A Convenient and Efficient Method for the Preparation of 6-Acyl-2(3*H*)-benzoxazolones

Hocine Aichaoui, Daniel Lesieur and Jean-Pierre Hénichart*

Institut de Chimie Pharmaceutique,
Rue du Professeur Laguesse,
59045 Lille, France

Received October 18, 1990

Benzoxazolinone derivatives have been found to exhibit various pharmacological properties and 6-acyl-2(3*H*)-benzoxazolones are considered as key starting materials for the preparation of these compounds. Reported here are the optimal conditions for a regioselective acylation at the 6-position of the benzoxazolinone ring. A general method leading to the expected products in excellent yields consists in using a mixture of aluminum chloride-dimethylformamide as catalyst and acid anhydrides or chlorides as acylating agents.

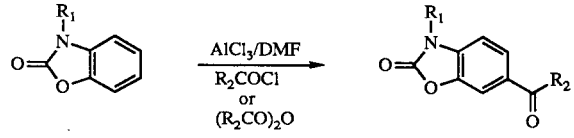
J. Heterocyclic Chem., **29**, 171 (1992).

Since the first report on the hypnotic properties of 2-benzoxazolinone [1], a number of derivatives have been tested for various activities including anticonvulsive, antipyretic, analgesic [2-5], antispasmodic [6], antitubercular [7-8] or antibacterial, antimicrobial and antifungal [9-21] effects. The potential of the benzoxazolinone structure has been recently emphasized by the finding that 6-methoxybenzoxazolinone, a natural occurring compound agonist of melatonin could serve as an environmental stimulus for reproductive activity [22,23]. At least, it is interesting to note that benzoxazolinone ring could be considered as a cyclic bioisostere of pyrocatechol. This analogy has been confirmed by the biological study of compounds in the structure of which the benzoxazolinone ring was linked to phenylethylamine chains. Such compounds exhibited a remarkable potential for use as agonists or antagonists of dopamine or norepinephrine [24,25].

Numerous works are currently in progress in this way and it is clear that the key step for the medicinal chemist is a flexible means of obtaining starting material such as acyl derivatives of benzoxazolinone.

The 6-acylbenzoxazolinones in particular exhibit analgesic properties largely higher than those of the parent heterocycle and constitute the basis of pharmacological developments in the field of CNS drugs. Electrophilic substitution such as chlorination, sulfonation, and nitration have been achieved using classical reagents but acylation yielding 6-acyl derivatives has been found to require particular conditions such as polyphosphoric acid as the solvent and catalyst with free acids serving as the acylating agents [3]. Nevertheless these conditions presented some limitations for the preparation of a number of 6-acylbenzoxazolinones. For example, they were not applicable to diacids or halogenoacids. Thus we now propose a new general method providing 6-acyl derivatives in excellent yields using the mixture aluminum chloride-dimethylformamide as the solvent and catalyst with acids anhydrides or chlorides as the acylating agents (Scheme 1).

Scheme 1



$R_1 = H$
$R_1 = CH_3$

1 (**a-o**) $R_1 = H$
2 (**a-o**) $R_1 = CH_3$

In the course of a systematic study, the temperature and the time of the reactions were optimized but the essential feature was the determination of the aluminum chloride/-benzoxazolinone ratio. It was found that the reagent was efficient only in the case of 7 to 11 equivalents *versus* benzoxazolinone derivatives. It is clear that aluminum chloride cannot be considered, in such conditions, as a catalyst. We have to admit the formation of a complex between aluminum chloride, dimethylformamide and benzoxazolinone involving the π and n electrons of the heterocycle.

We report in Table 1 the comparative yields obtained by the polyphosphoric acid (A) and aluminum chloride-dimethylformamide (B) methods.

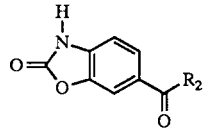
EXPERIMENTAL

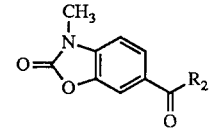
Melting points were taken on a Tottoli melting-point apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 177 infrared-spectrometer using potassium bromide pellets. The ^{1}H nmr spectra were recorded with a Bruker WP80-SY spectrometer. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Elemental analyses were performed by the "Service Central d'Analyses", CNRS, Vernaison, France.

