Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.20; H, 6.99; N, 19.01.

Preparation of Azides 1. General Procedure. A solution of sodium nitrite (0.052 mol) in water (10 ml) was added dropwise to a solution of aniline **2** (0.050 mol) in 4 *N* HCl (60 ml) under vigorous stirring and ice cooling. The mixture was then neutralized by $NaHCO_3$ and a solution of sodium azide (0.050 mol) in water (35 ml) was slowly added at ca. 5°. After 30 min, the mixture was extracted with ether and the organic solution was dried over $MgSO_4$. The solvent was removed under reduced pressure and afforded practically pure azide **1**, with the exception of **1c** and **1d**, which were purified by silica gel chromatography using as eluent respectively benzene and a solution of diethyl ether–*n*-hexane (4:1). See Table I.

Decomposition of Azides 1. General Procedure. A 0.1 *M* solution of azide **1** was refluxed until all the starting material was consumed (see Table II for solvents and reaction times). The solvent was then evaporated under reduced pressure and the residue was worked up according to the procedure indicated in Table II. Physical, spectral, and analytical data of compounds **3, 7,** and **8** are collected in Table III. Compound **4**[5] gave the following NMR spectrum ($CDCl_3$): τ 2.6–3.3 (4 H, m, aromatics), 5.53 (2 H, s, CH_2), 7.90 (3 H, s, CH_3).

Catalytic Hydrogenation of Aziridine 3a. A solution of **3a** in ethanol (40 ml) was stirred under hydrogen atmosphere in the presence of Pd/C. When the theoretical amount of hydrogen was absorbed, the catalyst was filtered off and the solvent was evaporated. Distillation in vacuo of the oily residue furnished compound **5a** in 65% yield: bp 80–83° (0.4 mm) [lit.[5] bp 150–152° (24 mm)]; NMR, see ref 23.

Catalytic Hydrogenation of Aziridine 3b. Compound **5b** was obtained from **3b** according to the above procedure in 72% yield: bp 85–88° (0.4 mm); NMR ($CDCl_3$) τ 3.1–3.6 (4 H, m, aromatics), 6.20 (2 H, s, CH_2), 6.70 (1 H, broad s, NH), 8.81 (6 H, s, two CH_3).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.65; H, 7.95; N, 8.37.

Catalytic Hydrogenation of Aziridine 3c. The above procedure, when starting from **3c** (0.2 g), led to **5c** in 67% yield: mp 63° (*n*-pentane); NMR ($CDCl_3$) τ 2.5–3.6 (9 H, m, aromatics), 5.6–6.5 (4 H, m, OCH_2CH and NH), 7.1–7.4 (2 H, m, CH_2).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.60; H, 6.58; N, 6.05.

Reduction of 4. A solution of ketimine **4** (0.155 g) in anhydrous THF (10 ml) was added under stirring to a suspension of $LiAlH_4$ (0.4 g) in THF (50 ml). After 5 hr refluxing, the excess of $LiAlH_4$ was decomposed by ethyl acetate, water was added, and the mixture was extracted several times with ether. The organic solution was dried over Na_2SO_4 and evaporated. The residue was distilled in vacuo to afford **5a** in 65% yield.

Registry No.—**1a,** 55000-07-2; **1b,** 55000-08-3; **1c,** 55000-09-4; **1d,** 55000-10-7; **1e,** 55000-11-8; **1f,** 55000-12-9; **1g,** 55000-13-0; **2a,** 27096-64-6; **2b,** 55000-14-1; **2c,** 55000-15-2; **2d,** 52536-39-7; **2e,** 52536-40-0; **2f,** 31507-29-6; **2g,** 55000-16-3; **3a,** 55000-17-4; **3b,** 55000-18-5; **3c,** 55000-19-6; **4,** 55000-20-9; **5a,** 32329-20-7; **5b,** 55000-21-0; **5c,** 55000-22-1; **6** (R_1 = H; R_2 = Me), 55012-68-5; **7a,** 235-23-4; **7b,** 55000-23-2; **8a,** 55000-24-3; **8b,** 35213-60-6; 2-methyl-3-(2-nitrophenoxy)propene, 13414-54-5; 2-nitrophenol, 88-75-5; cinnamyl bromide, 4392-24-9; 3-(2-nitrophenoxy)-1-phenylpropene, 55000-25-4; 2-nitrocinnamonitrile, 55000-26-5.

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Synthesis of 3,4-Dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones

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Two new routes to the title compounds have been developed. 3,4-Dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (**3**) was prepared by treating 2-carboalkoxyphenyl isocyanate (**1**) with methylhydrazine and cyclizing the semicarbazide ester (**2**) with base. The 4-methyl isomer of **3** (**7a**) was prepared by treating 2-isocyanatobenzoyl chloride (**6a**) with methylhydrazine. Two reports which disclose syntheses of extensive numbers of 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones are shown to be in error. These routes lead, instead, to 3-amino-2,4(1*H*,3*H*)-quinazolinediones.

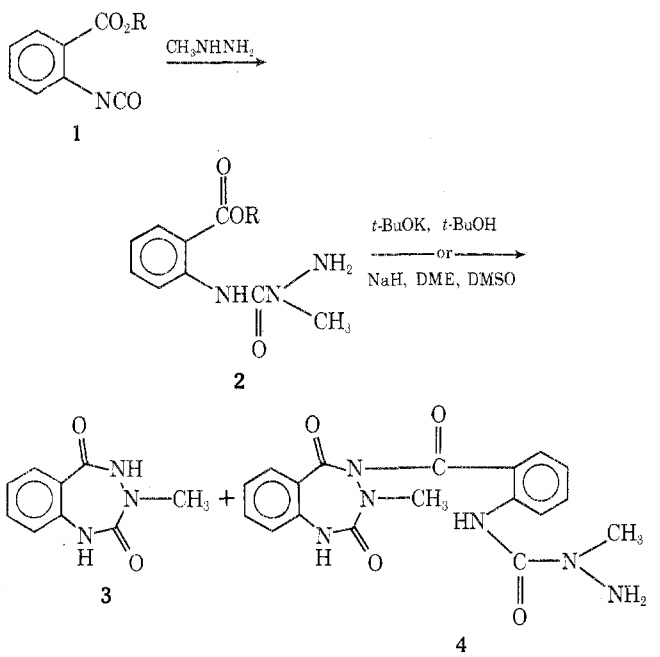
In the past several years much research effort has been expended on the preparation of benzodiazepines for evaluation as potential psychotherapeutic agents. All six classes are known, and their chemistry and pharmacology have been studied extensively.[1]

Pharmaceutical interest in the benzotriazepines has evolved from the benzodiazepines. Of the six possible classes[2] of benzotriazepines, only three have been studied to date. No representatives of the benzo-1,2,3-, 1,2,4-, or 2,3,4-triazepine classes are known. Benzo-1,3,4-triazepines[3] and benzo-1,2,5-triazepines[4] are well documented in the literature. Benzo-1,3,5-triazepines[5] are documented in a few instances.

