Pyrimidine Derivatives and Related Compounds. 38 (1). Synthesis of 1,3-Oxazine-2,4-diones and Their Reaction with Nucleophiles. Ring Transformation of 1,3-Oxazines to Pyrimidines

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5,6-Unsubstituted 1,3-oxazine-2,4-diones (**3**) and 6-unsubstituted 5-methyl-1,3-oxazine-2,4-diones (**4**) were prepared by reduction of the corresponding 6-chloro derivatives (**1** and **2**). Treatment of 6-chloro-3-methyl-1,3-oxazine-2,4-dione (**1a**) with sodium azide, sodium cyanide, secondary amines and aniline gave the corresponding 6-substituted compounds (**7**, **9**, **10** and **11**) while the reaction of **1a** and **2a,b** with primary aliphatic amines such as methylamine and ethylamine caused a ring transformation to pyrimidine ring system giving barbituric acids (**13a-d**).

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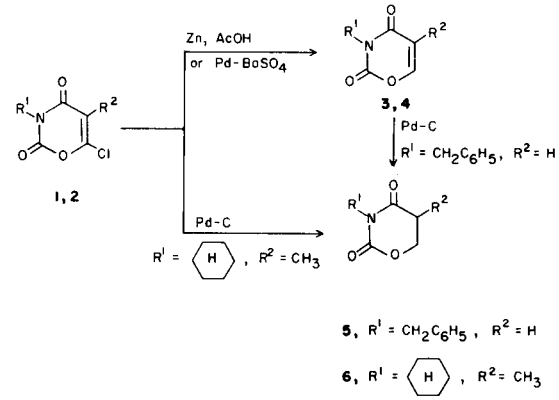
1,3-Oxazine-2,4-dione is a parent base of the nucleoside antibiotic oxazinomycin (2,3) which possesses antibacterial activity against gram-positive and gram-negative species (4) as well as significant activity against transplantable tumors (2,4). Furthermore, it is well known that some compounds of this type are effective as agricultural chemicals serving as fungicides, nematocides and viricides (5) as well as insecticides and plant protective agents (6). Therefore, we have been interested in 1,3-oxazine-2,4-dione derivatives from a viewpoint of their biological activities. Though there are already many reports on 1,3-oxazine-2,4-diones, most of them deal with the ring formation of 6-alkyl or 6-aryl derivatives and only a little is described about the reactivity in such reports (7).

We have investigated the reduction of 6-chloro-1,3-oxazine-2,4-diones (**1** and **2**) and their reaction with nucleophiles such as amines, azide and cyanide. In this report, synthesis of hitherto unknown 5,6- or 6-unsubstituted 1,3-oxazine-2,4-diones (**3** and **4**) and a novel ring transformation of 1,3-oxazines to barbituric acids are described.

Synthetic methods for the preparation of 6-chloro-1,3-oxazine-2,4-diones by the reaction of malonyl dichlorides and isocyanates were reported by Disselnkoetter (6) and Ziegler, *et al.* (8). We applied their methods to synthesize eleven 6-chloro derivatives (**1a-f** and **2a-e**) including eight new compounds (Table I). Then the reduction of the 6-chloro group under various conditions using **1a** was examined. Thus, the catalytic hydrogenolysis of **1a** in ethanol in the presence of palladium on charcoal and that of **1a** in acetic acid in the presence of palladium on charcoal and sodium acetate afforded 3-methyl-1,3-oxazine-2,4-dione (**3a**) in 38% and 11% yields, respectively. On the other hand, reduction of **1a** by refluxing in acetic acid with zinc powder resulted in a broad rise of the yield up to 87%; other 5,6-unsubstituted 1,3-oxazine-2,4-diones (**3b-e**) were obtained in high yield from the corresponding 6-chloro derivatives (**1b-e**) under the same conditions (9). Similar treatment of 6-chloro-5-methyl-1,3-oxazine-2,4-diones (**2a,e**) gave the corresponding 6-unsubstituted 5-methyl derivatives (**4a,b**) though the reaction required much more time. On the contrary, 6-chloro-3-cyclohexyl-5-methyl-1,3-oxazine-2,4-dione (**2c**) was not reduced under such conditions. But, when **2c** was subjected to a catalytic hydrogenolysis in methanol in the presence of palladium on charcoal at 60° and 45 kg/cm² pressure, a stable crystalline compound was obtained. The pmr spectral signals (10) at δ 4.31 (1H, dd, J = 6, 11 Hz), 4.00 (1H, t, J = 11 Hz), 2.78 (1H, m) and 1.27 (3H, d, J = 6 Hz) suggested

