Preparation of Fused 1,3-Oxazine-2,4-diones as Potential Antitumor Agents

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A series of indole, thiophene and pyrrole-fused 1,3-oxazine-2,4-diones, 2-methyl-1,3-oxazin-4-ones and 2-dimethylamino-1,3-oxazin-4-ones were synthesized and evaluated as antitumor agents.

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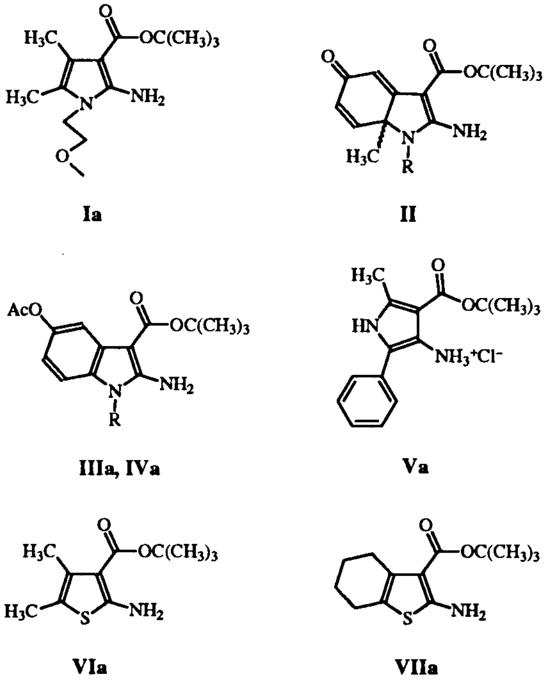
Introduction.

Much previous work in our laboratory has involved the synthesis of heterocyclic β-enamino esters as pharmaceutical intermediates [2-5]. Evaluation of these interesting compounds and their derivatives as antimicrobial agents [6], fungicides [7] and serine protease inhibitors [8] has also been a top priority.

We are aware that there are few reports in the literature of heterocyclic β-enamino esters or their fused oxazine derivatives having been evaluated for cytotoxic or antitumor activity [9-12]. Therefore we set out to produce a robust series of heterocyclic β-enamino *t*-butyl esters, as well as their fused oxazine derivatives, for antitumor evaluation.

Facile synthetic routes to a number of heterocyclic β-enamino *t*-butyl esters exist. A number of 1-substituted-2-amino-3-*t*-butoxycarbonyl-4,5-dimethyl pyrroles such as **Ia** are available *via* the condensation of acetoin, *t*-butyl cyanoacetate and a primary amine with the azeotropic removal of water (Figure 1) [2]. The 1-substituted-2-amino-3-*t*-butoxycarbonyl-5-oxo-7a-methyl-5,7a-dihydroindoles **II**, are in turn available *via* an unusual cycloaddition of ethyl propiolate to the aforementioned pyrroles **Ia** (Figure 1) [4]. Unfortunately, ring closure of the β-enamino *t*-butyl ester domain of these dihydroindoles **II** by means of doubly electrophilic reagents has, to date, not been possible. It is possible however, to convert **II** (where R = $C_2H_4OCH_3$ and Bz) to **IIIa** and **IVa** *via* a reductive aromatization utilizing Zn, pyridine and a trace of water, followed by acetylation of the free 5-OH group by acetic anhydride [5]. Formation of the 2-phenyl-3-amino-4-*t*-butoxycarbonyl-5-methylpyrrole (**Va**) occurs in high yield by condensation of *t*-butyl acetoacetate with (±)-2-phenylglycinonitrile followed by cyclization of the intermediate enamine with sodium ethoxide in ethanol [6]. The novel 4,5-disubstituted-2-amino-3-*t*-butoxycarbonylthiophenes **VIa**, **VIIa** may be produced by means of a modification of the procedure of Eger, *et al.* (Figure 1) [13]. Briefly, the appropriate ketone was condensed with *t*-butyl cyanoacetate in the presence of elemental sulfur to yield the 4,5-disubstituted-2-amino-3-*t*-butoxycarbonylthiophene **VIa**, **VIIa**.