This report deals specifically with 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones. We have developed new, unequivocal entries into this class of compound which allow us to critically examine the few reported entries, and the compounds which have been made by these routes and assigned as 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones.

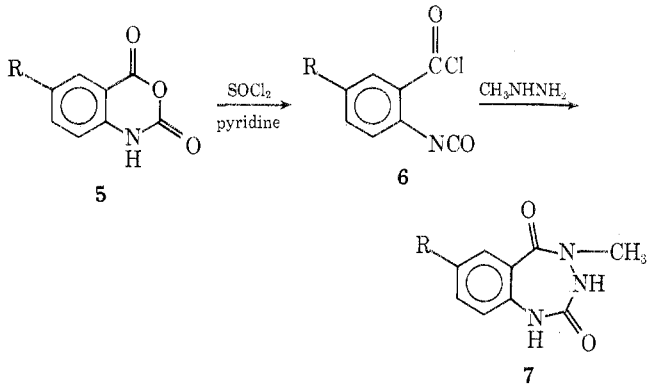
Treatment of 2-carboalkoxyphenyl isocyanates **1a** and

Scheme I



a, R = CH_3
b, R = CH_2CH_3

Scheme II



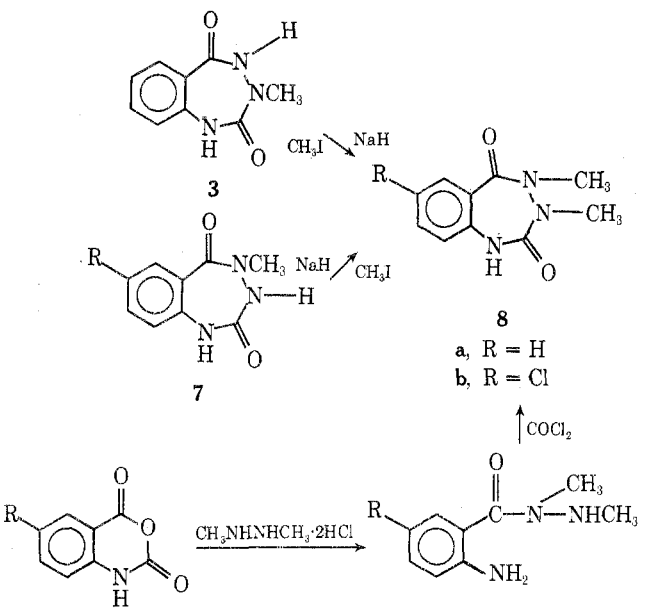
a, R = H
b, R = Cl

1b with methylhydrazine gave the semicarbazides **2a**[6] and **2b**. Cyclization of **2a** with potassium *tert*-butoxide in *tert*-butyl alcohol or **2b** with sodium hydride in dimethoxyethane (DME) and dimethyl sulfoxide (DMSO) gave a mixture of benzotriazepinedione **3** and a compound to which we assign structure **4**, as shown in Scheme I. Compounds **3** and **4** were separated by subjecting the mixture to Soxhlet extraction with dioxane. The electron impact mass spectrum of **4** contained no parent peak. The fragmentation pattern resembled that of **3**.

Treatment of isatoic anhydride (**5a**) with thionyl chloride and a catalytic amount of pyridine gave 2-isocyanatobenzoyl chloride (**6a**), as reported.[8] Reaction of **6a** with methylhydrazine yielded benzotriazepinedione **7a**, isomeric with **3**. A solid polymeric material was also formed in the reaction, but it is worthy of note that **7a** was the *only isolable monomeric material*. Likewise, 2-isocyanato-5-chlorobenzoyl chloride (**6b**) was prepared and treated with methylhydrazine to yield **7b** as the sole monomeric product. (See Scheme II.) Thus, by varying the electrophilic reactivity of the o-carboxy-derived group on the phenyl isocyanate from carboalkoxy to carbonyl chloride, groups which are less and more susceptible to nucleophilic attack, respectively, than the isocyanato group, we have controlled the site for initial attack by the methyl-bearing nitrogen of methylhydrazine and effected selective syntheses for the isomeric benzotriazepinediones **3** and **7a**.

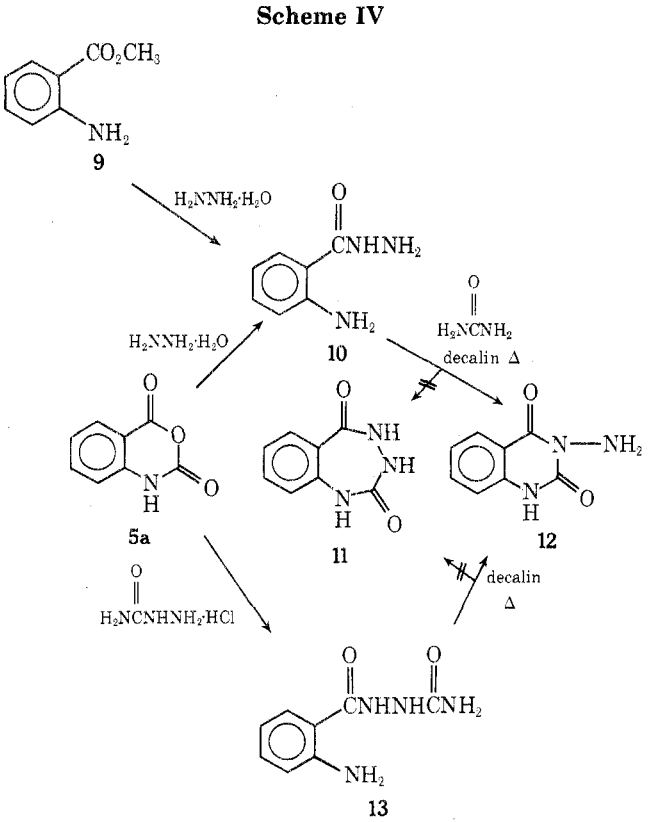
Alkylation of either **3** or **7a** with methyl iodide, using sodium hydride as the base in DMF, yielded the same dimethylbenzotriazepinedione **8a**. The results of these experiments served to relate **3** and **7a** to each other and to the known literature compound **8a**, which was prepared from isatoic anhydride and *sym*-dimethylhydrazine by Hromatka et al.[9] as shown in Scheme III. Compound **7b** was also converted to the known compound **8b** in similar fashion. Hromatka et al. report two other authentic benzo-

