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# A General Route for the Facile Synthesis of 4-Thioxopyrimidin-2-one Derivatives via the Annulation of Cyclic *o*-Aminonitriles Using Carbonyl Sulfide[1]

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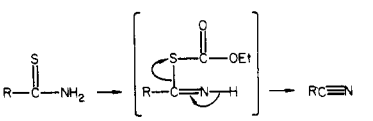
A facile synthesis of 4,5-diamino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one (**6**) from an appropriately substituted pyrrolo[2,3-*d*]pyrimidine has been accomplished. A key reaction in this synthesis involves the ring closure of a cyclic *o*-aminonitrile precursor by using carbonyl sulfide to obtain the versatile 4-thioxopyrimidin-2-one intermediate **3**. A study involving the generality of this reagent for the annulation of cyclic *o*-aminonitriles under different reaction conditions is also discussed.

The significant antitumor activity observed[2,3] for certain tricyclic nucleosides prepared in our laboratory, e.g., 4,5-diamino-8-(β-D-ribofuranosyl)pyrazolo[3',4':5,4]pyrrolo-[2,3-*d*]pyrimidine[4] and 6-amino-4-methyl-8-(β-D-ribofuranosyl)-4*H*,8*H*-pyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]-pyridazine[5] prompted us to continue our research efforts in the tricyclic nucleoside area. We have recently synthesized[12] a new class of tricyclic nucleoside in which the aglycon has a [6:5:6] "linear" geometry with the ribosyl moiety residing on the five-membered ring. However, we were unable to prepare, in this series, the adenosine–isoguanosine analogue 4,5-diamino-9-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one (**6**) using the standard synthetic routes.

Our initial attempts to synthesize **6** directly by ring annulation[6] of 6-aminotoyocamycin[7] (**2**) with ethyl chloroformate, followed by treatment with ammonia, were unsuccessful. Also, a fusion of **2** with urea[6] resulted in a black reaction mixture from which no identifiable products could be isolated. These results indicated that the 5-cyano group of **2** should be converted into a more reactive form[8] such as an amidine or alkyl imino ether group which would then function more effectively in a ring-closing reaction. However, attempts to form the above derivatives were unproductive since the cyano group was found to be essentially resistant toward attack by nucleophiles. These results further confirmed some of our earlier findings,[7] that in this ring system, a 4- and/or 6-amino group serves to deactivate a cyano group located at the 5-position. The synthesis of isoguanosine, per se, has been accomplished[9] by using 5-amino-4-cyano-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole as the starting material. This nucleoside was converted into 5-amino-1-(β-D-ribofuranosyl)imidazole-4-thiocarboxamide which was then cyclized with diethyl carbonate in ethanolic sodium ethoxide solution to give 6-thioxanthosine (5% yield from the 2',3'-*O*-isopropylidene derivative of 5-amino-4-cyanoimidazole ribonucleoside). The nucleoside 6-thioxanthosine was then methylated and treated with ammonia to afford isoguanosine. However, our attempts to use this procedure for the synthesis of 4-amino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one (**3**) from 6-amino-thiosangivamycin[7] (**1**) only resulted in the isolation[10] of **2**.

†CONICIT Venezuelan Predoctoral Fellow.

(1) Chung, F-L.; Earl, R. A.; Townsend, L. B. *Tetrahedron Lett.* **1980**, 1599.
(2) Townsend, L. B.; Bhat, G. A.; Chung, F-L.; Schram, K. H; Panzica, R. P.; Wotring, L. L. *INSERM* **1979**, *81*, 37.
(3) Roti Roti, L. W.; Roti Roti, J. L.; Townsend, L. B. *Proc. Am. Assoc. Cancer Res.* **1978**, *19*, 40.
(4) Tolman, R. L.; Townsend, L. B. *Tetrahedron Lett.* **1968**, 4815.
(5) Schram, K. H.; Townsend, L. B. *Tetrahedron Lett.* **1971**, 4757.
(6) Taylor, E. C.; McKillop, A. "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles"; Interscience Publishers: New York, 1970.
(7) Schram, K. H.; Townsend, L. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1253.
(8) Schoefer, F. C. "The Chemistry of the Cyano Group", Rappoport, Z., Ed.; Interscience: New York, 1970; Chapter 6.
(9) Yamazaki, A.; Kumashiro, I.; Takenishi, T.; Ikehara, M. *Chem. Pharm. Bull.* **1968**, *16*, 2172.
(10) A possible mechanism for the conversion of the thiocarboxamide group of **1** into a cyano group is as follows:



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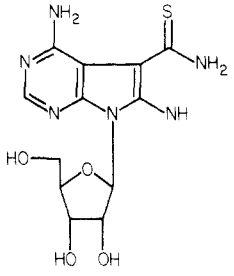

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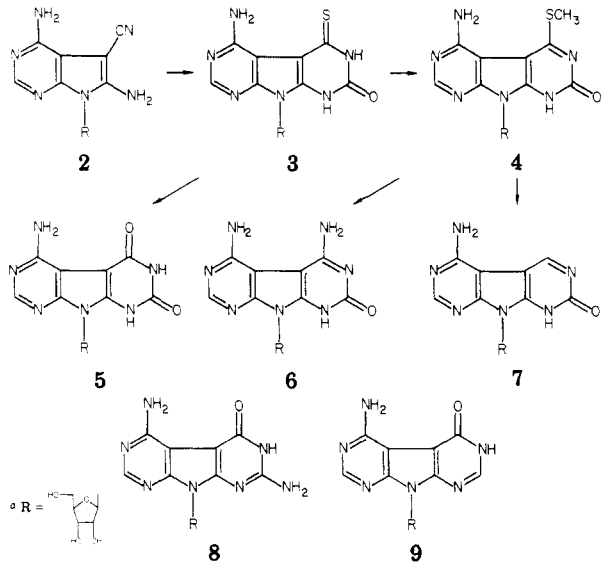
These unsuccessful attempts at the synthesis of **3** by using standard procedures prompted us to investigate a novel synthetic approach involving the reagent carbonyl sulfide. This reagent was used for the facile ring closure of the *o*-aminonitrile grouping. Treatment of **2** with an excess of carbonyl sulfide yielded a light yellow product which lacked an absorption band for a cyano group (region near 2200 $cm^{-1}$) in the IR spectrum. The UV spectrum indicated that ring closure had probably occurred since the product (**3**) showed a significant bathochromic shift in comparison to the starting material[7] **2** [$\lambda_{max}(CH_3OH)$ of 292 nm for **3** and a $\lambda_{max}(CH_3OH)$ of 274 nm for **2**]. Furthermore, this bathochromic shift in the UV spectrum is also indicative[11,17] that the thione group is adjacent to the pyrrole ring, i.e., at the 5-position of the tricyclic ring rather than the 7-position.