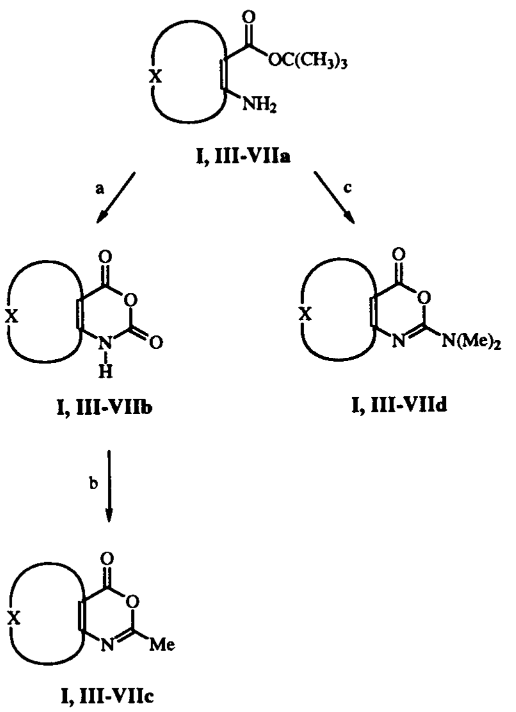
where R = 2-methoxyethyl for **IIIa-d**, and benzyl for **IVa-d**

Figure 1

It was found that treatment of the heterocyclic β-enamino *t*-butyl esters **I**, **III-VIIIa** with Triphosgene® resulted in smooth formation of the fused oxazine-2,4-diones **I**, **III-VIIIb**, which precipitated from the reaction mixture within minutes (Scheme 1). This method uses no base and gives less exposure to toxic phosgene than standard methods [14]. In order to convert the fused oxazine-2,4-diones **I**, **III-VIIIb** to fused 2-methyloxazin-4-ones **I**, **III-VIIIc** we used a modification of Jacobs' procedure by which any alkyl group may be placed at the 2-position by use of the appropriate anhydride (Scheme 1) [15].

Phosgene iminium salts have been used previously to prepare 2-dimethylamino-4-chloroquinazolines from *o*-aminobenzonitriles in anhydrous acidic dichloroethane [16]. Closure of the heterocyclic β-enamino *t*-butyl esters **I**, **III-VIIIa** with phosgene iminium chloride proceeded similarly and afforded the fused 2-dimethylaminooxazin-

Scheme 1



where X = any of the heterocyclic β-enamino *t*-butyl esters in Figure 1

a) Triphosgene®, CH_2Cl_2, 38°C, 2 hours

b) Acetic Anhydride, Pyridine, 100°C, 1 hour

c) Phosgene iminium chloride, $HCl/(C_2H_5)_2O$, $ClCH_2CH_2Cl$, 83°C, 2 hours

4-ones **I**, **III-VIIId** in high yield (Scheme 1).

Biological Results.

Each compound was evaluated using the National Cancer Institutes new *in vitro* disease-oriented primary antitumor screen [17]. Although several compounds showed total growth inhibition (TGI) in the 10^{-6} range, the most interesting compound was **II** where R = benzyl [4]. This dihydroindole caused TGI in the 10^{-5} range and showed some cell line selectivity for several types of renal and non-small cell lung cancers. Additional evaluation of this compound is underway.

EXPERIMENTAL

Mass spectroscopy was performed using either a heated direct insertion probe or by the fast atom bombardment or electrospray techniques. The pmr spectra were obtained on a Brücker AM500 nmr spectrometer using default parameters. The infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. The melting points were determined on an Electrothermal apparatus and are uncorrected. The tlc was run on precoated silica gel plates ($60F_{254}$, 0.2 mm thick, Merck). Flash chromatography was performed with 32-63 μm silica gel from Selecto, Inc., Kennesaw, GA. Compounds used as starting materials have been previously synthesized and reported, **Ia** [2], **II** [4], **II-IVa** [5] and **Va** [6].

General Procedure for the Preparation of the 4,5-Disubstituted-2-amino-3-*tert*-butoxycarbonylthiophenes **VI-VIIa**.

Elemental sulfur (0.1 g-atom), *t*-butyl cyanoacetate (0.1 mole), morpholine (0.1 mole) and the appropriate ketone (0.1 mole) were added to 100 ml of absolute ethanol and stirred at reflux for 18 hours. After cooling the ethanol was removed *in vacuo*. The crude product was purified *via* flash chromatography using a hexanes:ethyl acetate (1:1) mobile phase to yield a straw-colored oil.