General Procedure for the Reaction of Acid Anhydrides with 2-benzoxazolinone **1a-i**.

Dimethylformamide (8.6 ml, 115 mmoles) was slowly added to aluminum chloride (53.3 g, 400 mmoles). The mixture was stirred

Table





R_2	No.	Comparative yields (%) Procedure A	B	R_2	No.	Comparative yields (%) Procedure A	B
CH_3	**1a**	55	68	CH_3	**2a**	62	70
CH_2CH_3	**b**	50	66	CH_2CH_3	**b**	64	69
$CH_2CH_2CH_3$	**c**	62	69	$CH_2CH_2CH_3$	**c**	68	75
CH_2CH_2COOH	**d**	0	55	CH_2CH_2COOH	**d**	0	65
$CH{=}CHCOOH$	**e**	0	48	$CH{=}CHCOOH$	**e**	0	60
$CH_2{-}C(=CH_2){-}COOH$	**f**	0	30	$CH_2{-}C(=CH_2){-}COOH$	**f**	0	42
$CH_2{-}CH(CH_3){-}COOH$	**g**	0	32	$CH_2{-}CH(CH_3){-}COOH$	**g**	0	40
	**h**	56	67		**h**	68	76
	**i**	0	48		**i**	0	59
CH_2Br	**j**	48	64	CH_2Br	**j**	52	80
$CH(Br)CH_3$	**k**	52	64	$CH(Br)CH_3$	**k**	62	70
CH_2CH_2Cl	**l**	0	70	CH_2CH_2Cl	**l**	0	88
CH_2CH_2Br	**m**	0	66	CH_2CH_2Br	**m**	0	75
	**n**	0	62		**n**	0	73
	**o**	0	60		**o**	0	70

and maintained at 45° and benzoxazolinone (5.4 g, 40 mmoles) and acid anhydride (60 mmoles) were added. The reaction mixture was warmed at 75° under stirring for 2 hours, poured on ice and the crude product was collected by filtration, air-dried and crystallized.

6-Acetyl-2(3*H*)-benzoxazolone (**1a**).

This compound was obtained as colorless needles (ethanol), mp 227-228°; ir: ν NH 3180, ν CO 1775, 1655 cm^{-1}; pmr (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 7.17 (d, 1H, 4-H, J = 8.6 Hz), 7.77 (s, 1H, 7-H), 7.84 (dd, 1H, 5-H, J = 8.6 Hz, J = 1.6 Hz), 11.88 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.92; H, 3.82; N, 8.00.

6-Propionyl-2(3*H*)-benzoxazolone (**1b**).

This compound was obtained as colorless needles (ethanol), mp 204-205°; ir: ν NH 3180, ν CO 1770, 1655 cm^{-1}; pmr (DMSO-d_6): δ 1.08 (t, 3H, CH_3), 3.05 (q, 2H, CH_2), 7.11 (d, 1H, 4-H, J = 9 Hz), 7.73 (d, 1H, 7-H, J = 1.8 Hz), 7.80 (dd, 1H, 5-H, J = 9 Hz, J = 1.8 Hz), 11.70 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.82; H, 4.76; N, 7.61.

6-Butyroyl-2(3*H*)-benzoxazolone (**1c**).

This compound was obtained as colorless needles (ethanol), mp 154-156°; ir: ν NH 3200, ν CO 1745, 1670 cm^{-1}; pmr (deuteriochloroform): δ 1.00 (t, 3H, CH_3), 1.75 (m, 2H, CH_2), 2.95 (t, 2H, CH_2), 7.10 (d, 1H, 4-H, J = 9 Hz), 7.80 (s, 1H, 7-H), 7.85 (dd, 1H, 5-H, J = 9 Hz, J = 1.8 Hz), 10.60 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.64; H, 5.31; N, 6.90.