Scheme III



a, R = H
b, R = Cl

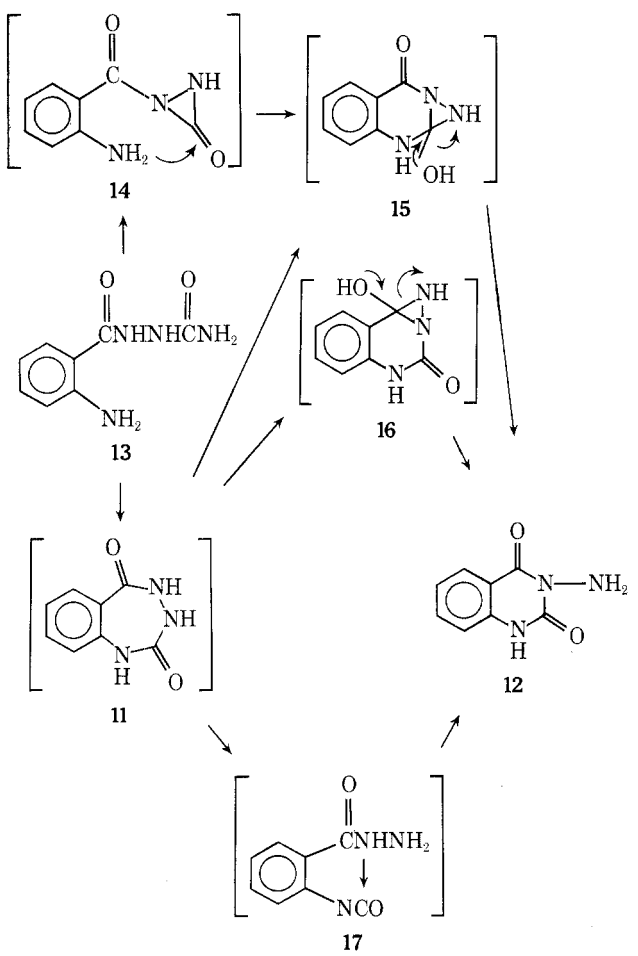
Scheme IV



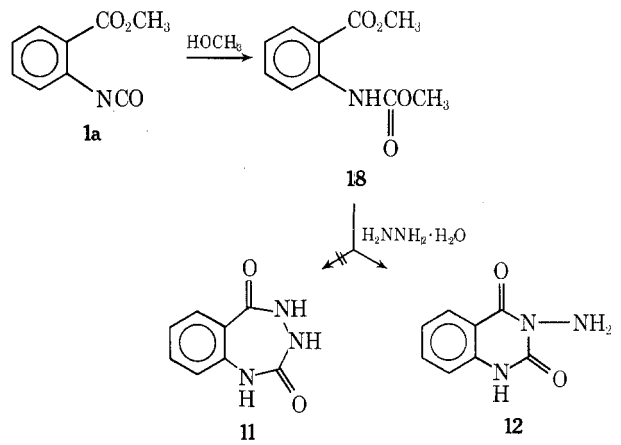
triazepinediones in addition to compounds **8a** and **8b**. These compounds represent the only authentic group of 3,4-dihydro-1*H*-1,3,4-benzotriazepinediones in the literature (vide infra). It is interesting to note that compounds **3** and **7** are selectively alkylated in the 4 and 3 positions, respectively, with no apparent competitive alkylation at position 1, since *N*-phenylamides are N-alkylated under these conditions.[10] This selectivity is apparently another demonstration of the α effect.[11]

Langis and Charest[12] report two methods for the preparation of 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione (**11**) and derivatives of **11**. Their methods for **11** involve the cyclization of 1-(2-aminobenzoyl)semicarbazide in decalin at reflux and treatment of 2-aminobenzoylhydrazine (**10**) with urea in decalin at reflux. In a reexamination of their work, we treated **10** with urea in decalin at reflux and found that the product of this reaction was 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**12**) and not **11** (Scheme IV). The product of this reaction was identical in all respects with a sample of **12** whose synthesis is reported in the literature.[13] We feel that 19 of the 21 additional compounds reported as benzotriazepinediones by Langis and Charest, which were prepared (with one exception) by treating 2-aminobenzoylhydrazines (most of which contained substituents on the terminal hydrazide nitrogen) with urea in decalin at reflux, are probably 3-amino-2,4(1*H*,3*H*)-quinazolinediones.[14]

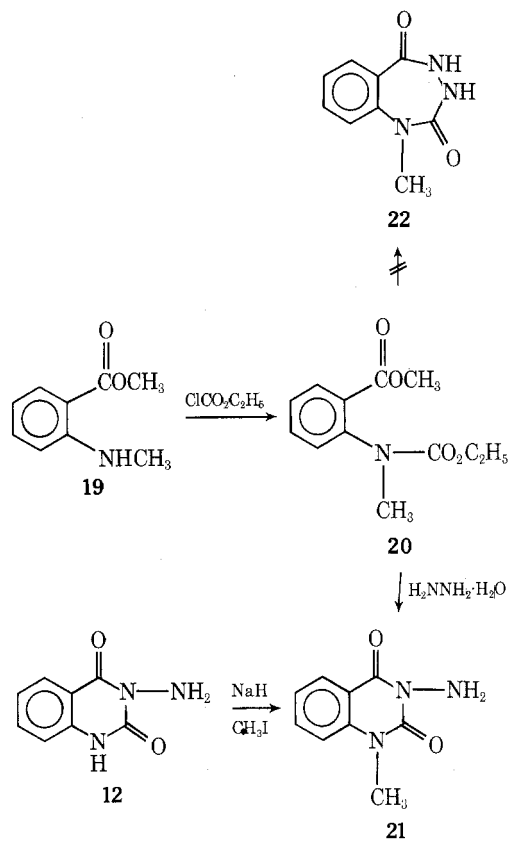
Thermal cyclization of 1-(2-aminobenzoyl)semicarbazide (**13**) in decalin also yielded 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**12**) in good yield (Scheme IV). This transformation is less obvious than the conversion of **10** to **12**. It is possible that **11** is an intermediate in this cyclization, generating **12** through the secondary intermediates **15, 16,** or **17**. Alternatively, **12** could arise from intermediate **14**.



