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The title compounds, **7a** and its 9-chloro analog **7b**, were prepared in three steps from methyl *N*-phenylanthranilates. Thus, methyl *N*-phenylanthranilate (**3a**) was treated with oxalyl chloride to yield 2-[(2-chloro-1,2-dioxoethyl)phenylamino]benzoic acid methyl ester (**4a**). Treatment of **4a** with methylhydrazine gave 2-([2-(1-methylhydrazino)-1,2-dioxoethyl]phenylamino)benzoic acid methyl ester (**6a**), which was cyclized with sodium hydride in dimethylformamide to produce **7a**. Alkylation of **7a** and **7b** with iodomethane afforded the respective 5-methyl derivatives **8a** and **8b**. A survey of the known literature benzotriazocines is presented.

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Of the eight benzotriazocine systems which are theoretically possible, only two are known (1). These are the 1,3,4- and the 1,4,5-benzotriazocine systems.

The syntheses of benzotriazocines are confined to the very recent chemical literature, with one exception. The older chemical literature contains a report describing the synthesis of 1,2,4,5-tetrahydro-1,4,5-benzotriazocine-3,6-dione (2). The recent patent literature describes many derivatives of 6-phenyl-3,4-dihydro-1,4,5-benzotriazocin-2(1*H*)one (3), some of which (3b,d) are cited as central nervous system agents. The oxime of 8-chloro-3,4-dihydro-3-methyl-6-phenyl-1,4,5-benzotriazocin-2(1*H*)one and its derivatives have also recently been reported (4), as well as related benzotriazocinium salts (5).

Only one member of the other known class of benzotriazocines has been reported. Recently described was the preparation of 6-phenyl-2,5-di-2-pyridinyl-1,3,4-benzotriazocine (6).

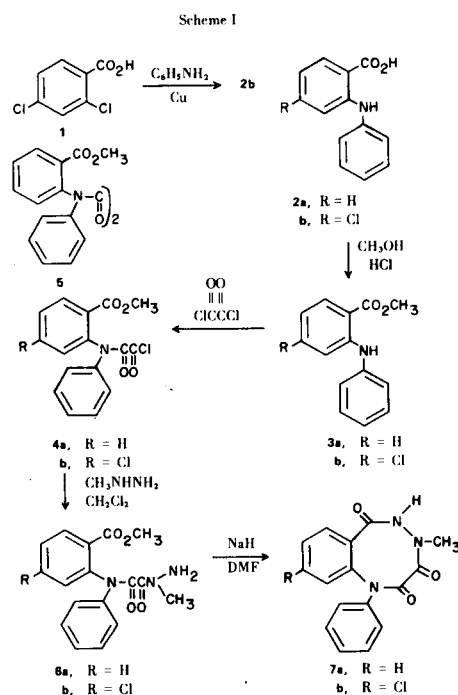
In this report we describe the preparation of additional members of the 1,4,5-benzotriazocine class. These compounds are, namely, 4,5-dihydro-4-methyl-1-phenyl-1,4,5-benzotriazocine-2,3,6(1*H*)triones and their 5-methyl derivatives.

N-Phenylanthranilic acid (**2a**) and its 4-chloro derivative **2b**, which was prepared from 2,4-dichlorobenzoic acid and aniline in the presence of copper powder, were esterified to yield the corresponding methyl esters **3a** and **3b**. Amides **4a** and **4b**, respectively, resulted when esters **3a** and **3b** were treated with oxalyl chloride. In the preparation of **4a**, a small amount of the symmetric oxamide **5** was also isolated.

Treatment of **4a** and **4b** with methylhydrazine yielded the hydrazides **6a** and **6b**, respectively. Cyclization of these hydrazides with sodium hydride in dimethylformamide produced the respective benzotriazocines **7a** and **7b**. These cyclization reactions are similar to those reported earlier by us (7) in the preparation of benzotriazepinediones from hydrazide-ester precursors. Benzotriazocines **7** were cleanly produced in high yield from the

hydrazide-esters **6**. The cyclizations were easily monitored by thin layer chromatography, and the formation of coproducts was not observed. See Scheme I.

Alkylation of benzotriazocines **7a** and **7b** with methyl iodide in dimethylformamide, using sodium hydride as the base, afforded good yields of the respective benzotriazocines **8a** and **8b**. These methylations produced derivatives of the parent compounds which displayed



higher melting points and were less polar (as determined by thin layer chromatography). See Scheme II.

An examination of the nmr spectra of compounds **4a**, **4b**, **5**, **6a** and **6b**, all of which contain oxamide functionality, was interesting and informative. With each compound, the presence of more than one amide rotamer was indicated by the presence of multiple methyl signals. The ambient-temperature nmr spectra for these compounds are described in the Experimental Section.

