Diethyl *N,N*-Dimethylaminomethylenemalonate in the Synthesis of Fused Heterocyclic Systems

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Dedicated with best wishes to Professor Miha Tišler, University of Ljubljana, on the occasion of his 70th birthday.

The reactions of diethyl *N,N*-dimethylaminomethylenemalonate (**3**) with *N*- and *C*- nucleophiles were studied. In the reaction of **3** with heterocyclic amines **4**, with the amino group attached at α-position in respect to the ring nitrogen atom, substitution of the dimethylamino group in **3** with the heterocyclic amino took place to give diethyl heteroarylaminomethylenemalonates **5**, which can cyclize into fused azino- **6** or azolopyrimidinones **7**. In the reaction of **3** with the compound with an active methylene group attached at α-position in regard to the ring nitrogen atom, such as pyridinylacetonitrile (**8**), ethyl pyridinyl- (**9**), and quinolinylacetate (**10**), fused quinolizines **11** and **12**, and benzo[*c*]quinolizine **13** were formed, respectively. Heterocyclic systems with an active or potentially active methylene group incorporated in the ring system, such as pyrazole **14**, pyrimidine **15**, and pyridine derivative **18**, gave with **3** fused pyranones **16**, **17**, and **19**, and dihydroxynaphthalenes **22** and **23** naphtho[2,1-*b*]pyranones **24** and **25**.

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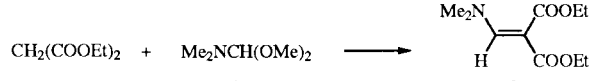
N-Aryl and *N*-heteroaryl substituted aminomethylenemalonates are of great importance in the synthesis, especially as intermediates in the preparation of fused heterocycles, such as azolo and azinopyridines [1] and azolo and azinopyrimidines [2]. The most widely used method of preparation of this type of compounds is the treatment of heterocyclic amines with dialkyl ethoxymethylenemalonates and their congeners [1,2].

In the course of our studies of amino substituted propenoates, such as ethyl 2-benzoylamino-3-dimethylaminopropenoate [3] and ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate [4], as masked aldehydo compounds, we have found that these compounds are useful building blocks for the construction of various heterocyclic systems. Therefore, we decided to extend our investigations to some other compounds of related structure.

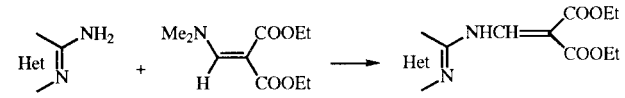
Scheme 1



1 **2** **3**

In this connection we selected diethyl *N,N*-dimethylaminomethylenemalonate (**3**), prepared from diethyl malonate (**1**) and *N,N*-dimethylformamide dimethyl acetal (**2**) (Scheme 1), as described previously [5], and studied its reactions with *N*- and *C*- nucleophiles. The following amino substituted heterocycles were selected as *N*-nucloephiles: 3-aminoisoxazole (**4a**), 3-amino-1,2,4-triazole (**4b**), 2-amino-3-methylpyridine (**4c**), 2-amino-4-methylpyridine (**4d**), 2-amino-3-hydroxypyridine (**4e**), 3-amino-6-chloropyridazine (**4f**), 2-aminopyrimidine (**4g**), and 3-aminoindazole (**4h**). When the reaction between heterocyclic amine **4** and the reagent **3** was carried out in acetic acid, the substitution of the dimethylamino group in **3** took place to give the corresponding diethyl *N*-heteroarylaminomethylenemalonates **5**. More reactive amines, such as **4a** and **4h**, react at room temperature, while other amines, such as **4c**, **4e**, and **4f**, react at higher temperatures, 60-100°. In the case of **4g** the addition of catalytic amounts of hydrogen bromide in acetic acid was required for the reaction to take place. (Scheme 2). Some of these intermediates, such as **4c**, **4e**, and **4h**, cyclize by prolonged heating into fused pyrimidones **6**, while more reactive amines, such as **4d**, cyclize without the isolation of the intermediate **5**. (Scheme 3).

