

## Heterocyclic Compounds. VII Synthesis of Thiadiazasteroid Analogs (1)

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The synthesis of a number of  $\beta$ -northiadiaza steroid analogs has been described. Suitable *o*-aminonitriles were acylated with  $\gamma$ -chlorobutyryl chloride. These amidonitriles were cyclized to substituted  $\gamma$ -lactams and subsequently to the tetracyclic products. To functionalize the "17-position" in these steroids, the intermediate  $\gamma$ -lactams were converted to arylidene derivatives before cyclization to the tetracyclic derivatives.

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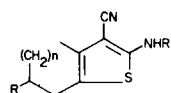
During the last few years considerable attention has been focussed on the synthesis of heterocyclic steroids because of their potential therapeutic importance (2,3). Recently Taylor and Shvo (4) have described the preparation of a heterocyclic steroid from 1-cyano-2-aminonaphthalene. We wish to report here the synthesis of some hitherto unknown thiadiazasteroid analogs.

Cyclohexanone on treatment with malononitrile, diethylamine and elemental sulfur was smoothly converted into 2-amino-3-cyano-4,5-tetramethylenethiophene (1) (5). Acylation of 1 with  $\gamma$ -chlorobutyryl chloride gave the amide (2) which on treatment with sodium methoxide or sodium hydride gave the  $\gamma$ -lactam (9); compound 1 could also be converted to 9 in one step by treating it with  $\gamma$ -chlorobutyryl chloride and triethylamine according to the procedure described by Bose, Manhas and Ghosh-Mazumdar (6). Warming an ethanolic solution of 9 saturated with dry hydrogen chloride gave the thiadiazasteroid compound (13) in almost quantitative yield.

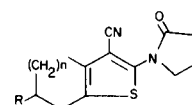
Using essentially the same reaction conditions as described above, cycloheptanone was converted to the thiophene derivative (7) which was acylated to 8. This cyanoamide (8) was then transformed to the corresponding  $\gamma$ -lactam (12) and subsequently cyclized to afford the A-homo- $\beta$ -northiadiazasteroid analog (14).

It was also possible to introduce a substituent at C<sub>3</sub> in 13. 4-Benzoyloxycyclohexanone was prepared from 1,4-dihydroxycyclohexane by the method of Jones and Sondheimer (7). The 4-benzoyloxycyclohexanone was converted to aminonitrile (5) which then afforded the 3-benzoyloxy heterosteroid (16) by a series of reactions outlined above. In a similar fashion 4-methylcyclohexanone could be converted to the corresponding 3-methyl

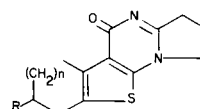
heterocyclic steroid (15) through the sequence 3 → 4 → 10 → 15.



1. R = R' = H, n = 2
2. R = H, R' = CO(CH<sub>2</sub>)<sub>3</sub>Cl, n = 2
3. R = CH<sub>3</sub>, R' = H, n = 2
4. R = CH<sub>3</sub>, R' = CO(CH<sub>2</sub>)<sub>3</sub>Cl, n = 2
5. R = COPh, R' = H, n = 2
6. R = OCOPh, R' = CO(CH<sub>2</sub>)<sub>3</sub>Cl, n = 2
7. R = R' = H, n = 3
8. R = H, R' = CO(CH<sub>2</sub>)<sub>3</sub>Cl, n = 3



9. R = H, n = 2
10. R = CH<sub>3</sub>, n = 2
11. R = OCOPh, n = 2
12. R = H, n = 3



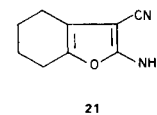
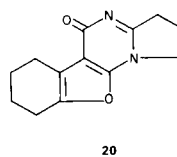
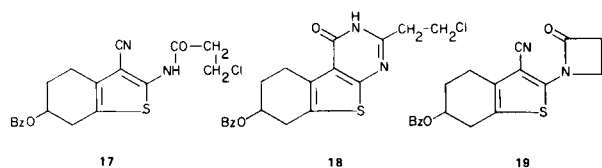
13. R = H, n = 2
14. R = H, n = 3
15. R = CH<sub>3</sub>, n = 2
16. R = OCOPh, n = 2

Acylation of 5 with  $\beta$ -chloropropionyl chloride gave 17. Attempts to cyclize this compound to 18 in absolute alcohol saturated with dry hydrogen chloride were not successful. Furthermore, treatment of 17 to yield the  $\beta$ -lactam (19) by using such basic reagents as sodium methoxide, sodium-liquid ammonia (8) or sodium hydride-dimethylsulfoxide (9) also did not succeed.

