Synthesis and novel reactions of 2,3-dimethyl-1H-pyrrolo[1,2-a]-benzimidazol-1-one with secondary amines and N-bromosuccinimide

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N,N-Disubstituted-β-(2-benzimidazolyl)-α,β-dimethylacrylamides 5Aa-g and 5Ba-g, 2-bromomethyl-3-methyl-1H-pyrrolo[1,2-a]benzimidazol-1-one 8A and 2,3-dimethyl-1H-pyrrolo[1,2-a]benzimidazole-1-thione 10A have been synthesized from 2,3-dimethyl-1H-pyrrolo[1,2-a]benzimidazol-1-one 4A. Compounds 5Aa-g and 5Ba-g have been synthesized via two different routes. These compounds have been screened for their antimicrobial and anthelmintic activities.

In our earlier publication we have reported the synthesis of N-substituted-β-(2-benzimidazolyl)-α,β-dimethylacrylamides by the ring opening of 2,3-dimethyl-1H-pyrrolo[1,2-a]benzimidazol-1-one with primary amines. Benzimidazole and related derivatives have shown various biological activities such as anthelmintic, antimicrobial, etc. In view of this we have prepared N,N-disubstituted-β-(2-benzimidazolyl)-α,β-dimethylacrylamides (5Aa-g and 5Ba-g) via two different routes.

The course of reaction of 1,2-diamino benzene 1A with dimethylmaleic anhydride 2 to afford N-(2-aminophenyl)dimethylmaleimide 3A has been shown in Scheme 1. The N-(2-aminophenyl)dimethylmaleimide undergoes facile dehydrative cyclisation on heating with glacial acetic acid to give 2,3-dimethyl-1H-pyrrolo[1,2-a]benzimidazol-1-one 4A which on subsequent treatment with secondary amines in chloroform at room temperature yielded 5Aa-g. We have reported a synthesis of 5Aa-g by a novel multistep method where 4A is first converted to acrylic acid 6A and then to the methyl ester 7A. The ester 7A reacts with secondary amines to give 5Aa-g (cf. Table I). The compounds obtained from both these routes were identical as confirmed by mmp determination co-TLC and superimposable IR spectra.

We have further studied the bromination of 4A using N-bromosuccinimide (NBS) in the presence of benzyol peroxide as a catalyst in carbon tetracloride. The bromination product by this method was obtained in pure form and in good yield. Bromination was confirmed by chemical means such as Lassaiogene's test, and also by spectroscopic methods. Unfortunately the position of attack of bromine atom at C-2 or C-3 methyl was unidentified. To confirm structure of the bromination product, we have comparatively studied its IR, 1H NMR and mass spectra. In the IR spectra, 4A showed a sharp peak at 1741 cm⁻¹ and 8A or 9A showed a sharp peak at 1730 cm⁻¹ for >C=O group. The mass spectrum of 4A exhibited the molecular ion peak at m/z 198 and that of 8A or 9A showed the molecular ion peaks at m/z 276 and 278 m/z indicating bromination.

The 1H NMR spectrum of 4A showed a singlet at δ 2.1 for three protons of C-2 methyl and another singlet at δ 2.3 for three protons of C-3 methyl group. In 8A or 9A the values are shifted to, singlet at δ 4.2 for two protons and singlet at δ 2.25 for three protons of C-3 methyl group.

From the above considerations it is clear that bromination took place at C-2 methyl group with respect to >C=O group and the correct structure is 9A.

In the recent literature it has been found that the structure of such compounds can be confirmed by thionation reaction. In the present study thionation reaction was carried out with Lawesson's reagent (LR) which converted the carbonyl of 4A to the
thiocarbonyl group (10A). The usefulness of Lawesson's reagent was taken into consideration while confirming the structure of the bromination product 8A or 9A.

To confirm the structure of the bromination product we have comparatively studied the IR, $^1$H NMR and mass spectra of compounds 4A, 8A or 9A and 10A.

