Potential Antitumor Agents. IV. Pyrrole Analogues of Oncodazole

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The synthesis of alkyl [5-(1*H*-pyrrol-2-ylcarbonyl)-1*H*-benzimidazol-2-yl]carbamates and alkyl [5-(1*H*-pyrrol-1-ylmethyl)-1*H*-benzimidazol-2-yl]carbamates is described. The new pyrrole derivatives are related to oncodazole, a recent synthetic derivative showing antifungal, antitumor and anthelmintic properties.

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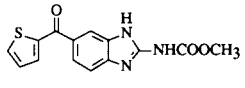
Methyl [5-(2-thienylcarbonyl)-1*H*-benzimidazol-2-yl]carbamate (**1**) (oncodazole, nocodazole) is a new synthetic chemotherapeutic agent with antineoplastic antifungal and anthelmintic activities [1,2].

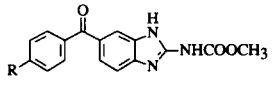
Development of this compound has led to derivatives which demonstrated higher antineoplastic activity in the P 388 mouse leukemia model, although the analogues with higher solubility showed significantly less activity than the parent **1** [3-5].

Oncodazole belongs to the class of alkyl (5-acyl-1*H*-benzimidazol-2-yl)carbamates which have proven anthelmintic activity (*e.g.*, mebendazole (**2**), and flubendazole (**3**) [6]).

Pursuing our studies on pyrrole analogues of biologically active compounds, we decided to prepare derivatives **4-7** related to oncodazole **1**.

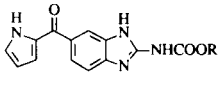


1



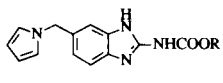
2 R = H

3 R = F



4 R = CH_3

5 R = C_2H_5

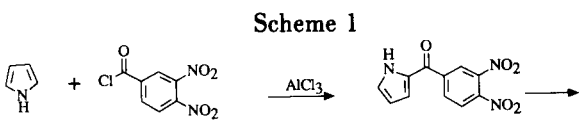


6 R = CH_3

7 R = C_2H_5

The synthesis of derivatives **4** and **5** began with a Friedel-Crafts reaction between 3,4-dinitrobenzoyl chloride and pyrrole in the presence of aluminum trichloride (Scheme 1). The product, 2-(3,4-dinitrobenzoyl)-1*H*-pyrrole (**8**), which formed was reduced to the corresponding diamino derivative **9** by hydrogenation in the presence of 10% palladium on carbon.

Scheme 1



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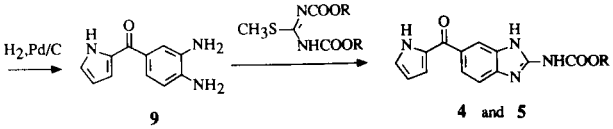


9

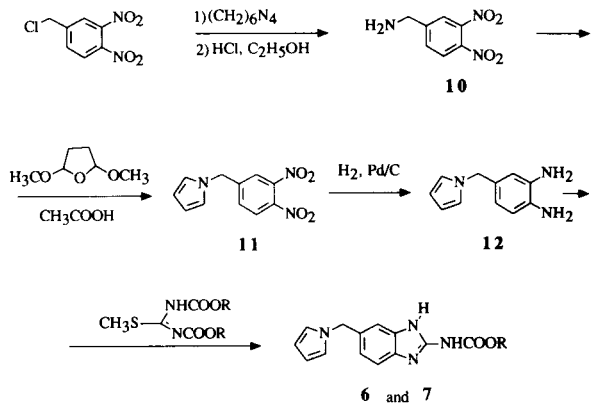
4 and **5**

R = CH_3, C_2H_5

Transformation of **9** into benzimidazoles **4** and **5** was accomplished using 1,3-bis(alkoxycarbonyl)-*S*-methylisothiourea, which was prepared from *S*-methylisothiourea and methyl or ethyl chlorocarbonate [4].

Synthesis of derivatives **6** and **7** was carried out as shown in Scheme 2.