The novel 1,4,5-benzotriazocines described in this report were prepared efficiently and in straight-forward fashion. We are currently exploring synthetic routes to other benzotriazocine systems.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727 Spectrophotometer, nmr with Varian T-60 and Perkin-Elmer R32 (90 MHz) spectrometers, and mass spectra with a Finnigan GC/MS Model 3000D (electron impact and chemical ionization) mass spectrometer at 70 eV. Combustion analyses for C, H, and N were performed by Dow Analytical Laboratories.

Materials.

4-Chloro-*N*-phenylanthranilic acid (**2b**), m.p. 190-194° [lit. (8a) m.p. 198-200°; lit. (8b) m.p. 201°] was prepared from **1** using the method of Chertsov (8a). Methyl *N*-phenylanthranilate (**3a**), b.p. 140° (0.10 mm), m.p. 53-56° [lit. (9a) m.p. 57-58°; lit. (9b) m.p. 58-59°] and methyl 4-chloro-*N*-phenylanthranilate (**3b**), b.p. 127-130° (1.5 mm), m.p. 58-59° [lit. (10) m.p. 58.5-59°] were prepared from **2a** and **b**, respectively, using standard esterification procedures.

2-[(2-Chloro-1,2-dioxoethyl)phenylamino]benzoic Acid Methyl Ester (**4a**) and 2,2-[(1,2-Dioxo-1,2-ethanediylo)bis(phenylimino)]-bisbenzoic Acid Dimethyl Ester (**5**).

A 44.2-g. (0.200 mole) quantity of **3a** was dissolved in 200 ml. toluene and 50.5 g. (0.398 mole) of oxalyl chloride (Aldrich) in 50 ml. of toluene was added over a 10-minute period with icebath cooling. Gas evolution was noted throughout the addition. After 30 minutes, an ir spectrum of an aliquot indicated the absence of starting material. The solution was concentrated and 50 ml. of carbon tetrachloride was added. The mixture was concentrated and this process was twice more performed to leave a viscous oil. Trituration with 75 ml. of ether caused a white solid to separate, which was collected and air-dried to yield 7.44 g. (7.3%) of crude **5**. The crude material was dissolved in chloroform, concentrated to a small volume and treated with ether to yield a white solid. This solid was recrystallized from ethyl acetate to yield pure **5** as pale yellow prisms: m.p. 233-235°; ir (Nujol): 1725 (C=O), 1675 (broad C=O) cm⁻¹; nmr (DMSO-*d*₆): δ 8.28-6.44 (m, 18H, aromatic), 3.80-3.48 (3 or more singlets, CH₃ groups); mass spectrum (70 eV, electron impact): *m/e* 254 (fragment of highest mass); ms (70 eV, chemical ionization, methane): *m/e* 509 (M⁺ +1), 537 (M⁺ +29), 549 (M⁺ +41).

Anal. Calcd. for C₃₀H₂₄N₂O₆: C, 70.85; H, 4.76; N, 5.51. Found: C, 70.90; H, 4.68; N, 5.56.

The ether filtrate was concentrated and triturated with hexane to yield a pale green solid which was collected and air-dried to yield 55.2 g. (87%) of **4a**; m.p. 64-67°; ir (Nujol): 1780 (C=O), 1725 (C=O), 1680 (C=O) cm⁻¹; nmr (deuteriochloroform): δ

8.09-7.72 (m, 2H, protons *ortho* to ester groups), 7.47-6.90 (m, 16H, remaining aromatic), 3.84 and 3.78 (2 singlets in *ca.* 2:1 ratio, respectively, 6H, CH₃ groups); nmr (acetone-*d*₆): δ 8.14-7.62 (m, 2H, protons *ortho* to ester groups), 7.62-7.01 (m, 16H, remaining aromatic), 3.87 and 3.82 (2 singlets in *ca.* 1:2 ratio, respectively, 6H, CH₃ groups); mass spectrum (70 eV, electron impact): *m/e* 317 (molecular ion). Compound **4a** appeared to be unstable in storage, and combustion analysis was not attempted.

An ether solution of **4a** was treated with ammonium hydroxide and the resulting amide was collected and recrystallized (ethanol) to yield the corresponding oxamide derivative, m.p. 153.5-155°.

Anal. Calcd. for C₁₆H₁₄N₂O₄: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.26; H, 4.98; N, 9.19.

4-Chloro-2-[(2-chloro-1,2-dioxoethyl)phenylamino]benzoic Acid Methyl Ester (**4b**).