The IR spectrum of 4A showed a sharp peak at 1741 cm$^{-1}$ for $>$C=O group, but it disappeared in 10A. In compound 10A a sharp peak appeared at 1504.0 cm$^{-1}$ indicating the presence of $>$C=S group. This proved that thionation took place at C-1 carbon atom. From a careful study of $^1$H NMR spectra, 4A, 8A or 9A and 10A showed that, on bromination the signal shifted downfield compared to 4A whereas on

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>H-N</th>
<th>Mol. formula</th>
<th>mp, °C (Crystal. from)</th>
<th>Analysis Found (Calcd)</th>
<th>Spectral data</th>
</tr>
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<tr>
<td>5Aa</td>
<td>H</td>
<td>Morpholine</td>
<td>C$<em>{16}$H$</em>{18}$N$_2$O$_2$</td>
<td>210 (aq. EtOH)</td>
<td>C:67.18(67.34) H:66.66(66.71) N:15.00(14.72)</td>
<td>IR: 3392.4, 3080.1, 2981.8, 1598.0, 1440.2, 1361.7 cm$^{-1}$</td>
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<tr>
<td>5Ab</td>
<td>H</td>
<td>Piperidine</td>
<td>C$<em>{17}$H$</em>{21}$N$_3$O</td>
<td>167-168 (aq. MeOH)</td>
<td>C:58.86(58.86) H:66.18(66.10) N:30.38(30.42)</td>
<td>IR: 3483.6, 3077.1, 2990.5, 1583.7, 1549.2, 1449.5, 1415.5 cm$^{-1}$ $^1$H NMR: 2.1 (s, 3H, $\alpha$-CH$_3$), 2.3 (s, 3H, $\beta$-CH$_3$), 3.25 (t, 4H, $\text{N(CH}_2_2$), 7.2-7.6 (m, 4H, ArH) MS: m/z 283 (M$^+$), 199, 173 (base peak) 156, 143, 119 &amp; 92</td>
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<tr>
<td>5Ac</td>
<td>H</td>
<td>Piperazine</td>
<td>C$<em>{16}$H$</em>{19}$N$_3$O</td>
<td>292-94 (DMF-H$_2$O)</td>
<td>C:67.42(67.58) H:7.10(7.09) N:19.70(19.70)</td>
<td>IR: 3256.4, 3190.0, 2925.4, 1594.4, 1520.7, 1463.2, 1411.6 cm$^{-1}$</td>
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Table I - Contd
Table I — Characterization data of compounds 5 prepared — Contd