4-Oxo-4-[2(3*H*)-benzoxazolon-6-yl]butyric Acid (**1d**).

This compound was obtained as colorless prisms (ethanol:water, 1:4), mp 218-219°; ir: ν OH 3290, ν NH 3060, ν CO 1740, 1705, 1670 cm^{-1}; pmr (DMSO-d_6): δ 2.50 (t, 2H, CH_2), 3.11 (t, 2H, CH_2), 7.21 (d, 1H, 4-H, J = 9 Hz), 7.81 (s, 1H, 7-H), 7.96 (d, 1H, 5-H, J = 9 Hz), 11.90 (s, 1H, COOH, exchangeable in deuterium oxide), 12.00 (s, 2H, NH, COOH, exchangeables in deuterium oxide).

Anal. Calcd. for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.95. Found: C, 56.11; H, 3.97; N, 6.11.

4-Oxo-4-[2(3*H*)-benzoxazolon-6-yl]-2-butenoic Acid (**1e**).

This compound was obtained as colorless prisms (ethanol:water, 2:5), mp 235-236°; ir: ν OH 3220, ν NH 3000, ν CO 1755,

1700, 1650 cm^{-1}; pmr (DMSO-d_6): δ 6.66 (d, 1H, CH=C*H*-COOH, J = 15 Hz), 7.23 (d, 1H, 4'-H, J = 8.6 Hz), 7.91 (d, 1H, 7'-H, J = 1.7 Hz), 7.92 (d, 1H, C*H*=CH-COOH, J = 15 Hz), 7.94 (dd, 1H, 5'-H, J = 8.6 Hz, J = 1.7 Hz), 12.50 (s, 1H, NH, exchangeable in deuterium oxide), 12.60 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{11}H_7NO_5$: C, 56.65; H, 3.03; N, 6.00. Found: C, 56.69; H, 3.25; N, 6.05.

2-Methylen-4-oxo-4-[2(3*H*)-benzoxazolon-6-yl]butyric Acid (**1f**).

This compound was obtained as colorless prisms (ethanol:water, 1:5), mp 222-223°; ir: ν OH 3300, ν NH 3080, ν CO 1745, 1695, 1665 cm^{-1}; pmr (DMSO-d_6): δ 4.01 (s, 2H, CH_2), 5.73 (d, 1H, $C=C<^{H}_{H}$, J = 2 Hz), 6.20 (d, 1H, $C=C<^{H}_{H}$, J = 2 Hz), 7.19 (d, 1H, 4'-H, J = 8.4 Hz), 7.81 (s, 1H, 7'-H), 7.88 (d, 1H, 5'-H, J = 8.4 Hz), 12.13 (s, 1H, NH, exchangeable in deuterium oxide), 12.20 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{12}H_9NO_5$: C, 58.30; H, 3.67; N, 5.67. Found: C, 58.79; H, 3.38; N, 5.40.

2-Methyl-4-oxo-4-[2(3*H*)-benzoxazolon-6-yl]butyric Acid (**1g**).

This compound was obtained as colorless prisms (ethanol:water, 1:4), mp 206-208°; ir: ν OH, ν NH 3250-2900, ν CO 1760, 1690, 1675 cm^{-1}; pmr (DMSO-d_6): δ 1.11 (d, 3H, CH_3, J = 6.5 Hz), 2.73-3.00 (m, 1H, CH), 3.04 (dd, 1H, CH_2, J = 3.20 Hz, J = 18.7 Hz), 3.40 (dd, 1H, CH_2, J = 7.50 Hz), 7.03 (d, 1H, 4'-H, J = 8.5 Hz), 7.84 (d, 1H, 7'-H, J = 1.4 Hz), 7.86 (dd, 1H, 5'-H, J = 8.5 Hz, J = 1.4 Hz), 12.08 (s, 1H, NH, exchangeable in deuterium oxide), 12.20 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.61; H, 4.35; N, 5.52.

6-Benzoyl-2(3*H*)-benzoxazolone (**1h**).