Scheme 2



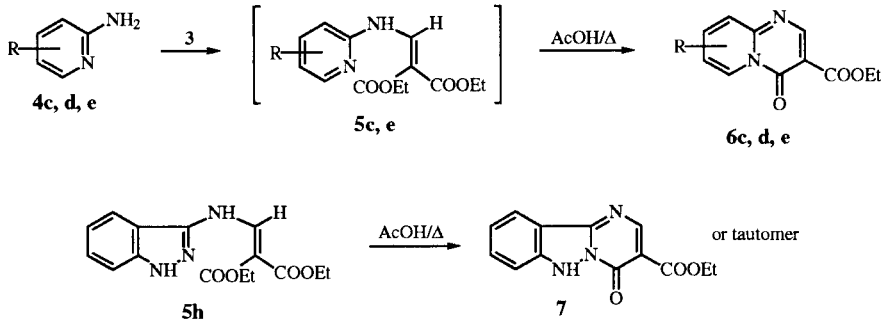
4a, c, e, g, f, h **3** **5a, c, e, f, g, h**

Compounds **4,5**	Heterocycle
a	3-aminoisoxazole
b	3-amino-1,2,4-triazole
c	2-amino-3-methylpyridine
d	2-amino-4-methylpyridine
e	2-amino-3-hydroxypyridine
f	3-amino-6-chloropyridazine
g	2-aminopyrimidine
h	3-aminoindazole

It has been reported that the reagent **3** reacts with *C*-nucleophiles to give substituted 2-pyranones in 50-70% yield [6]. In this connection, we extended our investigation to the compounds with an active methylene group attached to the heterocyclic ring, such as 2-pyridinylacetonitrile (**8**), ethyl 2-pyridinylacetate (**9**), and methyl 2-quinolinylacetate (**10**).

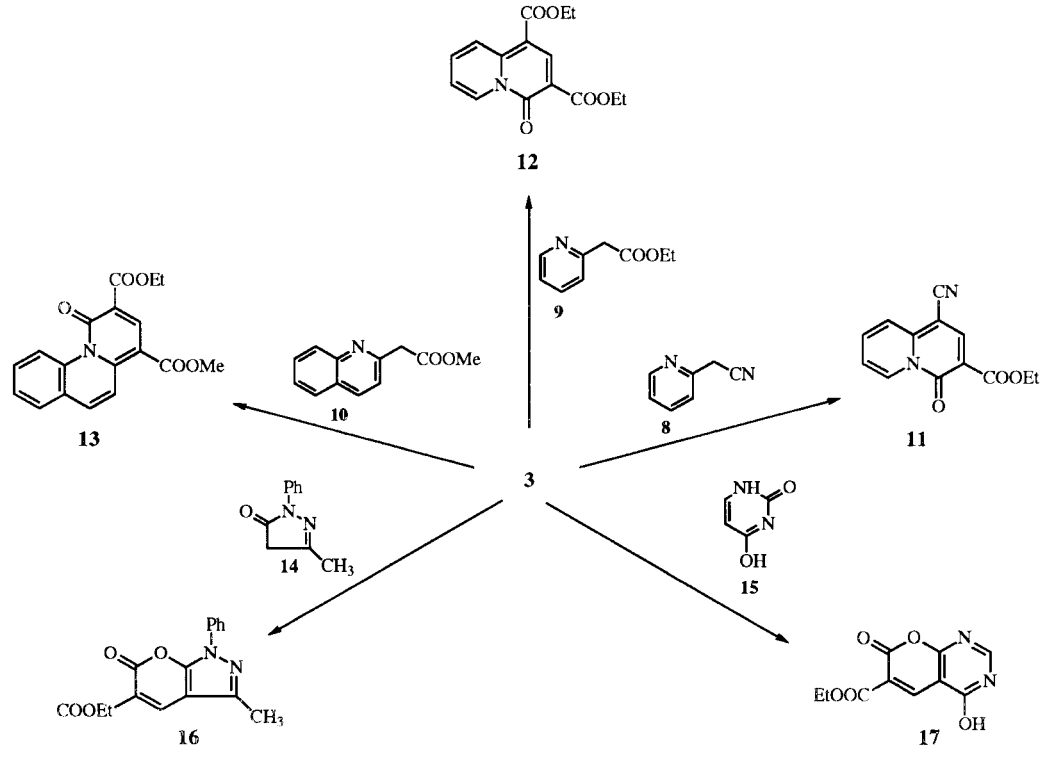
Under the employed reaction conditions the fused pyridinones, *i.e.* 1-cyano-3-ethoxycarbonyl-4-oxo-4*H*-