Scheme 2



10

11

12

6 and **7**

Reaction of 3,4-dinitrobenzyl chloride with hexamethylenetetramine followed by acid hydrolysis according to the Delépine method [7] furnished 3,4-dinitrobenzylamine (**10**). This compound was converted to 1-(3,4-dinitrobenzyl)-1*H*-pyrrole (**11**) by reaction with 2,5-dimethoxytetrahydrofuran in glacial acetic acid. The use of the Clauson-Kaas method [8] led to a much higher yield of **11** than other attempts, such as by alkylation of pyrrole with 3,4-dinitrobenzyl chloride in the presence of a base (sodium hydride, potassium *t*-butylate and 18-crown-6). The dinitro compound, 1-(3,4-dinitrobenzyl)-1*H*-pyrrole (**11**), was reduced with palladium on carbon and hydrogen to the corresponding diaminobenzylpyrrole **12**. Treatment of **12** with 1,3-bis(methoxycarbonyl) and 1,3-bis(ethoxycarbonyl)-*S*-methylisothiourea gave compounds **6** and **7**, respectively.

EXPERIMENTAL

Melting points were taken on a Büchi 530 melting point apparatus and are uncorrected. Infrared spectra (nujol mulls) were recorded on a Perkin-Elmer 297 spectrometer. The pmr spectra were recorded on a Varian EM-390 and on a Varian XL-300 (for compounds **4-7**) spectrometers, using tetramethylsilane as an internal standard. Merck silica gel and alumina (70-230 mesh ASTM) were used for chromatographic purifications. Microanalyses were performed by A. Pietrogrande, Padova, Italy.

1,3-Bis(alkoxycarbonyl)-*S*-methylisothiourea.

A solution of *S*-methylisothiourea sulfate (11.1 g, 0.04 mole) and 4-dimethylaminopyridine (29.3 g, 0.24 mole) in anhydrous dioxane (300 ml) was stirred for 10 minutes, followed by dropwise addition of a solution of ethyl chloroformate (0.32 mole) in anhydrous dioxane (160 ml). After the addition was complete, the mixture was refluxed for 2 hours, then cooled to room temperature and treated again with 4-dimethylaminopyridine (14.6 g, 0.12 mole) and ethyl chloroformate (0.32 mole). After stirring for 15 hours at room temperature, the mixture was filtered and the insoluble material washed with dioxane. The organic solution was evaporated under reduced pressure and the residue chromatographed on silica gel column (chloroform as eluent). Removal of solvent from collected eluates gave about 50% of 1,3-bis(ethoxycarbonyl)-*S*-methylisothiourea [9], mp 43-44° (from *n*-hexane); ir: ν 3160 (NH), 1745 (CO) and 1645 cm^{-1} (C=N); pmr (carbon tetrachloride): δ 1.38 (m, 6H, CH_2CH_3), 2.33 (s, 3H, SCH_3), 4.18 (m, 4H, CH_2CH_3), 11.82 (broad, 1H, NH).

Anal. Calcd. for $C_8H_{14}N_2O_4S$: C, 41.01; H, 6.02; N, 11.96; S, 13.69. Found: C, 41.13; H, 5.98; N, 11.86; S, 13.73.

For 1,3-bis(methoxycarbonyl)-*S*-methylisothiourea, see ref [10].

2-(3,4-Dinitrobenzoyl)-1*H*-pyrrole (**8**).

3,4-Dinitrobenzoylchloride (5.0 g, 0.0217 mole) was dissolved in dichloromethane (20 ml) and added into a suspension of aluminum trichloride (2.9 g, 0.0217 mole) in the same solvent (20 ml). The clear solution was added dropwise during 20 minutes into a solution of pyrrole (1.3 g, 0.0197 mole) in dichloromethane (10 ml) cooled to -20°. After stirring for an additional 20 minutes, the solution was poured onto crushed ice (150 mg) and acidified by adding concentrated hydrochloric acid (3 ml). The organic phase was separated, washed with saturated sodium bicarbonate solution, then with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on an alumina column (chloroform as eluent) to give 1.66 g (32% yield) of **8**, mp 158-160° (from ethanol); ir: ν 3270 (NH), 1530 and 1355 cm^{-1} (NO_2); pmr (DMSO-d_6): δ 6.35 (m, 1H, pyrrole H-4), 7.00 (m, 1H, pyrrole H-3), 7.42 (m, 1H, pyrrole H-5), 8.38 (m, 2H, benzene H-5,6), 8.55 (m, 1H, benzene H-2), 12.40 (broad, 1H, NH).

