Synthesis and Tautomerism of Ethyl 2-(2-Benzothiazolyl)-2-(6-purinyl)acetate and Related Compounds

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Reaction of 6-chloro-9*H*-(2-tetrahydropyranyl)purine (**2d**) with the sodium salt of ethyl benzothiazole-2-acetate (**1**) in dimethylformamide effects condensation of the two compounds (with loss of sodium chloride) to give the corresponding ethyl diarylacetate **4** (35%), present largely as an enol chelate tautomer. Isolated as a by-product is 6-(2-aminophenyl-1-thio)-9*H*-(2-tetrahydropyranyl)-purine (4%), formed *via* opening of the thiazole ring. Removal of the tetrahydropyranyl protective group from **4** occurs by treatment with *p*-toluenesulfonic acid in aqueous ethanol to produce ethyl benzothiazole-2-(6-purinyl)acetate (80%), existent largely as two enol chelate isomers. Spectral data for the various products are presented. An attempt to use 6-chloro-9-acetyl-9*H*-purine in place of **2d** in the first reaction gives acetylation of **1** instead of condensation.

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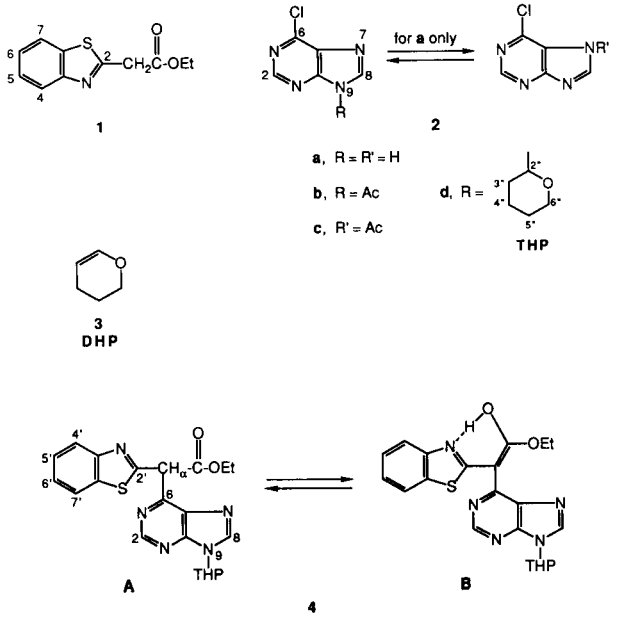
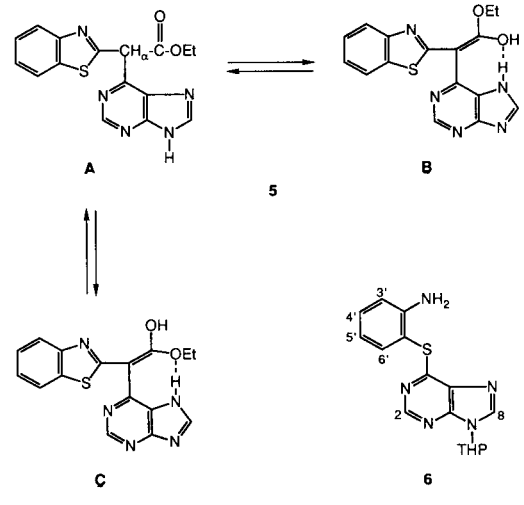
In previous publications [3,4] we described the synthesis and tautomerism of 2,2-disubstituted ethyl acetates bearing the cyano group and either a quinolyl or a thienopyridyl substituent. The present paper is concerned with an analogous study in another system of 2,2-disubstituted ethyl acetates in which the substituents are a 2-benzothiazolyl group and a 6-purinyl group, as exemplified by compound **5**. The plan of the synthesis is to condense the sodium salt of ethyl benzothiazole-2-acetate (**1**) with 6-chloropurine (**2a**) bearing a protective group at N-7 or N-9 (with elimination of sodium chloride) and then to remove the protective group to form ester **5**.