Scheme 3



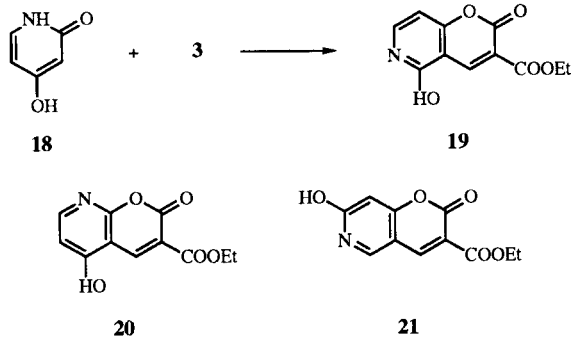
quinolizine (**11**), 1,3-(diethoxycarbonyl)-4-oxo-4*H*-quinolizine (**12**), and 2-ethoxycarbonyl-3-methoxycarbonyl-4-oxo-4*H*-benzo[c]quinolizine (13), were formed, respectively. Furthermore, also heterocyclic compounds with a methylene or potential methylene group incorporated in the cyclic system, such as 3-methyl-1-phenylpyrazol-4(5*H*)-one (**14**) and uracil (**15**), react in acetic acid to give fused pyranones, 5-ethoxycarbonyl-3-methyl-1-phenyl-6-oxo-1(6*H*)-pyrano[2,3-*c*]pyrazole (**16**) and 6-ethoxycarbonyl-4-hydroxy-7-oxo-7*H*-pyrano[2,3-*d*]pyrimidine (**17**), respectively (Scheme 4).

Scheme 4



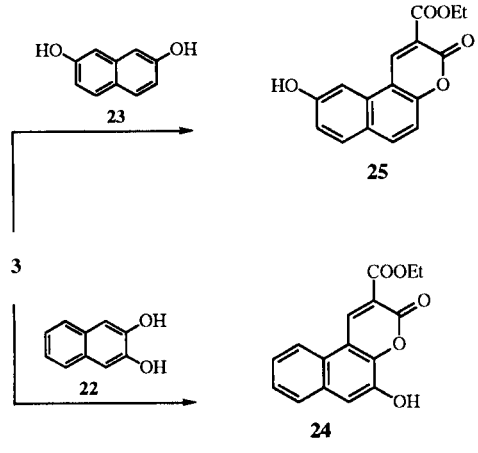
In the case of 4-hydroxypyridin-2(1*H*)-one (**18**) three isomeric structure **19**, **20**, and **21** can be formed, dependent on the initial attack of the reagent either at postion **3** or **5**, and further cyclization to adjacent hydroxy group attached either at position **2** or **4**. On the basis of the magnitude of the coupling constant, J = 7.0 Hz, between two protons at δ = 6.32 ppm and δ = 7.75 ppm, characteristic for ortho protons, the structure **21** was eliminated. The chemical shifts for these two protons are characteristic for structure **19**, and are in agreement with those found in other derivatives of this system [7], while the pyridine protons of the isomeric structure **20** would appear at around δ = 7.5 ppm and δ = 8.5 ppm, as shown in some other derivatives of this system [8] (Scheme 5).

Scheme 5



Compound **3** reacts also with dihydroxynaphthalenes, such as 2,3-dihydroxy **22** and 2,7-dihydroxynaphthalene (**23**) at position 1, in boiling acetic acid, to give 2-ethoxycarbonyl-5-hydroxy-3-oxo-3*H*-naphtho[2,1-*b*]pyran (**24**) and 2-ethoxycarbonyl-9-hydroxy-3-oxo-3*H*-naphtho-[2,1-*b*]pyran (**25**), respectively (Scheme 6).

Scheme 6

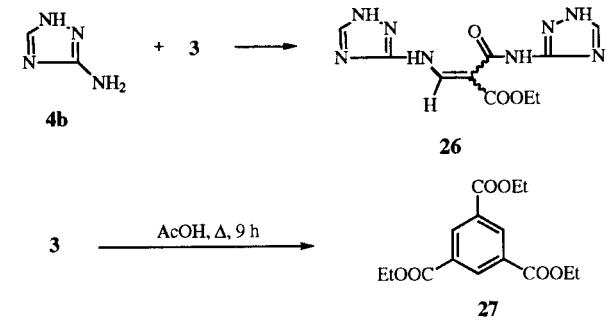


During these investigations, we observed, that by the heating of 3-amino-1,2,4-triazole (**4b**) with the compound **3** in acetic acid, in the presence of catalytic amounts of hydrobromic acid (36%), under reflux for seven hours, one of the ester groups was transformed to give ethyl 3-[(1,2,4-triazolyl-3)amino]-2-[(1,2,4-triazolyl-3)carbamoyl]propenoate (**26**) in 34% yield. No attempts were made in order to establish the orientation around the double bond.