Table I

| Compound No. (a) | M.p. °C | Yield % | Formula   | C                    | Analysis H     | N                |
|------------------|---------|---------|---|----------------------|----------------|------------------|
| 1                | 165     | 80      | C <sub>9</sub> H <sub>10</sub> N <sub>2</sub> S                   |                      |                |                  |
| 2                | 186-187 | 60      | C <sub>13</sub> H <sub>15</sub> ClN <sub>2</sub> OS               | 55.10 (b)<br>(55.22) | 5.30<br>(5.66) | 9.68<br>(9.91)   |
| 3                | 196     | 70      | C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> S                  | 62.41<br>(62.50)     | 6.20<br>(6.25) | 14.40<br>(14.38) |
| 4                | 165-166 | 65      | C <sub>14</sub> H <sub>17</sub> ClN <sub>2</sub> OS               | 56.64<br>(56.66)     | 5.68<br>(5.70) | 9.60<br>(9.44)   |
| 5                | 151-152 | 82      | C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> S   | 64.48<br>(64.42)     | 4.70<br>(4.70) | 9.30<br>(9.39)   |
| 6                | 182-183 | 65      | C <sub>20</sub> H <sub>14</sub> ClN <sub>2</sub> O <sub>3</sub> S | 59.10<br>(59.62)     | 4.65<br>(4.72) | 7.41<br>(6.95)   |
| 7                | 198-200 | 70      | C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> S                  | 62.39<br>(62.50)     | 6.42<br>(6.25) | 14.50<br>(14.58) |
| 8                | 163-165 | 60      | C <sub>14</sub> H <sub>17</sub> ClN <sub>2</sub> OS               |                      |                |                  |
| 9                | 202-204 | 38      | C <sub>13</sub> H <sub>14</sub> N <sub>2</sub> OS                 | 63.54<br>(63.40)     | 5.68<br>(5.73) | 11.43<br>(11.38) |
| 10               | 210-211 | 50      | C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> OS                 | 64.50<br>(64.60)     | 6.30<br>(6.20) | 10.90<br>(10.76) |
| 11               | 145-146 | 80      | C <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S   | 65.80<br>(65.57)     | 4.90<br>(4.95) | 7.86<br>(7.65)   |
| 12               | 165-166 | 12      | C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> OS                 | 64.57<br>(64.60)     | 6.26<br>6.26   | 10.61<br>10.61   |
| 13               | 260-261 | 40      | C <sub>13</sub> H <sub>14</sub> N <sub>2</sub> OS                 | 63.41<br>(63.40)     | 5.69<br>(5.73) | 11.38<br>(11.38) |
| 14               | 250-252 | 80      | C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> OS                 | 64.40<br>(64.60)     | 6.12<br>(6.20) | 10.61<br>(10.76) |
| 15               | 260-261 | 65      | C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> OS                 | 64.40<br>(64.60)     | 6.32<br>(6.20) | 10.66<br>(10.76) |
| 16               | 255-256 | 27      | C <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S   | 65.39<br>(65.57)     | 4.97<br>(4.95) | 7.40<br>(7.65)   |
| 23               | 217-218 | 80      | C <sub>21</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> S   | 68.92<br>(69.92)     | 5.51<br>(5.53) | 7.60<br>(7.69)   |
| 24               | 218-220 | 85      | C <sub>22</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> S   | 69.75<br>(69.83)     | 5.53<br>(5.86) | 7.69<br>(7.40)   |
| 25               | 230-233 | 60      | C <sub>21</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> S   | 69.32<br>(69.22)     | 5.53<br>(5.53) | 7.69<br>(7.69)   |
| 26               | 261-262 | 55      | C <sub>22</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> S   | 69.70<br>(69.83)     | 5.92<br>(5.86) | 7.49<br>(7.40)   |

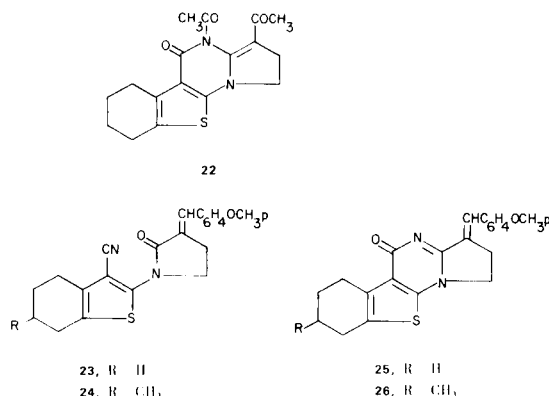
(a) All the compounds gave satisfactory ir, nmr, and mass spectra. (b) Values in parentheses refer to the calculated percentages.



Efforts were then directed towards the synthesis of **20**, the oxygen analog of **13**. 2-Amino-3-cyano-4,5-tetramethylenefuran (**21**) was prepared by a known method (10). However, when **21** was treated with  $\gamma$ -chlorobutyryl chloride a product was obtained which could neither be induced to crystallize nor could it be purified by column chromatography.