2-Amino-3-*tert*-butoxycarbonyl-4,5-dimethylthiophene (**VIa**).

After recrystallization from acetone (100 ml), this compound was obtained as yellow crystals in 48% yield (10.9 g), tlc R_f, hexanes:ethyl acetate:dichloromethane (2:1:1), 0.75, mp 66-67°; ir: ν 3450, 3300, 1620, 1570, 1250, 1140 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.53 (s, 9H, *t*-butyl CH_3), 2.12 (s, 6H, 4- and 5-CH_3); eims: (m/z) 227 (M^+).

Anal. Calcd. for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16. Found: C, 57.93; H, 7.54; N, 6.04.

2-Amino-3-*tert*-butoxycarbonyl-4,5,6,7-tetrahydrobenzothiophene (**VIIa**).

This compound was obtained as a straw colored oil in 86% yield (21.8 g); ir: ν 3470, 3310, 1645, 1560, 1250, 1130 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.52 (s, 9H, *t*-butyl CH_3), 2.12 (m, 4H, 5- and 6-CH_2), 2.48 (m, 2H, 4-CH_2), 2.62 (m, 2H, 7-CH_2).

Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.54; H, 7.60; N, 5.48.

General Procedure for the Preparation of the Fused 1,3-Oxazine-2,4-diones **I**, **III-VIIb** from Heterocyclic β-Enamino *t*-Butyl Esters **I**, **III-VIIa**.

The appropriate heterocyclic β-enamino *t*-butyl ester, **I**, **III-VIIa**, (0.003 mole) was dissolved in dichloromethane (25 ml), and Triphosgene® (0.001 mole) was added. The reaction mixture was refluxed for two hours, cooled to 0° and filtered to yield the crude products, **I**, **III-VIIb**, which were recrystallized from diethyl ether to yield bright white crystals.

5,6-Dimethyl-7-(2-methoxyethyl)pyrrolo[2,3-*d*]-1,3-oxazine-2,4(1*H*,7*H*)-dione (**Ib**).

This compound was obtained in 86% yield (0.62 g), mp 209-210° dec; ir: ν 3000, 1700, 1550, 1380, 1100, 890 cm^{-1}; ^1H-nmr (acetone-d_6): δ 2.16 (s, 3H, 5-CH_3), 2.18 (s, 3H, 6-CH_3), 3.29 (s, 3H, $NCH_2CH_2OCH_3$), 3.64 (t, 2H, $NCH_2CH_2OCH_3$), 4.19 (t, 2H, $NCH_2CH_2OCH_3$), 12.25 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.42; H, 5.93; N, 11.84.

6-Acetoxy-9-(2-methoxyethyl)-1,3-oxazino[4,5-*b*]indole-2,4-(1*H*,9*H*)-dione (**IIIb**).

This compound was obtained in 37% yield (0.35 g), mp 217-219° dec; ir: ν 2880, 1700, 1565, 1445, 1195, 975 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 2.28 (s, 3H, $COCH_3$), 3.20 (s, 3H, $NCH_2CH_2OCH_3$), 3.63 (t, 2H, $NCH_2CH_2OCH_3$), 4.46 (t, 2H, $NCH_2CH_2OCH_3$), 7.01 (m, 1H, 7-H), 7.40 (m, 1 H, 8-H), 7.59

(m, 1H, 5-*H*); hrms: fab (m/z) 319.0925, error 1.6 ppm (M^+).

Anal. Calcd. for $C_{15}H_{14}N_2O_6 \cdot 3/4H_2O$: C, 54.30; H, 4.71; N, 8.44. Found: C, 54.58; H, 4.55; N, 8.41.

6-Acetoxy-9-benzyl-1,3-oxazino[4,5-*b*]indole-2,4-(1*H*,9*H*)-dione (**IVb**).

This compound was obtained in 74% yield (0.78 g), mp 224-224.5° dec; ir: ν 3060, 1770, 1720, 1570, 1455, 1200 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 2.26 (s, 3H, $COCH_3$), 5.55 (s, 2H, $NCH_2C_6H_5$), 6.94 (m, 1H, 7-*H*), 7.23-7.36 (s, 5H, phenyl *H*), 7.24 (m, 1 H, 8-*H*), 7.41 (m, 1H, 5-*H*); hrms: fab (m/z) 351.0977, error 1.1 ppm (M^+).