The reagent **3** is thermally unstable. By heating in acetic acid under reflux for nine hours 1,3,5-triethoxycarbonylbenzene (**27**) was formed in 11% yield. This compound was always found as an impurity present in the reaction mixtures when longer heating was required (Scheme 7).

The structures of all new compounds were determined on the basis of elemental analyses for C, H, and N, and ^{1}H nmr spectra.

Scheme 7



EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Varian EM 360 L spectrometer, ir spectra on a Perkin-Elmer 1310 instrument, and microanalyses for C, H and N on Perkin-Elmer Analyser 2400.

Diethyl *N,N*-dimethylaminomethylenemalonate (**3**) was prepared according to the procedure described in the literature [5].

Diethyl *N*-(Isoxazolyl-3)aminomethylenemalonate (**5a**).

3-Aminoisoxazole (**4a**, 216 mg, 0.0026 mole) and diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 1.376 g, 0.0064 mole) were dissolved in acetic acid (3 ml) and the solution was allowed to stand at room temperature for one day. Then one half of the solvent was evaporated *in vacuo* and the mixture was allowed to stand at 5° for 24 hours. The precipitate was collected by filtration to give **5a** in 32% yield, mp 62-63° (from ethanol/water); ^{1}H nmr (deuteriochloroform): δ 1.30 (3H, t, CH_3CH_2), 1.33 (3H, t, CH_3CH_2), 4.22 (2H, q, CH_2CH_3), 4.26 (2H, q, CH_2CH_3), 6.25 (1H, d, $H_{4'}$), 8.32 (1H, d, $H_{5'}$), 8.49 (1H, d, CHNH), 10.87 (1H, br d, NHCH), J_{CH3CH2} = 7.0 Hz, $J_{H4'H5'}$ = 2.0 Hz, J_{NHCH} = 13.0 Hz.

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 52.74; H, 5.64; N, 11.04.

In the same manner the following compounds were prepared:

Diethyl *N*-(3-Methylpyridinyl-2)aminomethylenemalonate (**5c**).

This compound was prepared from 2-amino-3-methylpyridine (**4c**, 1.000 g, 0.0093 mole) and diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 2.000 g, 0.0128 mole) by heating at 70° for 16 hours to give **5c** in 35% yield, mp 64-65° (from ethanol/water), lit [9] mp 61-62°; ^{1}H nmr (deuteriochloroform): δ 1.23 (3H, t, CH_3CH_2), 1.26 (3H, t, CH_3CH_2), 2.28 (3H, s, 3'-Me), 4.17 (2H, q, CH_2CH_3), 4.20 (2H, q, CH_2CH_3), 7.09 (1H, t, $H_{5'}$), 7.70 (1H, dd, $H_{4'}$), 8.22 (1H, dd, $H_{6'}$), 9.10 (1H, d, CHNH), 11.00 (1H, br d, NHCH), J_{CH3CH2} = 7.0 Hz, $J_{H4'H5'}$ = 5.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, $J_{H4'H6'}$ = 2.0 Hz, J_{NHCH} = 13.0 Hz.

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.66; H, 6.42; N, 10.46.

Diethyl *N*-(3-Hydroxypyridinyl-2)aminomethylenemalonate (**5e**).

This compound was prepared from 2-amino-3-hydroxypyridine (**4e**, 600 mg, 0.0055 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 1.376 g, 0.0064 mole) by heating

at 60° for 8 hours, to give **5e** in 30% yield, mp 179-185° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.33 (3H, t, CH_3CH_2), 1.36 (3H, t, CH_3CH_2), 4.35 (2H, q, CH_2CH_3), 4.39 (2H, q, CH_2CH_3), 7.00 (1H, t, $H_{5'}$), 7.30 (1H, dd, $H_{4'}$), 7.39 (1H, s, OH), 8.06 (1H, dd, $H_{6'}$), 9.40 (1H, d, CHNH), 11.63 (1H, br d, NHCH), J_{CH3CH2} = 7.0 Hz, $J_{H4'H5'}$ = 5.0 Hz, $J_{H5'H6'}$ = 5.0 Hz, $J_{H4'H6'}$ = 2.0 Hz, J_{NHCH} = 13.0 Hz.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 10.00. Found: C, 56.00; H, 5.67; N, 10.27.