Scheme I

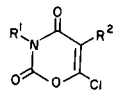


1 and 2, see Table I, 3 and 4, see Table II

that the compound was not the expected product (**4c**) but further reduced 5,6-dihydro derivative (**6**). On the other hand, catalytic hydrogenolysis of **2c** in ethanol at room temperature and atmospheric pressure over palladium on

0022-152X/81/061095-06$02.25

Table I



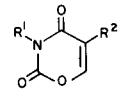
Compound No.	R^1	R^2	Mp, °C	Yield, %	Formula	Analysis (%) Calcd. (Found) C	H	N	Pmr C_5-H	C_5-CH_3	Others
1a	CH_3	H	101-103 (a)	74	$C_5H_4ClNO_3$	37.17 (37.36)	2.50 (2.47)	8.67 (8.62)	6.05		3.33 (3H, s, N-CH_3)
1b	C_2H_5	H	77-79	49	$C_6H_6ClNO_3$	41.04 (40.98)	3.44 (3.39)	7.98 (7.96)	6.04		3.95 (2H, q, J = 7 Hz, N-CH_2-), 1.26 (3H, t, J = 7 Hz, -CH_3)
1c	C_4H_9	H	58-59 (b)	69	$C_8H_{10}ClNO_3$	47.19 (47.10)	4.95 (4.85)	6.88 (6.96)	6.01		3.87 (2H, t, J = 7 Hz, N-CH_2-), 1.10-2.00 (4H, m, -CH_2CH_2-), 0.95 (3H, t, J = 7 Hz, -CH_3)
1d	C_6H_{11}	H	130-131 (c)	78	$C_{10}H_{12}ClNO_3$	52.30 (52.08)	5.27 (5.29)	6.10 (6.10)	5.96		4.30-4.90 (1H, m, N-CH<), 0.80-2.80 (10H, m, $(CH_2)_5$)
1e	$C_6H_5CH_2$	H	77-78	57	$C_{11}H_8ClNO_3$	55.59 (55.78)	3.39 (3.33)	5.89 (5.83)	6.03		7.20-7.60 (5H, m, C_6H_5), 5.00 (2H, s, N-CH_2-)
1f	C_6H_5	H	190-192 (d)	8	$C_{10}H_6ClNO_3$	53.71 (53.94)	2.70 (2.70)	6.26 (6.28)	6.15		7.10-7.70 (5H, m, N-C_6H_5)
2a	CH_3	CH_3	81-82	72	$C_6H_6ClNO_3$	41.04 (41.17)	3.44 (3.44)	7.98 (8.04)		2.02	3.33 (3H, s, N-CH_3)
2b	C_2H_5	CH_3	oil	66	$C_7H_8ClNO_3$	44.34 (43.75)	4.25 (4.23)	7.39 (7.31)		2.01	1.24 (3H, t, J = 7 Hz, -CH_3), 3.94 (2H, q, J = 7 Hz, N-CH_2-)
2c	C_6H_{11}	CH_3	75-76	51	$C_{11}H_{14}ClNO_3$	54.22 (54.38)	5.79 (5.80)	5.75 (5.74)		2.00	4.30-4.95 (1H, m, N-CH<), 0.80-2.80 (10H, m, $(CH_2)_5$)
2d	$C_6H_5CH_2$	CH_3	75- 76	70	$C_{12}H_{10}ClNO_3$	57.26 (57.11)	4.01 (3.92)	5.57 (5.57)		2.05	7.25-7.65 (5H, m, C_6H_5), 5.12 (2H, s, N-CH_2-)
2e	C_6H_5	CH_3	111-112	58	$C_{11}H_8ClNO_3$	55.59 (55.79)	3.39 (3.42)	5.89 (5.98)		2.06	7.10-7.70 (5H, m, N-C_6H_5)

(a) Lit (6) mp 102-104°. (b) Lit (6) mp 61°. (c) Lit (6) mp 132°. (d) Melts with decomposition.

barium sulfate gave desired 5-methyl-1,3-oxazine-2,4-dione (**4c**) (11). Furthermore, reduction of 3-benzyl-1,3-oxazine-2,4-dione (**3e**) in ethanol in the presence of palladium on charçoal was carried out in order to obtain the simplest compound, *i.e.* 1,3-oxazine-2,4-dione. However, the isolated product did not appear to be the desired compound but the 3-benzyl-5,6-dihydro derivative (**5**) from the results of various spectral data and elemental analysis.