Anal. Calcd. for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.10; H, 4.07; N, 8.00.

5-Methyl-7-phenylpyrrolo[3,4-*d*]-1,3-oxazine-2,4(1*H*,6*H*)-dione (**Vb**).

This compound was obtained in 91% yield (0.66 g), mp 269-271° dec; ir: ν 3220, 1750, 1695, 1470, 1120, 975 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 1.54 (s, 3H, 5-CH_3), 7.2-7.7 (m, 5H, phenyl *H*), 10.94 (s, 1H, 6-*H*), 12.51 (s, 1H, 1-*H*); ms: fab (m/z) 243 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.21; H, 4.25; N, 11.50.

5,6-Dimethylthieno[2,3-*d*]-1,3-oxazine-2,4(1*H*)-dione (**VIb**).

This compound was obtained in 56% yield (0.29 g), mp 197-198° dec; ir: ν 3120, 1750, 1490, 1310, 970 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 2.21 (s, 3H, 5-CH_3), 2.26 (s, 3H, 6-CH_3), 12.43 (s, 1H, 1-*H*); ms: fab (m/z) 198 (M^+).

Anal. Calcd. for $C_8H_7NO_3S$: C, 48.72; H, 3.58; N, 7.10. Found: C, 48.56; H, 3.58; N, 7.02.

5,6,7,8-Tetrahydrobenzothieno[2,3-*d*]-1,3-oxazine-2,4(1*H*)-dione (**VIIb**).

This compound was obtained in 56% yield (0.37 g), mp 217-217.5° dec; ir: ν 3080, 2850, 1645, 1400, 1320, 940 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 1.73 (m, 4H, 6- and 7-CH_2), 2.59 (m, 2H, 5-CH_2), 2.64 (m, 2H, 8-CH_2), 12.39 (s, 1H, 1-*H*).

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.75; H, 4.11; N, 6.29.

General Procedure for the Preparation of the Fused 2-alkyl-1,3-oxazin-4-ones **I, III-VIIc** from Fused 1,3-Oxazine-2,4-diones **I, III-VIIb**.

The appropriate fused 1,3-oxazine-2,4-diones **I, III-VIIb** (0.005 mole) was dissolved in pyridine (0.05 mole) and acetic anhydride (0.025 mole) was added. This solution was heated in boiling water bath for 1 hour. After cooling, 50 ml of an aqueous 1*M* sodium carbonate solution was slowly added and this mixture was stirred at rt for 1 hour. After dilution with 150 ml of ethyl acetate, the organic layer was washed successively with 100 ml of aqueous 1*M* hydrochloric acid, 100 ml of aqueous 1*M* sodium hydroxide and saturated aqueous sodium chloride. The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo* to yield the crude product.

2,5,6-Trimethyl-7-(2-methoxyethyl)pyrrolo[2,3-*d*]-1,3-oxazin-4(7*H*)-one (**Ic**).

After recrystallization from methanol:water (5:1) this compound was obtained as off-white crystals in 86% yield (0.52 g), mp 124-124.5° dec; ir: ν 3680, 1750, 1580, 1250, 850, 570 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.55 (s, 3H, 2-CH_3), 2.20 (s, 3H, 5-CH_3), 2.24 (s, 3H, 6-CH_3), 3.29 (s, 3H, $NCH_2CH_2OCH_3$), 3.59 (t, 2H, $NCH_2CH_2OCH_3$), 4.16 (t, 2H, $NCH_2CH_2OCH_3$).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.11; H, 6.89; N, 11.83.

6-Acetoxy-2-methyl-9-(2-methoxyethyl)-1,3-oxazino[4,5-b]indol-4(9*H*)-one (**IIIc**).

After recrystallization from methanol this compound was obtained as yellow crystals in 40% yield (0.63 g), mp 203-204°; ir: ν 2870, 1745, 1450, 1200, 1000 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 2.32 (s, 3H, $COCH_3$), 2.53 (s, 3H, 2-CH_3), 3.28 (s, 3H, $NCH_2CH_2OCH_3$), 3.73 (t, 2H, $NCH_2CH_2OCH_3$), 4.47 (t, 2H, $NCH_2CH_2OCH_3$), 7.09 (m, 1H, 7-*H*), 7.48 (m, 1 H, 8-*H*), 7.75 (m, 1H, 5-*H*); ms: (electrospray) (m/z) 317 (M^+).