Diethyl *N*-(6-Chloropyridazinyl-3)aminomethylenemalonate (**5f**).

This compound was prepared from 3-amino-6-chloropyridazine (**4f**, 300 mg, 0.0026 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 1.376 g, 0.0064 mole) under reflux for 7 hours to give **5f** in 13% yield, mp 164-166° (from ethanol/water), lit [10] mp 169°; ^{1}H nmr (deuteriochloroform): δ 1.30 (3H, t, CH_3CH_2), 1.35 (3H, t, CH_3CH_2), 4.26 (2H, q, CH_2CH_3), 4.31 (2H, q, CH_2CH_3), 7.10 (1H, s, $H_{4'}$), 7.49 (1H, d, $H_{5'}$), 9.18 (1H, d, CHNH), 11.44 (1H, br d, NHCH), J_{CH3CH2} = 7.0 Hz, $J_{H4'H5'}$ = 9.0 Hz, J_{NHCH} = 13.0 Hz.

Anal. Calcd for $C_{12}H_{14}ClN_3O_4$: C, 48.09; H, 4.71; N, 14.02. Found C, 48.41; H, 4.62; N, 13.98.

Diethyl *N*-(Pyrimidinyl-2)aminomethylenemalonate (**5g**).

This compound was prepared from 2-aminopyrimidine (**4g**, 400 mg, 0.0042 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 1.376 g, 0.0064 mole) by heating at 100° for 8 hours to give **5g** in 56% yield, mp 114-116° (from ethanol/water), lit [11] mp 113°; ^{1}H nmr (deuteriochloroform): δ 1.31 (3H, t, CH_3CH_2), 1.35 (3H, t, CH_3CH_2), 4.29 (2H, q, CH_2CH_3), 4.34 (2H, q, CH_2CH_3), 7.00 (1H, t, $H_{5'}$), 8.58 (2H, d, $H_{4'}$ and $H_{6'}$), 9.12 (1H, d, CHNH), 11.00 (1H br d, NHCH), J_{CH3CH2} = 7.0 Hz, $J_{H4'H5'}$ = $J_{H5'H6'}$ = 5.0 Hz, J_{NHCH} = 13.0 Hz.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.63; H, 5.63; N, 15.65.

Diethyl *N*-(Indazolyl-3)aminomethylenemalonate (**5h**).

This compound was prepared from 3-aminoindazole (**4h**, 400 mg, 0.003 mole) and diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 1.376 g, 0.0064 mole) was allowed to stand at 20° for 24 hours to give **5h** in 49% yield, mp 167-169° (from ethanol), lit [12] mp 153-156°; ^{1}H nmr (deuteriochloroform): δ 1.33 (3H, t, CH_3CH_2), 1.39 (3H, t, CH_3CH_2), 4.29 (2H, q, CH_2CH_3), 4.35 (2H, q, CH_2CH_3), 7.00-7.80 (4H, m, Ar), 8.97 (1H, d, CHNH), 10.26 (1H, broad peak, $H_{1'}$), 11.44 (1H, br d, NHCH), J_{CH3CH2} = 7.0 Hz, J_{NHCH} = 13.0 Hz.

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.49; H, 5.53; N, 13.89.

3-Ethoxycarbonyl-9-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**6c**).

A mixture of diethyl *N*-(3-methylpyridinyl-2)aminomethylenemalonate (**5c**, 300 mg, 0.0011 mole) and acetic acid (3 ml) was heated under reflux for 2 hours, the solvent was evaporated *in vacuo* and the solid residue recrystallized from ethyl acetate to give **6c** in 60% yield, mp 153-155° (from ethyl acetate), lit [9] mp 149-150°; ^{1}H nmr (deuteriochloroform): δ 1.40 (3H, t, CH_3CH_2), 2.68 (3H, s, 9-Me), 4.43 (2H, q, CH_2CH_3), 7.24 (1H, dd, H_7), 7.81 (1H, dd, H_8), 9.00 (1H, s, H_2), 9.20 (1H, dd, H_6), J_{CH3CH2} = 7.0 Hz, J_{H6H7} = 7.0 Hz, J_{H6H8} = 1.0 Hz, J_{H7H8} = 7.0 Hz.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.11; H, 4.94; N, 12.21.