It is well known that chloro groups located at a β-position of an α,β-unsaturated ketone moiety contained in a heterocyclic ring can be readily replaced by various nucleophiles. For example, 6-chlorouracils react with nucleophiles to give 6-substituted uracils (12). Anticipating that similar nucleophilic substitution may take place, we investigated the nucleophilic reaction of **1a** with some nucleophiles.

Table II

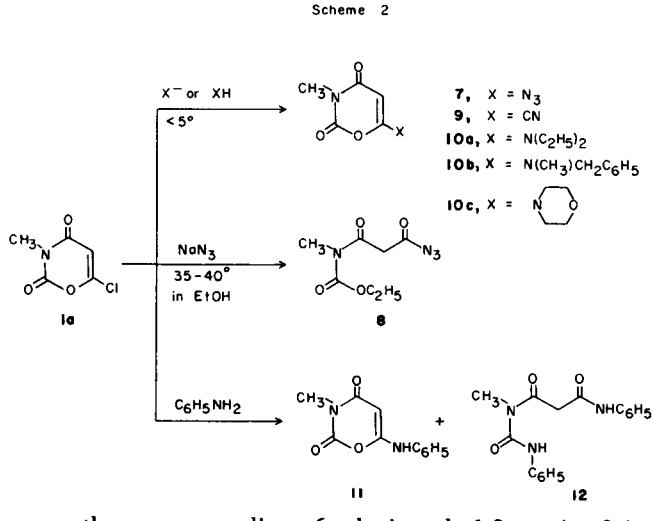


Compound No.	R^1	R^2	Mp or Bp/mm (a), °C	Yield, %	Formula	Analysis (%) Calcd. (Found) C	H	N	Pmr C_5-H	C_5-CH_3	C_6-H	Others
3a	CH_3	H	90-92 (b)	87	$C_5H_5NO_3$	47.25 (47.02)	3.97 (3.82)	11.20 (11.06)	6.00 (d, J = 6 Hz)		7.43 (d, J = 6 Hz)	3.33 (3H, s, N-CH_3)
3b	C_2H_5	H	45-47 80/2	80	$C_6H_7NO_3$	51.06 (50.78)	5.00 (5.02)	9.93 (9.78)	6.00 (d, J = 6 Hz)		7.45 (d, J = 6 Hz)	3.96 (2H, q, J = 7 Hz, N-CH_2-), 1.24 (3H, t, J = 7 Hz, -CH_3)
3c	C_4H_9	H	100/2	91	$C_8H_{11}NO_3$	56.79 (56.32)	6.55 (6.72)	8.28 (8.24)	5.98 (d, J = 6 Hz)		7.43 (d, J = 6 Hz)	3.89 (2H, t, J = 7 Hz, N-CH_2-), 1.00-2.00 (4H, m, -CH_2CH_2-), 0.95 (3H, t, J = 7 Hz, -CH_3)
3d	C_6H_{11}	H	105-107 (c)	85	$C_{10}H_{13}NO_3$	61.52 (61.65)	6.71 (6.82)	7.18 (7.19)	5.91 (d, J = 6 Hz)		7.33 (d, J = 6 Hz)	4.30-4.95 (1H, m, N-CH<), 0.80-2.70 (10H, m, $(CH_2)_5$
3e	$C_6H_5CH_2$	H	39-40 160/2	92	$C_{11}H_9NO_3$	65.02 (64.79)	4.46 (4.37)	6.89 (6.96)	5.92 (d, J = 6 Hz)		(d)	7.05-7.63 (6H, m, -C_6H_5 + C_6-H), 5.00 (2H, s, N-CH_2-)
4a	CH_3	CH_3	60-60.5 (e)	76	$C_6H_7NO_3$	51.06 (50.96)	5.00 (5.02)	9.93 (9.87)		1.91 (d, J = 2 Hz)	7.28 (q, J = 2 Hz)	3.35 (3H, s, N-CH_3)
4b	C_6H_5	CH_3	112-113 (f)	39	$C_{11}H_9NO_3$	65.02 (65.29)	4.46 (4.43)	6.89 (6.83)		1.89 (d, J = 2 Hz)	(d)	7.05-7.63 (6H, m, N-C_6H_5 + C_6-H)
4c	C_6H_{11}	CH_3	81-82 (g)	60	$C_{11}H_{15}NO_3$	63.14 (62.59)	7.23 (7.19)	6.69 (6.60)		1.88 (d, J = 2 Hz)	7.15 (q, J = 2 Hz)	4.35-5.05 (1H, m, N-CH<), 0.80-2.80 (10H, m, $(CH_2)_5$)

(a) Bath temperature. (b) Recrystallized from ethanol. (c) Recrystallized from hexane. (d) C_6-H proton is overlapped by the aromatic proton multiplet. (e) Recrystallized from petroleum benzin (bp 30-70°). (f) Recrystallized from benzene-hexane. (g) Recrystallized from water.