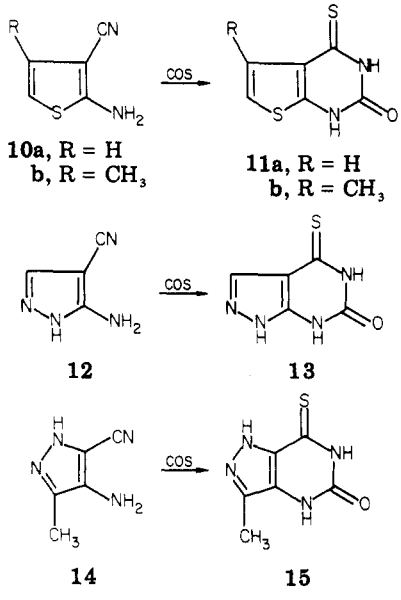
Although we assumed that this product was the "linear" tricyclic nucleoside **3**, there was a possibility that ring closure had taken place between the 5-cyano group and the 4-amino group (rather than the 6-amino group), which would yield a "triangular"-type tricyclic nucleoside containing a seven-membered ring. However, the annulation of **2** with carbonyl sulfide has been shown to yield a "linear" tricyclic nucleoside on the basis of the following chemical conversions: Treatment of **3** with methyl iodide under basic conditions furnished the 5-methylthio derivative **4**. That methylation had occurred on the exocyclic sulfur atom rather than a ring nitrogen was established by the appearance of a sharp 3-proton singlet at $\delta$ 2.18 in the $^1H$ NMR spectrum. Subsequent treatment of **4** with ammonium hydroxide at 130 °C provided nucleoside material which was subsequently established as being the desired tricyclic adenosine–isoguanosine analogue **6**. The $^1H$ NMR spectrum of **6** ($Me_2SO$-$d_6$) was compared and found to be similar to, but not identical with the $^1H$ NMR spectrum of the tricyclic adenosine–guanosine[12] analogue **8**. The signal for the anomeric proton (H-1′) of **6** was observed at $\delta$ 5.05 (compared to $\delta$ 5.10 for **8**) and H-2′ appeared at $\delta$ 6.23 (compared to $\delta$ 6.20 for **8**). However, in direct contrast to the $^1H$ NMR spectrum, the UV spectra of **6** was quite different from the UV spectra of the tricyclic adenosine–guanosine[12] analogue **8**. Oxidative hydrolysis of **3** provided the known[12] "linear" tricyclic nucleoside 4-amino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d*′]dipyrimidin-5,7-dione (**5**) which established the "linear" nature of the original ring-closed product **3**. Finally, dethiation of **4** with Raney nickel has provided a keto derivative (**7**) with an empirical formula identical with the adenosine–inosine nucleoside 4-amino-9-(β-D-ribofuranosyl)pyrrolo-[2,3-*d*:5,4-*d*′]dipyrimidin-5-one[12] (**9**); however, the spectral data ($^1H$ NMR, UV) for the dethiation product **7** is also significantly different from the spectral data obtained[12] for **9**. Therefore, on the basis of the above, the tricyclic nucleoside obtained from the carbonyl sulfide ring closure of **2** must possess the structure **3** with the thione group located in the 5-position of the tricyclic ring rather than the isomeric structure with the thione group in the 7-position.

Scheme I[a]



[a] R = 1-β-D-ribofuranosyl

Scheme II



**10a**, R = H
**b**, R = $CH_3$

**11a**, R = H
**b**, R = $CH_3$

**12** **13**

**14** **15**

In order to test the generality of this interesting reaction, we examined other *o*-aminonitriles. After several preliminary investigations, two different sets of reaction conditions were found which furnished high yields of the desired products. The starting materials and the products are shown in Scheme II. The products formed by both method A and method B had identical melting points and spectral data. Proof that cyclization had occurred was provided by the spectral data. First, the UV spectra of the products showed a significant bathochromic shift with respect to their corresponding starting materials. For example, compound **14** showed a maximum at $\lambda_{max}(CH_3OH)$ of 276 nm, while compound **15** showed a maximum at $\lambda_{max}(CH_3OH)$ of 344 nm. As stated previously, these large bathochromic shifts indicate[11,17] that the thione group is in the 4-position of the pyrimidine moiety of the heterocycle rather than in the 2-position of the pyrimidine moiety. The IR spectra of the products lacked an absorption band for a cyano group (region near 2200 $cm^{-1}$) but did show strong absorption bands in the 1700–1680

(11) Beaman, A. G. *J. Am. Chem. Soc.* **1954**, *76*, 5633.
(12) Chung, F-L.; Schram, K. H.; Panzica, R. P.; Earl, R. A.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem.* **1980**, *23*, 1158.

