

Pyrazolo[3,4-*e*][1,4]thiazepines: Synthesis and Structure Proof

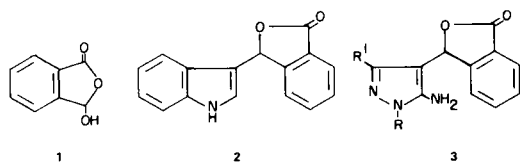
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Pyrazolo[3,4-*e*][1,4]thiazepine derivatives were obtained by reacting 5-amino-1,3-dimethylpyrazole with arylaldehydes or ketones and mercaptoacetic acid. The structure proof of these derivatives was carried out by identifying the benzylpyrazole products obtained by desulfurization and subsequent hydrolysis, and by comparison of the spectral data of a series of analogous pyrazolothiazepines. Treating the pyrazolothiazepines with sodium hydride and methyl iodide in dimethylformamide or dimethylsulfoxide resulted in a ring contraction with the elimination of sulfur, to yield the pyrazolopyridones in addition to the *N*-methylpyrazolothiazepines.

Indole is known to react with *o*-phthalaldehydic acid **1** to form 3-phthalidylindole **2** (1). In a previous communication (2), we reported on a similar reaction product **3** obtained by the condensation of **1** with 5-aminopyrazoles.



We also reported that **3**, like its indole counterpart **2**, underwent hydrogenolysis of the lactone ring to form the corresponding amino acid (**2**). Compounds like **2** and **3** are expected to be highly reactive species toward nucleophilic reagents. When a solution of **4** in toluene was heated

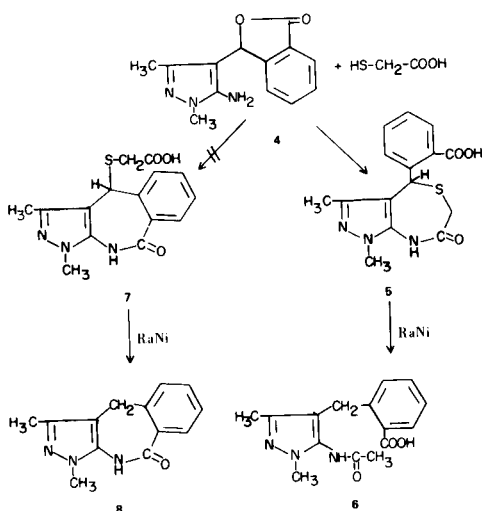
at reflux with an equimolar quantity of mercaptoacetic acid, the pyrazolothiazepine derivative **5** was obtained in a high yield (Scheme I).

We could envision the formation of either **5** or **7**, depending on whether the lactam was formed from the carboxyl group of mercaptoacetic acid as in **5** or from the opening of the lactone ring of **4** as in **7**. The spectral data obtained (ir, nmr) could not distinguish between **5** and **7**.

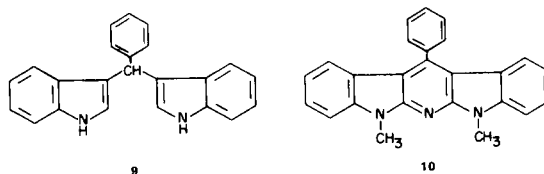
Treatment of this product with Raney nickel gave rise to **6** easily discernible from the alternative **8** by spectral means (ir, nmr) and by direct comparison with an authentic sample of **8** prepared earlier by us in an unequivocal procedure (2). Based on these data, structure **5** rather than **7** was assigned to the product obtained from the reaction of **4** with mercaptoacetic acid.

Since 5-aminopyrazoles and indoles form similar phthalidyl derivatives, **3** and **2**, it can be assumed that these reactions involve a common mechanism. In the case of indoles, it has been proposed (1) that this reaction proceeds by a nucleophilic attack of the indole on the aldehydic carbon in the open ring *o*-formylbenzoic form of **1**, followed by lactonization. Based on this premise, a study was initiated to examine the reaction of 5-aminopyrazoles with other aromatic aldehydes.