Thus, treatment of **1a** with sodium azide in ethanol at 3-5°, followed by quenching with water immediately after the reaction gave 6-azido-3-methyl-1,3-oxazine-2,4-dione (**7**) in 37% yield. However, warming of the reaction mixture at 35-40° after the reaction afforded the red oily product. Its mass spectrum showed the molecular ion peak at m/e 214 and the ir spectrum suggested the presence of an azide group by absorption band at 2160 cm^{-1}. Its pmr spectrum showed signals at δ 4.20 (2H, q, J = 7 Hz), 3.90 (2H, s), 3.20 (3H, s) and 1.27 (3H, t, J = 7 Hz). All of those spectral data fully support that this compound is ethyl *N*-azidoformylacetyl-*N*-methylcarbamate (**8**) which would be formed by further attacking of the 2-carbonyl group in **7** with ethoxide anion. The reaction in acetone resulted in a slight rise of the yield up to 56%. Treatment of **1a** with sodium cyanide in acetone at −12 to −6° gave 6-cyano-3-methyl-1,3-oxazine-2,4-dione (**9**) though the yield was low (4%). Similarly, the reaction of **1a** with secondary amines such as diethylamine, benzylmethylamine and morpholine

Scheme 2

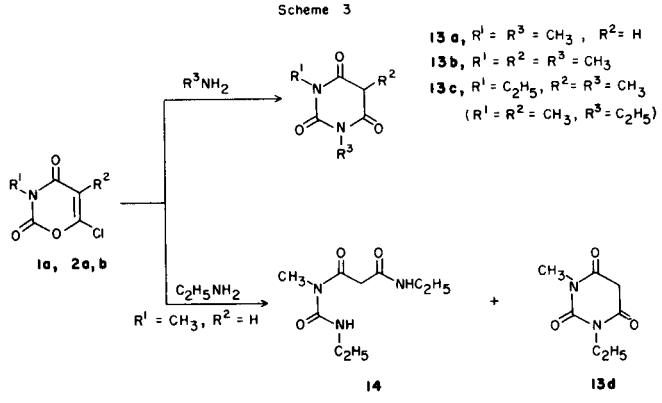


gave the corresponding 6-substituted 1,3-oxazine-2,4-diones (**10a-c**) in 26%, 91% and 19% yields, respectively.

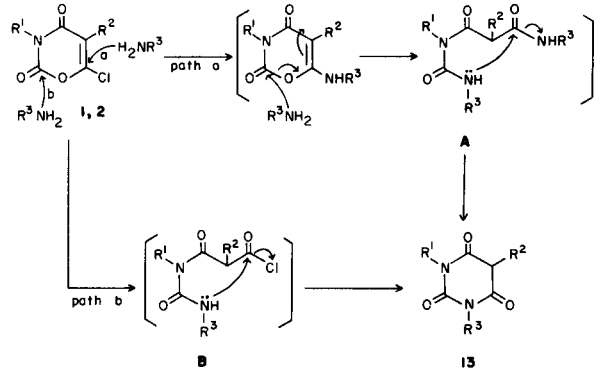
Subsequently, primary amines were used as nucleo-

philes. The reaction of **1a** with aniline gave the 6-anilino compound (**11**) in 76% yield along with 1-methyl-3-phenyl-1-(*N*-phenylmalonamoyl)urea (**12**) as a by-product. On the other hand, when methylamine was used, the reaction of **1a** caused a ring transformation to pyrimidine ring system. Thus, treatment of **1a** with an aqueous solution of methylamine in tetrahydrofuran at 0-5° afforded colorless sticks, mp 122-124°, in 45% yield. This compound was not

Scheme 3



Scheme 4



the expected 6-methylamino compound but assumed to be 1,3-dimethylbarbituric acid (**13a**) from their various spectral data. The structure was confirmed by direct comparison with an authentic sample (13). To our knowledge, such a ring transformation into barbituric acid systems has not yet been reported (14). Similar treatment of **2a,b** with methylamine or ethylamine gave the corresponding barbituric acids (**13b,c**). In the reaction of **1a** with ethylamine, a ring-opened compound, 3-ethyl-1-(*N*-ethylmalonamoyl)-1-methylurea (**14**), was obtained in 58% yield along with the corresponding barbituric acid (**13d**).