3-Ethoxycarbonyl-8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**6d**).

A mixture of 2-amino-4-methylpyridine (**4d**, 540 mg, 0.005 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (5 ml) was heated under reflux for 90 minutes, two thirds of the solvent evaporated *in vacuo* and cooled. The precipitate was collected by filtration and washed with water and diethyl ether to give **6d** in 35% yield, mp 165-169° (from toluene), lit [13] mp 171-172°; ^{1}H nmr (deuteriochloroform): δ 1.42 (3H, t, CH_3CH_2), 2.59 (3H, s, 8-Me), 4.46 (2H, q, CH_2CH_3), 7.20 (1H, br d, H_7), 7.61 (1H, br s, H_9), 9.08 (1H, s, H_2), 9.22 (1H, br d, H_6), J_{CH3CH2} = 7.0 Hz, J_{H6H7} = 7.0 Hz.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.16; H, 5.10; N, 11.94.

3-Ethoxycarbonyl-9-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**6e**).

A mixture of diethyl *N*-(3-methylpyridinyl-2)aminomethylenemalonate (**5e**, 200 mg, 0.0007 mole) and acetic acid (3 ml) was heated under reflux for 8 hours. Then the reaction mixture was cooled and some water was added. The precipitate was collected by filtration and washed with water and diethyl ether to give **6e** in 78% yield, mp 171-173° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.41 (3H, t, CH_3CH_2), 4.44 (2H, q, CH_2CH_3), 6.95-7.55 (3H, m, H_7, H_8 and OH), 8.80 (1H, dd, H_6), 8.99 (1H, s, H_2), J_{CH3CH2} = 7.0 Hz, J_{H6H7} = 7.0 Hz, J_{H6H8} = 2.0 Hz, J_{H7H8} = 7.0 Hz.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.70; H, 4.13; N, 11.90.

3-Ethoxycarbonyl-4-oxo-4(6*H*)-pyrimido[1,2-*b*]indazole (**7**).

A mixture of diethyl *N*-(indazolyl-3)aminomethylenemalonate (**5h**, 303 mg, 0.001 mole) and acetic acid (5 ml) was heated under reflux for 6 hours, cooled and the precipitate collected by filtration to give **7** in 31% yield, mp 280-310° dec (from DMSO/water), lit [12] mp 315°; ^{1}H nmr (deuteriotrifluoroacetic acid) δ 1.08 (3H, t, CH_3CH_2), 4.16 (2H, q, CH_2CH_3), 7.10-8.10 (4H, m, H_7, H_8, H_9 and H_{10}), 8.83 (1H, s, H_2), J_{CH3CH2} = 7.0 Hz.

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.94; H, 4.19; N, 16.54.

1-Cyano-3-ethoxycarbonyl-4-oxo-4*H*-quinolizine (**11**).

A solution of ethyl 2-pyridylacetonitrile (**8**, 500 mg, 0.0042 mole) and diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) in acetic acid (5 ml) was allowed to stand at room temperature for 10 days, the precipitate collected by filtration and washed with water and diethyl ether to give **11** in 84% yield, mp 179-181° (from ethanol), lit [14] mp 174°; ^{1}H nmr (deuteriochloroform): δ 1.39 (3H, t, CH_3CH_2), 4.42 (2H, q, CH_2CH_3), 7.46 (1H, m, H_7), 8.05 (2H, m, H_8 and H_9), 8.73 (1H, s, H_2), 9.55 (1H, dd, H_6), J_{CH3CH2} = 7.0 Hz, J_{H6H7} = 7.0 Hz, J_{H6H8} = 1.5 Hz.

Anal Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found C, 64.78; H, 3.96; N, 11.75.

1,3-Diethoxycarbonyl-4-oxo-4*H*-quinolizine (**12**).