The reaction of indole with benzaldehyde gave the bis-indolylmethane **9** in 20% yield as the only isolable

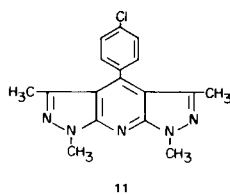


Scheme I

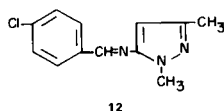


product (1). On the other hand, 2-aminoindoles, which might be considered more analogous to 5-aminopyrazoles, gave rise to the pyridine derivative **10** (3,4).

*p*-Chlorobenzaldehyde and 5-amino-1,3-dimethylpyrazole were heated at reflux in toluene without the aid of a catalyst. The theoretical amount of water was collected in two hours. By thin layer chromatography, the reaction product was shown to be a mixture unlikely to be resolved by column chromatography. Distillation of this mixture gave **11**, identified by its ir and nmr spectral data, as the only isolable product.



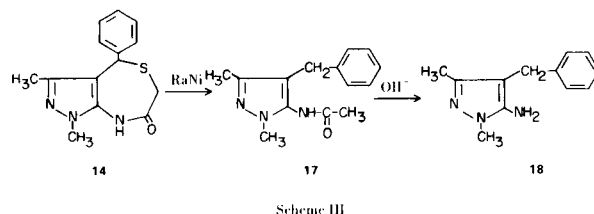
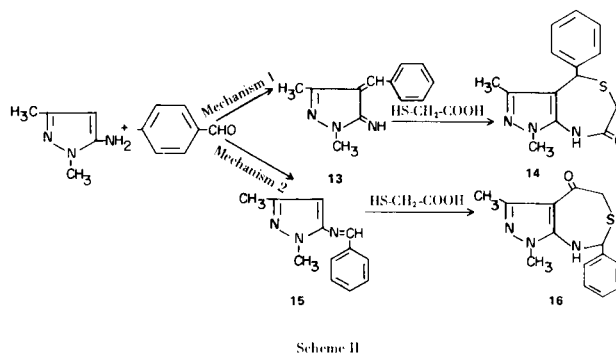
The formation of **11** suggested that the initial reaction proceeded by a condensation at the C-4 position of the pyrazole ring rather than through the formation of Schiff base **12**.



Since interesting biological activities are associated with thiazepines (5), we decided to investigate their synthesis from 5-amino-1,3-dimethylpyrazole, substituted benzaldehydes and acetophenones, and mercaptoacetic acid. After the theoretical amount of water was eliminated from the reaction of 5-amino-1,3-dimethylpyrazole and benzaldehyde, an equimolar amount of mercaptoacetic acid was added and the mixture heated at reflux in toluene. In 18 hours another mole of water was collected, the reaction mixture was worked up, and a good yield (81%) of a pyrazolothiazepine derivative was obtained.

The pyrazolothiazepine product could be postulated as **14** or **16**, depending on the intermediate formed (Scheme II). This intermediate, shown previously to be a complex mixture, could not be characterized as **13**, although we had shown that *o*-phthalaldehydic acid formed the 4-phthalidyl derivatives **3** (2) with 5-aminopyrazoles. It could not be assumed that other arylaldehydes and arylketones react in a similar fashion (Mechanism 1) (Scheme II). If indeed a Schiff base was formed as in **15** (6) (Mechanism 2) (Scheme II), it also was capable of reacting with mercaptoacetic acid (7).