Scheme V



Scheme VI



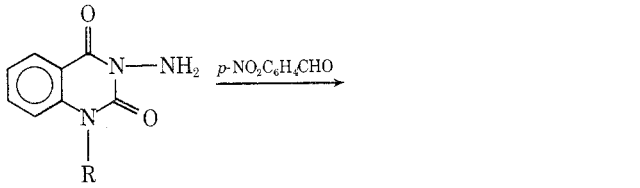
A recent U.S. Patent by Bailey[15a] discloses a preparative method for 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones. The general method of preparation involves the condensation of alkyl *N*-carboxyanthranilates with hydrazines. In a reexamination of this reaction, we treated methyl *N*-carbomethoxyanthranilate (**18**) with hydrazine hydrate and isolated only the quinazolinedione **12**, in good yield (Scheme V).

We next prepared intermediate **20**, which is also reported by Bailey, and treated it with hydrazine hydrate. The product isolated was 1-methyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione (**21**) and not **22**, as reported by Bailey. Confirmation of structure was achieved by methylating **12** to yield **21**. See Scheme VI.

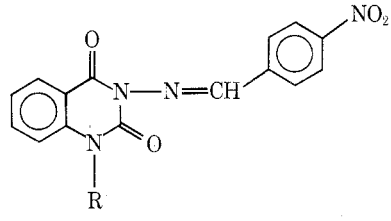
We feel that the above results cast serious doubt on the structures of at least 70 of the 77 compounds disclosed as benzotriazepinediones by Bailey.[15b] It appears that the six-membered quinazolinedione ring system is thermodynamically favored over the seven-membered benzotriaze-

pinedione ring system, and that even in well-intentioned experiments designed to produce the latter system, quinazolinediones result where possible.

Additional confirmation for the presence of primary amino functionalities in **12** and **21** was established chemically. Both **12** and **21** were condensed with *p*-nitrobenzaldehyde to yield the respective Schiff bases **23** and **24.**

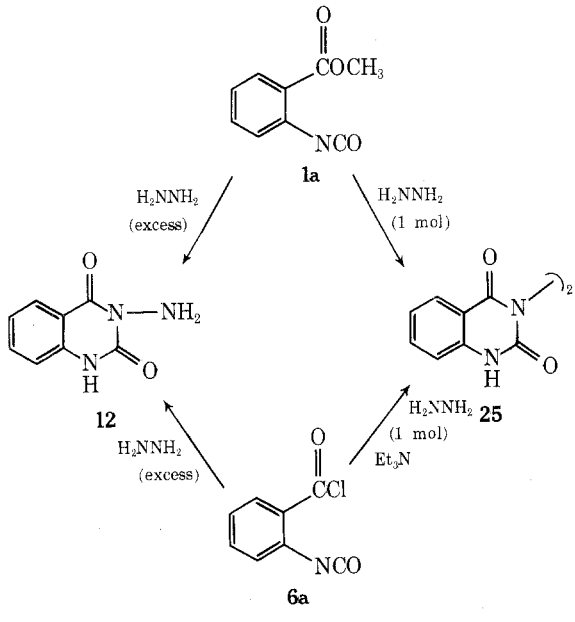


12, R = H
21, R = CH_3



23, R = H
24, R = CH_3

Other available possible precursors to **12** (or **11**) were **1a** or **6a.** The addition of **1a** or **6a** to excess hydrazine afforded almost quantitative yields of **12.** However, when the order of addition was reversed and equimolar amounts of hydrazine were used, good yields of bis compound **25** resulted.



Experimental Section

Preparation of Methyl 2-{[(1-Methylhydrazino)carbonyl]-amino}benzoate (2a). A 422-g (2.38 mol) quantity of 2-carbomethoxyphenyl isocyanate (**1a**)[16] in 500 ml of CH_2Cl_2 was added to a solution of 110 g (2.38 mol) of methylhydrazine (Aldrich) in 500 ml of CH_2Cl_2 over a 60-min period with ice-bath cooling. The solution (whose ir spectrum showed no N=C=O stretch) was concentrated and the resulting solid was recrystallized in crops from CH_2Cl_2–hexane to yield 406 g (77%) of **2a** as clear prisms: mp 123.5–125.5°; ir (Nujol) 3350, 3260, and 3210 (NH), 1700 (ester C=O), 1670 cm^{-1} (semicarbazide C=O); NMR ($CDCl_3$) δ 11.64 (s, 1, NH), 8.82–8.58 (m, 1, aromatic), 8.00–7.85 (m, 1, aromatic), 7.64–7.30 (m, 1, aromatic), 7.07–6.75 (m, 1, aromatic), 3.97 (s, 2, NH_2), 3.83 (s, 3, OCH_3), 3.19 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.80; H, 5.87; N, 18.61.

A 4.46-g (20.0 mmol) quantity of **2a** and 3.02 g (20.0 mmol) of *p*-nitrobenzaldehyde (Aldrich) in 150 ml of ethanol were heated at reflux for 3 hr. The precipitate was removed by filtration to yield 5.93 g (83%) of the Schiff base: mp 232–242° (EtOH); ir (Nujol) 3200, 1680, 1580 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.73. Found: C, 57.10; H, 4.59; N, 15.83.