Benzothiazole ester **1** was described by three research groups [5-7] with varying indications of its stability toward distillation. We have found that **1** is easily prepared from 2-aminobenzenethiol by the procedure of Baudet and Otten [5] and is easily purified (albeit with considerable loss) by molecular distillation at 90-95° (0.1 mm).

As a protective group for 6-chloropurine (**2a**) we first chose the acetyl function since a crystalline derivative, either **2b** or **2c**, was reported by Montgomery [8] who found it easily undergoes deprotection by warming with aqueous sodium hydroxide. In a simple modification of the Montgomery synthesis, we refluxed a solution of **2a** in acetic anhydride, removed by-product acetic acid by distillation, and subjected the residual liquid to fractional precipitation with ether. The precipitate proved to be a mixture of **2b** and **2c** (minor component) on the basis of its ^{1}H nmr spectrum, which showed a doubling of the three expected singlet signals. We attribute the upfield set of singlets at 8.55, 8.20, and 2.82 ppm to **2c**, the 7-acetyl isomer in which the carbonyl group of the acetyl substituent should be sterically hindered from attainment of coplanarity with the purine ring. Correspondingly, the downfield set at 9.13 (H-2), 8.96 (H-8), and 2.93 (Ac), is assigned to the 9-acetyl isomer **2b**, where coplanarity by the carbonyl group should be possible and cause withdrawal of electronic charge from the purine π-system. The ether-soluble fraction contained only the **2b** isomer, as based on the ^{1}H nmr spectrum. Unfortunately, reaction of **2b** with the sodium salt of **1** did not cause coupling of the benzothi-





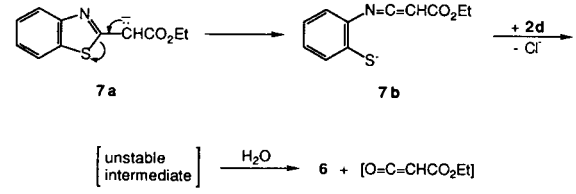
azole and purine moieties. Although sodium chloride was formed, the only organic product isolated, identified by ^{1}H nmr only, contained a mixture of mono and diacetyl derivatives of **1**. This action of **2b** as an acetylating agent is analogous to previous observations on *N*-acetyl derivatives in the quinoline and thieno[2,3-*b*]pyridine systems [3,4].

Successful coupling of the benzothiazole and purine systems was subsequently accomplished by using the tetrahydropyranyl (THP) protective group on 6-chloropurine, instead [9]. Thus, compound **2d** was synthesized from **2a** and dihydropyran (**3**, DHP) according to the published procedure of Robins *et al.* [10], who assigned the location of the THP group of the crystalline product to N-9 on the basis of its ultraviolet spectrum [11]. Reaction of **1** in dimethylformamide first with sodium hydride at 0-25° and then with **2d** at a temperature up to 140° gave **4** (35%) as non-fluorescent, canary yellow crystals, mp 158-160.5° [12].

Crystalline compound **4** is assigned the structure of a chelated enol (tautomer **B**) on the basis of its ir spectrum in a potassium bromide pellet (bands at 3440 cm^{-1} for a bonded hydroxyl group and at 1617 cm^{-1} for the structural feature C=C-O). Moreover, there is no band at 1745-1770 cm^{-1}, expected for the ester group of tautomer **A** [13]. The ^{1}H nmr spectrum of **4** in hexadeuteriodimethyl sulfoxide, however, shows the presence of both tautomers **B** (broad singlet for the N··H··O chelate group at δ 13.7 [14]) and **A** (doubling of signals for H-2, H-8, H-4′, H-7′, and H-2″, plus a singlet at 6.44 for the α proton) in the ratio of *ca.* 8:1. Because of the presence of tautomer **A** in solution, we expected to be able to saponify the carboethoxy group with a base and retain the THP protective unit [9]. However, refluxing **4** with either aqueous sodium hydroxide or methanolic potassium hydroxide gave only product devoid of identifiable benzothiazole or purine ^{1}H nmr signals. Fragmentation of **4** under electron impact involves loss of carboethoxy and dihydropyran (DHP) units, as well as four molecules of hydrogen cyanide [15].