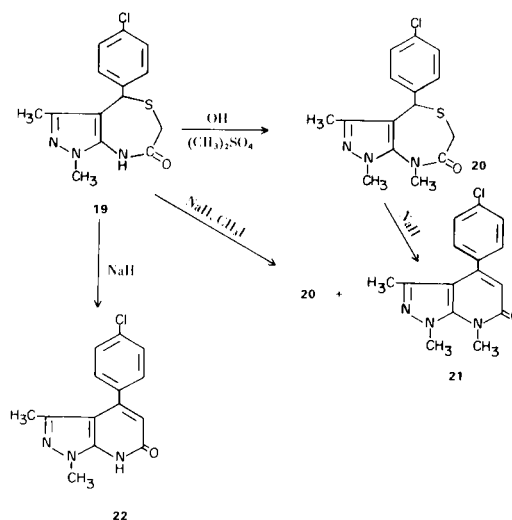
Concerning the structure proof of the pyrazolothiazepine product, we envisioned the decarboxylation of **5**, whose structure had been established, to provide **14**. Unable to accomplish this, the pyrazolothiazepine **14** was subjected to desulfurization by the aid of Raney nickel,



followed by hydrolysis (Scheme III). The product obtained was characterized to be **18** by spectral analysis (ir, nmr), indicating the structure of the pyrazolothiazepine to be **14**, and not **16**.

The reaction was found to be general in nature, being applicable to all aromatic aldehydes and ketones used by us. However, since the intermediate of the reaction could not be purified, we could not eliminate the possibility that a Schiff base **15** was formed, which in turn rearranged to **13** in the presence of mercaptoacetic acid to eventually yield **14** rather than **16**. Table I lists the examples of products obtained from substituted benzaldehydes and acetophenones. The reaction conditions were kept identical throughout and no catalysts were used.

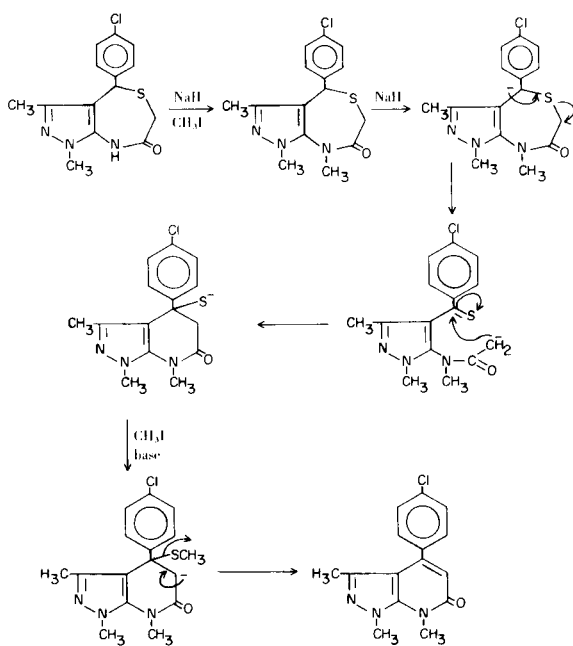
Structure proof through desulfurization was carried out



with only two members of this series (**5**, **14**). Spectral analyses (nmr, ir) were carried out on all the pyrazolothiazepines that were synthesized.

Table II gives the chemical shifts in ppm ( $\delta$ ) of the C-CH<sub>3</sub>, N-CH<sub>3</sub>, S-CH<sub>2</sub>-, Ar-CH- and -NH- protons. The chemical shifts, being sufficiently close, suggests all members belong to the same series. The chemical shift of the Ar-CH- proton in **5** is significantly different than those in the other related compounds. This difference can be explained by a substituent effect and evidence for this effect was obtained by comparison with substituted toluenes (**8**).

Another interesting aspect of this investigation was uncovered in the alkylation of the pyrazolothiazepines. By using alkali and dimethylsulfate, the expected *N*-methylpyrazolothiazepine derivative **20** was obtained. When the alkylating reagents were changed to sodium hydride and methyl iodide in dimethylformamide or dimethylsulfoxide, a ring contraction occurred with the elimination of sulfur to yield the pyrazolopyridone **21** in addition to **20** (Scheme IV). The yield of **21** could be controlled by the amount of sodium hydride used and the temperature of the reaction. In this regard, **22** and **21** were the only products formed when **19** and **20**, respectively, were treated with sodium hydride in dimethylformamide or dimethylsulfoxide (Scheme IV). A possible mechanism for this ring contraction is proposed in Scheme V, a precedent of which is reported in the literature concerning carbanions formed from benzylsulfides (9).



