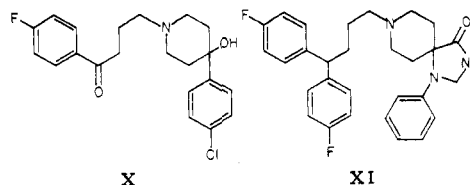


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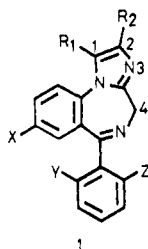
## Diazepines. 5. Synthesis and Biological Action of 6-Phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines<sup>1-3</sup>

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A series of 6-phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines (**2**) has been prepared with 2-phthalimidomethylfurans (**12**) and 1-phthalimidoalkane-2,5-diones (**15**) or 2,5-dimethoxy-2-phthalimidomethyltetrahydrofurans (**16**) as the key intermediates and subsequently evaluated for CNS activity. The structure-activity data generated indicate that, in general, introduction of the methyl and/or ethyl group(s) in the pyrrole ring and a chlorine atom at the ortho position of the 6-phenyl group increases the activity and that substitution of the above chlorine atom for a fluorine atom decreases the activity. 8-Chloro-6-(2-chlorophenyl)-1,3-dimethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**2p**), the most potent among the compounds synthesized, was equipotent in taming and sedative activities to diazepam. The acute LD<sub>50</sub> of **2p** in mice was larger than 3000 mg/kg po.

Previously we have observed that the introduction of an alkyl group (particularly the methyl and the ethyl group) at the 2 position of 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepines (**1**) greatly enhances the CNS activity of

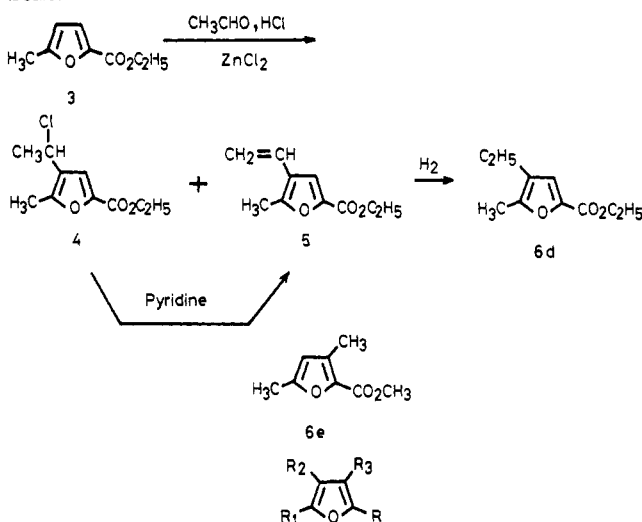


the compounds.<sup>4</sup> The present study was undertaken in order to synthesize 6-phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines<sup>5</sup> (**2**) by an efficient method and to investigate the CNS activity of the compounds particularly in terms of the effect of the alkyl group(s) on the pyrrole ring upon the pharmacological action. The potential effect of the introduction of an alkyl group at the 3 position is of interest, for compounds **1** cannot possess an alkyl group at this position.

**Chemistry.** The tricyclic diazepine compounds **2** were synthesized (Scheme III) with the furans **12** (Scheme I) and the 1,4-diketones **15** or the tetrahydrofurans **16** (Scheme II) as the key intermediates.

**Phthalimidomethylfurans.** Compound **4** obtained by distillation in the  $\alpha$ -chloroethylation<sup>7</sup> of ethyl 5-methyl-2-furoate (**3**) using acetaldehyde and hydrogen chloride with zinc chloride as the catalyst was accompanied by the olefin **5**, apparently arising from the dehydrochlorination of the  $\alpha$ -chloroethyl derivative **4** in the distillation flask. The mixture of **4** and **5** so obtained was heated with pyridine to yield pure **5**, which was then hydrogenated over Raney nickel to give ethyl 4-ethyl-5-methyl-2-furoate (**6d**). The ester **6d** was hydrolyzed to the acid **7d**, which was

Scheme I



### Five Series Synthesized

- a: R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=H  
 b: R<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=R<sub>3</sub>=H  
 c: R<sub>1</sub>=R<sub>2</sub>=CH<sub>3</sub>, R<sub>3</sub>=H  
 d: R<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=C<sub>2</sub>H<sub>5</sub>, R<sub>3</sub>=H  
 e: R<sub>1</sub>=R<sub>3</sub>=CH<sub>3</sub>, R<sub>2</sub>=H

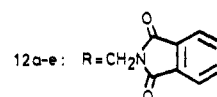
7d,e: R=CO<sub>2</sub>H

8d,e: R=H

9d,e: R=CHO

10d,e: R=CH=NOH

11a-e: R=CH<sub>2</sub>NH<sub>2</sub>



12a-e: R=CH<sub>2</sub>N

decarboxylated<sup>8</sup> to **8d** by heating in an oil bath of 250–265 °C with copper powder and quinoline. The formylation of **8d** under Vilsmeier conditions<sup>9</sup> afforded the aldehyde **9d**. The phthalimidomethylfuran **12d** was prepared from **9d** via the oxime **10d** and the amine **11d** according to the

Table I. 1,4-Diketones 15, Tetrahydrofurans 16, and Their Synthetic Intermediates 12-14

| Compd | Mp, °C                 | Recrystn solvent <sup>a</sup> | % yield         | Formula   | Analyses <sup>b</sup> |
|-------|------------------------|-------------------------------|-----------------|---|-----------------------|
| 12d   | 144-144.5              | E                             | 70 <sup>c</sup> | C <sub>16</sub> H <sub>15</sub> NO <sub>3</sub> | C, H, N               |
| 12e   | 114.5-115              | M                             | 89 <sup>c</sup> | C <sub>15</sub> H <sub>13</sub> NO <sub>3</sub> | C, H, N               |
| 13a   | 147.5-148 <sup>d</sup> | MC-H                          | 73 <sup>e</sup> | C <sub>15</sub> H <sub>15</sub> NO <sub>5</sub> | C, H, N               |
| 13d   | 127-129.5 <sup>f</sup> | EE-H                          | 98 <sup>g</sup> | C <sub>16</sub> H <sub>21</sub> NO <sub>5</sub> | H, N; C <sup>h</sup>  |
| 13e   | 142-154 <sup>i</sup>   | M                             | 71 <sup>c</sup> | C <sub>17</sub> H <sub>19</sub> NO <sub>5</sub> | C, H, N               |
| 14d   | 100.5-101              | MC-H                          | 65 <sup>j</sup> | C <sub>16</sub> H <sub>15</sub> NO <sub>4</sub> | C, H, N               |
| 14e   | 171-171.5              | MC-H                          | 78 <sup>j</sup> | C <sub>15</sub> H <sub>13</sub> NO <sub>4</sub> | C, H, N               |
| 15a   | 136-137.5              | MC-C                          | 97 <sup>g</sup> | C <sub>15</sub> H <sub>11</sub> NO <sub>4</sub> | C, H, N               |
| 15d   | 79.5-80.5              | EE-H                          | 96 <sup>g</sup> | C <sub>16</sub> H <sub>17</sub> NO <sub>4</sub> | C, H, N               |
| 15e   | 101.5-102.5            | M                             | 98 <sup>g</sup> | C <sub>15</sub> H <sub>15</sub> NO <sub>4</sub> | C, H, N               |
|       |                        |                               | 96 <sup>j</sup> |   |                       |
| 16a   | 113-114.5 <sup>k</sup> | MC-H                          | 98 <sup>g</sup> | C <sub>15</sub> H <sub>17</sub> NO <sub>5</sub> | C, H, N               |