This compound was obtained as colorless needles (toluol), mp 169-170°; ir: ν NH 3140, ν CO 1780, 1635 cm^{-1}; pmr (DMSO-d_6): δ 7.21 (d, 1H, 4-H, J = 8.6 Hz), 7.44-7.75 (m, 7H, 5-H, 7-H, phenyl), 11.97 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.34; H, 3.60; N, 6.02.

6-(2'-Carboxy)benzoyl-2(3*H*)-benzoxazolone (**1i**).

This compound was obtained as colorless prisms (ethanol:water, 1:3), mp 243-244°; ir: ν OH 3470, ν NH 3360, ν CO 1770, 1690, 1650 cm^{-1}; pmr (DMSO-d_6): δ 7.15 (d, 1H, 4-H, J = 8.5 Hz), 7.38 (m, 2H, 4'-H, 5'-H), 7.58 (m, 1H, 3'-H), 7.69 (s, 1H, 7-H), 7.70 (dd, 1H, 5-H, J = 8.5 Hz, J = 2 Hz), 7.84 (m, 1H, 6'H), 12.05 (s, 1H, NH, exchangeable in deuterium oxide), 13.10 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{15}H_9NO_5$: C, 63.60; H, 3.20; N, 4.94. Found: C, 63.29; H, 3.18; N, 4.92.

General Procedure for the Reaction of Acid Chlorides with 2-Benzoxazolinone **1j-o**.

Dimethylformamide (6.0 ml, 80 mmoles) was slowly added to aluminum chloride (37.3 g, 280 mmoles). The mixture was stirred and maintained at 45° and benzoxazolinone (5.4 g, 40 mmoles) and acid chloride (60 mmoles) were added. The reaction mixture was warmed at 75° under stirring for 2 hours, poured on ice and the crude product was collected by filtration, air-dried and crystallized.

6-Bromoacetyl-2(3*H*)-benzoxazolone (**1j**).

This compound was obtained as colorless needles (ethanol), mp 228°; ir: ν NH 3250, ν CO 1790, 1680 cm^{-1}; pmr (DMSO-d_6): δ 4.91 (s, 2H, CH_2), 7.26 (d, 1H, 4-H, J = 9 Hz), 7.94 (d, 1H, 7-H, J = 1.8 Hz), 7.97 (dd, 1H, 5-H, J = 9 Hz, J = 1.8 Hz), 12.18 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_9H_6NO_3Br$: C, 42.21; H, 2.36; N, 5.47. Found: C, 42.46; H, 2.56; N, 5.49.

6-(2-Bromopropionyl)-2(3*H*)-benzoxazolone (**1k**).

This compound was obtained as colorless needles (ethanol), mp 191-192°; ir: ν NH 3170, ν CO 1780, 1660 cm^{-1}; pmr (DMSO-d_6): δ 1.85 (d, 3H, CH_3, J = 6.5 Hz), 5.87 (q, 1H, CH, J = 6.5 Hz), 7.31 (d, 1H, 4-H, J = 9 Hz), 8.00 (d, 1H, 7-H, J = 1.8 Hz), 8.05 (dd, 1H, 5-H, J = 9.0 Hz, J = 1.8 Hz), 12.00 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{10}H_8NO_3Br$: C, 44.47; H, 2.98; N, 5.18. Found: C, 44.71; H, 3.17; N, 5.30.

6-(3-Chloropropionyl)-2(3*H*)-benzoxazolone (**1l**).

This compound was obtained as colorless needles (dioxane), mp 164° dec; ir: ν NH 3145, ν CO 1745, 1680 cm^{-1}; pmr (DMSO-d_6): δ 3.50 (t, 2H, C*H*$_2$-CH$_2$-Cl), 3.92 (t, 2H, CH$_2$-C*H*$_2$-Cl), 7.11 (d, 1H, 4-H, J = 8.4 Hz), 7.74 (s, 1H, 7-H), 7.85 (d, 1H, 5-H, J = 8.4 Hz), 11.83 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{10}H_8NO_3Cl$: C, 53.22; H, 3.57; N, 6.21. Found: C, 53.41; H, 3.58; N, 6.34.