Two plausible mechanisms (path a and b) for the formation of **13a-d** are shown in Scheme 4. In path a, displacement of 6-chloro group with an amine followed by attack of one more amine on the 2-position affords an intermediate (A) which cyclizes to **13**. In path b, the reaction proceeds *via* formation of an intermediate (B) and further recyclization. The posturated intermediate (A) in path a corresponds to the urea (**14**) obtained above and our attempts to convert **14** into **13** were unsuccessful. This fact suggests that the ring transformation may take place in accordance with path b.

Results of examination on biological activities of the new compounds obtained above will be reported later.

EXPERIMENTAL

All melting points are uncorrected. Mass spectra were recorded on a JEOL JMS-D300 spectrometer and ir spectra were obtained on a Hitachi Model 215 spectrophotometer. Unless otherwise stated, pmr spectra were recorded on a Hitachi Perkin-Elmer R-20B 60-MHz nuclear magnetic resonance spectrometer and deuteriochloroform was used as a solvent with tetramethylsilane as an internal standard. Chemical shifts were quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Thin-layer chromatograms (tlc) were run on Silica-gel $60F_{254}$ plastic sheets (Merck). Column chromatographies were run using Silica-gel C-200 (Wako) and unless otherwise stated, chloroform was used as an eluent.

Benzyl Isocyanate.

To a stirred solution of phenylacetyl chloride (27.4 g, 0.177 mole) in acetone (70 ml), a solution of sodium azide (13.8 g, 0.212 mole) in water (60 ml) was added at 10-20° and the mixture was stirred for 30 minutes. After addition of water (60 ml), the mixture was extracted three times with 100 ml portion of benzene, washed with water and dried over magnesium sulfate. The benzene extract was added dropwise to a refluxing benzene (50 ml) and the mixture was heated to reflux for 30 minutes. The solvent was evaporated *in vacuo* and the residue was distilled under reduced pressure to give benzyl isocyanate as colorless oil (16 g, 60%), bp 97-99°/23 mm [lit (15) bp 90°/12 mm].

3-Substituted 6-Chloro-3,4-dihydro-2*H*-1,3-oxazine-2,4-diones (**1a-f**) (Table I).

Application of the method of Disselnkoetter (5) to malonyl dichloride (20 mmoles) and isocyanates (25 mmoles) such as methyl, ethyl, butyl, cyclohexyl, benzyl and phenyl isocyanate gave the corresponding **1a-e**, which could be purified by recrystallization from hexane, and **1f**, which could be purified by column chromatography using benzene as an eluent and recrystallization from benzene.

3-Substituted 6-Chloro-5-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-diones (**2a-e**) (Table I).

Application of the method of Ziegler *et al.* (6) to methylmalonyl dichloride (20 mmoles) and isocyanates (25 mmoles) such as methyl, ethyl, cyclohexyl, benzyl and phenyl isocyanate gave the corresponding **2a-e**, which was purified by column chromatography using benzene as an eluent and recrystallization from hexane.

3-Methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (**3a**).

Method a.

A solution of **1a** (600 mg, 3.7 mmoles) in ethanol (15 ml) was hydrogenated catalytically using 5% palladium on charcoal (60 mg). The progress of the reaction was followed by tlc using ether as a developer. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was recrystallized from ethanol to give **3a** (180 mg, 38%).

Method b.

A mixture of **1a** (600 mg, 3.7 mmoles), 5% palladium on charcoal (60 mg), sodium acetate (310 mg, 3.8 mmoles) and acetic acid (10 ml) was hydrogenated catalytically. After the usual treatment, a small quantity of water was added to the residue. The mixture was neutralized with sodium

bicarbonate, extracted with chloroform, washed with water and dried over magnesium sulfate. Evaporation of the solvent and recrystallization of the residue gave **3a** (50 mg, 11%).

Method c.