Scheme V

## EXPERIMENTAL

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin Elmer Model 521 spectrophotometer. Absorption bands are reported in reciprocal centimeters ( $\text{cm}^{-1}$ ). Proton magnetic resonance spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane (TMS) as the internal standard. The chemical shifts are reported in parts per million ( $\delta$ ). Elemental analyses were performed by Abbott Laboratories, North Chicago, Illinois. All solvents were of reagent and analytical grade.

4-(*o*-Carboxyphenyl)-1,3-dimethyl-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-one (**5**).

A mixture of 5-amino-1,3-dimethyl-4-phthalidylpyrazole (24.3 g., 0.1 mole) and mercaptoacetic acid (10.0 g., 0.11 mole) in 250 ml. of toluene was heated under reflux overnight using a water separator. The toluene was decanted, the residue treated with hot 95% ethanol and filtered. The solid material obtained (9 g.) was crystallized from DMF and water to afford **5** in a yield of 7.2 g., m.p. 259-261°; ir (nujol):  $\gamma$  max 3300-2500 (broad), 1703, 1660, 1592, 1561 and 1540  $\text{cm}^{-1}$ ; pmr (DMSO-*d*<sub>6</sub>):  $\delta$  1.68 (s, 3H, C-CH<sub>3</sub>), 3.72 (s, 3H, N-CH<sub>3</sub>), 3.24 (d x d, *J* = 12 Hz, 2H, CH<sub>2</sub>), 6.52 (s, 1H, CH-Arom.), 7.03-7.50 (m, 4H, aromatic) and 9.96 (s, 1H, NH).

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>S: C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.67; H, 4.72; N, 13.09; S, 9.82.

5-Acetamido-4-(*o*-carboxybenzyl)-1,3-dimethylpyrazole (**6**).

A mixture of **5** (20.0 g., 0.063 mole) and Raney nickel (20.0 g.) in 250 ml. of ethanol was stirred and heated under reflux for 3 hours. The mixture was filtered hot, the filtrate evaporated *in vacuo* and the residue obtained dissolved in water. The solution was made slightly acidic with hydrochloric acid. This resulted in the precipitation of white feathery needles upon standing overnight. The crystals were harvested, washed with water and dried. The yield was 0.60 g. (33%), m.p. 208-210°; ir (nujol):  $\gamma$  max 3275, 3100-2400 (broad), 1698, 1667, 1598, 1570 and 1535  $\text{cm}^{-1}$ ; pmr (DMSO-*d*<sub>6</sub>):  $\delta$  1.88 (s, 3H, C-CH<sub>3</sub>), 1.97 (s, 3H, C-CH<sub>3</sub>), 3.51

(s, 3H, N-CH<sub>3</sub>), 3.98 (s, 2H, -CH<sub>2</sub>-), 7.20-8.00 (m, 4H, aromatic), and 9.53 (s, 1H, COOH).

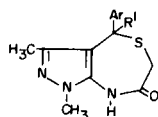
4-(*p*-Chlorophenyl)-1,3,5,7-tetramethyl-1*H*,7*H*-dipyrazolo[3,4-*b*:4',3'-*e*]pyridine (**11**).