Preparation of 3,4-Dihydro-3-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (3). A. *tert*-Butoxide Method. A solution of 53.4 g (0.239 mol) of **2a** and 26.8 g (0.239 mol) of potassium *tert*-butoxide (Aldrich) in 1100 ml of *tert*-butyl alcohol was heated at reflux under a nitrogen atmosphere for 18 hr. The solution was evaporated to one-third volume, diluted with water (1 l.), and acidified with concentrated HCl. The resulting precipitate was collected and washed with ether to yield 28.4 g of a mixture containing **3** and **4**, mp 229–231°. The mixture was subjected to Soxhlet extraction with dioxane to remove, as prisms from the cooled dioxane extract, 16.1 g (35%) of **3:** mp 242–245°; ir (Nujol) 3240 and 3110 (NH), 1710 (C=O), 1670 cm^{-1} (C=O); NMR (DMSO) δ 10.10 (s, 1, NH), 9.54 (s, 1, NH), 7.85–6.97 (m, 4, aromatic), 2.93 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 191 (molecular ion).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.70; H, 4.81; N, 21.70.

The material remaining in the thimble, after additional lixiviation with hot dioxane (4 × 100 ml), yielded 7.83 g (17%) of **4:** mp 237–239°; ir (Nujol) 3350 and 3230 (NH), 1675 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 217 (1), 191 (33), 163 (83), 162 (97), 146 (93), 30 (100). A field ionization mass spectrum displayed a parent peak at *m/e* 382.

Anal. Calcd for $C_{18}H_{18}N_6O_4$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.40; H, 5.05; N, 22.25.

A 100-MHz NMR spectrum of **4** was obtained in DMSO-d_6 and in DMSO-d_6 with added trifluoroacetic acid (TFA). The added TFA served to sharpen the spectrum and to shift any signals due to H_2O or exchangeable protons downfield. The DMSO-d_6–TFA spectrum indicated the presence of two or more conformers in solution, showing NH resonances at δ 11.78, 11.72, 11.17, 10.14, and 8.86, aromatic multiplets at 8.14–7.89 (4), 7.80–7.34 (6), and 7.34–7.00 (6), and methyl signals at 3.34 (broad, 3), 3.23 (sharp, 3), 2.79 (sharp, 3), and 2.71 (broad, 3). The integral intensities of the NH signals could not be accurately determined, but it was clear that the integral ratio of total aromatic protons to total NCH_3 protons was 4:3, respectively.

B. Sodium Hydride Method. A 31.9-g (0.167 mol) quantity of **2b** (mp 152–154°, prepared in similar fashion to **2a** in 84% yield) and 10.2 g (0.423 mol) of NaH (Alfa) in 600 ml of dimethoxyethane and 30 ml of DMSO were heated at reflux for 15 hr. (The reaction was monitored by withdrawing aliquots and diluting them with water. When starting ester still remained, its presence was evident at this point by its appearance as a precipitate.) The reaction mixture was cooled, diluted with 3 l. of ice-cold water, and acidified with concentrated HCl to yield a tan precipitate which was collected and dried to yield 22.4 g. Lixiviation with several portions of hot dioxane left 4.31 g (14%) of **4.** Crystallization of **3** from the hot dioxane extract yielded 6.97 g (22%).

Preparation of 2-Isocyanatobenzoyl Chlorides 6a and 6b. 2-Isocyanatobenzoyl chloride (**6a**) was prepared as reported[8] in 82% yield, bp 85° (0.3 mm) [lit.[8] bp 105° (6 mm)].

A 496-g (2.51 mol) quantity of 5-chloroisatoic anhydride (Aldrich), 2 kg of $SOCl_2$, and 3 ml of pyridine were heated at reflux. After 8 days (solution had not resulted), an additional 1 kg of $SOCl_2$ and 2 ml of pyridine were added. After 2 weeks, 2 l. of dioxane was added. After 3 weeks at reflux, solution had resulted, and the reaction solution was cooled and concentrated to yield a slurry. Filtration removed 176 g of yellow solid.[17] The filtrate (475 g) was distilled to yield 153 g (31%) of **6b:** mp 53–57°; bp 115–117° (1.3 mm); ir (Nujol) 3100 (CH), 2280 (NCO), 1740 cm^{-1} (C=O).

Preparation of 3,4-Dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (7a). To a stirred solution of 20.5 g (0.113 mol) of **6a** in 1 l. of CH_2Cl_2 at 0° was added a solution of 5.21 g (0.113 mol) of methylhydrazine and 114 g (0.113 mol) of triethylamine in 200 ml of CH_2Cl_2 over a 30-min period. The reaction solution was cloudy during the addition, clear at the end, and after ca. 15 min a precipitate began forming. After 20 hr, the precipitate was collected, washed with H_2O, and dried to yield 3.04 g of solid. The filtrate was washed with H_2O and concentrated to 150 ml. An additional 0.08 g of solid was precipitated and collected as above: total yield of **7a** 3.12 g (14.4%);[18] mp 266–267°; ir (Nujol) 3270 and 3190 (NH), 1725 (C=O), 1630 cm^{-1} (C=O); NMR (DMSO) δ 9.44 (s, 1, NH), 8.84 (s, 1, NH), 7.90–6.93 (m, 4, aromatic), 3.30 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 191 (molecular ion).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.70; H, 4.73; N, 22.17.

Preparation of 3,4-Dihydro-4-methyl-7-chloro-1*H*-1,3,4-benzotriazepine-2,5-dione (7b). To a stirred solution of 131 g (0.607 mol) of **6b** in 1200 ml of CH_2Cl_2 at 0° was added a solution of 28.0 g (0.607 mol) of methylhydrazine and 61.4 g (0.607 mol) of triethylamine in 400 ml of CH_2Cl_2 over a 30-min period. The reaction appearance was identical with that of **7a.** After 1 hr the precipitate was collected and dried to yield 19.8 g (14%), mp 280–284°, of **7b:** mp 293–295° (dioxane–hexane); ir (Nujol) 3250 and 3150 (NH), 1725 (C=O), 1630 cm^{-1} (C=O); NMR (DMSO) δ 9.73 (s, 1, NH), 9.03 (s, 1, NH), 7.88–7.02 (m, 3, aromatic), 3.27 (s, 3, CH_3).

Anal. Calcd for $C_9H_8ClN_3O_2$: C, 47.90; H, 3.57; N, 18.62. Found: C, 48.10; H, 3.64; N, 18.99.