A mixture of **1a** (600 mg, 3.7 mmoles), zinc powder (500 mg, 7.7 mmoles) and acetic acid (10 ml) was refluxed under vigorous agitation until tlc showed the disappearance of **1a**. The mixture was filtered while hot to remove insoluble matter, and the filtrate was concentrated *in vacuo*. The residue was dissolved in chloroform and the solution was washed with successive water, sodium bicarbonate solution and water and dried over magnesium sulfate. Evaporation of the solvent to dryness and recrystallization gave **3a** (410 mg, 87%).

Similarly, other 1,3-oxazine-2,4-diones (**3b-e** and **4a,b**) were prepared by method c (Table II).

3-Cyclohexyl-5-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (**4c**).

Catalytic hydrogenolysis using **2c** (480 mg, 2 mmoles), 5% palladium on barium sulfate (100 mg) and ethanol (50 ml) at room temperature was carried out in the usual way to give **4c** (250 mg, 60%).

3-Benzyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazine-2,4-dione (**5**).

A mixture of **3e** (500 mg, 2.5 mmoles) and ethanol (10 ml) was hydrogenated in the presence of 5% palladium on charcoal (50 mg) at room temperature. A usual treatment of the reaction mixture and recrystallization from hexane gave colorless needles (**5**) (450 mg, 89%), mp 62-63°; ms: m/e 205 (M^+); pmr: δ 7.16-7.53 (5H, m, C_6H_5), 4.95 (2H, s, NCH_2), 4.33, 2.79 (each 2H, each t, J = 6 Hz, $CH_2 \times 2$).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.58; H, 5.44; N, 6.70.

3-Cyclohexyl-5-methyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazine-2,4-dione (**6**).

A mixture of **2c** (500 mg, 2.1 mmoles) and methanol (70 ml) was hydrogenated catalytically in the presence of 5% palladium on charcoal at 60° and 45 kg/cm² pressure. The reaction mixture was treated in the usual way and recrystallized from hexane to give colorless prisms (**6**) (340 mg, 78%), mp 61-62°; ms: m/e 211 (M^+); pmr: δ 4.24-4.60 (1H, m, NCH), 4.31 (1H, dd, J = 6, 11 Hz, C_6-H), 4.00 (1H, t, J = 11 Hz, C_6-H), 2.78 (1H, m, C_5-H), 0.70-2.28 (10H, m, $(CH_2)_5$), 1.27 (3H, d, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.53; H, 8.37; N, 6.53.

6-Azido-3-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (**7**).

a) To a stirred solution of **1a** (600 mg, 3.7 mmoles) in ethanol (50 ml) was added a solution of sodium azide (260 mg, 4 mmoles) in water (1 ml) dropwise at 3-5° and the mixture was stirred for 15 minutes. After addition of water, the mixture was extracted with chloroform, washed with water and dried over magnesium sulfate. Evaporation of the solvent to dryness and recrystallization from ethanol gave pale yellow needles (**7**) (230 mg, 37%), mp 115-117° dec; ms: m/e 168 (M^+); ir (potassium bromide): 2120 cm^{-1} (N_3); pmr: δ 5.47 (1H, s, C_5-H), 3.32 (3H, s, NCH_3).

Anal. Calcd. for $C_5H_4N_4O_3$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.98; H, 2.41; N, 33.32.

b) To a stirred solution of **1a** (600 mg, 3.7 mmoles) in acetone (7 ml) was added a solution of sodium azide (260 mg, 4 mmoles) in water (1 ml) dropwise at 3-5° and the mixture was stirred for 1.5 hours. After addition of acetic acid (0.2 ml) to the mixture, the solvent was removed *in vacuo*. The residue was washed with a small quantity of water and recrystallized to give **7** (350 mg, 56%).

Ethyl *N*-Azidoformylacetyl-*N*-methylcarbamate (**8**).

To a stirred solution of **1a** (600 mg, 3.7 mmoles) in ethanol (50 ml), was added a solution of sodium azide (300 mg, 4.6 mmoles) in water (1 ml) dropwise at 3-5° and the mixture was stirred for 10 minutes. The solvent was evaporated at 35-40° *in vacuo* to give the oily product, which was subsequently dissolved in chloroform, washed with water and dried over magnesium sulfate. After evaporation of the solvent, the residual oily product was purified by column chromatography to give a red oil (**8**) (550 mg, 69%); ms: m/e 214 (M^+); ir (neat): 2160 cm^{-1} (N_3); pmr: δ 4.20 (2H, q, J = 7 Hz, OCH_2), 3.90 (2H, s, CH_2), 3.20 (3H, s, NCH_3), 1.27 (3H, t, J = 7 Hz, CH_3).