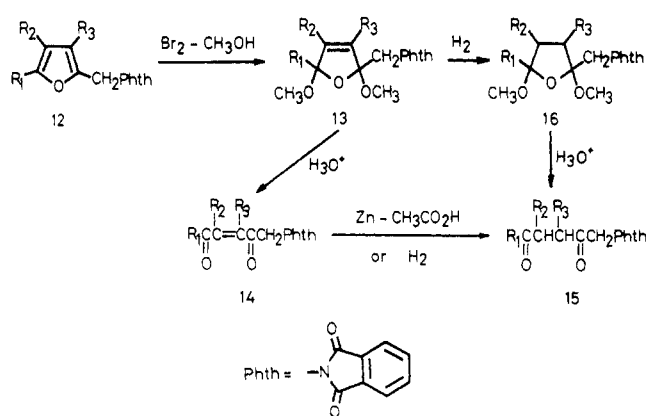
<sup>a</sup> E = EtOH; M = MeOH; MC = CH<sub>2</sub>Cl<sub>2</sub>; H = *n*-hexane; EE = ether; C = CCl<sub>4</sub>. <sup>b</sup> Analyses for the elements indicated were within  $\pm 0.4\%$  of the theoretical values unless otherwise noted. <sup>c</sup> Yield of recrystallized material. <sup>d</sup> Melting point of the less soluble isomer obtained by fractional recrystallization. <sup>e</sup> Yield of recrystallized material plus material obtained by silica gel column chromatography of the mother liquor. <sup>f</sup> Melting point of a mixture of *E* and *Z* isomers (major isomer:minor isomer = 22:1). <sup>g</sup> Yield of crude material identified by NMR spectroscopy. <sup>h</sup> C: calcd, 65.24; found, 65.69. <sup>i</sup> Melting point of a mixture of *E* and *Z* isomers (major isomer:minor isomer = 12.6:1). <sup>j</sup> Yield of material purified by silica gel column chromatography with benzene-AcOEt. <sup>k</sup> Melting point of one isomer obtained from the corresponding, less soluble isomer of 13a.

standard procedure.<sup>10,11</sup> Compounds 12a-c,e were prepared similarly from 11a-c<sup>11,12</sup> and 6e<sup>13</sup> (Scheme I).

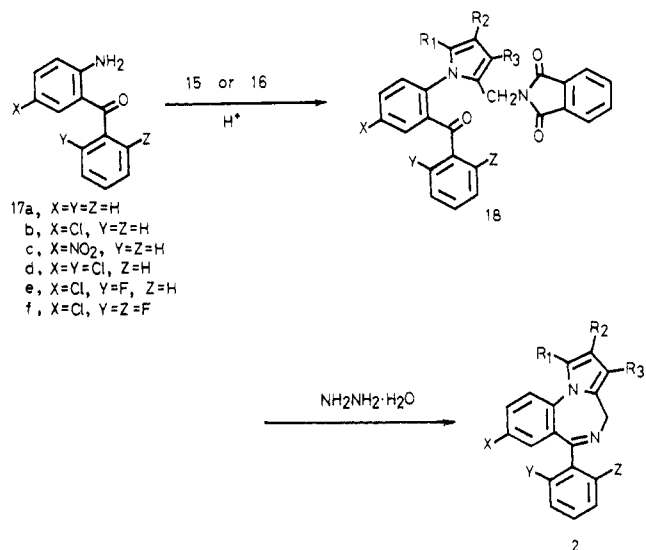
**Phthalimido-1,4-dicarbonyl Compounds and Dimethoxyphthalimidomethyltetrahydrofurans.** Compounds 15a-e were prepared<sup>14</sup> from 12 via the dihydrofurans 13 and the unsaturated 1,4-diketones 14. In the methoxylation of 12 to 13, methylene chloride was used as the cosolvent of methanol because of the high solubility of 12 in methylene chloride even at the low reaction temperature of -50 to -20 °C. Compounds 13a,d,e were, as in the cases of 13b,c,<sup>2,14</sup> obtained as a mixture of *E* and *Z* isomers as indicated by two sets of the NMR signals of the methoxy groups and the methyl group at C-2 (or C-5). Hydrogenation of 13a,b over Raney nickel proceeded smoothly under atmospheric pressure at room temperature to give 16a,b, which on hydrolysis in a mixture of benzene and 2 N or 3 N HCl at the refluxing temperature afforded 15a,b. This hydrolysis required stronger conditions than the conversion of 13 to 14 (Scheme II).

**6-Phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines.** The condensation of the 2-aminobenzophenones 17 with 15 or 16 with *p*-toluenesulfonic acid or trichloroacetic acid as the catalyst gave the pyrrolylbenzophenones 18, which were then converted to the desired pyrrolobenzodiazepines 2 by the treatment with hydrazine hydrate (Scheme III). The transformation of 17 to 18 and then to 2 could also be operated, as a so-called one-vessel reaction, continuously without any workup of the first reaction mixture. Compounds 2 gave satisfactory IR, NMR, and mass spectra. In the NMR spectra the C-4 protons of 2, except for 2b and 2c,<sup>15</sup> appeared as an AB quartet with  $\delta_{AB}$  of about 1.0 ppm, whereas the  $\delta_{AB}$  of the AB quartets of the corresponding methylene protons in 18 were smaller than or equal to 0.54 ppm. Another characteristic, NMR spectral change associated with the conversion of 18 having a methyl group at C-2' of the pyrrole ring to the corresponding pyrrolobenzodiazepines 2 is a fairly large downfield shift (0.38-0.48 ppm in CDCl<sub>3</sub>) of the methyl proton signal. These observations are consistent with the structure of 2: the former observation is firstly due to the rigid tricyclic molecular structure retarding the flapping of the methylene group up and down the plane of the pyrrolobenzodiazepine structure considerably enough in the NMR time scale for each of the methylene protons to have a different chemical shift; the second observation is due to the anisotropic deshielding effect of the benzene

Scheme II



Scheme III



ring of the benzodiazepine skeleton on the methyl group which is now close to the plane of the benzene ring. See Tables I-III.