When the synthesis of **4** was conducted under somewhat modified reaction conditions a white by-product, mp 160-162°, $C_{16}H_{17}N_5OS$ (4%), was also obtained. This by-product is assigned structure **6** since (a) it shows infrared absorption peaks at 3416 and 3303 cm^{-1} for a free, primary amino group [16] and (b) it loses DHP plus four molecules of hydrogen cyanide in mass spectrometry. Corroborating this structure is the ^{1}H nmr spectrum of **6** in hexadeuteriodimethyl sulfoxide which retains signals for the purine and THP portions as in **4**, but lacks signals for an ethyl group. In addition **6** exhibits a broad singlet at 5.33 ppm for the two amino protons, plus a pattern of two doublets and two triplets (albeit in a modified order of chemical shifts from that in **4**) for an intact *ortho*-disubstituted benzene ring. A rationale for the formation of **6** involves the assumption that the carbanion from **1**, **7a**, undergoes opening of the heterocyclic ring either before or during reaction with **2d**, as suggested formally in Scheme I, where the sulfide ion **7b** gives nucleophilic displacement of chloride ion from **2d**.

Scheme I



Warming **4** with aqueous *p*-toluenesulfonic acid readily removes the THP protective group and gives a good yield (80%) of compound **5**, obtained as a bright yellow hydrate on crystallization from dichloromethane, mp 171.5-173°. As for **4**, the infrared spectrum of **5** in the solid state indicates the presence of a vinyl ether function such as would occur in tautomeric enol form **B** or **C**. Likewise the ^{1}H nmr spectrum of **5** in hexadeuteriodimethyl sulfoxide shows no evidence for a keto form **A**. However, in deuteriochloroform one can clearly recognize the presence of three isomeric forms in the ratio of *ca.* 3.8:3.1:1.0, possibly for either **B**:**C**:**A** or **C**:**B**:**A**. Thus, in the latter solvent there are three clearly distinguishable sets of signals for the ethyl group and one singlet at 4.07 ppm, ascribed to H-α in tautomer **A**. The mass spectrum of **5** is straightforward, with the molecular ion as the most abundant species plus strong peaks for loss of ethanol and a carboethoxy unit.

It is clear that systems **4** and **5** show many of the properties of enolization and chelation that were noted in the 2-heteroaryl cyanoacetate systems studied earlier [3,4]. Associated with these properties are (a) changes in the ratios of various isomeric and/or tautomeric structural modifications of each compound brought about by changes in the chemical environment and (b) loss of physicochemical properties normally expected for a simple ester [17].

EXPERIMENTAL [18]

Acetylation of 6-Chloropurine (**2a**).

A mixture of 0.5 g of 6-chloropurine (**2a**) [Aldrich, mp >300° dec]; ^{1}H nmr (hexadeuteriodimethyl sulfoxide): δ 13.9 (broad s, NH), 8.75 (s, H-2), 8.70 (s, H-8)] and 10 ml of acetic anhydride was refluxed in an atmosphere of nitrogen for one hour. Excess solvent (including acetic acid formed) was removed by slow distillation and rotoevaporation under anhydrous conditions. Addition of ether to the cooled residue gave crystals (119 mg, mp 130-132°); ^{1}H nmr (hexadeuteriodimethyl sulfoxide): δ 9.13 (s, 1H, H-2), 8.96 (s, 1H, H-8), 2.93 (s, 3H, Ac) for **2b**, plus 8.55 (s, 1H, H-2), 8.20 (s, 1H, H-8), 2.82 (s, 3H, Ac) for **2c** in the ratio of **2b**/**2c**

= 1.5. Evaporation of the mother liquor from the preceding precipitate yielded 224 mg of isomerically pure **2b**, mp 128-132°, lit 140-142° [8]; total yield of both isomers 343 mg (54%).