A mixture of 5-amino-1,3-dimethylpyrazole (11.1 g., 0.1 mole) and *p*-chlorobenzaldehyde (14.1 g., 0.1 mole) in 250 ml. of toluene was heated under reflux for 3 hours, using a Dean-Stark water separator. The toluene was removed from the reaction mixture by distillation, the residue was cooled and taken up in ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated to dryness *in vacuo* to yield 22.0 g. of an oil. The oil was distilled and chromatographed on silica gel using benzene-95% ethanol (20:1). The major product from the column was a yellow material which after washing with petroleum ether (b.p. 63-68°) gave a white sample of **11** in a yield of 4.0 g., m.p. 178-180°; ir (deuteriochloroform):  $\gamma$  max at 2940, 2240, 1600, 1500, 1320, 1200, 990, 920, 825  $\text{cm}^{-1}$ ; pmr (deuteriochloroform):  $\delta$  2.00 (s, 6H, 2C-CH<sub>3</sub>), 4.03 (s, 6H, 2N-CH<sub>3</sub>), 7.40 (d x d, *J* = 8 Hz, 4H, aromatic).

*Anal.* Calcd. for C<sub>17</sub>H<sub>16</sub>ClN<sub>5</sub>: C, 62.67; H, 4.91; N, 21.50. Found: C, 62.67; H, 5.12; N, 21.62.

Table I

Reaction of 5-Amino-1,3-dimethylpyrazole and Mercaptoacetic Acid with Arylaldehydes or with Arylketones



Arylaldehyde or Arylketone	Reaction Product	Ar.	R <sub>1</sub>	Yield %	M.p., °C
4-Chlorobenzaldehyde	<b>19</b>		H	59	204-206
Benzaldehyde	<b>14</b>		H	81	205-207
3,4-Dimethoxybenzaldehyde	<b>23</b>		H	70	170-172
4-Fluorobenzaldehyde	<b>24</b>		H	75	197-199
2-Carboxybenzaldehyde	<b>5</b>		H	23	259-261
4-Hydroxybenzaldehyde	<b>25</b>		H	56	268-270
4-Nitrobenzaldehyde	<b>26</b>		H	10	225-227
<i>p</i> -Chloroacetophenone	<b>27</b>		CH <sub>3</sub>	30	248-250
<i>p</i> -Fluoroacetophenone	<b>28</b>		CH <sub>3</sub>	23	206-208

1,3-Dimethyl-4-phenyl-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-one (**14**).

A mixture of 5-amino-1,3-dimethylpyrazole (11.1 g., 0.1 mole) and benzaldehyde (10.6 g., 0.1 mole) in 100 ml. of dry toluene was heated under reflux for 1.5 hours, during which time the theoretical amount of water was collected. The solution was cooled, mercaptoacetic acid (9.2 g., 0.1 mole) was added, and the mixture heated at reflux for 3 hours. The solution was cooled, concentrated *in vacuo* to about one half of its volume, and an equal amount of diethyl ether was added. A pink colored crystalline material was obtained in a yield of 22.2 g. Recrystallization from benzene-petroleum ether (b.p. 63-68°) afforded 16.8 g. of **14** (62% yield) with a m.p. 205-207°; ir (chloroform):  $\gamma$  max 3390, 3220, 3152, 1672, 1583, 1532 and 1490 cm<sup>-1</sup>; pmr (deuteriochloroform):  $\delta$  2.30 (s, 3H, C-CH<sub>3</sub>), 3.42 (s, 3H, N-CH<sub>3</sub>), 3.28 (d x d, J = 14 Hz, 2H, S-CH<sub>2</sub>), 5.37 (s, 1H, CH-Ar), 7.33 (s, 5H, aromatic) and 8.06 (s, 1H, NH).

*Anal.* Calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>OS: C, 61.54; H, 5.53; N, 15.37. Found: C, 61.78; H, 5.42; N, 15.49.

5-Acetamido-4-benzyl-1,3-dimethylpyrazole (**17**).

