (mass spectra) 224.

3,6-Dicarbomethoxy-5-methyl-1,2,4-triazine (XIa).

To a stirred solution containing 5 g. of 3,6-dicarbomethoxytetrazine in 75 ml. of dioxane was slowly added 2.25 g. of ethylacetimidate in 25 ml. of dioxane at room temperature. The mixture was then stirred at 60° for 10 hours when the colour had changed to yellow-green. A T.L.C. examination on silica gel using a mixture of benzene-ethyl acetate (2:8) as the developing agent indicated the presence of one major reaction product, R_f 0.8, Removal of the solvent *in vacuo* gave 5.1 g. of an oil which was chromatographed on a column (80 x 3 cm.) of silica gel (100-200 Mesh). Initial development with a mixture of ethyl acetate-benzene (2:3) eluted a bright yellow impurity. The major reaction product was eluted as a light yellow band using a mixture of ethyl acetate-benzene (1:1) as eluant. Removal of the solvents from this fraction gave an oil which on trituration with cold ether gave 3,6-dicarbomethoxy-5-methyl-1,2,4-triazine as a light yellow crystalline solid. Yield 630 mg. (13%), m.p. 82-83°; U.V. λ max 264 (ϵ, 4,430), 355 nm (ϵ, 430); infrared cm^{-1} included major bands at 2960, 1740, 1730, 1510, 1440, 1380, 1260, 1200, 1170, 820 (potassium bromide disc); NMR spectrum (deuteriochloroform) showed two singlets τ 5.9, 5.87 (each 3H), $-CO_2CH_3$ protons, and a singlet τ 7.1 (3H), aromatic-CH_3 protons.

Anal. Calcd. for $C_8H_9N_3O_4$: C, 45.5; H, 4.3; N, 19.9; *M*, 211. Found: C, 45.4; H, 4.5; N, 20.0; *M*, (mass spectra) 211.

3,6-Dicarbomethoxy-5-phenyl-1,2,4-triazine (XIb).

A stirred solution of 1 g. of 3,6-dicarbomethoxytetrazine and 0.75 g. of ethylbenzimidate in 15 ml. of dioxane was kept at 80° for six hours. Removal of the solvent gave a yellow oil which was chromatographed on a column (35 x 3 cm.) of silica gel (100-200 Mesh). Development with a mixture of ethyl acetate-benzene (2:3) eluted a yellow band which was collected and on evaporation of the solvents gave an oil. Trituration with ether gave 3,6-dicarbomethoxy-5-phenyl-1,2,4-triazine as yellow plates. Yield 190 mg. (27%), m.p. 110-113°; U.V. λ max 295 (ϵ,9,570), 360 nm (ϵ, 440); infrared cm^{-1} included major bands at 2960, 1740, 1520, 1490, 1440, 1220, 1070, 768, 695 (potassium bromide disc); NMR spectrum (deuteriochloroform) showed a multiplet between τ 1.9-2.6 (5H), phenyl protons, and two singlets τ 5.8, 6.0 (each 3H), $-CO_2CH_3$ protons.

Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.1; H, 4.1; N, 15.4; *M*, 273. Found: C, 57.3; H, 4.1; N, 15.6; *M*, (mass spectra) 273.

Acknowledgment.

We thank Drs. N. Franklin and D. Rackham for helpful discussions and Drs. W. Salmond, W. Hargrove, and Mr. M. Harper for mass spectral facilities.

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(11) Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Ultraviolet spectra (in methanol) were determined on a Unicam S.P. 800 spectrophotometer; infrared spectra on a Perkin Elmer 475 spectrophotometer; nuclear magnetic resonance spectra (at 60 MHz) on a Varian A60 spectrometer using tetramethylsilane as internal reference and mass spectra on an A.E.I., MS9 spectrometer. The toluene and dioxane were freshly distilled, the latter from sodium pellets; silica gel used for T.L.C. was Kieselgel F_{254}, Merk; that for column chromatography was Koch-Light, 100-200 Mesh.

Received March 10, 1969

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