Ethyl Benzothiazole-2-acetate (**1**).

This compound was prepared from 2-aminobenzenethiol (Sigma) and ethyl malonyl chloride (Aldrich) according to the procedure of Baudet and Otten [5]. The crude product was purified by molecular distillation at 90-95° (0.1 mm) to give a lemon yellow liquid, stored at 20°; ir (neat): 1736 cm^{-1} (carbonyl); ^1H nmr (deuteriochloroform): δ 7.98 and 7.82 (2d, J = 8 Hz, 1H each, H-4 and H-7), 7.42 and 7.33 (2 overlapping t, J ≅ 7.6 Hz, H-5 and H-6), 4.18 (q, J_{Et} = 7.1 Hz, 2H, OCH_2CH_3) which overlaps 4.09 (s, 2H, CH_2CO_2Et), 1.18 (t, methyl); ms: m/e 221 (M^+, 40), 149 (71), 148 (M^+ - CO_2Et, 100), 69 (20), 45 (CHS^+, 56), 44 (43), 43 (79).

6-Chloro-9*H*-(2-tetrahydropyranyl)purine (**2d**).

This compound was synthesized from 6-chloropurine (Aldrich) and purified 2,3-dihydropyran [19] by the method of Robins and co-workers [10]; ^1H nmr (deuteriochloroform): δ 8.70 (s, H-2), 8.33 (s, H-8), 5.76 (d, J = 10 Hz, 1H, H-2″), 4.16 (partially split d, J = 10 Hz, 1H) and 3.76 (m, 1H, 2H-6″ combined), 1.6-2.3 (2m, 6H, 2H-3″, 2H-4″, 2H-5″); ms: m/e 240 (M^+, 2.4) and 238 (M^+, 7), 212 (3) and 210 (M^+ - H_2CN, 8), 157 (6) and 155 (18), 119 (9), 86 (9), 85 (DHP•H^+, 100), 84 (17).

Ethyl 2-(2-Benzothiazolyl)-2-(9*H*-[2-tetrahydropyranyl]purin-6-yl)-acetate (**4**) [20].

Into a nitrogen-filled, well-dried flask protected from moisture in the air was placed 0.62 g (15.6 mmoles) of 60% sodium hydride (emulsion in mineral oil) and 5 ml of petroleum ether (35-60°). The mixture was stirred briefly and the petroleum ether was removed by suction using a filter stick. The residual sodium hydride was washed twice more with petroleum ether and then suspended in 6 ml of dried, purified dimethylformamide [21] and treated (with stirring) with a solution of 3.16 g (14.3 mmoles) of ethyl benzothiazole-2-acetate (**1**) in 9 ml of dimethylformamide. After the foam had dissipated a solution of 3.41 g (14.3 mmoles) of 6-chloro-9*H*-(2-tetrahydropyranyl)purine (**2d**) in 30 ml of dimethylformamide was added. The greenish black mixture was heated to 105° over 25 minutes and then to 120° over the next 2.3 hours. Most of the voluminous precipitate which formed dissolved when the temperature was raised to 140° over the next 0.5 hour. Heating was then discontinued.

