Reactions of 2-Isocyanatobenzoyl Chloride and 2-Carbomethoxyphenyl Isocyanate with 5-Aminotetrazole

Norton P. Peet

Merrell Dow Research Institute, Indianapolis Center, 9550 Zionsville Road, Indianapolis, IN 46268

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Treatment of 2-isocyanatobenzoyl chloride (**4**) with 5-aminotetrazole (5-AT) gave 3-(5-tetrazolyl)quinazoline-2,4(1*H*,3*H*)-dione (**1**) directly. Treatment of 2-carbomethoxyphenyl isocyanate (**5**) with 5-AT gave 2-[((5-amino-1*H*-tetrazol-1-yl)carbonyl)amino]benzoic acid methyl ester (**6**) as a kinetic product, which was thermally isomerized to 2-[((1*H*-tetrazol-5-ylamino)carbonyl)amino]benzoic acid methyl ester (**7**), the thermodynamically more stable urea. Cyclization of **7** with polyphosphoric acid gave 2-(1*H*-tetrazol-5-ylamino)-4*H*-3,1-benzoxazin-4-one (**2**). Urea **6** was quite labile in solution, as shown by nmr, and readily reacted with methanol to give 2-[(methoxycarbonyl)amino]benzoic acid methyl ester (**10**).

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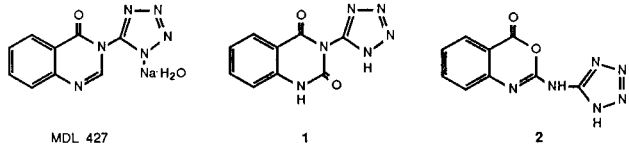
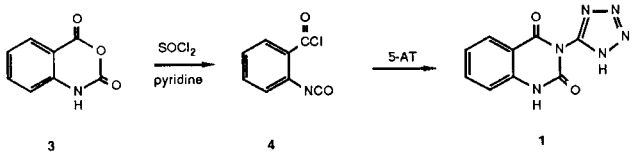
In a synthetic program designed to make compounds related to MDL 427 [1,2], an antiallergic agent which is presently being evaluated clinically, one objective was to prepare a pair of similar tetrazoles, namely, quinazolinedione **1** and benzoxazinone **2**. These isomeric compounds share certain structural features with MDL 427 which we feel are necessary for biological activity. This report describes the synthesis of the novel heterocyclic compounds **1** and **2** [3].



MDL 427 1 2

The preparation of 1,4-dihydro-3(2*H*)-(5-tetrazolyl)quinazoline-2,4-dione (**1**) was straightforward and is shown in Scheme I. 2-Isocyanatobenzoyl chloride (**4**) was prepared from isatoic anhydride (**3**), thionyl chloride and a catalytic amount of pyridine [5-8]. Treatment of **4** with 5-aminotetrazole (5-AT) gave **1** directly [9].

Scheme I



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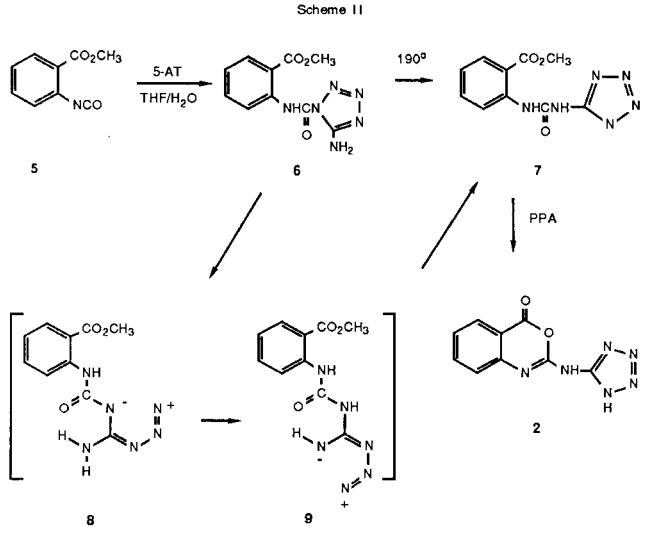
2-(1*H*-Tetrazol-5-ylamino)-4*H*-3,1-benzoxazine-4-one (**2**) was prepared as shown in Scheme II. Treatment of 2-carbomethoxyphenyl isocyanate (**5**) [12] with 5-AT in tetrahydrofuran containing a small amount of water gave an 81% yield of 2-[((5-amino-1*H*-tetrazol-1-yl)carbonyl)amino]-benzoic acid methyl ester (**6**). Rearrangement of **6** in decahydronaphthalene at reflux gave urea **7** in 96% yield. Cyclization of **7** with polyphosphoric acid gave the desired benzoxazinone **2** in 27% yield.