Anal. Calcd. for $C_{16}H_{16}N_2O_5 \cdot 1/2H_2O$: C, 59.07; H, 5.27; N, 8.61. Found: C, 59.03; H, 5.27; N, 8.38.

6-Acetoxy-2-methyl-9-benzyl-1,3-oxazino[4,5-*b*]indol-4(9*H*)-one (**IVc**).

After recrystallization from methanol:water (9:1) this compound was obtained as yellow crystals in 62% yield (1.07 g), mp 235-236° dec; ir: ν 3450, 1750, 1595, 1495, 1210 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 2.30 (s, 3H, $COCH_3$), 2.55 (s, 3H, 2-CH_3), 5.51 (s, 2H, $NCH_2C_6H_5$), 7.01 (m, 1H, 7-*H*), 7.19 (m, 1 H, 8-*H*), 7.23-7.36 (s, 5H, phenyl *H*), 7.77 (m, 1H, 5-*H*); ms: fab (m/z) 349 (M^+).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.71; H, 4.61; N, 7.92.

2,5-Dimethyl-7-phenylpyrrolo[3,4-*d*]-1,3-oxazin-4(6*H*)-one (**Vc**).

After recrystallization from methanol:water (9:1) this compound was obtained as tan crystals in 64% yield (0.76 g), mp 308-310° dec; ir: ν 3200, 1700, 1600, 1160, 1020 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 2.32 (s, 3H, 5-CH_3), 2.57 (s, 3H, 2-CH_3), 7.1-8.0 (m, 5H, phenyl *H*), 12.38 (s, 1H, 6-*H*); ms: fab (m/z) 240 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_2O_2 \cdot 1/4H_2O$: C, 68.70; H, 5.15; N, 11.44. Found: C, 68.90; H, 5.24; N, 11.20.

2,5,6-Trimethylthieno[2,3-*d*]-1,3-oxazine-4-one (**VIc**).

After recrystallization from methanol:water (3:1) this compound was obtained as yellow spicules in 92% yield (0.89 g), mp 110-111°; ir: ν 2910, 1745, 1595, 1415, 880 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 2.36 (s, 3H, 5-CH_3), 2.37 (s, 3H, 6-CH_3), 2.43 (s, 3H, 2-CH_3); ms: ei (m/z) 195 (M^+).

Anal. Calcd. for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17. Found: C, 55.09; H, 4.68; N, 7.07.

2-Methyl-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-1,3-oxazin-4-one (**VIIc**).

After recrystallization from methanol:water (9:1) this compound was obtained as yellow crystals in 50% yield (0.55 g), mp 132-132.5°; ir: ν 2840, 1710, 1580, 1320, 880 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.83 (m, 4H, 6- and 7-CH_2), 2.42 (s, 3H, 2-CH_3), 2.78 (m, 2H, 5-CH_2), 2.83 (m, 2H, 8-CH_2); ms: ei (m/z) 221 (M^+).

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.88; H, 5.06; N, 6.34.

General Procedure for the Preparation of the Fused 2-Dimethylamino-1,3-oxazin-4-ones **I, III-VIId** from Heterocyclic β-Enamino *t*-Butyl Esters **I, III-VIIa**.

VIIa (0.01 mole) was dissolved in warm dichloroethane (25 ml), and phosgene iminium chloride (0.01 mole) was added. After cooling to 0°, 2 ml of anhydrous 1*M* ethereal hydrogen chloride was added. The reaction mixture was refluxed for one hour, cooled and the solvent was removed *in vacuo*. The oily residue was dissolved in 100 ml of ethyl acetate and filtered through a short bed of silica gel. After removal of the ethyl acetate *in vacuo*, recrystallization of the residue from methanol:water (3:1) yielded **I**, **III-VIId** as white crystals.

2-Dimethylamino-5,6-dimethyl-7-(2-methoxyethyl)pyrrolo[2,3-*d*]-1,3-oxazine-4(7*H*)-one (**Id**).