6-Cyano-3-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (**9**).

To a stirred solution of **1a** (600 mg, 3.7 mmoles) in acetone (7 ml) was added a solution of sodium cyanide (240 mg, 4.9 mmoles) in water (1 ml) dropwise at −12 to −6°. After addition of acetic acid (0.2 ml) to the reaction mixture, the solvent was removed *in vacuo*. The residue was dissolved in chloroform, washed with water and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography and recrystallization from hexane to give colorless leaves (**9**) (20 mg, 4%), mp 97-99°, in addition to the starting **1a** (70 mg); ms: m/e 152 (M^+); ir (potassium bromide): 2240 cm^{-1} (CN); pmr: δ 6.53 (1H, s, C_5-H), 3.37 (3H, s, NCH_3).

Anal. Calcd. for $C_6H_4N_2O_3$: C, 47.38; H, 2.65; N, 18.42. Found: C, 47.34; H, 2.60; N, 18.12.

6-Diethylamino-3-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (**10a**).

To a stirred solution of **1a** (600 mg, 3.7 mmoles) in chloroform (10 ml) was added a solution of diethylamine (900 mg, 12.3 mmoles) in chloroform (5 ml) dropwise at −13 to −10°. After stirring for 30 minutes, the mixture was washed with water and dried over magnesium sulfate, followed by evaporation of the solvent. The residual oily product was purified by column chromatography and recrystallization from hexane to give colorless prisms (**10a**) (190 mg, 26%), mp 68-69°; ms: m/e 198 (M^+); pmr: δ 4.74 (1H, s, C_5-H), 3.37 (4H, q, J = 7 Hz, $N(CH_2)_2$), 3.26 (3H, s, NCH_3), 1.22 (6H, t, J = 7 Hz, $CH_3 \times 2$).

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.81; H, 7.10; N, 14.16.

6-Benzylmethylamino-3-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (**10b**).

To a stirred solution of **1a** (600 mg, 3.7 mmoles) in chloroform (10 ml) was added a solution of benzylmethylamine (900 mg, 7.4 mmoles) in chloroform (5 ml) dropwise at −10 to −5° and the mixture was stirred for 1 hour. After addition of acetic acid (0.1 ml), the reaction mixture was washed with water and dried over magnesium sulfate, followed by evaporation of the solvent to give the crude oily product which was purified by column chromatography to give colorless oil (**10b**) (690 mg, 91%), bp 220°/3 mm (bath temperature), along with recovering the starting **1a** (100 mg); ms: m/e 246 (M^+); pmr: δ 7.04-7.20 (5H, m, C_6H_5), 4.74 (1H, s, C_5-H), 4.45 (2H, s, C_6-NCH_2), 3.18 (3H, s, N_3-CH_3), 2.86 (3H, s, C_6-NCH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.27; H, 5.79; N, 11.20.

3-Methyl-6-morpholino-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (**10c**).

To a stirred solution of **1a** (320 mg, 2 mmoles) in tetrahydrofuran (10 ml) in an ice-bath was added morpholine (1390 mg, 16 mmoles) dropwise and the mixture was stirred for 3 hours. After addition of acetic acid (1 ml), the insoluble matter was filtered off and the solvent was evaporated *in vacuo* to give the red oily product. Water was added thereto and the resulting white precipitate was filtered and recrystallized from petroleum benzin (bp 75-120°) to give colorless needles (**10c**) (80 mg, 19%), mp 86-87°; ms: m/e 212 (M^+); pmr: δ 4.84 (1H, s, C_5-H), 3.80, 3.43 (each 4H, each m, $CH_2 \times 4$), 3.32 (3H, s, NCH_3).

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.80; H, 6.32; N, 13.34.

6-Anilino-3-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (**11**) and 1-Methyl-3-phenyl-1-(*N*-phenylmalonamoyl) urea (**12**).

To a stirred solution of **1a** (3.2 g, 20 mmoles) in tetrahydrofuran (40 ml) was added aniline (3.8 g, 40.9 mmoles) dropwise at room temperature and the mixture was stirred for 22 hours. After addition of acetic acid (2 ml), the solvent was evaporated to dryness and the residue was triturated with water, filtered and washed with water. Fractional recrystallization from ethanol gave colorless needles (**11**) (3.3 g, 76%), mp 201-202° dec;

ms: m/e 218 (M^+); pmr (deuteriodimethylsulfoxide): δ 9.90 (1H, br, NH), 6.87-7.50 (5H, m, C_6H_5), 5.02 (1H, s, C_5-H), 3.15 (3H, s, NCH_3).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.55; H, 4.58; N, 12.72.