**Biological Studies.** The pyrrolobenzodiazepines 2 were subjected to tests designed to measure CNS activities. In these tests the previously described methods<sup>1</sup> (see Experimental Section) were employed. The results are shown

Table II. 2-(2-Phthalimidomethylpyrrol-1-yl)benzophenones (18)

| Compd | R <sub>1</sub>  | R <sub>2</sub>                | R <sub>3</sub>  | X               | Y  | Z | Mp, °C               | Recrystn solvent <sup>a</sup> | % yield <sup>b,c</sup> | Method <sup>d</sup> | Rxn conditions <sup>e</sup> | Formula  | Analyses <sup>f</sup> |
|-------|-----------------|-------------------------------|-----------------|-----------------|----|---|----------------------|-------------------------------|------------------------|---------------------|-----------------------------|--|-----------------------|
| 18a   | H               | H                             | H               | Cl              | H  | H | 188-189.5            | H                             | 88 <sup>g</sup>        | A                   | TCA, 2 <sup>h</sup>         | C <sub>26</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>3</sub>                | C, H, N               |
| 18b   | H               | H                             | H               | Cl              | Cl | H | 237-239 <sup>i</sup> |                               | 87 <sup>g</sup>        | A                   | TCA, 2 <sup>h</sup>         |  | IR <sup>j</sup>       |
| 18c   | H               | H                             | H               | Cl              | F  | H | 217.5-218            | MC-C                          | 64 <sup>g</sup>        | A                   | TCA, 2 <sup>h</sup>         | C <sub>26</sub> H <sub>16</sub> ClFN <sub>2</sub> O <sub>3</sub>               | C, H, N               |
| 18d   | CH <sub>3</sub> | H                             | H               | H               | H  | H | 117.5-118            | MC-H                          | 92                     | B                   | TCA, 1                      | C <sub>27</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>                  | H, N; C <sup>k</sup>  |
| 18e   | CH <sub>3</sub> | H                             | H               | Cl              | H  | H | 148.5-149.5          | EE-H                          | 93                     | B                   | TCA, 2                      | C <sub>27</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>3</sub>                | C, H, N               |
| 18f   | CH <sub>3</sub> | H                             | H               | NO <sub>2</sub> | H  | H | 174-175              | MC-H                          | 59                     | B                   | PTS, 3.5                    | C <sub>27</sub> H <sub>19</sub> N <sub>3</sub> O <sub>5</sub>                  | C, H, N               |
| 18g   | CH <sub>3</sub> | H                             | H               | Cl              | Cl | H | 170-170.5            | MC-H                          | 95 <sup>i</sup>        | B                   | PTS, 1.5                    | C <sub>27</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>  | C, H, N               |
|       |                 |                               |                 |                 |    |   |                      |                               | 80                     | A                   | PTS, 1.5                    |  |                       |
| 18h   | CH <sub>3</sub> | H                             | H               | Cl              | F  | H | 184-185              | MC-H                          | 88                     | B                   | PTS, 1                      | C <sub>27</sub> H <sub>18</sub> ClFN <sub>2</sub> O <sub>3</sub>               | C, H, N               |
|       |                 |                               |                 |                 |    |   |                      |                               | 75                     | A                   | PTS, 1.8                    |  |                       |
| 18i   | CH <sub>3</sub> | CH <sub>3</sub>               | H               | H               | H  | H | 186-187              | MC-H                          | 89                     | B                   | PTS, 1.5                    | C <sub>28</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>                  | H, N; C <sup>m</sup>  |
| 18j   | CH <sub>3</sub> | CH <sub>3</sub>               | H               | Cl              | H  | H | 160-160.5            | MC-H                          | 92                     | B                   | PTS, 2                      | C <sub>28</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>3</sub>                | C, H, N               |
| 18k   | CH <sub>3</sub> | CH <sub>3</sub>               | H               | Cl              | Cl | H | 162-163              | MC-H                          | 97                     | B                   | PTS, 1                      | C <sub>28</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>  | C, H, N               |
| 18l   | CH <sub>3</sub> | CH <sub>3</sub>               | H               | Cl              | F  | H | 152-153              | MC-H                          | 94                     | B                   | PTS, 1                      | C <sub>28</sub> H <sub>20</sub> ClFN <sub>2</sub> O <sub>3</sub>               | C, H, N               |
| 18m   | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub> | H               | Cl              | Cl | H | 168-169.5            | MC-H                          | 65                     | B                   | PTS, 4                      | C <sub>29</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>  | C, H, N               |
| 18n   | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub> | H               | Cl              | F  | H | 185-186              | MC-H                          | 54 <sup>n</sup>        | B                   | PTS, 20                     | C <sub>29</sub> H <sub>22</sub> ClFN <sub>2</sub> O <sub>3</sub>               | C, H, N               |
| 18o   | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub> | H               | Cl              | F  | H | 198-199              | MC-H                          | 80                     | B                   | PTS, 24                     | C <sub>29</sub> H <sub>21</sub> ClF <sub>2</sub> N <sub>2</sub> O <sub>3</sub> | C, H, N               |
| 18p   | CH <sub>3</sub> | H                             | CH <sub>3</sub> | Cl              | Cl | H | 168.5-169.5          | B-H                           | 90 <sup>i</sup>        | B                   | PTS, 3.5                    | C <sub>28</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>  | C, H, N               |
| 18q   | CH <sub>3</sub> | H                             | CH <sub>3</sub> | Cl              | F  | H | 168-168.5            | MC-H                          | 82 <sup>i</sup>        | B                   | PTS, 5                      | C <sub>28</sub> H <sub>20</sub> ClFN <sub>2</sub> O <sub>3</sub>               | C, H, N               |
| 18r   | CH <sub>3</sub> | H                             | CH <sub>3</sub> | Cl              | F  | F | 187.5-188.5          | MC-H                          | 91 <sup>i</sup>        | B                   | PTS, 16.5                   | C <sub>28</sub> H <sub>19</sub> ClF <sub>2</sub> N <sub>2</sub> O <sub>3</sub> | C, N; C <sup>o</sup>  |

<sup>a</sup> H = *n*-hexane; MC = CH<sub>2</sub>Cl<sub>2</sub>; C = CCl<sub>4</sub>; EE = ether; B = benzene. <sup>b</sup> Yield of material purified, unless otherwise indicated, by silica gel column chromatography with benzene-AcOEt as the eluent; no efforts were made to optimize yields.