A 20 g. (0.073 mole) sample of **14** was stirred at reflux temperature in 250 ml. of ethanol containing a suspension of Raney nickel catalyst (~80 g.) for two hours. The nickel catalyst was removed by

filtration, and the filtrate concentrated *in vacuo* to a solid residue. Crystallization of this residue from hot water-95% ethanol (9:1) afforded **17** in 12.1 g. yield (61%), with a m.p. of 140-142°; ir (deuteriochloroform):  $\gamma$  max 2900, 2250, 1690, 1590, 1500, 1420, 1350, 1090, 1020, 840 and 810 cm<sup>-1</sup>; pmr (DMSO-d<sub>6</sub>):  $\delta$  1.93

(s, 3H, C-CH<sub>3</sub>), 2.03 (s, 3H, C-CH<sub>3</sub>), 3.53 (s, 3H, N-CH<sub>3</sub>), 3.60 (s, 2H, -CH<sub>2</sub>-Ar), 7.20 (s, 5H, aromatic), 9.47 (s, 1H, -NH).

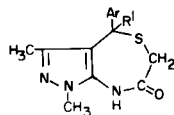
*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>O: C, 69.11; H, 7.04; N, 17.27. Found: C, 68.96; H, 7.01; N, 17.08.

5-Amino-4-benzyl-1,3-dimethylpyrazole (**18**).

A 2.0 g. sample of **17** was heated under reflux with 20 ml. of 5% sodium hydroxide for two hours. At the end of the heating, an oily layer appeared which solidified upon cooling. The solid material was filtered, washed with water and crystallized from 95% ethanol-petroleum ether (63-68°) to afford **18** in 1.2 g. yield (60%), with a m.p. of 102-105°; ir (deuteriochloroform):  $\gamma$  max 3450, 3375, 2940, 2220, 1650, 1540, 1395, 1300 and 920 cm<sup>-1</sup>; pmr (deuteriochloroform):  $\delta$  2.08 (s, 3H, C-CH<sub>3</sub>), 3.56 (s, 3H, N-CH<sub>3</sub>), 3.66 (s, 2H, CH<sub>2</sub>-Ar) and 7.23 (s, 5H, aromatic).

*Anal.* Calcd. for C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.82; H, 7.76; N, 21.11.

Table II  
Pmr Data for the Pyrazolothiazepine Derivatives



Compound	Ar.	R <sub>1</sub>	Chemical Shift, ppm (δ)					
			C-CH <sub>3</sub>	N-CH <sub>3</sub>	S-CH <sub>2</sub>	Ar-CH (a)	NH	Solvent
22		H	1.83	3.85	3.28	5.22	9.64	CDCl <sub>3</sub>
			1.73	3.64	3.22	5.50	--	DMSO-d <sub>6</sub>
14		H	2.30	3.42	3.28	5.37	8.06	CDCl <sub>3</sub>
			1.77	3.70	3.27	5.51	9.96	DMSO-d <sub>6</sub>
23		H	1.85	3.87	3.30	5.27	9.55	CDCl <sub>3</sub>
24		H	1.75	3.67	3.25	5.51	9.87	DMSO-d <sub>6</sub>
5		H	1.68	3.72	3.24	6.52	9.96	DMSO-d <sub>6</sub>
25		H	1.73	3.67	3.24	5.42	9.85	DMSO-d <sub>6</sub>
26		H	1.77	3.68	3.27	5.69	10.00	DMSO-d <sub>6</sub>
27		CH <sub>3</sub>	1.68	3.68	3.28	--	9.87	DMSO-d <sub>6</sub>
28		CH <sub>3</sub>	1.66	3.70	3.30	--	9.83	DMSO-d <sub>6</sub>

(a) If R<sub>1</sub> = H.

4-(*p*-Chlorophenyl)-1,3-dimethyl-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-one (**19**).