Scheme II



5 6 7 8 9 2

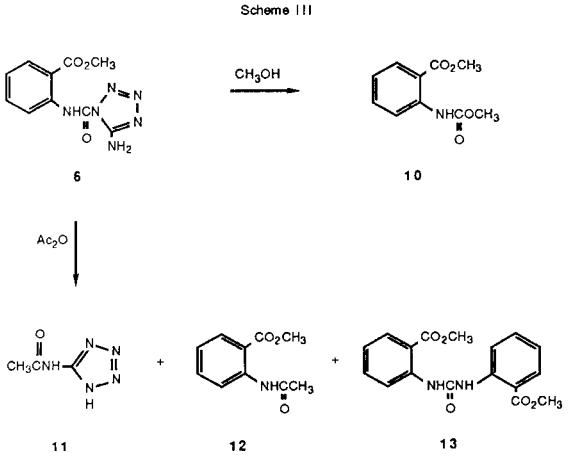
The structure of **6** was verified on the basis of its facile and efficient thermal rearrangement to the isomeric urea **7**. This rearrangement may proceed through guanyl azide intermediate **8**, which, after proton transfer occurs to produce **9**, can cyclize by forming a new nitrogen-nitrogen bond to give **7**. Thus, in the interaction of isocyanate **5** with 5-AT, urea **6** is the kinetic product while urea **7** is the thermodynamically more stable product. Compounds related to **6**, produced from alkyl isocyanates and 5-AT, have been prepared and thermally rearranged in analogous fashion [13]. An earlier, related study described the preparation of 1-acetyl-5-arylaminotetrazoles and their rearrangement to 1-acetylamino-5-aryltetrazoles [14]. In addition, an analogous study with phenyl isothiocyanate and 3-amino-1,2,4-triazole described the initial production of 5-amino-1-[phenylamino(thiocarbonyl)]-1,2,4-triazole, which was then thermally rearranged to *N*-(1,2,4-triazol-3-yl)-*N'*-phenylthiourea [15]. However, the production of compounds like **6** from aryl isocyanates and 5-AT have not been reported previously. The reaction of 4-carboethoxyphenyl isocyanate with 5-AT, in benzene at reflux, has

been reported to give the urea corresponding to **7** directly [16].

Urea **6** was labile in solution. We were able to obtain an nmr spectrum of **6** in dimethylsulfoxide-d_6 if the spectrum was recorded immediately after **6** was solubilized. However, nmr signals ascribed to **6** decreased with time and eventually disappeared. When a solution of **6** in dimethylsulfoxide was stirred for 60 hours and quenched with water, the isolated products were methyl anthranilate (**12**) and dimethyl 2,2′-[carbonylbis(imino)]bisbenzoate (**13**).

The lability of **6** was also demonstrated by heating **6** in methanol. Replacement of the 5-aminotetrazolyl group in **6** with methoxyl occurred, either by direct displacement or by elimination to the isocyanate followed by reaction with methanol, to give carbamate **10** in 88% yield (Scheme III).

Scheme III



In addition, simple acetylation of **6** was not possible. When **6** was warmed in acetic anhydride, 5-(acetylamino)-tetrazole (**11**) crystallized directly from the resulting solution in 72% yield. Concentration of the filtrate and treatment with sodium carbonate solution gave a product mixture derived from the anthranilate portion of the molecule, which was separated by flash chromatography. The major product was methyl *N*-acetylanthranilate (**12**), isolated in 74% yield, while the minor product was dimethyl 2,2′-[carbonylbis(imino)]bisbenzoate (**13**), isolated in 6% yield.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Beckman Model 4240 spectrophotometers, nmr spectra with Varian EM-360A and Perkin-Elmer R-32 (90 MHz) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, OH.

3-(5-Tetrazolyl)quinazoline-2,4-(1*H*,3*H*)-dione (**1**).

To a solution of 10.3 g (0.100 mole) of 5-aminotetrazole monohydrate in 300 ml of tetrahydrofuran and 15 ml of water was rapidly added a solution of 9.08 g (50.0 mmoles) of 2-isocyanatobenzoyl chloride (**4**) [6] in 50 ml of tetrahydrofuran. A white precipitate soon formed. After 30 minutes of stirring, the mixture was diluted with 150 ml of water and the white solid was collected. The filtrate was diluted with 850 ml of water and a second crop of white solid was collected. The combined, oven-dried crops (5.63 g) were recrystallized (dimethylformamide-methanol) to give 3.53 g (31%) of **1**, mp 273° dec; ir (Nujol): 3300-2300 (NH), with spike at 3180, 1735 (C=O), 1650 (C=O), 1620, 1595, 1470, 1330, 1265, 1230, 1010 and 765 cm^{-1}; nmr: [17]; ms: (70 eV, electron impact) m/e 230 (molecular ion).