Anal. Calcd. for $C_{11}H_7N_3O_5$: C, 50.58; H, 2.70; N, 16.09. Found: C, 50.47; H, 2.56; N, 15.98.

2-(3,4-Diaminobenzoyl)-1*H*-pyrrole (**9**).

A solution of **8** (5.06 g, 0.0194 mole) in ethyl acetate (200 ml) was hydrogenated in a Parr apparatus at 45° with palladium on charcoal (10%) at an initial pressure of 4 atmospheres. The catalyst was filtered off and the filtrate evaporated at reduced pressure until dry to give **9** in almost quantitative yield (3.2 g). The diamino derivative **9** was recrystallized from toluene, mp 125-127°; ir: ν 3370, 3300 and 3180 (NH, NH_2), 1570 (CO); pmr (perdeuteriodimethylformamide): δ 5.07 (broad s, 4H, NH_2), 6.23 (m, 1H, pyrrole H-4), 6.73 (d, 1H, J = 9 Hz, benzene H-5), 6.87 (m, 1H, pyrrole H-3), 7.13-7.43 (m, 3H, pyrrole H-5 and benzene H-2,5), 11.66 (broad, 1H, NH).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.84; H, 5.65; N, 20.62.

2-(Ethoxycarbonylamino)-5-(1*H*-pyrrol-2-ylcarbonyl)-1*H*-benzimidazole (**5**).

A solution of **9** (0.54 g, 0.0028 mole), 1,3-bis(ethoxycarbonyl)-*S*-methylisothiourea (1.05 g, 0.0045 mole) and *p*-toluenesulfonic acid (70 mg) in dry ethanol (50 ml) was refluxed for 4 hours. The precipitate was separated from the hot solution by filtration and washed successively on the filter with DMF, dry ethanol and light petroleum ether. Compound **5** (540 mg, 65% yield) was subjected to elemental analysis without further purification; mp >300°; ir: ν 3320 and 3280 (NH), 1700 (CO carbamate), 1610 and 1590 cm^{-1} (CO ketone and C=N); pmr (DMSO-d_6): δ 1.29 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 6.29 (m, 1H, pyrrole H-4), 6.84 (m, 1H, pyrrole H-3), 7.19 (m, 1H, pyrrole H-5), 7.50 (d, 1H, J = 8.1 Hz, benzimidazole H-7), 7.64 (dd, 1H, J = 8.1 Hz, benzimidazole H-6), 7.96 (d, 1H, benzimidazole H-4), 11.95 (broad, 3H, NH).

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60,37; H, 4.73; N, 19.00.

2-Methoxycarbonylamino-5-(1*H*-pyrrol-2-ylcarbonyl)-1*H*-benzimidazole (**4**).

This compound was prepared from **9** and 1,3-bis(methoxycarbonyl)-*S*-methylisothiourea as described for the carbamate **5**, yield 68%; mp >300°; ir: ν 3320 (NH), 1720 (CO carbamate), 1650 and 1620 cm^{-1} (CO ketone and C=N); pmr (DMSO-d_6): δ 3.78 (s, 3H, CH_3), 6.27 (m, 1H, pyrrole H-4), 6.81 (m, 1H, pyrrole H-3), 7.18 (m, 1H, pyrrole H-5), 7.49 (d, 1H, J = 8.3 Hz, benzimidazole H-7), 7.64 (dd, 1H, J = 8.3 Hz, benzimidazole H-6), 7.96 (d, 1H, benzimidazole H-4), 11.96 (broad, 3H, NH).

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.26; N, 19.71. Found: C, 59.09; H, 4.32; N, 19.83.

3,4-Dinitrobenzylamine (**10**).

Finely powdered hexamethylentetramine (5.48 g, 0.039 mole) in dry ethanol (400 ml) was treated with a solution of 3,4-dinitrobenzyl chloride (7.0 g, 0.0323 mole) in chloroform (20 ml) and the resulting solution was stirred at room temperature for 10 minutes. Sodium iodide (4.84 g, 0.0323 mole) was added and the mixture was stirred for an additional 20 hours. After cooling at 0-5°, the suspension was filtered and the solid washed with ethanol (17 ml). A suspension of this solid in dry ethanol (80 ml) was treated with concentrated hydrochloric acid (13 ml) and heated at 50-55° for 4 hours. The precipitate formed on cooling at 5° was filtered, washed with ethanol and dissolved in water. The solution was made alkaline by adding sodium carbonate and then shaken with ethyl acetate. The organic extracts were collected, washed with brine and dried over anhydrous sodium sulfate. Removal of solvent gave 4.37 g (69% yield) of **10** as an unstable yellowish solid, which was used for the next reaction without further purification.