A 30.0-g. (0.114 mole) quantity of **3b** was dissolved in 125 ml. of toluene and 32.0 g. (0.250 mole) of oxalyl chloride was added over a 10-minute period. After 20 hours, the orange solution was concentrated and 50 ml. of carbon tetrachloride was added. The mixture was concentrated and this process was twice more performed to leave a viscous oil. The oil was dissolved, with vigorous stirring, in 100 ml. of ether. Upon standing, light yellow crystals formed which were collected and air-dried to yield 33.8 g. (84%) of **4b**, m.p. 105-109°; m.p. 109-111° (benzene-hexane); ir (Nujol): 1760 (C=O), 1715 (C=O), 1650 (C=O) cm⁻¹; nmr (deuteriochloroform): δ 7.83 (d, J = 8 Hz, 1H, H *ortho* to ester group), 7.45-6.88 (m, 7H, remaining aromatic), 3.84 and 3.80 (2 singlets, 3H, CH₃); ms (70 eV, chemical ionization, methane): *m/e* 352 (M⁺ +1), 380 (M⁺ +29), 392 (M⁺ +41).

Anal. Calcd. for C₁₆H₁₁Cl₂NO₄: C, 54.46; H, 3.15; N, 3.98. Found: C, 54.30; H, 3.22; N, 4.13.

2-[(2-(1-Methylhydrazino)-1,2-dioxoethyl)phenylamino]benzoic Acid Methyl Ester (**6a**).

A 10.0-g. (31.5 mmoles) quantity of **4a** in 50 ml. of dichloromethane was added, over a 15-minute period with icebath cooling, to a solution of 25 ml. of methylhydrazine in 100 ml. of dichloromethane. The organic layer was washed with water, dried (sodium sulfate) and concentrated. The resulting oil crystallized upon standing to yield 8.13 g. (79%) of **6a**; m.p. 155.5-156.5°; ir (Nujol): 3340 and 3240 (NH), 1720 (C=O), 1680 (C=O), 1660 (C=O) cm⁻¹; nmr (deuteriochloroform): δ 8.00-7.67 (m, 1H, H *ortho* to ester group), 7.53-6.97 (m, 8H, remaining aromatic), 8.99 (broad s, 2H, NH₂, deuterium oxide-exchangeable), 3.81, 3.84 and 3.86 (three singlets, 3H, OCH₃), 3.25, 2.90 and 2.83 (three singlets, 3H, NCH₃); ms (70 eV, electron impact): *m/e* 327 (molecular ion).

Anal. Calcd. for C₁₇H₁₇N₃O₄: C, 62.37; H, 5.24; N, 12.84. Found: C, 62.40; H, 5.36; N, 12.58.

4-Chloro-2-[(2-(1-methylhydrazino)-1,2-dioxoethyl)phenylamino]benzoic Acid Methyl Ester (**6b**).

A 26.5-g. (75.2 mmoles) quantity of **4b** in 150 ml. of methylene chloride was added, over a 25-minute period with icebath cooling, to a solution of 70 ml. of methylhydrazine in 250 ml. of methylene chloride. After 45 minutes of stirring, the solution was washed with water, saturated sodium chloride solution, and dried (sodium sulfate). The solution was concentrated and the resulting solid was recrystallized from benzene-hexane to give 19.8 g. (73%) of **6b**; m.p. 162-164°; ir (Nujol) 3310 and 3210 (NH), 1730 (C=O), 1665 (broad C=O) cm⁻¹; nmr (deuteriochloroform): δ 7.94-7.64 (m, 1H, H *ortho* to ester group), 7.53-7.00 (m, 7H, remaining aromatic), 3.98 (broad s, 2H, NH₂, deuterium oxide-exchangeable), 3.85 and 3.82 (2 singlets, 3H, OCH₃), 3.20 and 2.88 (2 singlets,

ca. in 1:2 ratio, respectively, 3H, NCH₃); ms (70 eV, chemical ionization, methane): m/e 362 (M⁺ +1), 390 (M⁺ +29), 402 (M⁺ +41).

Anal. Calcd. for C₁₇H₁₆ClN₃O₄: C, 56.43; H, 4.46; N, 11.60. Found: C, 56.14; H, 4.42; N, 11.75.

4,5-Dihydro-4-methyl-1-phenyl-1,4,5-benzotriazocine-2,3,6(1H)-trione (**7a**).

To a stirred slurry of 1.20 g. (25.0 mmoles) of sodium hydride, 50% oil dispersion (Alfa), in 40 ml. of dimethylformamide (freshly distilled from 4Å^o molecular sieve) under a nitrogen atmosphere was added, dropwise, 7.70 g. (23.5 mmoles) of **6a** in 50 ml. of dry dimethylformamide. The reaction was monitored by tlc (Silica Gel, 9:1::chloroform:methanol). After stirring for 15 hours, the brown solution was poured into water and the resulting yellow solution was acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic extract was dried (sodium sulfate) and concentrated to leave 5.50 g. (79%) of **7a**: m.p. 215-217° (methanol); ir (Nujol): 3175 (broad NH), 1665 (broad C=O) cm⁻¹; nmr (DMSO-d₆): δ 7.90-7.10 (m, 10H, aromatic and NH), 2.97 (s, 3H, CH₃); ms (70 eV, chemical ionization, methane): m/e 296 (M⁺ +1), 324 (M⁺ +29), 336 (M⁺ +41).