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<tr>
<th>Compd</th>
<th>R</th>
<th>H-N</th>
<th>Mol. formula</th>
<th>mp °C (Crystal. from)</th>
<th>Analysis Found</th>
<th>Spectral data</th>
</tr>
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<tbody>
<tr>
<td>5Ad</td>
<td>H</td>
<td>N-Ethyl-piperazine</td>
<td>C₁₈H₂₄N₄O₁₆</td>
<td>163 (C₆H₅-Pet. ether)</td>
<td>C:68.89(69.20) H:07.63(07.74) N:18.00(17.93)</td>
<td>IR:3349, 3042, 2901, 1601, 1528, 1470 cm⁻¹</td>
</tr>
<tr>
<td>5Ae</td>
<td>H</td>
<td>Dimethylamine</td>
<td>C₁₈H₂₄N₄O₁₆</td>
<td>245 (aq. EtOH)</td>
<td>C:69.00(69.11) H:07.10(07.04) N:17.28(17.28)</td>
<td>IR:3245, 3031, 1609, 1550, 1495, 1470 cm⁻¹ ¹H NMR: δ 2.08(s, 3H, CH₃), 2.35 (s, 3H, β-CH₂), 2.85 (s, 3H, N-CH₃), 3.0 (s, 3H, N-CH₃), 7.19-7.82 (m 4H, ArH)</td>
</tr>
<tr>
<td>5Af</td>
<td>H</td>
<td>Diethylamine</td>
<td>C₁₈H₃₀N₄O₂₄</td>
<td>184-85 (aq. EtOH)</td>
<td>C:70.62(70.82) H:07.68(07.80) N:15.20(15.48)</td>
<td>IR:3342, 3030, 1641, 1593, 1508, 1450, 1396 cm⁻¹ ¹H NMR: δ 2.08(s, 3H, CH₃), 2.35 (s, 3H, β-CH₂), 2.85 (s, 3H, N-CH₃), 3.0 (s, 3H, N-CH₃), 7.19-7.82 (m 4H, ArH)</td>
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<td>5Ag</td>
<td>H</td>
<td>Diphenylamine</td>
<td>C₁₈H₃₀N₄O₂₄</td>
<td>229-30 (aq. EthOH)</td>
<td>C:70.62(70.82) H:07.68(07.80) N:15.20(15.48)</td>
<td>IR:3342, 3030, 1641, 1593, 1508, 1450, 1396 cm⁻¹ ¹H NMR: δ 2.08(s, 3H, CH₃), 2.35 (s, 3H, β-CH₂), 2.85 (s, 3H, N-CH₃), 3.0 (s, 3H, N-CH₃), 7.19-7.82 (m 4H, ArH)</td>
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<tr>
<td>5Ba</td>
<td>Cl</td>
<td>Morpholine</td>
<td>C₁₈H₂₄N₄O₂₄</td>
<td>216-18 (aq. EthOH)</td>
<td>C:60.12(60.09) H:05.62(05.67) N:11.42(11.43)</td>
<td>IR:3450, 3080, 2925, 1593, 1519, 1465, 1441, 1403 cm⁻¹ ¹H NMR: δ 2.16(s, 3H, α-CH₃), 3.3 [s, 4H, -N(CH₂)₂], 3.6 [s, 4H, -O(CH₂)₂], 7.0-7.6 (m, 3H, ArH)</td>
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<tr>
<td>5Bb</td>
<td>Cl</td>
<td>Piperidine</td>
<td>C₁₈H₂₄N₄O₂₄</td>
<td>163-64 (aq. EthOH)</td>
<td>C:64.20(64.25) H:06.12(06.34) N:12.90(12.22)</td>
<td>IR:3450, 3080, 2925, 1593, 1519, 1465, 1441, 1403 cm⁻¹ ¹H NMR: δ 2.16(s, 3H, α-CH₃), 3.3 [s, 4H, -N(CH₂)₂], 3.6 [s, 4H, -O(CH₂)₂], 7.0-7.6 (m, 3H, ArH)</td>
</tr>
<tr>
<td>5Be</td>
<td>Cl</td>
<td>Piperazine</td>
<td>C₁₈H₂₄N₄O₂₄</td>
<td>285 (DMF-H₂O)</td>
<td>C:60.00(60.28) H:5.97(6.00) N:17.43(17.57)</td>
<td>IR:3460, 3160, 3030, 1594, 1539, 1440 cm⁻¹</td>
</tr>
<tr>
<td>5Bd</td>
<td>Cl</td>
<td>N-Ethyl-piperazine</td>
<td>C₁₈H₂₄N₄O₂₄</td>
<td>155-56 (C₆H₅-Pet. ether)</td>
<td>C:62.21(62.33) H:06.48(06.68) N:16.00(16.15)</td>
<td>IR:3435, 3060, 2900, 1597, 1539, 1512, 1443 cm⁻¹</td>
</tr>
<tr>
<td>5Be</td>
<td>Cl</td>
<td>Dimethylamine</td>
<td>C₁₈H₂₄N₄O₂₄</td>
<td>220 (aq. EthOH)</td>
<td>C:60.12(60.54) H:05.78(05.81) N:15.10(15.13)</td>
<td>IR:3450, 3189, 2930, 1610, 1575, 1541, 1458 cm⁻¹</td>
</tr>
<tr>
<td>5Bf</td>
<td>Cl</td>
<td>Diphenylamine</td>
<td>C₁₈H₂₄N₄O₂₄</td>
<td>178-80 (aq. EthOH)</td>
<td>C:62.57(62.84) H:06.52(06.60) N:13.58(13.74)</td>
<td>IR:3415, 3075, 2989, 1583, 1542, 1518, 1456 cm⁻¹</td>
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<tr>
<td>5Bg</td>
<td>Cl</td>
<td>Diphenylamine</td>
<td>C₁₈H₂₄N₄O₂₄</td>
<td>150-51 (aq. EthOH)</td>
<td>C:71.53(71.73) H:5.12(05.02) N:10.28(10.45)</td>
<td>IR:3486, 3126, 2988, 1593, 1508, 1450 cm⁻¹</td>
</tr>
</tbody>
</table>

thionation it shifted further downfield as in 10A for C-2 methyl group; the values are: δ 2.1 for 4A, δ 4.2 for 8A or 9A and δ 4.5 for 10A.