The cold, purplish brown mixture was filtered (sintered glass) and the precipitate (identified as sodium chloride, 0.59 g, 70%) was washed with chloroform. The filtrate (plus washing) was diluted with three times its volume of ether and extracted five times with 200-ml portions of saturated, aqueous sodium chloride solution (to remove dimethylformamide). The brown organic layer was filtered to remove a scum, concentrated to a small volume, and refrigerated to provide 2.11 g (35%) of **4** as yellow crystals, mp 148-158° dec. Thin layer chromatography of this crude product with silica gel/ethyl acetate showed two spots, R_f 0.32 for **4** and 0.67 for a fluorescent by-product [22]. The crude product was chromatographed on a column of silica gel (92 g per g of product) with ethyl acetate and fractions containing only **4** were recrystallized from ethyl acetate to give fine, canary yellow, non-fluorescent needles, mp 158-160.5° with sintering at 148°; ir: 3440 (broad, bonded OH) and 1617 cm^{-1} (strong, C=C-O) [23]; ^1H nmr (hexadeuteriodimethyl sulfoxide): tautomer *B* (89%), δ 13.7 (broad s, N••H••O) [4], 8.74 (s, H-2), 8.52 (s, H-8), 7.84 and 7.68 (2d, J = 7.5 Hz, 1H each, H-4′ and H-7′), 7.37 and 7.22 (2t, J = 7.5 Hz, 1H each, H-5′ and H-6′), 5.70 (d, J = 11 Hz, H-2″), 4.16 (q, J_{Et} = 7 Hz, 2H, OCH_2CH_3), 3.6-4.1 and 1.7-2.4 (2m, 10H total, 8H in THP; plus 2H for **A**, *vide infra*), 1.12 (t, 3H, methyl group); additional signals for tautomer **A** (11%), δ 8.98 and 8.86 (2s, H-2 and H-8), 8.07 and 7.94 (2d, J = 7.5 Hz, H-4′ and H-7′), 7.45 (t, other t obscured), 6.44 (s, $CHCO_2Et$), 5.78 (d, J = 11 Hz, H-2″), 3.6-4.1 and 1.7-2.4 (total of *ca.* 2H for THP and ethyl groups); ms: m/e 423 (M^+, 19), 350 (M^+ - CO_2Et, 45), 340 (25), 339 (M^+ - DHP, 32), 293 (22), 268 (21), 267 (60), 266 (M^+ - CO_2Et - DHP, 100), 85 (DHP•H^+, 31). There is also an apparent fragmentation series for successive emissions of 4 molecules of hydrogen cyanide, thus 293 → 266 → 239 (10) → 212 (10) → 185 (5), in the mass spectrum.

Anal. Calcd. for $C_{21}H_{21}N_5O_3S$: C, 59.56; H, 5.00; N, 16.54; S, 7.57; exact mass, 423.1368. Found: C, 59.77; H, 5.02; N, 16.36; S, 7.18; exact mass, 423.1365.

6-(2-Aminophenyl-1-thio)-9*H*-(2-tetrahydropyranyl)purine (**6**).

In a variation of the preceding condensation reaction equimolar quantities (10.6 mmoles) of sodium hydride, **1**, and **2d** were used and the reaction mixture was maintained at 60-95° for 3 hours. The filtered, cold reaction mixture was diluted with 200 ml of ether and washed three times with an equal volume of saturated aqueous sodium chloride solution. Concentration of the ether solution left a viscous syrup which deposited tan crystals on standing, yield 178 mg (4%), mp 140-143° (sintering at 136°). Recrystallizations from ethyl acetate gave white needles of **6**, mp 160-162°; ir: 3416 and 3303 (amino), 2938, 1574 cm^{-1} [16]; ^1H nmr (hexadeuteriodimethyl sulfoxide): δ 8.71 (s, 1H, H-2), 8.55 (s, 1H, H-8), 7.29 and 6.79 (2d, J_{ortho} = 8.3 Hz, 1H each, H-3′ and H-6′), 7.19 and 6.59 (2 pseudotriplets, J ≅ 8.0 Hz, 1H each, H-4′ and H-5′), 5.73 (d, $J_{2'',3''}$ = 11 Hz, 1H, H-2″), 5.33 (broad s, *ca.* 2H, amino group), 4.00 (d, 1H, H-6″), 3.7, 2.3, and 2.1-1.5 (3m, 7H total, other protons on THP group); ms: m/e 327 (M^+, 5) 244 (19), 243 (M^+ - DHP, 100), 227 (243$^+$ - NH_2, 34), 217 (11), 216 (243$^+$ - HCN, 75), 210 (47), 85 (THP•H^+, 25), 41 (42). Successive losses of hydrogen cyanide molecules in the mass spectrum are also apparent in the fragmentation pattern 243 → 216 → 189 (7) → 162 (7) → 135 (7).