From the filtrate was obtained colorless needles (**12**) (230 mg, 4%), mp 176°; ms: m/e 311 (M^+); pmr (deuteriodimethylsulfoxide): δ 11.22 (1H, br, NH), 9.85 (1H, br, NH), 6.90-7.78 (10H, m, C_6H_5 × 2), 3.83 (2H, s, CH_2), 3.38 (3H, s, NCH_3).

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.52; H, 5.24; N, 13.60.

1,3-Dimethylbarbituric Acid (**13a**).

To a stirred solution of **1a** (600 mg, 3.7 mmoles) in tetrahydrofuran (10 ml) was added 40% aqueous solution of methylamine (2 ml) dropwise and the mixture was stirred for 15 minutes. Acetic acid (1 ml) was added to the reaction mixture and the solvent was evaporated *in vacuo*. The residue was dissolved in chloroform, washed with water and dried over magnesium sulfate. After evaporation of the solvent, the residue was recrystallized from benzene to give colorless sticks (**13a**) (260 mg, 45%), which was identified with an authentic sample (13).

1,3,5-Trimethylbarbituric Acid (**13b**).

According to the same procedure as described above, **2a** (650 mg, 3.7 mmoles) was allowed to react with 40% aqueous solution of methylamine (2 ml) to give colorless sticks (**13b**) (120 mg, 19%), which was identified with an authentic sample (16).

1-Ethyl-3,5-dimethylbarbituric Acid (**13c**).

Method a.

According to the same procedure as described above, **2b** (700 mg, 3.7 mmoles) was allowed to react with 40% aqueous solution of methylamine (2 ml) and recrystallized from hexane to give colorless sticks (**13c**) (380 mg, 56%), mp 78-79.5°; ms: m/e 184 (M^+); pmr: δ 3.95 (2H, q, J = 6 Hz, NCH_2), 3.48 (1H, q, J = 7 Hz, C_5-H), 3.30 (3H, s, NCH_3), 1.62 (3H, d, J = 7 Hz, C_5-CH_3), 1.20 (3H, t, J = 6 Hz, CH_3).

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.18; H, 6.59; N, 15.11.

Method b.

According to the same procedure as described above, **2a** (650 mg, 3.7 mmoles) was allowed to react with 70% aqueous solution of ethylamine (1 ml) to give the crude oily product, which was purified by column chromatography and recrystallization to give **13c** (280 mg, 41%).

1-Ethyl-3-methylbarbituric Acid (**13d**) and 3-Ethyl-1-(*N*-ethylmalonamoyl)-1-methylurea (**14**).

To a solution of **1a** (600 mg, 3.7 mmoles) in tetrahydrofuran (10 ml) was added 40% aqueous solution of ethylamine (2 ml) dropwise at 0-5° and the mixture was stirred for 15 minutes. After addition of acetic acid (1 ml), the solvent was evaporated *in vacuo* to give a pale yellow oily product, which was dissolved in chloroform, washed with water and dried over magnesium sulfate, followed by evaporation of the solvent. To the residue was added 50 ml of hexane and the mixture was refluxed for a while. After cooling to room temperature, the insoluble matter was filtered and recrystallized from benzene to give colorless needles (**14**) (460 mg, 58%), mp 108-109°; ms: m/e 215 (M^+); pmr: δ 8.90 (1H, br, NH), 6.95 (1H, br, NH), 3.53 (2H, s, CH_2), 3.30 (3H, s, NCH_3), 3.27 (4H, q, J = 7 Hz, NCH_2 × 2), 1.18 (6H, t, J = 7 Hz, CH_3 × 2).

Anal. Calcd. for $C_9H_{17}N_3O_3$: C, 50.22; H, 7.96; N, 19.52. Found: C, 50.37; H, 7.96; N, 19.45.

The hexane filtrate was evaporated and the residue was recrystallized from ether to give colorless sticks (**13d**) (80 mg, 13%), mp 73-75°; ms: m/e 170 (M^+); pmr: δ 3.92 (2H, q, J = 7 Hz, NCH_2), 3.64 (2H, s, CH_2), 3.28 (3H, s, NCH_3), 1.23 (3H, t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.29; H, 5.90; N, 16.38.

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