<sup>c</sup> Unless otherwise indicated, compound 15 or 16 was used in a stoichiometric amount or in a small excess to 17 (1:1-1.07), and the yield is based on 17. <sup>d</sup> A = reaction of 17 with 16; B = reaction of 17 with 15. <sup>e</sup> The reactions were run in, unless otherwise indicated, benzene by heating at reflux with a catalyst. The catalyst employed and refluxing time (h) are indicated: PTS = *p*-toluenesulfonic acid; TCA = CCl<sub>3</sub>CO<sub>2</sub>H. <sup>f</sup> Analyses for the elements indicated were within ±0.4% of the theoretical values unless otherwise noted. <sup>g</sup> Yield of material collected by filtration of the cooled reaction mixture.

<sup>h</sup> In EtOH. <sup>i</sup> Of a product not recrystallized because of the very low solubility in solvents. <sup>j</sup> The symbol "IR" indicates that structure determination was by this method alone at this reaction step because of the very low solubility in solvents.

<sup>k</sup> C: calcd, 77.12; found, 77.55. <sup>l</sup> Compound 17 was used in a small excess to 16b or 16e (1:1.05), and the yield is based on 16b or 16e. <sup>m</sup> C: calcd, 77.40; found, 76.96. <sup>n</sup> 42% of 17d was recovered. <sup>o</sup> C: calcd, 66.60; found, 67.07.

Table III. 6-Phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines

| Compd | R <sub>1</sub>  | R <sub>2</sub>                | R <sub>3</sub>  | X               | Y  | Z | Mp, °C                   | Recrystn solvent <sup>a</sup> | % yield <sup>b</sup> | Rxn conditions <sup>c</sup> | Formula   | Analyses <sup>d</sup> |
|-------|-----------------|-------------------------------|-----------------|-----------------|----|---|--------------------------|-------------------------------|----------------------|-----------------------------|---|-----------------------|
| 2a    | H               | H                             | H               | Cl              | H  | H | 130.5-131.5 <sup>e</sup> | H                             | 78                   | A, 1.5                      | C <sub>18</sub> H <sub>13</sub> ClN <sub>2</sub>                | C, H, N               |
| 2b    | H               | H                             | H               | Cl              | Cl | H | 135.5-136.5              | H                             | 83                   | C, 2                        | C <sub>18</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub>  | C, H, N               |
| 2c    | H               | H                             | H               | Cl              | F  | H | 123-124                  | MC-H                          | 76                   | C, 0.5                      | C <sub>18</sub> H <sub>12</sub> ClFN <sub>2</sub>               | C, H, N               |
| 2d    | CH <sub>3</sub> | H                             | H               | H               | H  | H | 142.5-143.5              | EE-H                          | 68                   | A, 1                        | C <sub>19</sub> H <sub>16</sub> N <sub>2</sub>                  | C, H, N               |
| 2e    | CH <sub>3</sub> | H                             | H               | Cl              | H  | H | 144-145                  | EE-H                          | 65                   | A, 1.5                      | C <sub>19</sub> H <sub>15</sub> ClN <sub>2</sub>                | C, H, N               |
| 2f    | CH <sub>3</sub> | H                             | H               | NO <sub>2</sub> | H  | H | 200-201.5                | MC-H                          | 71                   | B, 0.5                      | C <sub>19</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>   | C, H, N               |
| 2g    | CH <sub>3</sub> | H                             | H               | Cl              | Cl | H | 134-135.5                | MC-H                          | 87                   | A, 1.5                      | C <sub>19</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub>  | C, H, N               |
| 2h    | CH <sub>3</sub> | H                             | H               | Cl              | F  | H | 99.5-100.5               | EE-H                          | 54                   | A, 3                        | C <sub>19</sub> H <sub>14</sub> ClFN <sub>2</sub>               | H, N; C <sup>f</sup>  |
| 2i    | CH <sub>3</sub> | CH <sub>3</sub>               | H               | H               | H  | H | 140.5-141                | EE-H                          | 67                   | B, 0.5                      | C <sub>20</sub> H <sub>18</sub> N <sub>2</sub>                  | C, H, N               |
| 2j    | CH <sub>3</sub> | CH <sub>3</sub>               | H               | Cl              | H  | H | 190.5-191.5              | EE-H                          | 56                   | B, 0.83                     | C <sub>20</sub> H <sub>17</sub> ClN <sub>2</sub>                | C, H, N               |
| 2k    | CH <sub>3</sub> | CH <sub>3</sub>               | H               | Cl              | Cl | H | 132.5-133.5              | EE-H                          | 90                   | B, 0.5                      | C <sub>20</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub>  | H, N; C <sup>g</sup>  |
| 2l    | CH <sub>3</sub> | CH <sub>3</sub>               | H               | Cl              | F  | H | 182.5-183.5              | MC-H                          | 68                   | B, 0.33                     | C <sub>20</sub> H <sub>16</sub> ClFN <sub>2</sub>               | C, N; H <sup>h</sup>  |
| 2m    | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub> | H               | Cl              | Cl | H | 136.5-137.5              | EE-H                          | 82                   | B, 1                        | C <sub>21</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub>  | C, H, N               |
| 2n    | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub> | H               | Cl              | F  | H | 169.5-170.5              | EE-H                          | 54                   | B, 1                        | C <sub>21</sub> H <sub>18</sub> ClFN <sub>2</sub>               | C, H, N               |
| 2o    | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub> | H               | Cl              | F  | F | 204.5-205                | MC-H                          | 87                   | B, 1                        | C <sub>21</sub> H <sub>17</sub> ClF <sub>2</sub> N <sub>2</sub> | C, H, N               |
| 2p    | CH <sub>3</sub> | H                             | CH <sub>3</sub> | Cl              | Cl | H | 132-133                  | EE-H                          | 86                   | B, 0.5                      | C <sub>20</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub>  | C, H, N               |
| 2q    | CH <sub>3</sub> | H                             | CH <sub>3</sub> | Cl              | F  | H | 99.5-101                 | EE-H                          | 48                   | B, 1.5                      | C <sub>20</sub> H <sub>16</sub> ClFN <sub>2</sub>               | C, H, N               |
| 2r    | CH <sub>3</sub> | H                             | CH <sub>3</sub> | Cl              | F  | F | <i>i</i>                 |                               | 83                   | B, 0.83                     | C <sub>20</sub> H <sub>15</sub> ClF <sub>2</sub> N <sub>2</sub> |                       |

<sup>a</sup> H = *n*-hexane; MC = CH<sub>2</sub>Cl<sub>2</sub>; EE = ether. <sup>b</sup> Yield of material purified by silica gel column chromatography with benzene-AcOEt as the eluent; no efforts were made to optimize yields. <sup>c</sup> The conversion of 18 to 2 with hydrazine hydrate was run by heating in a solvent or a mixture of solvents: A, heating at reflux in EtOH; B, heating at reflux in a mixture of EtOH and *N,N*-dimethylformamide; C, heating in an oil bath of 100 °C in *N,N*-dimethylformamide. Heating time (h) is indicated. <sup>d</sup> Analyses for the elements indicated were within ±0.4% of the theoretical values unless otherwise noted.