This compound was obtained as white spicules in 88% yield (2.25 g), mp 129-130°; ir: ν 2720, 1750, 1560, 1165, 975, 610 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.12 (s, 3H, 5-CH_3), 2.19 (s, 3H, 6-CH_3), 3.09 (s, 6H, 2-N(CH_3)$_2$), 3.32 (s, 3H, $NCH_2CH_2OCH_3$), 3.57 (t, 2H, $NCH_2CH_2OCH_3$), 4.02 (t, 2H, $NCH_2CH_2OCH_3$).

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.92; H, 7.26; N, 15.76.

2-Dimethylamino-6-acetoxy-9-(2-methoxyethyl)-1,3-oxazino[4,5-*b*]indol-4(9*H*)-one (**IIId**).

After recrystallization from acetone this compound was obtained as white crystals in 63% yield (2.16 g), mp 186.5-187°; ir: ν 2910, 1740, 1595, 1205, 995 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.29 (s, 3H, COCH_3), 3.20 (s, 6H, 2-N(CH_3)$_2$), 3.29 (s, 3H, $NCH_2CH_2OCH_3$), 3.69 (t, 2H, $NCH_2CH_2OCH_3$), 4.30 (t, 2H, $NCH_2CH_2OCH_3$), 6.92 (m, 1H, 7-*H*), 7.28 (m, 1 H, 8-*H*), 7.57 (m, 1H, 5-*H*); ms: fab (m/z) 346 (M$^+$).

Anal. Calcd. for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.54; N, 12.17. Found: C, 59.27; H, 5.59; N, 12.22.

2-Dimethylamino-6-acetoxy-9-benzyl-1,3-oxazino[4,5-*b*]indol-4(9*H*)-one (**IVd**).

After recrystallization from acetone this compound was obtained as yellow crystals in 73% yield (2.74 g), mp 199-201°; ir: ν 2920, 1760, 1595, 1530, 1195 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.29 (s, 3H, COCH_3), 3.21 (s, 6H, 2-N(CH_3)$_2$), 5.34 (s, 2H, $NCH_2C_6H_5$), 6.84 (m, 1H, 7-*H*), 7.10 (m, 1 H, 8-*H*), 7.13-7.37 (s, 5H, phenyl *H*), 7.57 (m, 1H, 5-*H*); ms: (electrospray) (m/z) 378 (M$^+$).

Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.74; H, 5.05; N, 11.18.

2-Dimethylamino-5-methyl-7-phenylpyrrolo[3,4-*d*]-1,3-oxazin-4(6*H*)-one (**Vd**).

After recrystallization from acetonitrile this compound was obtained as tan crystals in 20% yield (0.50 g), mp 278-280° dec; ir: ν 3230, 1700, 1600, 1500, 980 cm^{-1}; ^{1}H-nmr (DMSO-d$_6$): δ 2.52 (s, 3H, 5-CH_3), 3.07 (s, 6H, 2-N(CH_3)$_2$), 7.0-8.0 (m, 5H, phenyl *H*), 11.92 (s, 1H, 6-*H*); ms: fab (m/z) 269 (M$^+$).

Anal. Calcd. for $C_{15}H_{15}N_3O_2 \cdot 1/2H_2O$: C, 64.74; H, 5.79; N, 15.10. Found: C, 64.59; H, 5.85; N, 15.10.

2-Dimethylamino-5,6-dimethylthieno[2,3-*d*]-1,3-oxazin-4-one (**VId**).

After recrystallization from diethyl ether this compound was obtained in 58% yield (1.27 g), mp 104-105°; ir: ν 2900, 1730, 1580, 1475, 1190 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.25 (s, 3H, 5-CH_3), 2.29 (s, 3H, 6-CH_3), 3.14 (s, 6H, 2-N(CH_3)$_2$); ms: ei (m/z) 224 (M$^+$).

Anal. Calcd. for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.33; H, 5.37; N, 12.47.

2-Dimethylamino-5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-1,3-oxazin-4-one (**VIId**).

This compound was obtained as beige crystals in 75% yield (1.86 g); mp 156-157°; ir: ν 2910, 1740, 1580, 1395, 1290 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.76 (m, 4H, 6- and 7-CH_2), 2.59 (m, 2H, 5-CH_2), 2.78 (m, 2H, 8-CH_2), 3.14 (s, 6H, 2-N(CH_3)$_2$); ms: ei (m/z) 250 (M$^+$).

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.53; H, 5.60; N, 11.24.

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