A mixture of 5-amino-1,3-dimethylpyrazole (111 g., 1.0 mole) and *p*-chlorobenzaldehyde (140 g., 1.0 mole) in 1 liter of dry toluene was heated under reflux for 4 hours, during which time the theoretical amount of water was collected. The solution was cooled, mercaptoacetic acid (92 g., 1.0 mole) was added, and the mixture heated at reflux overnight. The solution was cooled, the excess toluene decanted, and the solid material formed washed twice with 500 ml. of ethanol and dried. Crystallization was accomplished by dissolving the crude material in DMF at 70° and gradually adding water. The crystals were harvested and dried *in vacuo* at 45°. The sample obtained (452 g., 73.3% yield) exhibited a m.p. of 198.5-199.5°; ir (deuteriochloroform):  $\gamma$  max 3390, 2980, 1670, 1580, 1520, 1485, 1400, 1120, 1080 and 1005 cm<sup>-1</sup>; pmr (deuteriochloroform):  $\delta$  1.80 (s, 3H, C-CH<sub>3</sub>), 3.25 (d x d, J = 14 Hz, 2H, CH<sub>2</sub>), 3.82 (s, 3H, N-CH<sub>3</sub>), 5.24 (s, 1H, Ar-CH), 7.00-7.40 (m, 4H, aromatic), 9.66 (s, 1H, -NH).

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>ClN<sub>3</sub>OS: C, 54.63; H, 4.58; N, 13.65. Found: C, 54.81; H, 4.59; N, 13.52.

4-(*p*-Chlorophenyl)-1,3,8-trimethyl-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-one (**20**).

To a suspension of 30.7 g. (0.1 mole) of **19** in 150 ml. of water,

20 ml. of 50% sodium hydroxide was added with stirring. Solution was effected in about 10 minutes. To this solution, dimethylsulfate (25.2 g., 0.2 mole) was added dropwise. After the addition of dimethylsulfate, the reaction mixture was stirred for 30 minutes and filtered. The precipitate was washed with water and dried. The yield was 30.2 g. (94%). Crystallization from ethanol afforded **20** in a yield of 19.1 g., with a m.p. of 149-151°; ir (deuteriochloroform):  $\gamma$  max 2900, 2240, 1690, 1585, 1515, 1500, 1420, 1350, 1090, 1020, 920, 840, 820 cm<sup>-1</sup>; pmr (deuteriochloroform):

$\delta$  1.83 (s, 3H, C-CH<sub>3</sub>), 2.83 (s, 3H, -C-N-CH<sub>3</sub>), 3.28 (d x d, J = 12 Hz, 2H, CH<sub>2</sub>), 3.73 (s, 3H, N-CH<sub>3</sub>), 5.22 (s, 1H, Ar-CH) and 7.60 (s, 4H, aromatic).

*Anal.* Calcd. for C<sub>15</sub>H<sub>16</sub>ClN<sub>3</sub>OS: C, 55.98; H, 5.01; N, 13.06. Found: C, 55.72; H, 5.02; N, 13.03.

4-(*p*-Chlorophenyl)-6,7-dihydro-1,3,7-trimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-one (**21**).

a. Prepared from **19**.

Sodium hydride (9.6 g., 0.4 mole) was added to 400 ml. of DMF and to this suspension 61.6 g. (0.2 mole) of **19** was added in portions with constant stirring. Finally, 66.8 g. (0.4 mole) of methyl iodide in 400 ml. of DMF was added dropwise, and the mixture stirred at 90° for 6 hours. Upon cooling to room tempera-

ture, the reaction mixture solidified. Addition of 200 ml. of water and dilute hydrochloric acid (to pH 4-5) afforded a precipitate which was filtered and washed with ethanol. Crystallization from 95% ethanol yielded 15.4 g. of crystals (27%) with a m.p. of 207-209°; ir (deuteriochloroform):  $\gamma$  max 2925, 2250, 1650, 1600, 1500, 1380, 1100, 1030, 960 and 850  $\text{cm}^{-1}$ ; pmr (deuteriochloroform):  $\delta$  1.90 (s, 3H, C-CH<sub>3</sub>), 3.90 (s, 3H, N-N-CH<sub>3</sub>), 4.20 (s, 3H, -C-N-CH<sub>3</sub>), 6.15 (s, 1H, Ar-C=CH), 7.20-7.60 (d x d, J = 8 Hz, 4H, aromatic).