<sup>e</sup> Lit.<sup>5</sup> mp 125-126 °C (recrystallized from *n*-hexane). <sup>f</sup> C: calcd, 70.26; found, 70.81. <sup>g</sup> C: calcd, 67.61; found, 68.23.

<sup>h</sup> H: calcd, 4.76; found, 5.17. <sup>i</sup> A glassy solid obtained failed to be recrystallized.

in Table IV along with the data for diazepam.

In general, the introduction of the methyl and/or ethyl group(s) in the pyrrole ring and chlorine and/or fluorine atom(s) at the ortho position(s) of the 6-phenyl group increased the overall activities. The introduction of two alkyl groups in R<sub>1</sub> and R<sub>3</sub> (2p and 2q) produced a higher activity than their introduction in R<sub>1</sub> and R<sub>2</sub> (2k and 2l) or the introduction of only one in R<sub>1</sub> (2g and 2h)—in the last case the activity is the lowest among the three. Comparison of the data of 2m and 2n with those of 2k and

2l indicates that the ethyl group at C-2 is more effective in enhancing the CNS activity than the methyl group, which is consistent with our observation<sup>4</sup> with the 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine series.

Substitution of the chlorine atom in Y for a fluorine atom decreased the overall activities (compare 2h, 2l, and 2q with 2g, 2k, and 2p, respectively), though the opposite is observed<sup>16</sup> with the bicyclic benzodiazepines. The introduction of two fluorine atoms in Y and Z (2r) recovered the overall activities.

Table IV. Pharmacological Data<sup>a,b</sup>

| Compd    | Anticonvulsant act.     |                         | Taming act.,<br>fighting mouse | Muscle-relaxant<br>act., inclined<br>screen | Motor inco-<br>ordinating act.,<br>rotating rod | Sedation,<br>potentiation<br>of thiopental |
|----------|-------------------------|-------------------------|--------------------------------|---|---|--|
|          | Pentylene-<br>tetrazole | Maximal<br>electroshock |                                |   |   |  |
| 2a       | 78                      | >100                    | >100                           | >100  | >100  | 44   |
| 2b       | >100                    | >100                    | >100                           | >100  | >100  | 18   |
|          |                         |                         |                                |   |   | (11.5-28.8)                                |
| 2c       | 100                     | >100                    | 39                             | >100  | >100  | 5.2  |
|          |                         |                         | (23.2-65.5)                    |   |   | (2.3-12.0)                                 |
| 2d       | >100                    | >100                    | >100                           | >100  | >100  | 22   |
|          |                         |                         |                                |   |   | (11.4-42.5)                                |
| 2e       | 100                     | >100                    | >100                           | >100  | >100  | 46   |
| 2f       | >100                    | >100                    | >100                           | >100  | >100  | 5.8  |
|          |                         |                         |                                |   |   | (3.2-10.7)                                 |
| 2g       | 20                      | >100                    | 11                             | >100  | 100   | 2.8  |
|          | (15.9-25.2)             |                         | (5.4-22.4)                     |   |   | (1.1-7.1)                                  |
| 2h       | 36                      | >100                    | 55                             | >100  | >100  | 6.9  |
|          | (15.7-82.8)             |                         |                                |   |   | (2.9-16.2)                                 |
| 2i       | >100                    | >100                    | >100                           | >100  | >100  | >30  |
| 2j       | 13.5                    | >100                    | >30                            | >100  | >100  | 21   |
|          | (7.5-24.3)              |                         |                                |   |   | (12.0-36.8)                                |
| 2k       | 6.5                     | >100                    | 4.8                            | >100  | 40  | 2.6  |
|          | (3.0-14.3)              |                         | (3.6-6.5)                      |   |   | (1.7-3.9)                                  |
| 2l       | 10                      | >100                    | 17                             | >100  | >100  | 8.0  |
|          | (6.2-16.0)              |                         | (12.4-23.3)                    |   |   | (1.3-49.6)                                 |
| 2m       | 3.4                     | >30                     | 3.4                            | 14  | 16.2  | 0.6  |
|          | (2.6-4.5)               |                         | (2.2-5.2)                      | (7.8-25.2)                                  | (4.1-64.8)                                      | (0.3-1.1)                                  |
| 2n       | 5.5                     | >30                     | 5.5                            | 30  | >100  | 2.2  |
|          | (2.9-10.5)              |                         | (2.9-10.5)                     |   |   | (1.1-4.3)                                  |
| 2o       | 16.6                    | >30                     | 12.5                           | 69  | >100  | 3.0  |
|          | (5.8-47.3)              |                         | (4.7-33.1)                     |   |   | (1.2-7.3)                                  |
| 2p       | 1.4                     | 100                     | 1.6                            | 8.2   | 15.5  | 0.34                                       |
|          | (0.7-2.9)               |                         | (0.3-7.7)                      | (3.1-21.5)                                  | (12.2-19.7)                                     | (0.26-0.45)                                |
| 2q       | 5.5                     | >100                    | 8.8                            | 20.5  | >30   | 2.4  |
|          | (2.9-10.5)              |                         | (6.0-12.8)                     | (10.3-41.0)                                 |   | (1.7-3.4)                                  |
| 2r       | 2.0                     | 88                      | 1.6                            | 6.4   | 16.2  | 0.7  |
|          | (0.3-12.4)              |                         | (0.4-7.4)                      | (2.3-17.9)                                  | (5.6-47.0)                                      | (0.3-1.8)                                  |
| Diazepam | 0.6                     | 8.8                     | 1.6                            | 0.6   | 5.4   | 0.3  |
|          | (0.3-1.5)               | (5.2-15.0)              | (1.0-2.5)                      | (0.3-1.1)                                   | (4.4-6.6)                                       | (0.2-1.4)                                  |

<sup>a</sup> Values are ED<sub>50</sub>'s expressed in mg/kg. <sup>b</sup> Values in parentheses are the 95% confidence limits of ED<sub>50</sub>.

Compound **2p** is the most active among the compounds synthesized in the present study and is in comparison with diazepam, equipotent in taming and sedative activities, two to three times less potent in antipentylene-tetrazole and motor incoordinating activities, and 11-13 times less potent in muscle relaxant activity and in preventing maximal electroshock seizure.

Compound **2p** was found to be considerably nontoxic; in an acute toxicological study the compound did not cause any death, as observed for a period of 2 weeks, to eight mice tested at a dosage of 3000 mg/kg po, the highest dosage employed.<sup>17</sup>

## Experimental Section

**Chemistry.** Melting points were obtained on a Yanagimoto hot-stage apparatus and are uncorrected. Analyses were carried out by the Analytical Chemistry Laboratory of Central Research Institute, Teijin Ltd. IR spectra were recorded on a Hitachi EPI-500 spectrophotometer. NMR data were obtained on a JEOL JNM-MH-100 spectrometer with Me<sub>4</sub>Si as an internal standard. Mass spectra were run on a LKB 9000 spectrometer at 70 eV. Although no spectral data are included in this report for compounds 4-11, all structural assignments for these compounds were unambiguously confirmed by NMR, supplemented by IR spectroscopy when necessary.