A mixture of ethyl 2-pyridylacetate (**9**, 800 mg, 0.0049 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (5 ml) was heated at 60° for 5 hours, cooled, the precipitate collected by filtration and washed with water and

diethyl ether to give **12** in 64% yield, mp 127-128° (from ethanol), lit [15] mp 131- 132°; ^{1}H nmr (deuteriochloroform): δ 1.43 (6H, t, CH_3CH_2), 4.38 (2H, q, CH_2CH_3), 4.42 (2H, q, CH_2CH_3), 7.35 (1H, ddd, H_7), 7.90 (1H, ddd, H_8), 9.20 (1H, s, H_2), 9.50 (2H, dd, H_6 and H_9), J_{CH3CH2} = 7.0 Hz, J_{H6H7} = 8.0 Hz, J_{H6H8} = 2.0 Hz, J_{H7H8} = 6.0 Hz, J_{H8H9} = 8.0 Hz.

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.50; H, 5.08; N, 5.21.

2-Ethoxycarbonyl-3-methoxycarbonyl-1-oxo-1*H*-benz[*c*]quinolizine **13**.

A mixture of methyl 2-quinolylacetate (**10**, 90%, 700 mg, 0.0036 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (3 ml) was heated at 60° for 10 hours. Then one half of the solvent was evaporated *in vacuo*, some water and ethanol was added and the mixture was left at 5° for several days. The precipitate was collected by filtration and washed with water and diethyl ether to give **13** in 22% yield, mp 146-148° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.41 (3H, t, CH_3CH_2), 3.95 (3H, s, OMe), 4.45 (2H, q, CH_2CH_3), 7.65 (4H, m, H_5, H_7, H_8 and H_9), 8.91 (1H, s, H_3), 9.02 (1H, d, H_6), 9.39 (1H, m, H_{10}), J_{CH3CH2} = 7.0 Hz, J_{H5H6} = 6.0 Hz.

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.45; H, 4.65; N, 4.31. Found: C, 66.52; H, 4.48; N, 4.71.

5-Ethoxycarbonyl-3-methyl-1-phenyl-6-oxo-1(6*H*)-pyrano-[2,3-*c*]pyrazole (**16**).

A mixture of 3-methyl-1-phenyl-4(5*H*)-pyrazolone (**14**, 500 mg, 0.0029 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (5 ml) was heated under reflux for one hour. The reaction mixture was then cooled, some water was added, the precipitate collected by filtration and washed with water and diethyl ether to give **17** in 82% yield, mp 148-168° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.37 (3H, t, CH_3CH_2), 2.45 (3H, s, 3-Me), 4.39 (2H, q, CH_2CH_3), 7.20-8.10 (5H, m, Ph), 8.60 (1H, s, H_4), J_{CH3CH2} = 7.0 Hz.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.43; H, 4.73; N, 9.39. Found C, 64.79; H, 4.68; N, 9.25.

6-Ethoxycarbonyl-4-hydroxy-7-oxo-7*H*-pyrano[2,3-*d*]pyrimidine (**17**).

A mixture of 4,6-dihydroxypyrimidine (**15**, 450 mg, 0.004 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (5 ml) was heated under reflux for 3 hours. The reaction mixture was then cooled, three quarters of the solvent were evaporated *in vacuo*, some water was added, the precipitate collected by filtration and washed with water and diethyl ether to give **17** in 53% yield, mp 213-215° (from ethanol), lit [16] mp 210-213°; ^{1}H nmr (DMSO-d_6): δ 1.31 (3H, t, CH_3CH_2), 4.29 (2H, q, CH_2CH_3), 8.55 (1H, s, H_5), 8.56 (1H, s, H_2), J_{CH3CH2} = 7.0 Hz.

Anal. Calcd. for $C_{10}H_8N_2O_5$: C, 50.86; H, 3.41; N, 11.86. Found: C, 51.20; H, 3.33; N, 11.59.

3-Ethoxycarbonyl-5-hydroxy-2-oxo-2*H*-pyrano[4,3-*b*]pyridine (**19**).

A mixture of 2,4-dihydroxypyridine (**18**, 350 mg, 0.0032 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (5 ml) was heated under reflux for 45 minutes, cooled, and the precipitate collected by filtration and washed with water and diethyl ether to give **19** in 94% yield, mp 245-265° dec (from ethanol); ^{1}H nmr (DMSO-d_6): δ 1.30 (3H, t, CH_3CH_2), 4.21 (2H, q, CH_2CH_3), 6.32 (1H, d, H_8), 7.75 (1H, d, H_7), 8.51 (1H, s, H_4), 13.15 (1H, br s, OH), J_{CH3CH2} = 7.0 Hz, J_{H7H8} = 7.0 Hz.