Anal. Calcd. for $C_9H_6N_6O_2$: C, 46.96; H, 2.63; N, 36.51. Found: C, 46.80; H, 2.88; N, 36.70.

2-[[(5-Amino-1*H*-tetrazol-1-yl)carbonyl)amino]benzoic Acid Methyl Ester (**6**).

To a warm solution of 25.8 g (0.250 mole) of 5-amino-1*H*-tetrazole monohydrate in 750 ml of tetrahydrofuran and 30 ml of water was added 44.3 g (0.250 mole) of 2-carbomethoxyphenyl isocyanate (**5**) [12]. Midway through the addition a flocculent precipitate appeared. The white solid was collected, washed with ether and air-dried to yield 53.1 g (81%) of **6**, mp 244° dec; ir (Nujol): 3425, 3270 (sh), 3190 (sh) and 3110 (NH and NH_2), 1740 (ester C=O), 1700, 1650 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 12.1 (s, 1H, NH), 8.33 (dd, J = 8 Hz, J = 1 Hz, 1H, C6-H), 7.98 (dd, J = 8 Hz, J = 2 Hz, 1H, C3-H), 7.67 (dt, J = 8 Hz, J = 2 Hz, 1H, C5-H), 7.53 (s, 2H, NH_2), 7.23 (dt, J = 8 Hz, J = 1 Hz, 1H, C4-H); ms: (70 eV, electron impact) m/e 262 (molecular ion); ms: (70 eV, chemical ionization, methane) 263 ($M^+ + 1$), 291 ($M^+ + 29$).

Anal. Calcd. for $C_{10}H_{10}N_6O_3$: C, 45.80; H, 3.84; N, 32.05. Found: C, 45.79; H, 3.76; N, 31.80.

2-[[(1*H*-Tetrazol-5-ylamino)carbonyl)amino]benzoic Acid Methyl Ester (**7**).

A mixture of 53.1 g (0.202 mole) of **6** and 400 ml of decahydronaphthalene was heated at reflux for 15 minutes. The thick slurry which formed was agitated by mechanical stirring. The mixture was cooled, diluted with ether, and the white solid was collected, washed with ether and air-dried to give 50.5 g (96%) of **7**, mp 233° dec (dimethylsulfoxide-water); ir (Nujol): 3400-2300 (NH), 1695 (ester C=O), 1630 (urea C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 15.7 (very broad signal, 1H, tetrazole NH), 12.02 (s, 1H, urea NH), 10.33 (s, 1H, urea NH), 8.55 (dd, J = 8 Hz, J = 1 Hz, 1H, C6-H), 8.08 (dd, J = 8 Hz, J = 2 Hz, 1H, C3-H), 7.75 (dt, J = 8 Hz, J = 2 Hz, 1H, C5-H), 7.30 (dt, J = 8 Hz, J = 1 Hz, 1H, C4-H), 4.02 (s, 3H, CH_3); ms: (70 eV, electron impact) m/e 262 (molecular ion); ms: (70 eV, chemical ionization, methane) 263 ($M^+ + 1$), 291 ($M^+ + 29$), 303 ($M^+ + 41$).

Anal. Calcd. for $C_{10}H_{10}N_6O_3$: C, 45.80; H, 3.84; N, 32.05. Found: C, 45.60; H, 4.06; N, 32.08.

2-(1*H*-Tetrazol-5-ylamino)-4*H*-3,1-benzoxazin-4-one (**2**).

A mixture of 27.0 g (0.103 mole) of **7** and 400 g of polyphosphoric acid was heated to 160° and then held at 130-140° for 2 hours. The clear, viscous solution was poured into ice water, and after hydrolysis of the polyphosphoric acid was complete the white solid was collected and air-dried to yield 12.9 g. Recrystallization (acetone-hexane) gave 6.28 g (27%) of **2**, mp 261-262° dec; ir (Nujol): 3625, 3450 and 3290 (NH), 1725 (C=O), 1665 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 12.06 (s, 1H, NH, deuterium oxide-exchangeable), 11.23 (broad s, 1H, NH, deuterium oxide-exchangeable), 8.30-7.65 (m, 2H, aromatic), 7.65-7.20 (m, 2H, aromatic); ms: (70 eV, electron impact) m/e 230 (molecular ion).

Anal. Calcd. for $C_9H_6N_6O_2$: C, 46.96; H, 2.63; N, 36.51. Found: C, 46.88; H, 2.76; N, 36.63.

Treatment of **6** with Methanol.