**Ethyl 5-Methyl-4-vinyl-2-furoate (5).** To a stirred mixture of ethyl 5-methyl-2-furoate (**3**) (45.7 g, 0.296 mol) and ZnCl<sub>2</sub> (9.6 g, 0.070 mol) in dry CH<sub>2</sub>Cl<sub>2</sub> was added acetaldehyde (26.4 g, 0.599 mol) dropwise at 0 °C over a period of 45 min. To the mixture was introduced HCl gas at ca. 10 °C for 3 h. The mixture was warmed to room temperature, and stirring was continued overnight with the flask closed with stopcocks. The mixture was poured into cold water (300 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The

combined extracts were washed with water (2 × 150 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The residue was distilled, and 21.1 g of a mixture of ethyl 4-(1-chloroethyl)-5-methyl-2-furoate (**4**) and **5** (ca. 2:1) was obtained as a fraction boiling at 108-113 °C (3.7 mm).

The above mixture of **4** and **5** was heated with pyridine (20 mL) at reflux for 3 h, poured into water (800 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The residue was distilled to give 14.9 g (28% from **3**) of **5**, bp 73-77 °C (0.18 mm).

**Ethyl 4-Ethyl-5-methyl-2-furoate (6d).** Compound **5** (16.8 g, 93.2 mmol) was hydrogenated over Raney nickel in EtOH (300 mL) at room temperature to give 16.5 g (97%) of **6d**, bp 74-77 °C (0.4 mm).

**4-Ethyl-5-methyl-2-furoic Acid (7d).** A mixture of **6d** (27.6 g, 0.151 mol) and 20% aqueous NaOH solution (70 mL) was heated at reflux for 2 h and acidified by concentrated HCl under cooling with an ice bath. The precipitated crystals were collected by filtration and dried to give 21.1 g (91%) of **7d**.

**3-Ethyl-2-methylfuran (8d).** A mixture of **7d** (21.1 g, 0.137 mol), copper powder (5.1 g, 0.080 g-atom), and quinoline (50 g) was heated to boiling by raising the bath temperature gradually to 260 °C, and finally to 275 °C, during which 14.1 g (93%) of **8d** was collected as the distillate, bp 83-95 °C.

**4-Ethyl-5-methyl-2-furaldehyde (9d).** To a stirred mixture of *N,N*-dimethylformamide (10.9 g, 0.149 mol) and dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added POCl<sub>3</sub> (19.0 g, 0.124 mol) at 0 °C over a period of 1 h. After stirring at this temperature for an additional 30 min, a solution of **8d** (13.6 g, 0.123 mol) in dry CH<sub>2</sub>Cl<sub>2</sub> (35 mL) was added at 0 °C over a period of 1.5 h, and stirring was continued at 0 °C for 1 h and at room temperature for 40 min. The mixture was poured onto ice-water (250 mL), made alkaline with solid K<sub>2</sub>CO<sub>3</sub>, stirred at room temperature overnight, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed with water and

brine, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The residue was distilled to give 15.3 g (90%) of **9d**, bp 124–128 °C (32 mm).

**4-Ethyl-5-methyl-2-furaldehyde Oxime (10d).** To a stirred mixture of **9d** (7.63 g, 55.2 mmol) and hydroxylamine hydrochloride (4.61 g, 66.3 mmol) dissolved in water (10 mL) was dropwise added a solution of  $\text{Na}_2\text{CO}_3$  (3.81 g, 35.9 mmol) in water (16.5 mL), and the mixture was heated at reflux for 3 h and 45 min, cooled to room temperature, and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were washed with water and brine and dried ( $\text{Na}_2\text{SO}_4$ ). The evaporation of the solvent gave 8.28 g (98%) of **10d** as a mixture of *E* and *Z* isomers, which became an oily solid on standing at room temperature overnight.

**3,5-Dimethyl-2-furfurylamine (11e).** A mixture of  $\text{LiAlH}_4$  (4.17 g, 0.11 mol) and dry ether (125 mL) was heated at reflux for 3 h, and to the resulting slurry was added 3,5-dimethyl-2-furaldehyde oxime (**10e**) (7.65 g, 55.0 mmol) dissolved in ether (50 mL) over a period of 1 h and 55 min at gentle reflux. The mixture was refluxed for an additional 0.5 h, cooled with an ice bath, treated with water (10.7 mL) added dropwise over a period of 35 min, stirred at room temperature for 15 min, and finally heated at reflux for 45 min. The mixture was filtered, and the solid was extracted with ether ( $2 \times 60$  mL). The combined filtrate and extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give 6.74 g (98%) of **11e** as a slightly yellow liquid.

**2,4-Dimethyl-5-phthalimidomethylfuran (12e).** A stirred mixture of **11e** (10.8 g, 86.3 mmol) and phthalic anhydride (12.8 g, 86.4 mmol) was heated in an oil bath of 120–125 °C for 1.5 h. The cooled reaction product was recrystallized from EtOH to give 18.1 g (82%) of **12e**: mp 114.5–115.0 °C; IR (KBr) 1771, 1712, 1418, 1389, 1071  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  2.08 (s, 3 H,  $\text{CH}_3$ ), 2.16 (s, 3 H,  $\text{CH}_3$ ), 4.71 (s, 2 H,  $\text{CH}_2\text{N}$ ), 5.74 (s, 1 H, H-3), 7.60–7.88 (m, 4 H, aromatic).