Preparation of 3,4-Dihydro-3,4-dimethyl-1*H*-1,3,4-benzotriazepine-2,5-dione (8a). A. From 3. To a stirred mixture of 0.900 g (37.5 mmol) of NaH in 20 ml of DMF under nitrogen was added 5.73 g (30.0 mmol) of **3.** To the resulting yellow solution was slowly added 10 ml of CH_3I with ice-bath cooling. The reaction was exothermic and a white precipitate resulted. After 2 hr of stirring at room temperature, the reaction mixture was partitioned between H_2O and CH_2Cl_2 and the organic extracts were dried (Na_2SO_4) and concentrated to leave an oil which was triturated with ether to yield 3.80 g (62%) of **8a:** mp 185–188° (lit.[9] mp 189–190°); ir (Nujol) 3260 (NH), 1705 (C=O), 1625 cm^{-1} (C=O); NMR (DMSO) δ 9.78 (s, 1, NH), 8.05–7.05 (m, 4, aromatic), 3.23 (s, 3, CH_3), 2.94 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.50; H, 5.48; N, 20.59.

B. From 7a. To a stirred mixture of 1.20 g (50.0 mmol) of NaH in 25 ml of DMF under nitrogen was added 8.70 g (45.5 mmol) of **7a.** To the resulting yellow solution was slowly added 15 ml of CH_3I with ice-bath cooling. The reaction was exothermic and a white precipitate resulted. After 3 hr of stirring at room temperature the reaction mixture was partitioned between H_2O and CH_2Cl_2 and the organic extracts were dried (Na_2SO_4) and concentrated to yield 8.60 g of white solid after trituration with hexane, mp 175–185°. Crystallization from CH_2Cl_2–hexane yielded 5.40 g (58%) of **8a,** mp 186–189°; ir of this sample was identical with that made from **3,** and a mixture melting point of the two samples was undepressed.

Preparation of 3,4-Dihydro-3,4-dimethyl-7-chloro-1*H*-1,3,4-benzotriazepine-2,5-dione (8b). To a stirred mixture of 0.96 g (40.0 mmol) of NaH in 25 ml of DMF under nitrogen was added 9.02 g (40.0 mmol) of **7b.** After 5 min of stirring a 10-ml volume of CH_3I was added slowly with ice-bath cooling. The mixture was partitioned between H_2O and CH_2Cl_2 and the organic extracts were dried (Na_2SO_4) and concentrated to leave 12.9 g of sticky solid. Recrystallization (CH_2Cl_2–ethanol) afforded 5.34 g (55%) of **8b:** mp 218–220° (lit.[9] mp 222°); ir (Nujol) 3250 and 3175 (NH), 1705 (C=O), 1635 cm^{-1} (C=O); NMR (DMSO) δ 9.53 (s, 1, NH), 7.77–6.95 (m, 3, aromatic), 3.22 (s, 3, CH_3), 2.97 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{10}ClN_3O_2$: C, 50.11; H, 4.20; N, 17.53. Found: C, 50.40; H, 4.23; N, 17.63.

Preparation of 3-Amino-2,4(1*H*,3*H*)-quinazolinedione (12). A. From Methyl 2-[(Methoxycarbonyl)amino]benzoate (18). To 35.4 g (0.200 mol) of **1a** was added 10 ml of methanol with ice-bath cooling. After the exothermic addition the ir (neat) showed no remaining isocyanate. The excess methanol was evaporated to leave 40.69 (97%) of **18** as a light oil (lit.[19] mp 59–61°): ir (neat) 3300 (NH), 1715 (carbamate C=O), 1690 cm^{-1} (ester C=O).

To 40.6 g (0.194 mol) of **18** in 250 ml of absolute ethanol was added 85 ml of hydrazine hydrate (Eastman). After 15 min of stirring a voluminous precipitate was present.[20] After 16 hr at reflux, the reaction mixture was cooled and the precipitate was collected and dried to afford 30.7 g (89%) of **12:** mp 287.5–290° (lit.[14] mp 291.5–293°); ir (Nujol) 3340 (NH), 1725 (C=O), 1645 cm^{-1} (C=O); NMR (DMSO) δ 10.50–8.33 (broad signal, NH), 8.12–7.05 (m, 4, aromatic), 5.52 (s, 2, NH_2).

An 8.85-g (50.0 mmol) quantity of **12,** 7.88 g (52.1 mmol) of *p*-nitrobenzaldehyde (Aldrich), and 450 ml of absolute ethanol were heated at reflux for 36 hr. The mixture was cooled and the precipitate was removed by filtration and washed with ethanol to leave 14.4 g (93%) of Schiff base **23:** mp 318–319°; ir (Nujol) 3190 (NH), 1720 (C=O), 1665 cm^{-1} (C=O); NMR (DMSO) δ 8.75 (s, 1, aldimine), 8.35–6.90 (m, 8, aromatic).

Anal. Calcd for $C_{15}H_{10}N_4O_4$: C, 58.06; H, 3.25; N, 18.06. Found: C, 58.23; H, 3.30; N, 18.02.

B. From 2-Aminobenzoylhydrazine (10). 2-Aminobenzoylhydrazine, mp 118–122° (lit.[21] mp 120–121°), was prepared in 86% yield according to the method of Barlin.[21,22] A 30.2-g (0.200 mol) quantity of **10,** 12.0 g (0.200 mol) of urea, and 300 ml of decalin were heated at reflux until evolution of ammonia ceased (4 hr). The reaction mixture was cooled and the precipitate was collected, washed with ether, and recrystallized (DMSO–H_2O) to yield 28.69 g (82%) of **12** (mp 281–284°).

C. From 1-(2-Aminobenzoyl)semicarbazide (13). A sample of **13,** mp 194–196°, was prepared using the method described by Langis and Charest[12] for 1-(2-amino-5-chlorobenzoyl)semicarbazide. A 10.0-g (0.0515 mol) quantity of **13** and 75 ml of decalin were heated at reflux for 3 hr. The mixture was cooled and the precipitate was collected, washed with ether, and recrystallized (DMSO–H_2O) to yield 6.10 g (67%) of **12** (mp 286–290°).