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>ClN<sub>3</sub>O: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.88; H, 4.99; N, 14.83.

On standing, the original mother liquor afforded a second crop of crystals (13.1 g., 20.5% yield) with a m.p. of 147-149°, which was identified as **20**.

b. Prepared from **20**.

Twenty g. (0.063 mole) of **20** was dissolved in 100 ml. of DMSO and 2.7 g. of 57% sodium hydride (0.063 mole) was added with constant stirring. The reaction mixture was stirred at 90° for two hours and poured onto ice-dilute hydrochloric acid. A white precipitate was obtained which was filtered and washed with water. Crystallization of this material from ethanol yielded 12.1 g. of **21** with a m.p. of 207-209° (67% yield).

4-(*p*-Chlorophenyl)-6,7-dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]-pyridin-6-one (**22**).

To a suspension of 9.6 g. (0.4 mole) of sodium hydride in 100 ml. of DMF, 61.6 g. (0.2 mole) of **19** in 350 ml. of DMF was added dropwise. The reaction mixture was heated and stirred at reflux overnight. The resulting dark purple solution was poured into 500 ml. of ice water containing 50 ml. of concentrated hydrochloric acid. The purple color was discharged and a tan colored precipitate was obtained. The precipitate was collected, washed with water and triturated with 1*N* hydrochloric acid. It was again filtered, washed with water, dried and crystallized from DMF. The crystals were harvested, washed with ethanol and ether, respectively, and dried. The yield was 20.4 g. (33%), m.p. > 290°; ir (nujol):  $\gamma$  max 2920, 2850, 1670, 1610, 1450, 1390, 1100, 890 and 750  $\text{cm}^{-1}$ ; pmr (DMF):  $\delta$  2.00 (s, 3H, C-CH<sub>3</sub>), 3.83 (s, 3H, N-CH<sub>3</sub>), 6.17 (s, 1H, Ar-C=CH), 7.57 (s, 4H, aromatic).

*Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>2</sub>: C, 61.43; H, 4.42; N, 15.35. Found: C, 60.97; H, 4.47; N, 15.36.

4-(*p*-Fluorophenyl)-1,3,4-trimethyl-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-one (**28**).

A mixture of 5-amino-1,3-dimethylpyrazole (11.0 g., 0.1 mole) and *p*-fluoroacetophenone (13.8 g., 0.1 mole) in 100 ml. of dry

toluene was heated under reflux for 1.5 hours, during which time the theoretical amount of water was collected. The solution was cooled, mercaptoacetic acid (9.2 g., 0.1 mole) was added, and the mixture heated at reflux overnight. The solution was cooled and filtered. Crystallization was induced by the addition of diethyl ether to the filtrate. The harvested crystals (12.6 g.) were recrystallized from DMF-water to afford **28** in a yield of 7.2 g. with a m.p. of 206-208° (23% yield); ir (deuteriochloroform):  $\gamma$  max 3397, 3225, 3160, 3047, 2980, 2943, 1673, 1604, 1562, 1524 and 1505  $\text{cm}^{-1}$ ; pmr (DMSO-*d*<sub>6</sub>):  $\delta$  1.66 (s, 3H, C-CH<sub>3</sub>), 2.07 (s, 3H, Arom-C-CH<sub>3</sub>), 3.30 (d x d, J = 16 Hz, 2H, -CH<sub>2</sub>-), 3.70 (s, 3H, N-CH<sub>3</sub>) 7.00-7.50 (m, 4H, aromatic).

*Anal.* Calcd. for C<sub>15</sub>H<sub>16</sub>FN<sub>3</sub>OS: C, 59.00; H, 5.28; N, 13.76. Found: C, 59.05; H, 5.39; N, 13.64.

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