Anal. Calcd. for $C_{16}H_{17}N_5OS$: C, 58.70; H, 5.24; S, 9.80; exact mass, 327.115. Found: C, 58.32; H, 5.20; S, 9.55; exact mass, 327.116. Calcd. for $C_{11}H_9N_5S$ (m/e 243): exact mass, 243.058. Found: exact mass, 243.057.

Ethyl 2-(2-Benzothiazolyl)-2-(6-purinyl)acetate (**5**) [20].

A stirred mixture of 1.30 g (3.07 mmoles) of ester **4**, 0.64 g (3.37 mmoles) of *p*-toluenesulfonic acid monohydrate, 20 ml of 95% ethanol, and 20 ml of water was warmed to 55°. The amber solution was maintained at this temperature for 25 minutes. Thin layer chromatography indicated that all of ester **4** (R_f 0.42, ethyl acetate/silica gel) had reacted and only ester **5** (R_f 0.11) remained. Concentration of the solution caused deposition of yellow crystals of **5** hydrate, yield 0.83 g (80%), mp 164-170°. Recrystallizations from dichloromethane gave fine, bright yellow needles, mp 171.5-173°; ir: 3256 (complexed water), 3095 (O••H••N chelate?), 1678 (aliphatic C=C), and 1215 cm^{-1} (vinyl ether); ^1H nmr (hexadeuteriodimethyl sulfoxide): δ 8.79 (s, H-2), 8.43 (broad s, H-8), 7.86 and 7.74 (2d, $J_{4',5'}$ = $J_{6',7'}$ = 7.8 Hz, 1H each, H-4′ and H-7′),

7.38 and 7.22 (2t, J = 7.5 Hz, 1H each, H-5′ and H-6′), 4.26 (q, J_{Et} = 7 Hz, 2H, OCH_2), 1.17 (t, 3H, methyl group); ^1H nmr (deuteriochloroform): δ 8.59 and 8.53 (2s), 8.26 (broad s), 7.8-7.9 (2 overlapping d), 7.3-7.6 (m), 4.56, 4.47, and 3.76 (3q, integral ratios of 4.7:3.0:1.0, respectively, J_{Et} = 7 Hz, 3 OCH_2 groups), 4.07 (s, H-α, ratio 0.3), 1.75 (broad s, NH, OH, or water, ratio 1.0), 1.60, 1.38 and 1.28 (3t, integral ratios of 3.2:2.0:1.0, respectively, 3 methyl groups); ms: m/e 340 (26), 339 (M^+, 100) 293 (M^+ - EtOH, 44), 267 (55), 266 (M^+ - CO_2Et, 72), 265 (20), 211 (27).

Anal. Calcd. for $C_{16}H_{13}N_5O_2S \cdot \frac{1}{4}H_2O$: C, 55.89; H, 3.95; N, 20.36. Found: C, 55.95; H, 3.81; N, 20.02.

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[11] The poor resolution of the nmr signals for the protons on the THP ring of our sample of **2d** did not help to clarify this assignment. However, even the crude sample appeared to be a single isomer (no doubling of the signals for H-2 and H-8).

[12] Some minor by-products are also produced, but they were not investigated in detail.

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[14] Compare with the N••H••O chelate at 13.5 ppm in a quinoline system [4].

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[16] Reference [13], p 278.

[17] Limited efforts were made to effect hydrolysis of **5**, but these studies were discontinued partially because numerous separable products resulted.

[18] Infrared spectra were determined on potassium bromide wafers by means of a Nicolet 5-DXB FTIR instrument; ^1H nmr spectra, by means of a General Electric QE-300 instrument. Electron-impact mass spectra at 70 eV were obtained by Dr. Richard Wielesek of this laboratory on a VB 12-250 instrument. Elemental analyses were conducted by Desert Analytics, Tucson, Arizona.

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