Biological Activity

**Antimicrobial Activity.** Compounds 5Aa-g and 5Ba-g were screened for their antibacterial activity against the pathogenic micro-organisms *S. citrus*, *B. subtilis* and *E. coli* and for antifungal activity against *A. fumigatus*, *C. albicans* and *F. heterosporum* by single disc method at two different concentrations (25 and 50 μg/mL). But unfortunately, the low doses of the compounds were not promising.

**Anthelmintic Activity.** The compounds 5Aa-g and 5Ba-g were also screened for their anthelmintic
activity in vitro against the H. nana and C. elegans. However none of the compounds showed any noteworthy activity against the above two models.

The compounds 5Aa, 5Ad, 5Bb, 5Bd and 5Bg were also studied in vivo for their anthelmintic activity against N. muris infection in rats at a dose of 100 mg/kg × 5 times p.o. dose. No significant activity could be observed against this model even at higher doses.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer FTIR-1600 spectrophotometer, 1H NMR spectra on a Varian Perkin-Elmer R-32(90 MHz) spectrometer using CDCl3 as a solvent and TMS as internal standard (chemical shifts in δ, ppm). Mass spectra were recorded on Jel JMS-D300 and Shimadzu QP-1000 spectrometers. TLC was run on Silica gel-G plates and spots were located by iodine vapours. The required dimethylmaleic anhydride and Lawesson’s reagent were synthesized by reported methods.

N-(2-Aminophenyl)dimethylmaleimide 3A. A mixture of 0.01 mole of 1,2-diaminobenzene and 0.01 mole of dimethylmaleic anhydride was taken in ethanol and refluxed on a water-bath for half an hour. It was then cooled on room temperature and diluted with cold water till the solution became turbid. From the reaction mixture the solid that separated out was filtered and recrystallised from n-hexane, mp 101 °C (yield 92%); IR: 2918, 1741, 1610, 1549, 1430 cm⁻¹; 1H NMR: δ 1.9 (s, 3H, -CH3, C-3), 2.1 (s, 3H, -CH3, C-2), 7.1 (m, 2H, ArH), 7.5 (m, 2H, ArH); MS: m/z 198 [M⁺]. Anal. Calcd for C12H11N2O2: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.45; H, 5.11; N, 14.20%.

Similarly, 5-chloro-2,3-dimethyl-1H-pyrrolo[1,2-a]benzimidazol-1-one 4B was synthesized and recrystallised from pet. ether (60-80°), mp 117 °C (90%); IR: 2915, 1743, 1605, 1553, 1434 cm⁻¹. Anal. Calcd for C12H10N2OCl: C, 72.69; H, 5.09; N, 14.13%. Found: C, 72.70; H, 5.11; N, 14.20%.

Similarly, 5-chloro derivatives 5Ba-g were prepared and recrystallised (cf. Table I).

Method 2: Step (a). β-(2-Benzimidazolyl)-α,β-dimethylacrylic acid 6A. 2,3-Dimethyl-1H-pyrrolo[1,2-a]benzimidazol-1-one (0.01 mole) was added to 10 mL of 2N sodium hydroxide solution. The mixture was stirred at half an hour at room temperature and acidified with acetic acid (pH 6). The solid that separated out was filtered and recrystallised from ethanol, mp 200 °C, yield 80%; IR: 3300, 3050, 1639, 1587, 1450 cm⁻¹. Anal. Calcd for C12H12N2O2: C, 66.69; H, 5.60; N, 12.97. Found: C, 66.70; H, 5.60; N, 12.82%.

Similarly, β-(2-(5-chlorobenzimidazolyl))-α,β-dimethylacrylic acid 6B was synthesized and recrystallised in ethanol, mp 245 °C; IR: 3404, 3061, 1707, 1585, 1484 cm⁻¹. Anal. Calcd for C12H11N2OCl: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.38; H, 4.40; N, 10.98%.