Attempts to prepare the diacetyl derivative (**22**) by treating **13** with acetic anhydride using Taylor and Shvo's reaction conditions (4) were unsuccessful and the starting material was recovered in each case. Allylic oxidation of the D-ring in **13** using *t*-butyl chromate, sulfur trioxide-pyridine complex in dimethylsulfoxide or Jones reagent were also unsuccessful.

To functionalize the 17-position in **13** and **15** the  $\gamma$ -lactams **9** and **10** were alkylated using aldol condensation reaction. The lactams **9** and **10** were separately treated with sodium hydride in THF and then allowed to react with *p*-methoxybenzaldehyde. The arylidene compounds **23** and **24** were obtained in about 90% yield (11). The cyclization of **23** and **24** under acidic conditions led to the formation of **25** and **26**, respectively.



#### Acknowledgment.

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#### EXPERIMENTAL

Melting points were determined in open capillary tubes using "Mel-Temp" apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer infracord. Nmr spectra were recorded on a Varian A-60A spectrometer operating at 60 MHz using trimethylsilane as an internal standard with chemical shifts expressed in ppm downfield from TMS. Mass spectra were obtained with a Perkin-Elmer RMU-7 mass spectrometer. Elemental analyses were performed by A. Bernhardt, Max-Planck Institute,

Mulheim, West Germany and Central Drugs Research Institute, Lucknow, India.

#### 2-Amino-3-cyano-4,5-tetramethylenethiophene (**1**).

This compound was prepared by the method of Gewald, Schinke, and Bottcher (5).

Aminonitriles **3**, **5** and **7** were similarly prepared from the corresponding ketones. The analytical data are given in Table I.

#### 2-*N*-(4'-Chlorobutyryl)-3-cyano-4,5-tetramethylenethiophene (**2**).

4-Chlorobutyryl chloride (14.1 g., 0.1 mole) in dry methylene chloride (100 ml.) was added dropwise to a stirred solution of the 2-amino-3-cyano-4,5-tetramethylenethiophene (**1**, 17.8 g., 0.1 mole), triethylamine (10.1 g., 0.1 mole) in methylene chloride (200 ml.). After stirring overnight at room temperature the reaction product was washed with water and dried (magnesium sulfate). Removal of the solvent under reduced pressure gave 25 g. (80%) of the amide **2**, m.p. 186° (methylene chloride-*n*-hexane).

The amides **4**, **6** and **8** were similarly prepared by the acylation of the corresponding amino nitriles with 4-chlorobutyryl chloride. The analytical data are given in Table I.

#### 2-(*N*-Pyrrolidonyl)-3-cyano-4,5-tetramethylenethiophene (**9**).

To a suspension of sodium hydride (4.8 g., 0.1 mole 50%) in dry benzene (200 ml.) was added gradually the chloro compound **2** (28.5 g., 0.1 mole). After addition, the mixture was warmed at 50-60° for 3 hours and then refluxed for 12 hours. Benzene was removed under reduced pressure and the residue was dissolved in methylene chloride. The organic layer was washed with water, and dried (magnesium sulfate). Evaporation of the solvent gave the  $\gamma$ -lactam **9**, which was crystallized from methylene chloride-hexane mixture, m.p. 204° (16.7 g., 68%).

The compounds **10**, **11** and **12** were similarly prepared from the corresponding chloro compounds. The analytical data are given in Table I.

#### 2-[*N*-(3'-*p*-Methoxybenzylidene)pyrrolidonyl]-3-cyano-4,5-tetramethylenethiophene (**23**).

To a cooled oily suspension of sodium hydride (7.2 g., 0.15 mole, 50%) in tetrahydrofuran (300 ml.) was added dropwise with constant stirring over a period of one hour a solution of **9** (24.6 g., 0.1 mole), *p*-anisaldehyde (13.6 g., 0.1 mole) in tetrahydrofuran (160 ml.). The stirring was continued for an additional 12 hours at room temperature and the THF solvent was evaporated and the residue dissolved in methylene chloride. This solution was washed with water and dried (magnesium sulfate). Removal of the solvent gave 32 g. (90%) of **23**, m.p. 175-176° (methylene chloride).

This compound **24** was similarly prepared from compound **10**. The analytical data are given in Table I.

#### 2,3,6,7,8,9-Hexahydro[1]benzothieno[2',3',4,5]pyrimido[3,2-*a*]pyrrole-10[1*H*]one (**13**).

Hydrogen chloride gas was passed through a solution containing 24.6 g. of the 2-(*N*-pyrrolidonyl)-3-cyano-4,5-tetramethylenethiophene in 200 ml. of alcohol until it was saturated. The reaction was then heated on a steam bath for 1 hour and allowed to stand in the refrigerator overnight. The crude product which separated was filtered and recrystallized from DMF, m.p. 260° (14.7 g., 60%).

The compounds **14**, **15**, **16**, **25** and **26** were similarly prepared by the cyclization of the corresponding amides. The analytical data are given in Table I.

## REFERENCES AND NOTES

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