6-(3-Bromopropionyl)-2(3*H*)-benzoxazolone (**1m**).

This compound was obtained as colorless needles (dioxane), mp 162° dec; ir: ν NH 3240, ν CO 1760, 1655 cm^{-1}; pmr (DMSO-d_6): δ 3.24-4.00 (m, 4H, CH_2-CH_2), 7.15 (d, 1H, 4-H, J = 8.8 Hz), 7.79 (s, 1H, 7-H), 7.83 (dd, 1H, 5-H, J = 8.8 Hz, J = 2 Hz), 11.84 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{10}H_8NO_3Br$: C, 44.47; H, 2.98; N, 5.19. Found: C, 44.36; H, 3.04; N, 4.99.

6-(2-Furoyl)-2(3*H*)-benzoxazolone (**1n**).

This compound was obtained as colorless needles (dioxane), mp 233-234°; ir: ν NH 3100, ν CO 1775, 1620 cm^{-1}; pmr (DMSO-d_6): δ 6.77 (dd, 1H, 4'-H, J = 3.6 Hz, J = 1.7 Hz), 7.24 (d, 1H, 4-H, J = 7.6 Hz), 7.39 (d, 1H, 3'-H, J = 3.6 Hz), 7.80 (s, 1H, 7-H), 7.85 (dd, 1H, 5-H, J = 7.6 Hz, J = 1.4 Hz), 8.06 (d, 1H, 5'-H, J = 1.7 Hz), 11.90 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{12}H_7NO_4$: C, 62.88; H, 3.08; N, 6.11. Found: C, 62.65; H, 3.11; N, 5.97.

6-Nicotinoyl-2(3*H*)-benzoxazolone Hydrochloride (**1o**).

This compound was obtained as a white powder (0.1*N* hydrochloric acid), mp 259-260°; ir: ν NH 3200, ν CO 1775, 1645 cm^{-1}; pmr (DMSO-d_6): δ 7.26 (d, 1H, 4-H, J = 8.8 Hz), 7.67 (dd, 1H, 5-H, J = 8.8 Hz, J = 2.2 Hz), 7.72 (s, 1H, 7-H), 7.86 (dd, 1H, 3'-H, J = 7.8 Hz, J = 4.4 Hz), 8.45 (d, 1H, 4'-H, J = 7.8 Hz), 8.94 (m, 2H, 2'-H, 6'-H), 10.39 (s, 1H, 1'-NH, exchangeable in deuterium oxide), 12.33 (s, 1H, NH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{13}H_9N_2O_3Cl$: C, 56.43; H, 3.28; N, 10.12. Found: C, 56.30; H, 3.35; N, 10.00.

General Procedure for the Reaction of Acid Anhydrides with 3-Methyl-2(3*H*)-benzoxazolone **2a-i**.

Dimethylformamide (8.6 ml, 115 mmoles) was slowly added to aluminum chloride (53.3 g, 400 mmoles). The mixture was stirred and maintained at 45° and 3-methyl-2(3*H*)-benzoxazolone (6.0 g, 40 mmoles) and acid anhydride (60 mmoles) were added. The reaction mixture was warmed to 75° with stirring for 2 hours, poured on ice and the crude product was collected by filtration, air-dried and crystallized.

3-Methyl-6-acetyl-2(3*H*)-benzoxazolone (**2a**).

This compound was obtained as colorless needles (ethanol), mp 168°; ir: ν CO 1765, 1675 cm^{-1}; pmr (DMSO-d_6): δ 2.52 (s, 3H, CH_3), 3.30 (s, 3H, N-CH_3), 7.31 (d, 1H, 4-H, J = 9 Hz), 7.80 (d, 1H, 7-H, J = 1.8 Hz), 7.85 (dd, 1H, 5-H, J = 9 Hz, J = 1.8 Hz).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.90; H, 4.67; N, 7.24.

3-Methyl-6-propionyl-2(3*H*)-benzoxazolone (**2b**).