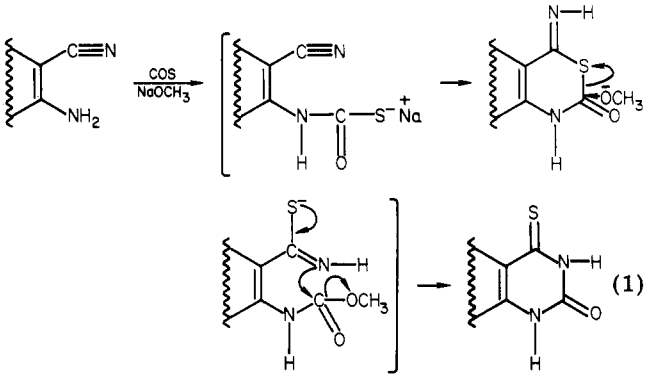
and 1150–1270 $cm^{-1}$ regions which were attributed to the newly formed keto and thio groups, respectively. In order to further substantiate the assignment of the C=S stretching band, we compared the IR spectrum of thieno[2,3-*d*]pyrimidin-2,4-dione[13] to that of thieno[2,3-*d*]-2-thioxopyrimidin-4-one.[14] As expected, the IR spectrum of thieno[2,3-*d*]pyrimidin-2,4-dione did not show a strong absorption band in the 1150–1270 $cm^{-1}$ region, while the IR spectrum of thieno[2,3-*d*]-2-thioxopyrimidin-4-one showed a strong absorption at 1270 $cm^{-1}$.

In order to further corroborate the structures as drawn for the products in Scheme II, we compared the UV and IR spectra of pyrazolo[3,4-*d*]-6-thioxopyrimidin-4-one[15] to those of compound **13**. As expected, the spectra were not identical; compound **13** showed a $\lambda_{max}(CH_3OH)$ of 324 nm, while the $\lambda_{max}(CH_3OH)$ of the isomeric compound was observed at 287 nm.

Even though the yields of the initial or preliminary reactions were high, reaction conditions were sought that would improve the yield even further. The cyclic *o*-aminonitrile[15] **12** was used for this study. It was found that the use of a few milligrams of 4-(dimethylamino)pyridine (DMAP), a well-known catalyst in acylation reactions,[16] not only improved the yield of compound **13** obtained by method A but also reduced the reaction time.

Compounds **13** and **15** are known and their spectra were identical with those previously reported.[15,17] To the best of our knowledge, compounds **11a** and **11b** have not been reported; however, the UV spectra of these compounds were very similar to those of their corresponding ribonucleosides[18] in methanol and in pH 1 buffer.

We propose that the mechanism of the ring-closure reaction with carbonyl sulfide is similar to that proposed[20] for reactions of *o*-aminonitriles with carbon disulfide. The mechanism would involve the initial formation of a monothiocarbamate salt, cyclization to a *m*-thiazine derivative through nucleophilic attack on the cyano group selectively, by a sulfur ion, followed by a ring-opening and a ring-closure sequence as illustrated by eq 1.




We believe that the relative ease and high yields obtained in these reactions will make carbonyl sulfide the reagent of choice in the synthesis of fused[21] pyrimidin-2-one-4-thione derivatives.

## Experimental Section

Proton magnetic resonance spectra were obtained in a JEOL C60H, a Varian A-60, or a Varian EM-390 spectrophotometer using dimethyl-$d_6$ sulfoxide as solvent and tetramethylsilane as an internal standard. The chemical shifts are recorded in $\delta$ units (parts per million) relative to the internal standard. Ultraviolet spectra were recorded on a Beckman Acta CIII or a Hewlett-Packard 8458 spectrophotometer. Infrared spectra were recorded on a Beckman IR10 or a Perkin-Elmer 281 spectrophotometer. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Mass spectra were obtained with the LKB 9000 S instrument and the Varian MAT 112S/SS100 C data system. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Az.

Thin-layer chromatography was run on glass plates coated (0.25 mm) with silica gel (SilicAR 7GF, Mallinckrodt). Silica gel suitable for column chromatography was purchased from J. T. Baker Chemical Co. All chromatographic separations were performed with glass columns dry-packed with silica gel under gravity flow unless otherwise stated.