**2,5-Dimethoxy-3,5-dimethyl-2-phthalimidomethyl-dihydrofuran (13e).** To a stirred solution of **12e** (4.00 g, 15.7 mmol) in a mixture of dry  $\text{CH}_2\text{Cl}_2$  (120 mL) and absolute MeOH (8 mL) was added a solution of  $\text{Br}_2$  (2.62 g, 16.4 mmol) in a mixture of dry  $\text{CH}_2\text{Cl}_2$  (6 mL) and absolute MeOH (2 mL) at –40 to –50 °C over a period of 35 min. After the mixture was stirred for an additional 1.5 h at –50 to –60 °C, gaseous  $\text{NH}_3$  was introduced to make the mixture basic. The mixture was warmed to room temperature,  $\text{CH}_2\text{Cl}_2$  (40 mL) added, the generated solid removed by filtration, and the filtrate washed with water ( $2 \times 50$  mL), dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The residual solid (4.50 g) was recrystallized from MeOH to give **13e** as colorless prisms (3.55 g, 71%), mp 142–154 °C, which was found to be a mixture of *E* and *Z* isomers (major isomer:minor isomer = 12.6:1) as determined from NMR spectroscopy: IR (KBr) 1767, 1713, 1611, 1464, 1420, 1392  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ ) (less soluble isomer<sup>18</sup>)  $\delta$  1.45 (s, 3 H,  $\text{CH}_3$ ), 1.89 (d, 3 H,  $J$  = 1.5 Hz,  $=\text{CCH}_3$ ), 2.92 (s, 3 H,  $\text{OCH}_3$ ), 3.10 (s, 3 H,  $\text{OCH}_3$ ), 4.00 and 3.88 (AB q, 2 H,  $J$  = 13.5 Hz,  $\text{CH}_2\text{N}$ ), 5.60 (q, 1 H,  $J$  = 1.5 Hz,  $=\text{CH}-$ ), 7.59–7.88 (m, 4 H, aromatic); NMR (more soluble isomer<sup>17</sup>)  $\delta$  1.11 (s, 3 H,  $\text{CH}_3$ ), 1.89 (d, 3 H,  $J$  = 1.5 Hz,  $=\text{CCH}_3$ ), 3.27 (s, 6 H,  $2 \times \text{OCH}_3$ ), 4.06 and 3.86 (AB q, 2 H,  $J$  = 13.5 Hz,  $\text{CH}_2\text{N}$ ), 5.63 (q, 1 H,  $J$  = 1.5 Hz,  $=\text{CH}-$ ), 7.60–7.93 (m, 4 H, aromatic).

**3-Methyl-1-phthalimidohex-3-ene-2,5-dione (14e).** To a solution of **13e** (1.44 g, 4.54 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was added 2 N HCl (3.5 mL), and the mixture was stirred at room temperature for 4 h and treated with saturated aqueous  $\text{NaHCO}_3$  solution. The  $\text{CH}_2\text{Cl}_2$  layer was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The residual solid was recrystallized from  $\text{CH}_2\text{Cl}_2$ -*n*-hexane to give 470 mg of **14e** as colorless prisms, mp 171–171.5 °C. The mother liquor was concentrated and chromatographed on silica gel with benzene-AcOEt (9:1) as eluent to give additional **14e** (494 mg) (964 mg in total, 78%): IR (KBr) 1769, 1714, 1689, 1614, 1464, 1414, 1390  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  2.06 (d, 3 H,  $J$  = 1.5 Hz,  $=\text{CCH}_3$ ), 2.22 (s, 3 H,  $\text{CH}_3\text{CO}$ ), 4.68 (s, 2 H,  $\text{CH}_2\text{N}$ ), 5.21 (q, 1 H,  $J$  = 1.5 Hz,  $=\text{CH}-$ ), 7.65–7.92 (m, 4 H, aromatic).

**3-Methyl-1-phthalimidohexane-2,5-dione (15e).** Compound **14e** (423 mg, 1.56 mmol) was hydrogenated over Raney nickel in AcOEt (45 mL). The calculated amount of  $\text{H}_2$  was absorbed in 12 min. The mixture was filtered, and the filtrate was evaporated to give 416 mg (97%) of **15e** as colorless crystals. Recrystallization from MeOH gave colorless prisms: mp 101.5–102.5 °C; IR (KBr) 1765, 1720, 1703, 1464, 1413  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.22 (d, 3 H,

$J$  = 7.0 Hz,  $\text{CH}_3$ ), 2.12 (s, 3 H,  $\text{CH}_3\text{CO}$ ), 2.40–3.36 (m, 3 H,  $\text{CH}_2\text{CH}$ ), 4.70 and 4.60 (AB q, 2 H,  $J$  = 18.0 Hz,  $\text{CH}_2\text{N}$ ), 7.61–7.95 (m, 4 H, aromatic).

**2,5-Dimethoxy-2-phthalimidomethyltetrahydrofuran (16a).** 2,5-Dimethoxy-2-phthalimidomethyl-dihydrofuran (**13a**) (21.7 g, 75.0 mmol) was hydrogenated over Raney nickel (10 mL of a MeOH suspension) in AcOEt (320 mL). The calculated amount of  $\text{H}_2$  was absorbed in 2 h. The mixture was filtered, and the filtrate was concentrated to ca. 50 mL and allowed to stand overnight. The precipitated **16a** was collected by filtration: yield 16.8 g; colorless needles; mp 112–113.5 °C. The mother liquor was concentrated and cooled to give 1.50 g of the second crop: mp 110.5–112 °C, 18.3 g (84%) in total. Recrystallization from  $\text{CH}_2\text{Cl}_2$ -*n*-hexane afforded colorless needles: mp 112.5–114 °C;<sup>19</sup> IR (KBr) 1771, 1711, 1613, 1468, 1449, 1422, 1391  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )<sup>20</sup>  $\delta$  1.72–2.41 (m, 4 H,  $\text{CH}_2\text{CH}_2$ ), 3.22 (s, 3 H,  $\text{OCH}_3$ ), 3.32 (s, 3 H,  $\text{OCH}_3$ ), 4.05 and 3.91 (AB q, 2 H,  $J$  = 14.0 Hz,  $\text{CH}_2\text{N}$ ), 5.05 (m, 1 H,  $\text{OCHO}$ ), 7.64–7.91 (m, 4 H, aromatic).

**1-Phthalimidohexane-2,5-dione (15b).** To a solution of 2,5-dimethoxy-2-methyl-5-phthalimidomethyltetrahydrofuran (**16b**) (100 mg, 0.328 mmol) in benzene (10 mL) was added 3 N HCl (2 mL), and the mixture was refluxed for 1 h. The mixture was cooled to room temperature, washed with water, saturated aqueous  $\text{NaHCO}_3$  solution, and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated to give 80 mg (94%) of **15b** as colorless crystals, mp 110.5–111 °C. Recrystallization from  $\text{CH}_2\text{Cl}_2$ -*n*-hexane gave colorless prisms, mp 118–119.5 °C. The IR and NMR data of this compound were identical with those<sup>14</sup> of **15b** obtained by Zn-AcOH reduction of 1-phthalimidohex-3-ene-2,5-dione (**14b**).