1-(3,4-Dinitrobenzyl)-1*H*-pyrrole (**11**).

A solution of **10** (210 mg, 0.0011 mole) and 2,5-dimethoxytetrahydrofuran (210 mg, 0.0016 mole) in glacial acetic acid (20 ml) was refluxed for 5 minutes. Removal of acetic acid gave a residue

which was dissolved in chloroform. The organic solution was washed with 5% sodium carbonate, then with brine and finally dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on an alumina column (chloroform as eluent). The eluates were collected and evaporated to afford 250 mg (92% yield) of **11** as a yellowish solid, mp 93-94° (from ethanol); ir: ν 1540 and 1355 cm^{-1} (NO_2); pmr (deuteriochloroform): δ 5.22 (s, 2H, CH_2), 6.23 (m, 2H, pyrrole β protons), 6.70 (m, 2H, pyrrole α protons), 7.35 (dd, 1H, J = 9 Hz, benzene H-6), 7.52 (d, 1H, benzene H-2), 7.90 (d, 1H, J = 9 Hz, benzene H-5).

Anal. Calcd. for $C_{11}H_9N_3O_4$: C, 53.44; H, 3.67; N, 17.00. Found: C, 53.70; H, 3.77; N, 16.92.

1-(3,4-Diaminobenzyl)-1*H*-pyrrole (**12**).

Prepared as described for **9**, compound **12** was obtained in almost quantitative yield after chromatographic purification on an alumina column (eluent: ethyl acetate-chloroform 1:1), mp 135-136° (from toluene); ir: ν 3430, 3400 and 3320 cm^{-1} (NH_2); pmr (perdeuteriodimethylformamide): δ 3.43 (broad s, 4H, NH_2), 4.83 (s, 2H, CH_2), 5.98 (m, 2H, pyrrole B protons), 6.28-6.62 (m, 3H, benzene protons), 6.72 (m, 2H, pyrrole α protons).

Anal. Calcd. for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.61; H, 7.01; N, 22.32.

2-(Ethoxycarbonylamino)-5-(1*H*-pyrrol-1-ylmethyl)-1*H*-benzimidazole (**7**).

Prepared as reported for **4**; reflux time was 45 minutes; yield 62%, mp 240-241° (from dimethylformamide with partial decomposition); ir: ν 3320 (NH), 1700 (CO) and 1620 cm^{-1} (C=N); pmr (DMSO-d_6): δ 1.27 (t, 3H, CH_3), 4.20 (q, 2H, CH_2CH_3), 5.11 (s, 2H, CH_2), 6.00 (m, 2H, pyrrole β protons), 6.80 (m, 2H, pyrrole α protons), 6.98 (dd, 1H, J = 8.2 Hz, benzimidazole H-6), 7.24 (d, 1H, benzimidazole H-4), 7.34 (d, 1H, J = 8.2 Hz, benzimidazole H-7), 11.55 (broad, 2H, NH).

Anal. Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 63.44; H, 5.76; N, 19.93.

2-(Methoxycarbonylamino)-5-(1*H*-pyrrol-1-ylmethyl)-1*H*-benzimidazole (**6**).

Prepared as reported for **4**; reflux time was 20 minutes, yield 50%, mp 242-244° (from dimethylformamide with partial decomposition); ir: ν 3320 (NH), 1710 (CO) and 1625 cm^{-1} (C=N); pmr (DMSO-d_6): δ 3.73 (s, 3H, CH_3), 5.12 (s, 2H, CH_2), 5.99 (m, 2H, pyrrole β protons), 6.80 (m, 2H, pyrrole α protons), 6.97 (dd, 1H, J = 8.1 Hz, benzimidazole H-6), 7.23 (d, 1H, benzimidazole H-4), 7.33 (d, 1H, J = 8.1 Hz, benzimidazole H-7), 11.62 (broad, 2H, NH).

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.28; H, 5.18; N, 20.69.

Acknowledgement.

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