This compound was obtained as colorless needles (ethanol), mp 157-158°; ir: ν CO 1770, 1675 cm^{-1}; pmr (DMSO-d_6): δ 1.09 (t, 3H, CH_3), 3.05 (m, 2H, CH_2), 3.34 (s, 3H, NCH_3), 7.32 (d, 1H, 4-H, J = 9 Hz), 7.84 (d, 1H, 7-H, J = 1.8 Hz), 7.90 (dd, 1H, 5-H, J = 9 Hz, J = 1.8 Hz).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.33; H, 5.42; N, 6.80.

3-Methyl-6-butyroyl-2(3*H*)-benzoxazolone (**2c**).

This compound was obtained as colorless needles (ethanol), mp 159-160°; ir: ν CO 1765, 1660 cm^{-1}; pmr (deuteriochloroform): δ 1.01 (t, 3H, CH_3), 1.78 (m, 2H, CH_2), 2.94 (t, 2H, CH_2), 3.45 (s, 3H, NCH_3), 7.01 (d, 1H, 4-H, J = 8 Hz), 7.82 (s, 1H, 7-H), 7.90 (dd, 1H, 5-H, J = 8 Hz, J = 1.5 Hz).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.71; H, 6.03; N, 6.37.

4-Oxo-4-(3-methyl-2(3*H*)-benzoxazolon-6-yl)butyric Acid (**2d**).

This compound was obtained as colorless prisms (ethanol:-water, 3:1), mp 179-180°; ir: ν OH 3300, ν CO 1755, 1730, 1660 cm^{-1}; pmr (CD_3COCD_3): δ 2.75 (t, 2H, CH_2), 3.33 (t, 2H, CH_2), 3.47 (s, 3H, NCH_3), 7.33 (d, 1H, 4-H, J = 9 Hz), 7.82 (d, 1H, 7-H, J = 2 Hz), 8.01 (dd, 1H, 5-H, J = 9 Hz, J = 2 Hz), 10.50 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.44; N, 5.62. Found: C, 57.62; H, 4.53; N, 5.83.

4-Oxo-4[3-methyl-2(3*H*)-benzoxazolon-6-yl]-2-butenoic Acid (**2e**).

This compound was obtained as colorless needles (ethanol), mp 220-221°; ir: ν OH 3280, ν CO 1760, 1720, 1655, ν C=C 1620, 1600 cm^{-1}; pmr (DMSO-d_6): δ 3.38 (s, 3H, N-CH_3), 6.67 (d, 1H, CH=C*H*-COOH, J = 15 Hz), 7.36 (d, 1H, 4-H, J = 8.0 Hz), 7.86 (s, 1H, 7-H), 7.89 (d, 1H, -C*H*=CH-COOH, J = 15 Hz), 8.00 (dd, 1H, 5-H, J = 8.0 Hz, J = 1.6 Hz), 13.16 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{12}H_9NO_5$: C, 58.30; H, 3.67; N, 5.67. Found: C, 58.06; H, 3.88; N, 5.65.

2-Methylen-4-oxo-4-[3-methyl-2(3*H*)-benzoxazolon-6-yl]butyric Acid (**2f**).

This compound was obtained as colorless needles (ethanol), mp 180°; ir: ν OH 3100-2800, ν CO 1745, 1710, 1670 cm^{-1}; pmr (DMSO-d_6): δ 3.35 (s, 3H, N-CH_3), 4.02 (s, 2H, CH_2), 5.76 (d, 1H, $\overset{H}{H}>C=C$, J = 2 Hz), 6.21 (d, 1H, $\overset{H}{H}>C=C$, J = 2 Hz), 7.34 (d, 1H, 4-H, J = 8.4 Hz), 7.86 (s, 1H, 7-H), 7.93 (dd, 1H, 5-H, J = 8.4 Hz, J = 2 Hz), 11.20 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.96; H, 4.19; N, 5.84.

2-Methyl-4-oxo-4-[3-methyl-2(3*H*)-benzoxazolon-6-yl]butyric Acid (**2g**).