A solution of 2.00 g (7.63 mmoles) of **6** in 200 ml of methanol was heated at reflux for 2 hours and concentrated. An nmr (dimethylsulfoxide-d_6) of the resulting white solid indicated a clean mixture of carbamate **10** and 5-aminotetrazole. The white solid was slurried with 20 ml

of 1 *N* sodium hydroxide solution and the insoluble portion was collected, washed with water and air-dried to give 1.40 g (88%) of 2-[(methoxycarbonyl)amino]benzoic acid methyl ester (**10**), mp 56-59° (lit [18] mp 59-61°); ir (Nujol): 3250 (NH), 1735 (ester C=O), 1695 (carbamate C=O); nmr (deuteriochloroform): δ 10.57 (br s, 1H, NH), 8.33 (dd, J = 8 Hz, J = 1 Hz, 1H, C6-H), 7.90 (dd, J = 8 Hz, J = 2 Hz, 1H, C3-H), 7.42 (dt, J = 8 Hz, J = 2 Hz, 1H, C5-H), 6.92 (dt, J = 8 Hz, J = 1 Hz, 1H, C4-H), 3.84 (s, 3H, CH_3), 3.70 (s, 3H, CH_3).

Treatment of **6** with Acetic Anhydride.

A mixture of 5.00 g (19.1 mmoles) of **6** and 50 ml of acetic anhydride was heated briefly until solution resulted. The white crystals which soon deposited were collected and air-dried to give 1.75 g (72%) of 5-(acetylamino)tetrazole (**11**), mp 277° dec (lit [19] mp 277-278° dec); ir (Nujol): 3400-2100 (NH), 1690 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 16.0 (very broad signal, 1H, tetrazole NH), 12.56 (broad s, 1H, CONH), 2.13 (s, 3H, CH_3).

The filtrate was concentrated and the resulting oil was treated with 25 ml saturated sodium carbonate solution. The oil which separated soon crystallized. The white solid was collected to give 3.55 g of a mixture of two components, as indicated by tlc. Separation of these components was accomplished with Baker Silica Gel for Flash Chromatography (7024-R, 700 ml dry volume) using 3:7 ethyl acetate:hexane as the eluent. Early fractions gave 0.40 g (6%) of dimethyl 2,2'-[carbonylbis(imino)]bisbenzoate (**13**), mp 142-144° (lit [12] mp 142-145°), whose infrared spectrum was identical to that of an authentic sample. Later fractions gave 2.73 g (74%) of methyl 2-(acetylamino)benzoate (**12**), mp 98-99° (lit [20] mp 101°); ir (Nujol): 3280 (NH), 1710 (ester C=O), 1695 (amide C=O); nmr (deuteriochloroform): δ 11.04 (br s, 1H, NH), 8.73 (dd, J = 8 Hz, J = 1 Hz, 1H, C6-H), 8.03 (dd, J = 8 Hz, J = 2 Hz, 1H, C3-H), 7.57 (dt, J = 8 Hz, J = 2 Hz, 1H, C5-H), 7.08 (dt, J = 8 Hz, J = 1 Hz, 1H, C4-H), 3.95 (s, 3H, OCH_3), 2.27 (s, 3H, $COCH_3$). Spectral data for **12** was identical to that obtained for an authentic sample prepared from methyl anthranilate and acetic anhydride.

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[3] When evaluated in the rat passive cutaneous anaphylaxis (PCA) test at 60 mg/kg as we recently described [4], compound **1** was essentially inactive and compound **2** produced 100% inhibition.

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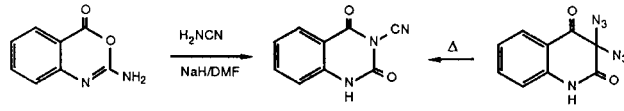
[9] Interestingly, preparations of another possible precursor to **1**, namely, 3-cyanoquinazoline-2,4(1*H*,3*H*)-dione (**ii**), have been reported. Treatment of 2-amino-3,1-benzoxazin-4-one (**i**) with cyanamide and



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sodium hydride in dimethylformamide gave **ii** [10]. Also, thermolysis of 3,3-diazidoquinazoline-2,4-(1*H*,3*H*)-dione (**iii**) furnished **ii** [11]. 1,3-Dipolar cycloaddition of **ii** with hydrazoic acid should give **1**.

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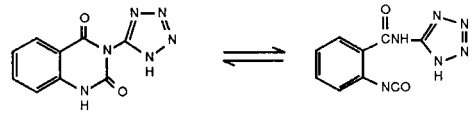
[17] The nmr (dimethylsulfoxide-d_6) spectrum of **1** indicated a mixture of species in solution. We recognize that **1** has latent isocyanate functionality, and that a solution equilibrium mixture of **1** and **i** could ac-



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count for the nmr spectrum. However, a solution infrared spectrum of **1** in dimethylsulfoxide failed to show appreciable absorption in the isocyanate region.

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