**4-Amino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]-5-thioxodipyrimidin-7-one (3). Method 1.** 6-Aminotoyocamycin[7] (**2**; 500 mg, 1.63 mmol) was suspended in a solution of sodium hydroxide (300 mg, 7.5 mmol) in methanol (18 mL). An excess of carbonyl sulfide[22] (1.5 mL) (liquefied with a dry-ice condenser) was added to the above mixture at −40 °C. The reaction mixture was then sealed in a steel reaction vessel and heated at 180 °C for 7 h. The reaction vessel was then cooled to room temperature before the excess carbonyl sulfide was allowed to slowly evaporate. The reaction mixture was then allowed to stand at 5 °C for 10 h. The yellow solid which had formed was collected by filtration. This disodium salt was dissolved in water (30 mL) and the pH of the solution was adjusted to 6 with 2 N HCl to afford 400 mg of **3** (61.4%) after crystallization from aqueous DMF (water/DMF, 5:5, v/v): mp 270 °C dec; $[\alpha]^{27}_D$ −57.2 (*c* 1.00, $Me_2SO$); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 4.68 (q, 1, $H_2'$, $J_{2',1'}$ = 8.0 Hz, $J_{2',3'}$ = 5.0 Hz), 6.38 (d, 1, $H_1'$, $J_{1',2'}$ = 8.0 Hz), 7.77 (br s, 1, NH), 8.27 (s, 1, $H_2$), 9.68 (br s, NH), 12.48 (s, 1, NHCO).

Anal. Calcd for $C_{13}H_{14}N_6O_5S$: C, 42.62; H, 3.83; N, 22.95. Found: C, 42.46; H, 3.91; N, 22.78.

**Method 2.** 6-Aminotoyocamycin (**2**; 1.0 g, 3.27 mmol) was suspended in pyridine (30 mL) and an excess of carbonyl sulfide (3 mL) was condensed (dry-ice condenser) into the suspension at −40 °C. The mixture was heated in a sealed steel reaction vessel at 95 °C. After 5 days, the volatile components were allowed to escape at 0 °C. The solvent was removed in vacuo and the residue was coevaporated with ethanol (2 × 20 mL). The residue was crystallized from aqueous DMF (water/DMF, 5:5, v/v) to afford 1.10 g (95%) of the product, which was shown to be identical with that obtained by method 1, using $^1H$ NMR and UV spectroscopy as well as TLC.

**4-Amino-5-(methylthio)-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one (4).** Concentrated ammonium hydroxide (28%, 0.4 mL) was added to a suspension of 4-amino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]-5-thioxodipyrimidin-7-one (**3**; 150 mg, 0.41 mmol) in water (25 mL). The reaction mixture was stirred at room temperature while methyl iodide (0.6 mL, 9.65 mmol) was added dropwise to the solution. After 3 h, a second portion of methyl iodide (0.3 mL, 4.9 mmol) was added to the solution. The reaction mixture was stirred for another 4 h and the solvent was then removed in vacuo. The residual solid was triturated with acetone (15 mL) and then

(13) Chacke, A. A., The University of North Carolina Dissertation, 1965.
(14) Unpublished compound synthesized in our laboratories.
(15) Robins, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 784.
(16) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(17) Long, R. A.; Gerster, J. F.; Townsend, L. B. *J. Heterocycl. Chem.* **1970**, *7*, 863.
(18) Patil, V. D.; Wise, D. S.; Townsend, L. B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1853.
(19) Gewald, K. *Chem. Ber.* **1965**, *98*, 3571.
(20) Taylor, E. C.; McKillop, A.; Warrener, R. N. *Tetrahedron* **1967**, *23*, 891.
(21) We tried two alicyclic compounds, 3-aminocrotonitrile and 3-aminopropionitrile, and both compounds failed to react with carbonyl sulfide under the reaction conditions used for this study. In this respect, it has been reported[6] that carbon disulfide will not effect a ring closure of alicyclic *o*-aminonitriles.
(22) Carbonyl sulfide was purchased from Matheson.
(23) Suzuki, K.; Kumashira, I. U.S. Patent 3450693, 1969; *Chem. Abst.* **1969**, *71*, 81698z.