Anal. Calcd. for C₁₆H₁₃N₃O₃: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.00; H, 4.58; N, 14.22.

9-Chloro-4,5-dihydro-4-methyl-1-phenyl-1,4,5-benzotriazocine-2,3,6(1H)-trione (**7b**).

To a stirred slurry of 2.00 g. (41.7 mmoles) of sodium hydride, 50% oil dispersion, in 75 ml. of dry dimethylformamide under a nitrogen atmosphere was added, over a 1-hour period, 14.4 g. (39.8 mmoles) of **6b** in 100 ml. of dry dimethylformamide. The reaction was monitored by tlc (Silica Gel, 9:1::chloroform:methanol). After stirring for 15 hours, the solution was poured into water and the resulting solution was acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic extract was washed with saturated sodium chloride solution, dried (sodium sulfate) and concentrated. The resulting oil, upon trituration with ether, gave a tan solid which was collected and air-dried to afford 8.19 g. (62%) of **7b**, m.p. 215-216.5° (ethanol); ir (Nujol): 3130 (NH), 1685 (C=O), 1650 (C=O) cm⁻¹; nmr (DMSO-d₆): δ 7.82-7.00 (m, 9H, aromatic and NH), 2.95 (s, 3H, CH₃); ms (70 eV, chemical ionization, methane): m/e 330 (M⁺ +1), 358 (M⁺ +29), 370 (M⁺ +41).

Anal. Calcd. for C₁₆H₁₂ClN₃O₃: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.10; H, 3.81; N, 12.69.

4,5-Dihydro-4,5-dimethyl-1-phenyl-1,4,5-benzotriazocine-2,3,6(1H)trione (**8a**).

To a stirred mixture of 0.170 g. (7.08 mmoles) of dry sodium hydride (Alfa) in 10 ml. of dry dimethylformamide under a nitrogen atmosphere was added a solution of 2.00 g. (6.77 mmoles) of **7a** in 10 ml. of dry dimethylformamide. The resulting solution was cooled in an icebath and a solution of 0.994 g. (7.00 mmoles) of iodomethane in 5 ml. of dry dimethylformamide was added, dropwise, over a 10-minute period. After 1 hour of stirring at icebath temperature, stirring was continued at 25° for 6 hours. The reaction was monitored by tlc (Silica Gel, 9:1::chloroform:methanol). The reaction solution was poured into water and the resulting solid was collected and air-dried to yield 1.38 g. (63%) of **8a**: m.p. 255-257°; ir (Nujol): 1700 (shoulder), 1670 (C=O) cm⁻¹; nmr (DMSO-d₆): δ 7.84-7.20 (m, 9H, aromatic), 3.33 (s, 3H, CH₃), 3.00 (s, 3H, CH₃); ms (70 eV, chemical ionization, methane): m/e 310 (M⁺ +1), 338 (M⁺ +29), 350 (M⁺ +41).

Anal. Calcd. for C₁₇H₁₅N₃O₃: C, 66.00; H, 4.89; N, 13.59.

Found: C, 65.80; H, 5.12; N, 13.62.

9-Chloro-4,5-dihydro-4,5-dimethyl-1-phenyl-1,4,5-benzotriazocine-2,3,6(1H)trione (**8b**).

To a stirred mixture of 0.680 g. (14.2 mmoles) of sodium hydride, 50% oil dispersion, in 15 ml. of dry dimethylformamide under a nitrogen atmosphere was added, dropwise, 4.00 g. (12.1 mmoles) of **7b** in 15 ml. of dry dimethylformamide. The resulting solution was cooled in an icebath and 2.13 g. (15.0 mmoles) of iodomethane in 10 ml. of dry dimethylformamide was added, dropwise, over a 15-minute period. After stirring for 1 hour at icebath temperature, stirring was continued at 25° for 2 hours. The reaction was monitored by tlc (Silica Gel, 9:1::chloroform:methanol). The reaction mixture was poured into water and the resulting precipitate was collected and air-dried to yield 3.35 g. (80%) of **8b**, m.p. 252-254°; m.p. 258.5-260° (methanol); ir (Nujol): 1720 (C=O), 1690 (C=O) cm⁻¹; nmr (DMSO-d₆): δ 7.67-6.94 (m, 8H, aromatic), 3.23 (s, 3H, CH₃), 2.94 (s, 3H, CH₃); ms (70 eV, chemical ionization): m/e 344 (M⁺ +29).

Anal. Calcd. for C₁₇H₁₄ClN₃O₃: C, 59.39; H, 4.10; N, 12.20. Found: C, 59.39; H, 4.21; N, 12.36.

REFERENCES AND NOTES

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