This compound was obtained as colorless prisms (ethanol:-water, 1:4), mp 186-187°; ir: ν OH 3060-2880, ν CO 1770, 1700, 1670 cm^{-1}; pmr (DMSO-d_6): δ 1.18 (d, 3H, CH_3, J = 6.4 Hz), 2.70-2.95 (m, 1H, CH), 3.05 (dd, 1H, CH_2 *trans*, J = 18.7 Hz, J = 3.2 Hz), 3.32 (s, 3H, N-CH_3), 3.46 (dd, 1H, CH_2 *cis*, J = 7.5 Hz), 7.31 (d, 1H, 4-H, J = 8.8 Hz), 7.89 (s, 1H, 7-H, J = 1.4 Hz), 7.94 (dd, 1H, 5-H, J = 8.8 Hz, J = 1.4 Hz), 12.13 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.17; H, 4.90; N, 5.39.

3-Methyl-6-benzoyl-2(3*H*)-benzoxazolone (**2h**).

This compound was obtained as colorless needles (ethanol), mp 147-148°; ir: ν CO 1760, 1645, ν C=C 1600 cm^{-1}; pmr (DMSO-d_6): δ 3.41 (s, 3H, N-CH_3), 7.35 (d, 1H, 4-H, J = 9 Hz), 7.56-7.72 (m, 7H, 5-H, 7-H, phenyl).

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.00; H, 4.32; N, 5.54.

3-Methyl-6-(2-carboxy)benzoyl-2(3*H*)-benzoxazolone (**2i**).

This compound was obtained as colorless needles (ethanol), mp 210-211°; ir: ν OH 3460, ν CO 1775, 1680, 1640 cm^{-1}; pmr (DMSO-d_6): δ 3.36 (s, 3H, N-CH_3), 7.26 (d, 1H, 4-H, J = 8.7 Hz), 7.41 (m, 2H, 4'-H, 5'-H), 7.56 (m, 1H, 3'-H), 7.67 (s, 1H, 7-H), 7.70 (dd, 1H, 5-H, J = 8.7 Hz, J = 2 Hz), 7.93 (m, 1H, 6'-H), 12.90 (s, 1H, COOH, exchangeable in deuterium oxide).

Anal. Calcd for $C_{16}H_{11}NO_5$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.54; H, 3.92; N, 4.74.

General Procedure for the Reaction of Acid Chlorides with 3-Methyl-2(3*H*)-benzoxazolone **2j-o**.

Dimethylformamide (7.7 ml, 103 mmoles) was slowly added to aluminum chloride (48.0 g, 360 mmoles). The mixture was stirred and maintained at 45° and 3-methyl-2(3*H*)-benzoxazolone (6.0 g, 40 mmoles) and acid chloride (60 mmoles) were added. The reaction mixture was warmed at 75° under stirring for 2 hours, poured on ice and the crude product was collected by filtration, air-dried and crystallized.

3-Methyl-6-bromoacetyl-2(3*H*)-benzoxazolone (**2j**).

This compound was obtained as colorless needles (ethanol), mp 178-179°; ir: ν CO 1775, 1695 cm^{-1}; pmr (DMSO-d_6): δ 3.40 (s, 3H, N-CH_3), 4.92 (s, 2H, CH_2), 7.41 (d, 1H, 4-H, J = 9 Hz), 7.93 (d, 1H, 7-H, J = 1.8 Hz), 8.00 (dd, 1H, 5-H, J = 9 Hz, J = 1.8 Hz).

Anal. Calcd. for $C_{10}H_8NO_3Br$: C, 44.47; H, 2.98; N, 5.18. Found: C, 44.81; H, 3.12; N, 5.21.

3-Methyl-6-(2-bromopropionyl)-2(3*H*)-benzoxazolone (**2k**).