Anal. Calcd. for $C_{11}H_9NO_5$: C, 56.18; H, 3.86; N, 5.95. Found: C, 56.27; H, 3.74; N, 6.12.

2-Ethoxycarbonyl-5-hydroxy-3-oxo-3*H*-naphtho[2,1-*b*]pyrane (**24**).

A mixture of 2,3-dihydroxynaphthalene (**22**, 300 mg, 0.002 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (5 ml) was heated under reflux for 7 hours. The reaction mixture was then cooled, some water was added, the precipitate collected by filtration and washed with water and diethyl ether to give **24** in 27% yield, mp 213-215° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 1.34 (3H, t, CH_3CH_2), 4.31 (2H, q, CH_2CH_3), 7.30 (4H, m, H_7, H_8, H_9, and H_{10}), 8.39 (1H, br s, H_6), 9.30 (1H, s, H_1), 10.71 (1H, s, OH), J_{CH3CH2} = 7.0 Hz.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.45; H, 4.07.

2-Ethoxycarbonyl-9-hydroxy-3-oxo-3*H*-naphtho[2,1-*b*]pyrane (**25**).

A mixture of 2,7-dihydroxynaphthalene (**23**, 300 mg, 0.002 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (5 ml) was heated under reflux for 7 hours. The reaction mixture was then cooled, some water was added, the precipitate collected by filtration and washed with water and diethyl ether to give **25** in 72% yield, mp 214-217° dec (from ethanol); ^{1}H nmr (DMSO-d_6): δ 1.37 (3H, t, CH_3CH_2), 4.31 (2H, q, CH_2CH_3), 7.17 (1H, d, H_6), 7.29 (1H, d, H_7), 7.65 (1H, d, H_{10}), 7.91 (1H, s, H_5), 8.16 (1H, dd, H_8), 9.09 (1H, s, H_1), 10.30 (1H, s, OH), J_{CH3CH2} = 7.0 Hz, J_{H5H6} = 9.0 Hz, J_{H7H8} = 9.0 Hz, J_{H8H10} = 2 Hz.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.31; H, 4.00.

Ethyl 2-[(1,2,4-Triazolyl-3)carbamoyl]-3-[(1,2,4-triazolyl-3)-amino]propenoate (**26**).

A mixture of 3-amino-1,2,4-triazole (**4b**, 160 mg, 0.0019 mole), diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0032 mole), acetic acid (3 ml) and the solution of hydrogen bromide in acetic acid (33% in acetic acid, a few drops) was heated at 100° for 6 hours. Then three quarters of the solvent were evaporated *in vacuo* and the reaction mixture was cooled. The precipitate was collected by filtration and washed with water and diethyl ether to give **26** in 34% yield, mp 190-196° (from ethanol/ethyl acetate); ^{1}H nmr (DMSO-d_6): δ 1.29 (3H, t, CH_3CH_2), 4.24 (2H, q, CH_2CH_3), 7.4 (4H, br s, NH+H_2O), 7.81 (1H, s, C*H*NH), 8.26 (1H, s, $H_{5'}$), 8.67 (1H, s, $H_{5'}$), J_{CH3CH2} = 7.0 Hz.

Anal. Calcd. for $C_{10}H_{12}N_8O_3$: C, 41.10; H, 4.14; N, 38.34. Found C, 41.08; H, 4.06; N, 38.31.

1,3,5-Triethoxycarbonylbenzene (**27**).

A mixture of diethyl *N,N*-dimethylaminomethylenemalonate (**3**, 0.0064 mole) and acetic acid (5 ml) was heated under reflux for 16 hours. Then three quarters of the solvent were evaporated *in vacuo*, cooled and some water was added. The precipitate was collected by filtration and washed with water and diethyl ether to give **27** in 11% yield, mp 130-135° (from ethanol water), lit [17] mp 133-134°; ^{1}H nmr (DMSO-d_6): δ 1.44 (3H, t, CH_3CH_2), 4.44 (2H, q, CH_2CH_3), 8.86 (1H, s, Ar), J_{CH2CH3} = 7.0 Hz.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.55; H, 6.08.

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