Step (b). Methyl β-(2-benzimidazolyl)-α,β-dimethylacrylate 7A. β-(2-Benzimidazolyl)-α,β-dimethylacrylic acid (0.01 mole) was refluxed in dry
methanol containing a few drops of conc. Sulphuric acid for 6-8 hr. Solvent was evaporated and the residue treated with a saturated solution of sodium bicarbonate. The solid that separated out was filtered and recrystallised from aq. Ethanol, mp 118 °C, (yield 85%); IR: 3480, 3336, 3088, 3019, 1698, 1648, 1526, 1442 cm⁻¹. Anal. Calcd for C₁₃H₁₄N₂O₂: C, 67.79; H, 6.13; N, 12.17%. Found: C, 68.00; H, 6.12; N, 12.20%.

Similarly, methyl β-[2-(5-chlorobenzimidazolyl)]-α,β-dimethylacrylate 7B was synthesized, and recrystallised from aq. ethanol, mp 118 °C, yield 85%; IR: 3502, 3332, 3109, 1698, 1643, 1582 cm⁻¹. Anal. Calcd for C₁₅H₁₅N₂Cl: C, 58.97; H, 4.95; N, 10.58. Found: C, 59.00; H, 5.00; N, 10.52%.

Step (c). Reaction between methyl β-(2-benzimidazolyl)-α,β-dimethylacrylate and secondary amines (Formation of 5Aa-g): General procedure. A mixture of methyl β-(2-benzimidazolyl)-α,β-dimethylacrylate (0.05 mole) and a secondary amine (0.05 mole) was heated on a water-bath for 2 hr. After cooling at room temperature, the compound obtained was recrystallised. (cf. Table I).

Similarly, 5-chloro derivatives 5Ba-g (Table I) were synthesized. All the compounds were obtained in 90-95% yields.

Bromination of 2,3-dimethyl-1H-pyrrolo[1,2-a]-benzimidazol-1-one 8A. A mixture of 2,3-dimethyl-1H-pyrrolo[1,2-a]benzimidazol-1-one (0.01 mole), N-bromosuccinimide (0.01 mole) in carbon tetrachloride and benzoyl peroxide (1g) was refluxed on a water-bath for 6-7 hr until succinimide separated out. The reaction mixture was cooled at room temperature, succinimide filtered and washed with carbon tetrachloride. The solvent was removed under reduced pressure and the product 2-bromomethyl-3-methyl-1H-pyrrolo[1,2-a]benzimidazo1-1-one 8A recrystallised from pet. ether (60-80 °C), mp 112 °C, yield 85%; IR: 3012, 1730, 1670, 1550, 144 cm⁻¹; 1H NMR: δ 2.25 (s, 3H, -CH₃, C-3), 4.2 (s, 2H, -CH₂, C-2), 7.1-7.7 (m, 4H, ArH); MS: m/z 179 [M⁺] and 281 (due to bromine). Anal. Calcd for C₁₅H₁₄N₂OBr: C, 51.98; H, 3.24; N, 10.10. Found: C, 52.00; H, 3.99; N, 10.18%.

Thionation of 2,3-dimethyl-1H-pyrrolo[1,2-a]-benzimidazol-1-one: Formation of (2,3-dimethyl-1H-pyrrolo[1,2-a]benzimidazole-1-thione 10A. 2,3-Dimethyl-1H-pyrrolo[1,2-a]benzimidazol-1-one (0.01 mole) and Lawesson’s reagent (0.005 mole) were heated in anhydrous benzene with stirring for 3-4 hr until no more of the starting material could be detected on TLC. After cooling to room temperature, the reaction mixture was evaporated on silica gel under reduced pressure and applied to silica gel column using 1:1 pet. ether (60-80)-benzene as a eluant. After evaporation of solvent the compound was recrystallised from pet. ether (60-80)-benzene (1:1), mp 168 °C, yield 65%; IR: 1598, 1504, 1453 cm⁻¹; 1H NMR: δ 3.5 (s, 3H, -CH₃, C-3), 4.5 (s, 3H, -CH₂, C-2); 6.9-7.8 (m, 4H, ArH). Anal. Calcd for C₁₃H₁₄N₂S: C, 67.26; H, 4.69; N, 13.07. Found: C, 67.50; H, 4.92; N, 12.70%.

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References