Table I. Reaction Conditions

| starting material | ref | method | amnt of compd, mmol | vol of base, mL | T, °C | reacn time, h | product | ref | % yield | mp, °C | C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **10a** | 19 | A | 8.07 | 9 | 95 | 62 | **11a** | 18 | 92 | 300 dec | 39.12[d] (39.08)[e] | 2.19 (2.38) | 15.20 (15.11) |
| | | B | 4.03 | 16.2 | reflux | 24 | | | 95 | 300 dec | | | |
| **10b** | 13 | A | 0.91 | 9 | 95 | 62 | **11b** | 18 | 92 | 300 dec | 42.41 (42.67) | 3.05 (3.07) | 14.13 (14.15) |
| | | B | 7.25 | 30 | reflux | 23 | | | 96 | 300 dec | | | |
| **12** | 15 | A | 1.85 | 9 | 95 | 62 | **13** | 15 | 74 | >400 | 35.71 | 2.40 | 33.31 |
| | | A[a] | 1.85 | 9 | 95 | 37 | | | quant.[b] | >400 | (35.55) | (2.59) | (33.46) |
| | | B | 1.85 | 9.2 | reflux | 26 | | | 81 | >400 | | | |
| **14** | 15 | A | 0.41 | 9 | 95 | 62 | **15** | 17 | 62 | 347-8 dec | 39.55 (39.33) | 3.32 (3.39) | 30.75 (30.97) |
| | | A[c] | 0.41 | 4 | 95 | 62 | | | 85 | 346-7 dec | | | |
| | | B | 0.41 | 1.7 | reflux | 25 | | | 51 | | | | |

[a] DMAP (10 mg) was added as catalyst. [b] Quantitative yield. [c] DMAP (2 mg) was added as catalyst. [d] Calculated. [e] (Found).

Table II

| no. | name of compound | $\lambda_{max}$(pH 1) | $\lambda_{max}$(methanol) | $\lambda_{max}$(pH 11) |
|---|---|---|---|---|
| 3 | 4-amino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]-5-thioxodipyrimidin-7-one | 367 (13.9)<br>355 (14.8)<br>301 (8.1) | 374 (14.6)<br>361 (sh) (12.4)<br>310 (11.7)<br>252 (sh) (11.0) | 370 (13.2)<br>357 (sh) (12.1)<br>307 (11.3)<br>251 (16.5) |
| 4 | 4-amino-5-methylthio-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one | 357 (5.7)<br>284 (11.8)<br>257 (16.7) | 334.5 (9.7)<br>290 (8.7)<br>250 (19.8) | 334 (13.0)<br>296 (11.4)<br>249 (18.8) |
| 6 | 4,5-diamino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one | 311 (sh) (11.5)<br>287 (13.9) | 294.5 (17.4)<br>228 (26.0) | 307 (16.7)<br>229 (27.3) |
| 7 | 4-amino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one | 335 (4.7)<br>286 (9.4)<br>250 (19.7) | 326 (3.7)<br>278 (sh) (8.7)<br>256 (18.0) | 323 (8.4)<br>287 (11.0)<br>243 (sh) (10.4) |
| 11a | thieno[2,3-*d*]-4-thioxopyrimidin-2-one | 349 (9.9)<br>297 (7.6)<br>278 (7.3)<br>249 (13.7) | 345 (10.3)<br>300 (inf, 5.5)<br>278 (8.3)<br>249 (12.3)<br>220 (inf, 8.6) | 275 (11.1)<br>246 (10.8) |
| 11b | 5-methylthieno[2,3-*d*]-4-thioxopyrimidin-2-one | 346 (13.9)<br>295 (sh, 6.8)<br>276 (8.1)<br>244 (14.7)<br>226 (12.4) | 348 (13.4)<br>337 (13.6)<br>278 (8.5)<br>244 (12.0)<br>236 (sh, 11.3)<br>226 (13.0) | 355 (13.2)<br>279 (14.5)<br>242 (16.6) |
| 13 | pyrazolo[3,4-*d*]-4-thioxopyrimidin-6-one | 256 (7.0)<br>324 (13.5) | 255 (6.2)<br>326 (12.5) | 230 (15.6)<br>258 (4.3)<br>330 (13.1) |
| 15 | 3-methylpyrazolo[4,3-*d*]-7-thioxopyrimidin-5-one | 206 (17.5)<br>262 (8.5)<br>314 (9.2)<br>346 (13.6) | 208 (12.9)<br>264 (7.8)<br>344 (14.8) | 231 (20.8)<br>256 (12.2)<br>294 (12.4)<br>377 (12.7) |

crystallized from water (20 mL) to furnish 100 mg (63.4%) of *4*, mp 231 °C. A sample for analysis was obtained by recrystallization from water: mp 231 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 2.80 (s, 3, $SCH_3$), 5.14 (t, 1, $H_2'$, $J_{2',1'}$ = 6.0 Hz, $J_{2',3'}$ = 6.0 Hz), 6.38 (d, 1, $H_1'$, $J_{1',2'}$ = 6.0 Hz), 7.30 (br s, 2, $NH_2$), 8.30 (s, 1, $H_2$).