Preparation of 1-Methyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione (21). A. From Methyl 2-[(Methyl)amino]benzoate (19). 2-[(Methyl)amino]benzoic acid was converted to ester **19,** bp 75° (0.15 mm) [lit.[23] bp 130–131° (15 mm)], using a standard procedure.[24] Carbamate ester **20,** bp 120–125° (0.50 mm) [lit.[15] bp 95–104° (0.12–0.20 mm)], was prepared from **19** and ethyl chloroformate in 66% yield. A solution of 5.50 g (23.2 mmol) of **20** and 13.0 ml of hydrazine hydrate in 40 ml of ethanol was heated at reflux for 2 hr. The mixture was cooled and the precipitate was collected, washed with ethanol, and dried to yield 2.23 g (50%) of **21:** mp 240–241°; ir (Nujol) 3310 and 3240 (NH), 1710 (C=O), 1640 cm^{-1} (C=O); NMR (TFA) δ 8.70–7.60 (m, 4, aromatic), 3.92 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 191 (molecular ion).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.30; H, 4.69; N, 22.15.

A 1.00-g (5.23 mmol) quantity of **21,** 0.790 g (5.23 mmol) of *p*-nitrobenzaldehyde, and 50 ml of absolute ethanol were heated at reflux for 8 hr. The mixture was cooled and the precipitate was removed by filtration and washed with ethanol to leave 1.30 g (77%) of Schiff base **24:** mp 246–247°; ir (Nujol) 1700 (C=O), 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.45; H, 3.44; N, 17.33.

B. From 12. To a stirring mixture of 2.27 g (94.5 mmol) of NaH in 40 ml of DMF under nitrogen was added 16.8 g (94.5 mmol) of **12.** After 5 min, a 20-ml volume of CH_3I was added slowly and with cooling, to produce a white precipitate in the exothermic reaction medium. After 4 hr of stirring the reaction mixture was diluted with water and the resulting precipitate was collected and dried to yield 10.7 g (59%) of **21** (mp 228–235°). Recrystallization of a portion from ethanol gave white plates, mp 238–241°, whose ir was identical with that of the material prepared in part A.

Preparation of 3,3′(2*H*,2′*H*)-biquinazoline-2,2′,4,4′-(1*H*,1′*H*)-tetrone (25). A. From 6a. To 18.2 g (0.100 mol) of **6a** in 100 ml of CH_2Cl_2 at 0° was added a solution of 3.22 g (0.100 mol) of 95% hydrazine (Eastman) and 10.1 g (0.100 mol) of triethylamine in 50 ml of CH_2Cl_2 over a 30-min period. The mixture was stirred for 1 hr and the precipitate was collected, washed with water, and dried to afford 21.1 g (66%) of **25:** mp >340° (DMSO–H_2O); ir (Nujol) 3280 (NH), 1625, 1605, 1580 cm^{-1}; NMR (DMSO) δ 8.45–7.25 (m, aromatic); mass spectrum (70 eV) *m/e* 322 (molecular ion).

Anal. Calcd for $C_{16}H_{10}N_4O_4$: C, 59.63; H, 3.13; N, 17.39. Found: C, 59.88; H, 3.05; N, 17.50.

B. From 1a. To 17.7 g (0.100 mol) of **1a** in 75 ml of CH_2Cl_2 at 0° was added 3.22 g (0.100 mol) of 95% hydrazine in 20 ml of CH_2Cl_2 over a 20-min period. After 1 hr the precipitate was collected to afford 13.6 g (42%) of **25** (mp >340°) whose ir was identical with that made in part A.

Additional Preparations of 12. A. From 6a. To an ice-cold solution of 16.0 g (0.500 mol) of hydrazine in 100 ml of CH_2Cl_2 was added 9.08 g (50.0 mmol) of **6a** in 50 ml of CH_2Cl_2 over a 35-min period. After 1 hr the precipitate was removed by filtration, washed with H_2O, and dried to yield 8.02 g (90%) of **12,** mp 280–284°.

B. From 1a. To an ice-cold solution of 32.0 g (1.00 mol) of hydrazine in 200 ml of CH_2Cl_2 was added 17.7 g (0.100 mol) of **1a** in 100 ml of CH_2Cl_2 over a 60-min period. After 1 hr the precipitate was removed by filtration and washed with CH_2Cl_2 to yield 15.6 g (88%) of **12,** mp 283–287°.

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ratories) for the 100-MHz NMR and field ionization mass spectral studies, respectively.

Registry No.—**1a,** 1793-07-3; **2a,** 55043-76-0; **2a** Schiff base, 55043-77-1; **2b,** 55043-78-2; **3,** 55043-79-3; **4,** 55043-80-6; **5b,** 4743-17-3; **6a,** 5100-23-2; **6b,** 18928-48-8; **7a,** 55043-81-7; **7b,** 55043-82-8; **8a,** 23829-79-0; **8b,** 23829-80-3; **10,** 1904-58-1; **12,** 30386-01-7; **13,** 55043-83-9; **18,** 7143-42-2; **19,** 85-91-6; **20,** 33923-02-3; **21,** 55043-84-0; **23,** 55043-85-1; **24,** 55043-86-2; **25,** 55043-87-3; methylhydrazine, 60-34-4; *p*-nitrobenzaldehyde, 555-16-8; potassium *tert*-butoxide, 3999-70-0; methanol, 67-56-1; urea, 57-13-6; ethyl chloroformate, 541-41-3.

References and Notes

(1) (a) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68,** 747 (1968); (b) L. H. Sternbach in "The Benzodiazepines", Raven Press, New York, N.Y., 1973, pp 1–27.

(2) Class here refers to position of the nitrogen atoms in the triazepine ring and not to positions of unsaturation. The six classes, thus, refer to nitrogen atoms in the following positions: 1,3,4; 1,2,5; 1,3,5; 1,2,4; 1,2,3; and 2,3,4.

(3) For example, see H. Kohl, P. D. Desai, A. N. Dohadwalla, and N. J. de Souza, *J. Pharm. Sci.*, **63,** 838 (1974).

(4) (a) For example, see S. Rossi, British Patent 1,219,847; *Chem. Abstr.*, **74,** 141901j (1971); S. Rossi, German Patent 2,064,207; *Chem. Abstr.*, **75,** 76854a (1971). (b) We have developed a new entry into this class of compound in our laboratories which will be the subject of a later report.