**Preparation of 2-(2-Phthalimidomethylpyrrol-1-yl)-benzophenones (18) (Table II).** General Method A. The preparation of **18** by the coupling of a 2-aminobenzophenone (**17**) with a 2,5-dimethoxy-2-phthalimidomethyltetrahydrofuran (**16**) is exemplified by the synthesis of 5-chloro-2'-fluoro-2-(2-methyl-5-phthalimidomethylpyrrol-1-yl)benzophenone (**18h**). A stirred solution of 2-amino-5-chloro-2'-fluorobenzophenone (**17e**) (330 mg, 1.32 mmol), **16b** (422 mg, 1.38 mmol), and *p*-toluenesulfonic acid monohydrate (30 mg) in benzene (5 mL) was heated at reflux for 1.8 h. The mixture was cooled to room temperature and treated with 10% aqueous  $\text{Na}_2\text{CO}_3$  solution, and the benzene layer was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The residual material was chromatographed on silica gel with benzene-AcOEt (98:2) as eluent to give 553 mg (89%) of **18h** as pale yellow crystals. Recrystallization from  $\text{CH}_2\text{Cl}_2$ -*n*-hexane gave pale yellow prisms: mp 184–185 °C; IR (KBr) 1767, 1722, 1661, 1610, 1481, 1416, 1391  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.87 (s, 3 H,  $\text{CH}_3$ ), 4.61 and 4.36 (AB q, 2 H,  $J$  = 15.0 Hz,  $\text{CH}_2\text{N}$ ), 5.62 (d, 1 H,  $J$  = 3.5 Hz, H on the pyrrole ring), 5.95 (d, 1 H,  $J$  = 3.5 Hz, H on the pyrrole ring), 6.88–7.84 (m, 11 H, aromatic).

General Method B. The preparation of **18** by the coupling of **17** with a 1-phthalimidohexane-2,5-dione (**15**) is exemplified by the synthesis of 2',5-dichloro-2-(2,4-dimethyl-5-phthalimidomethylpyrrol-1-yl)benzophenone (**18p**). A stirred solution of 2-amino-2',5-dichlorobenzophenone (**17d**) (375 mg, 1.41 mmol), **15e** (366 mg, 1.34 mmol), and *p*-toluenesulfonic acid monohydrate (30 mg) in benzene (15 mL) was heated at reflux for 3.5 h. The mixture was cooled, diluted with benzene (20 mL), washed with water, 10% aqueous  $\text{Na}_2\text{CO}_3$  solution, and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The residual material was chromatographed on silica gel first with benzene to give 43 mg of recovered **17c** and then with benzene-AcOEt (19:1) to give 608 mg (90%) of **18p**. Recrystallization from benzene-*n*-hexane gave pale yellow needles: mp 168.5–169.5 °C; IR (KBr) 1763, 1708, 1661, 1587, 1482, 1422, 1397  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.82 (s, 3 H,  $\text{CH}_3$ ), 1.90 (s, 3 H,  $\text{CH}_3$ ), 4.63 and 4.12 (AB q, 2 H,  $J$  = 15.5 Hz,  $\text{CH}_2\text{N}$ ), 5.52 (s, 1 H, H on the pyrrole ring), 7.01–7.78 (m, 11 H, aromatic).

**Preparation of 6-Phenyl-4H-pyrrolo[1,2-a][1,4]benzodiazepines (2) (Table III).** General Method. The preparation of **2** by the action of hydrazine hydrate on **18** is exemplified by the synthesis of 8-chloro-6-(2-chlorophenyl)-1,3-dimethyl-4H-pyrrolo[1,2-a][1,4]benzodiazepine (**2p**). Compound **18p** (608 mg, 1.21 mmol) was dissolved by heating in *N,N*-dimethylformamide (2 mL). To the solution were added EtOH (8 mL) and hydrazine hydrate (0.2 mL), and the mixture was heated at reflux for 0.5 h. The EtOH was evaporated, and benzene (30

mL) was added. The mixture was heated at reflux for 5 min, cooled to room temperature, and filtered. The filtrate was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The residual material was chromatographed on silica gel with benzene-AcOEt (49:1) as eluent to give 368 mg (86%) of **2p** as yellow crystals. Recrystallization from ether-*n*-hexane gave pale yellow prisms: mp 132–133 °C; IR (KBr) 1616, 1591, 1560, 1481, 1414  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  2.10 (s, 3 H,  $\text{CH}_3$ ), 2.28 (s, 3 H,  $\text{CH}_3$ ), 5.07 and 3.94 (AB q, 2 H,  $J = 13.0$  Hz,  $\text{CH}_2\text{N}$ ), 5.97 (s, 1 H, H-2), 7.06 (m, 1 H, aromatic), 7.23–7.62 (m, 6 H, aromatic).

**Pharmacology. Methods. CNS Actions.** Male ddY mice weighing 18–24 g were used for all studies reported here. The test compounds were suspended in 5% arabic gum solution and administered orally to a group of six mice per dose. The compounds were examined suitably at three or four dosage levels selected from 100, 30, 10, 3, 1, 0.3, and 0.1 mg/kg. The  $\text{ED}_{50}$  values were calculated by the method of Litchfield–Wilcoxon.<sup>21</sup> Procedures for measuring the activities of the test compounds—antipentylentetrazole activity, antimaximal electroshock activity, taming activity in fighting mice induced by electrofootshock, muscle relaxant activity using an inclined wooden board, motor incoordinating activity, and potentiation of thiopental—have been described previously.<sup>1</sup>

**Acute Toxicity.** Male ddY mice weighing 18–24 g were used. The test compounds were suspended in 5% arabic gum solution and administered orally to a group of four mice at a dosage of 1000 and 2000 mg/kg and to a group of eight mice at a dosage of 3000 mg/kg.

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## Synthesis and Antitumor Activity of Halogen-Substituted 4-(3,3-Dimethyl-1-triazeno)quinolines

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Halogenated 4-(3,3-dimethyl-1-triazeno)quinolines were synthesized as potential antitumor agents on the basis of the biochemical pharmacological properties of existing triazenes, their structural-activity relationships, and the high melanin binding of chloroquine and iodoquine in vivo and in vitro. They were synthesized by diazotization of appropriate halogen-substituted 4-aminoquinolines in fluoboric acid at  $-5$  °C followed by coupling with dimethylamine. Among these new compounds, 8-chloro-4-(3,3-dimethyl-1-triazeno)quinoline produces significant antitumor activity against both P-388 and L1210 murine leukemias. Although only marginally active or inactive against P-388, the other chloro, bromo, or iodo analogues show activity against L1210 comparable to that of dacarbazine (DIC). However, none of these compounds is active against B-16 melanoma. Compared with DIC these new agents demonstrate a higher in vitro affinity for melanin; however, this affinity is apparently not correlated with their antitumor activity.

Although metastatic melanoma is only one of the many varieties of malignant tumors, its virulence and high mortality have stimulated studies over the ages. It comprises about 2% of all cancers, and about 80–90% of them arise in the skin.<sup>1</sup> 5-(3,3-Dimethyl-1-triazeno)-imidazole-4-carboxamide (DIC) is by far the most useful

single agent against melanoma in man. However, it has produced only temporary responses in 19% of the patients with this disease.<sup>2</sup> The lack of effective agents against melanoma justifies the continuous search for better new agents. A large number of triazenes with diverse structures have been synthesized and tested in experimental systems.<sup>3</sup>