Anal. Calcd for $C_{14}H_{16}N_6O_5S\cdot0.5H_2O$ (verified by $^1$H NMR data): C, 43.19; H, 4.37; N, 21.59. Found: C, 42.96; H, 4.36; N, 21.50.

**4-Amino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-5,7-dione (5).** 4-Amino-9-(β-D-ribofuranosyl)pyrrolo-[2,3-*d*:5,4-*d'*]-5-thioxodipyrimidin-7-one (**3**; 150 mg, 0.41 mmol) was dissolved in aqueous ammonium hydroxide (10 mL of 28.7% solution). Hydrogen peroxide (2 mL of 30% solution) was added dropwise to the solution with stirring at room temperature. After 1 h, the reaction mixture was evaporated to dryness in vacuo to afford a white solid. The solid was crystallized from 50% aqueous ethanol (300 mL, v/v) to afford 80 mg of **5** (56.1%), which was found to be identical[12] by a comparison of UV, TLC, and $^1$H NMR data with the product obtained by a ring closure of 6-aminosangivamycin[7] with diethyl carbonate.

**4,5-Diamino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one (6).** The nucleoside **4** (300 mg, 0.79 mmol) was suspended in concentrated ammonium hydroxide (28%, 15 mL). The reaction mixture was heated at 130 °C for 14 h in a sealed steel vessel. The solvent was removed in vacuo and the residual solid was crystallized from water (55 mL) to give 200 mg (71.3%) of **6**, mp 310 °C dec. A small quantity (50 mg) of the product was recrystallized from water (15 mL) to furnish an analytical sample: $[\alpha]^{27}_D$ −40.0 (*c* 1.00, $Me_2SO$); $^1$H NMR ($Me_2SO$-$d_6$) δ 5.05 (t, 1, $H_2'$, $J_{2',1'}$ = 6.0 Hz, $J_{2',3'}$ = 6.0 Hz), 6.23 (d, 1, $H_1'$, $J_{1',2'}$ = 6.0 Hz), 6.51 (br s, 2, $NH_2$), 6.90 (br s, 2, $NH_2$), 8.20 (s, 1, $H_2$).

Anal. Calcd for $C_{13}H_{15}N_7O_5\cdot1.5H_2O$ (verified by $^1$H NMR data): C, 41.49; H, 4.79; N, 26.10. Found: C, 41.29; H, 4.63; N, 25.97.

**4-Amino-9-(β-D-ribofuranosyl)pyrrolo[2,3-*d*:5,4-*d'*]dipyrimidin-7-one (7).** The nucleoside **4** (100 mg, 0.26 mmol) was suspended in water (20 mL), Raney nickel (700 mg, wet weight) was added to the suspension, and the reaction mixture was heated at reflux temperature. After 2 h, the suspension was filtered and

the filter cake was washed with hot dimethylformamide (4 × 10 mL). The filtrate and washings were combined and evaporated to dryness in vacuo. The residue was crystallized from aqueous DMF (water/DMF, 4:6, v/v) to yield 60 mg (69.2%) of 7: mp 250 °C dec; $^1$H NMR ($Me_2SO$-$d_6$) δ 5.10 (t, 1, $H_{2'}$, $J_{2',1'}$ = 6.0 Hz, $J_{2',3'}$ = 6.0 Hz), 6.25 (d, 1, $H_{1'}$, $J_{1',2'}$ = 6.0 Hz), 7.22 (br s, 2, $NH_2$), 8.22 (s, 1, $H_2$ or $H_5$), 8.91 (s, 1, $H_5$ or $H_2$).