This compound was obtained as colorless needles (ethanol), mp 138-139°; ir: ν CO 1770, 1675 cm^{-1}; pmr (DMSO-d_6): δ 1.80 (d,

3H, CH_3, J = 6.5 Hz), 3.39 (s, 3H, N-CH_3), 5.84 (q, 1H, CH, J = 6.5 Hz), 7.35 (d, 1H, 4-H, J = 9 Hz), 7.90 (d, 1H, 7-H, J = 1.8 Hz), 7.98 (dd, 1H, 5-H, J = 9 Hz, J = 1.8 Hz).

Anal. Calcd. for $C_{11}H_{10}NO_3Br$: C, 46.48; H, 3.52; N, 4.93. Found: C, 46.48; H, 3.61; N, 5.09.

3-Methyl-6-(3-chloropropionyl)-2(3*H*)-benzoxazolone (**2l**).

This compound was obtained as colorless needles (ethanol), mp 187-188°; ir: ν CO 1765, 1660 cm^{-1}; pmr (deuteriochloroform): δ 3.41 (s, 3H, N-CH_3), 3.42 (t, 2H, CH_2-CH_2Cl), 3.90 (t, 2H, CH_2-CH_2Cl), 7.02 (d, 1H, 4-H, J = 8.0 Hz), 7.80 (d, 1H, 7-H, J = 1.7 Hz), 7.88 (dd, 1H, 5-H, J = 8.0 Hz, J = 1.7 Hz).

Anal. Calcd. for $C_{11}H_{10}NO_3Cl$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.05; H, 4.25; N, 5.73.

3-Methyl-6-(3-bromopropionyl)-2(3*H*)-benzoxazolone (**2m**).

This compound was obtained as colorless needles (ethanol), mp 183-184°; ir: ν CO 1765, 1660 cm^{-1}; pmr (DMSO-d_6): δ 3.37 (s, 3H, N-CH_3), 3.50-4.00 (m, 4H, CH_2-CH_2), 7.31 (d, 1H, 4-H, J = 8.8 Hz), 7.85 (s, 1H, 7-H), 7.92 (dd, 1H, 5-H, J = 8.8 Hz, J = 1.9 Hz).

Anal. Calcd. for $C_{11}H_{10}NO_3Br$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.62; H, 3.56; N, 4.88.

3-Methyl-6-(2-furoyl)-2(3*H*)-benzoxazolone (**2n**).

This compound was obtained as colorless needles (ethanol), mp 140-141°; ir: ν CO 1760, 1625 cm^{-1}; pmr (DMSO-d_6): δ 3.41 (s, 3H, N-CH_3), 6.79 (dd, 1H, 4'-H, J = 3.6 Hz, J = 1.7 Hz), 7.40 (d, 1H, 4-H, J = 7.8 Hz), 7.46 (d, 1H, 3'-H, J = 3.6 Hz), 7.84 (s, 1H, 7-H), 7.94 (dd, 1H, 5-H, J = 7.8 Hz, J = 1.6 Hz), 8.10 (d, 1H, 5'-H, J = 1.7 Hz).

Anal. Calcd. for $C_{13}H_9NO_4$: C, 64.19; H, 3.67; N, 5.67. Found: C, 64.26; H, 3.63; N, 5.86.

3-Methyl-6-nicotinoyl-2(3*H*)-benzoxazolone (**2o**).

This compound was obtained as colorless needles (ethanol), mp 163-164°; ir: ν CO 1770, 1635 cm^{-1}; pmr (DMSO-d_6): δ 3.40 (s, 3H, N-CH_3), 6.37 (d, 1H, 4-H, J = 8.4 Hz), 6.56 (m, 1H, 3'-H, J = 8.0 Hz, J = 4.8 Hz, J = 0.9 Hz), 6.68 (dd, 1H, 5-H, J = 8.4 Hz, J = 1.7 Hz), 6.70 (d, 1H, 7-H, J = 1.7 Hz), 8.08 (m, 1H, 4'-H, J = 8.0 Hz, J = 2.0 Hz), 8.70-8.88 (m, 2H, 2'-H, 6'-H).

Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.13; H, 3.96; N, 11.02. Found: C, 66.24; H, 3.96; N, 10.87.

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