(5) For example, see G. Doleschall, G. Hornyak, B. Agai, G. Simig, J. Fetter, and K. Lempert, *Tetrahedron Lett.*, 5069 (1973), and references cited therein.

(6) The structure of **2a** follows from spectral and chemical evidence. The NCH_3 and NH_2 signals in the NMR spectrum of **2a** appear as singlets at δ 3.19 and 3.97, respectively. Compound **2a** formed a Schiff base with *p*-nitrobenzaldehyde (see Experimental Section). Based on the known relative nucleophilicities of the nitrogen atoms in methylhydrazine, **2a** is the expected isomer from the reaction of **1a** with methylhydrazine. Other authors[7] have reported reactions of methylhydrazine with phenyl isocyanates to yield products analogous to **2,** but offer no evidence to distinguish their products from the other possible isomers.

(7) (a) M. Wilcox, *J. Med. Chem.*, **11,** 171 (1968); (b) French Patent 1,521,959; *Chem. Abstr.*, **71,** 3166k (1969).

(8) Y. Iwakura, K. Uno, and S. Kang, *J. Org. Chem.*, **31,** 142 (1966).

(9) O. Hromatka, F. Krenmüller, and M. Knollmüller, *Monatsh. Chem.*, **100,** 934 (1969).

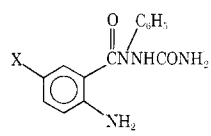
(10) (a) E. Thielepape, *Chem. Ber.*, **68,** 751 (1935); (b) W. S. Fones, *J. Org. Chem.*, **14,** 1099 (1949); (c) see also the preparation of **21** from **12** in the Experimental Section.

(11) A. K. Butler in "Organic Reaction Mechanisms", B. Capon and C. W. Rees, Ed., Wiley, New York, N.Y., 1972, p 189.

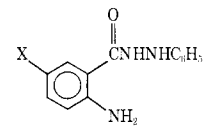
(12) A. L. Langis and M. P. Charest, *Chim. Ther.*, 349 (1967).

(13) R. L. Jacobs, *J. Heterocycl. Chem.*, **7,** 1337 (1970). We thank Dr. Jacobs, of Sherwin-Williams Chemicals, for an authentic sample of this compound. Compound **12** was also identical with a commercial sample of 3-amino-2,4(1*H*,3*H*)-quinazolinedione obtained from Carbolabs Inc., New Haven, Conn.

(14) Two of the benzotriazepinediones reported by Langis and Charest were prepared from the *N*-(2-aminobenzoyl)semicarbazides i and ii by thermal cyclization in decalin. Since the reported melting points for the products thus obtained from i and ii do not closely jibe, respectively, with those of compounds obtained from their treatment of iii and iv with urea in decalin (compounds which we suspect are quinazolinediones), the products derived from i and ii may be authentic benzotriazepinediones.



i, X = H
ii, X = Cl



iii, X = H
iv, X = Cl

(15) (a) D. M. Bailey, U.S. Patent 3,607,866 (1971); *Chem. Abstr.*, **75,** 140910v (1971); (b) Dr. Bailey has examined a preprint of this manuscript and concurs with these findings.

(16) N. P. Peet and S. Sunder, *J. Org. Chem.*, **39,** 1931 (1974).

(17) The structure of this material has been identified and will be disclosed in a future report.

(18) The reactant concentration in this preparation was 0.094 *M*. When run at a reactant concentration of 0.25 *M*, the yield of **7a** was 10.7%.

(19) E. Kühle and R. Wegler, *Justus Liebigs Ann. Chem.*, **616,** 183 (1958).

(20) An aliquot of the reaction mixture withdrawn at this point showed the precipitate to be **12.**

(21) G. B. Barlin, *J. Appl. Chem.*, **12,** 148 (1962).

(22) We have also prepared **10** by heating isotoic anhydride and hydrazine hydrate neat or in DMF at 50°.

(23) J. R. A. Pollack and R. Stevens, Ed., "Dictionary of Organic Compounds", Vol. . 4, Oxford University Press, London, 1965, p 2119.

(24) A. I. Vogel, "Practical Organic Chemistry", Longmans, Green and Co., New York, N.Y., 1956, p 1000.

Synthesis of Fused Phenothiazines. 2,3-Dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-1,3-dione and 6*H*,16*H*-[1,5]Diazocino[3,2,1-*kl*:7,6,5-*k'l'*]diphenothiazine-6,16-dione

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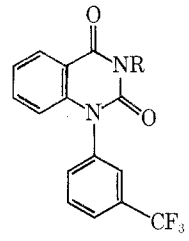
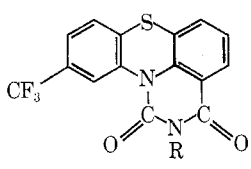
10-Trifluoromethyl-2,3-dihydro-1*H*-pyrimido[5,6,1-*kl*]phenothiazine-3-one-1-thione (**6**) was prepared starting from 8-trifluoromethylphenothiazine-1-carboxylic acid (**3**) by thermal cyclization of the acid isothiocyanate. This was converted to tee 1,3-dione by acid hydrolysis of the 1-methyl mercaptan derivative. Alkylation and oxidation to sulfoxide and sulfone derivatives are described. Pyrolysis of the anhydride of **3** gave 3,13-bis(trifluoromethyl)-6*H*,16*H*-[1,5]diazocino[3,2,1-*kl*:7,6,5-*k'l'*]diphenothiazine-6,16-dione.

Quinazoline-2,4-diones (**1**), derived from flufenamic acid, were recently described as anti-inflammatory agents.[1]



1



2

Since we previously observed anti-inflammatory properties with 8-trifluoromethylphenothiazine-1-carboxylic acid (**3**),[2] an analog of flufenamic acid, we undertook preparation of some pyrimidinediones (**2**) derived from **3.**

Typical syntheses of quinazolinediones such as **1** involve fusing the *N*-arylanthranilic acid, ester, or amide with urea, thiourea, or ethyl carbamate at 200°.[3] However, these reaction conditions using **3** returned unreacted starting material. Also treatment of the ethyl ester of **3** with sodium cyanate in trifluoroacetic acid, another quinazoline-1,3-dione synthesis,[4] also failed. A possible cause for these failures was a low reactivity of the diaryl nitrogen owing to it