Anal. Calcd for $C_{13}H_{14}N_6O_5 \cdot 1.5H_2O$ (verified by $^1$H NMR): C, 43.21; H, 4.71; N, 23.27. Found: C, 43.58; H, 4.47; N, 22.97.

**General Procedure.**[24] **Method A.** The *o*-aminonitrile was dissolved in pyridine, and 1 mL of liquefied carbonyl sulfide was added to the solution at −70 °C. The reaction mixture was then sealed in a steel vessel and heated for a suitable period of time. The reaction vessel was cooled to room temperature and the excess carbonyl sulfide was allowed to slowly evaporate. The reaction mixture was coevaporated several times with 2-propanol to remove the pyridine. The remaining solid was dissolved in a 1 N NaOH solution, activated charcoal was added, and the resulting mixture was filtered through a Celite bed. The pH of the filtrate was adjusted to 6.0 with a 1 N HCl solution and the solid that separated was collected by filtration. Analytical samples were obtained by one additional reprecipitation.

**General Procedure.**[24] **Method B.** Carbonyl sulfide was slowly bubbled through a 1 N sodium ethoxide solution for 10 min. The appropriate *o*-aminonitrile was added to this solution and the reaction mixture was heated to reflux temperature. After a suitable period of time, any solid that had formed was dissolved in a small amount of water and the volume of the reaction mixture was concentrated to ca. 4 mL. Activated charcoal was added, the mixture was filtered through a Celite bed, and the pH of the filtrate was adjusted to 6.0 with a 1 N HCl solution. One additional reprecipitation from a basic solution afforded analytical samples of the respective products.

(24) See Tables I and II for the exact quantities used and the results obtained.

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# Metalation of Diazepam and Use of the Resulting Carbanion Intermediate in a New Synthesis of 3-Substituted Diazepam Derivatives[1a,c]

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Treatment of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (diazepam, 1) with 1 equiv of LDA in THF–hexane produces an equilibrium mixture consisting of equal amounts of 1 and its monolithio salt 2 as shown by $^1$H NMR and $D_2O$ quenching. With 2 equiv of LDA, 2 is formed in sufficient concentration to react with alkyl halides, aldehydes, ketones, and esters to give 3-substituted derivatives of 1. $^1$H NMR studies of THF-$d_8$ solutions prepared from 1 and 2–3 equiv of LDA indicate partial twofold metalation of 1 in which both hydrogens at $C_3$ are removed to form dilithio derivative 10. The present metalations provide a convenient new method for direct modification of diazepam, without requiring the more cumbersome ring closure procedures traditionally employed for such syntheses.

As part of a program directed toward the preparation of new anticonvulsant agents, we sought a direct, general method for the synthesis of various 3-substituted derivatives of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (diazepam, 1).[2] Current syntheses of such compounds usually involve extensions of methods employed for the preparation of 1 such as condensations of 2-amino-5-chlorobenzophenone with α-substituted α-amino acids (esters)[3] or α-substituted α-haloacyl halides.[3] In these cases, the original α substituent of the acylating agent appears at the 3-position of the resulting diazepinone. Certain 3-substituted 1,4-benzodiazepin-2-ones can also be prepared from 3-hydroxy-1,4-benzodiazepin-2-ones,[4] which are available through reaction of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxides with acetic anhydride followed by hydrolysis,[5] by base-catalyzed cyclization of the syn oximes of 2-(haloacetamido)-5-chlorobenzophenones,[6] and by oxygenation of 1 and related compounds in the presence of potassium *tert*-butoxide.[7]

The present study was based on the concept that 3-substituted diazepams might be available directly from 1 through metalated derivative 2. Subsequent reactions of 2 with electrophilic reagents could then lead to introduction of 3-substituents without requiring construction of the diazepinone ring from acylic precursors each time a dif-

(1) (a) Supported by Grant No. NS 10197 from the National Institute of Neurological and Communicative Disorders and Stroke. (b) Taken in part from the MS thesis of B.E.R., Virginia Polytechnic Institute and State University, Aug 1979. (c) Presented in part at the 181st National Meeting of the American Chemical Society Atlanta GA, Mar 1981; ORGN 15.

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