Synthesis of 3,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-ones

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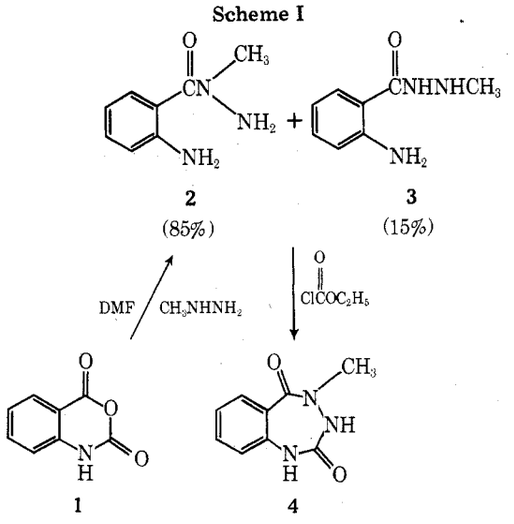
Received October 6, 1975

The reaction of isatoic anhydride (1) with methylhydrazine in dimethylformamide at 45–50 °C yielded predominantly 1-(*o*-aminobenzoyl)-1-methylhydrazine (2), whose structure was confirmed by conversion to the known 3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (4) with ethyl chloroformate. Hydrazide 2 was treated with triethyl ortho esters to produce 2-substituted 3,4-dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-ones **5a–d.**

The reactions of isatoic anhydride with hydrazines to yield anthraniloyl hydrazides has been frequently used to generate starting materials for heterocyclic syntheses. Thus, isatoic anhydride has been reacted with hydrazine hydrate,[1] phenylhydrazine,[2] acylhydrazines,[3] carboalkoxyhydrazines,[4] symmetrical[5] and unsymmetrical[6,7] dialkylhydrazines, semicarbazides,[8] and 2-pyridylamidrazone[9] to yield the corresponding anthraniloyl hydrazides. We wish to report the reaction of methylhydrazine with isatoic anhydride (1) to yield 1-(*o*-aminobenzoyl)-1-methylhydrazine (2), and the utility of 2 in the preparation of 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones.

Treatment of a dimethylformamide (DMF) solution of isatoic anhydride[10] with methylhydrazine at 45–50 °C yielded, after concentration and distillation, a 76% yield of 2 and the isomeric 2-(*o*-aminobenzoyl)-1-methylhydrazine (3) in a ratio of 85:15 (by NMR), respectively.[11] That the mixture was predominantly 2 was confirmed by its reaction product with ethyl chloroformate. Treatment of the 85:15 mixture of 2 and 3 with ethyl chloroformate and triethylamine in methylene chloride gave a 26% yield of 3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (4), which was identical with an authentic sample of 4 whose unequivocal synthesis has been reported.[1] See Scheme I.

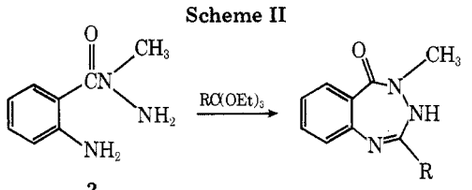
Scheme I



Hydrazide 2 (containing 15% of 3)[12] was then reacted with triethyl orthoformate in ethanol to yield 3,4-dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-one (**5a**). The other three benzotriazepinones shown in Scheme II were also prepared in good yield in similar fashion from the appropriate ortho esters.

The ultraviolet spectra of compounds **5a–d** all display absorption maxima at 229–231 nm with ϵ_{max} values of 17 000–21 000. These values are consistent with the expected[13] and reported[9a] values for the *N*-phenylimino chromophore.

Scheme II



5a, R = H (46%)
b, R = CH_3 (57%)
c, R = C_2H_5 (58%)
d, R = C_6H_5 (63%)

The benzotriazepinones **5a–d** were prepared for pharmacological evaluation as central nervous system agents, as an integral part of our research efforts in this area. A recent report by Takahashi et al.[9a] describes the synthesis of similar compounds, namely, 3,4-dihydro-2-(2-pyridyl)-5*H*-1,3,4-benzotriazepin-5-ones.

Experimental Section[14]

Reaction of Isatoic Anhydride (1) with Methylhydrazine.[11] An 81.6-g (0.500 mol) quantity of 1[10] was dissolved in 250 ml of dry DMF and warmed to 45 °C. A solution of 23.5 g (0.510 mol) of methylhydrazine (Aldrich) in 100 ml of DMF was added over a 15-min period. After 45 min at 45–50 °C, CO_2 evolution had ceased and the solution was concentrated to a viscous oil. Distillation afforded 62.7 g (76%) of an 85:15 mixture of 2 and 3, respectively: bp 170–180 °C (1.0–3.0 mm); ir (neat) 3450, 3350, and 3250 (NH), 1610 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.45–6.94 (m, 2, aromatic), 6.90–6.35 (m, 2, aromatic), 4.70 (broad s, 4, both NH_2 groups), 3.10 and 2.60 (two singlets, 85:15 ratio, corresponding to NCH_3 groups in 2 and 3, respectively);[15] mass spectrum (70 eV) *m/e* 165 (molecular ion).

Anal. Calcd for $C_8H_{11}N_3O$: C, 58.20; H, 6.71; N, 25.39. Found: C, 58.20; H, 6.57; N, 25.44.

Preparation of 3,4-Dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (4). An 8.42-g (51.0 mmol) quantity of 2, 5.53 g (51.0 mmol) of ethyl chloroformate, and 6.1 g (60 mmol) of triethylamine in 25 ml of CH_2Cl_2 were heated at reflux for 2 h. The resulting mixture (a white precipitate was present) was partitioned between water and CH_2Cl_2 and the organic layer was separated, dried (Na_2SO_4), and concentrated to yield 2.50 g (26%) of 4, mp 266–267 °C (lit.[1] mp 266–267 °C). The infrared spectrum of 4 was identical with that of an authentic sample,[1] and a mixture melting point of 4 with an authentic sample was undepressed.

Preparation of 3,4-Dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-one (5a). An 8.26-g (50.0 mmol) quantity of 2[12] and 7.41 g (50.0 mmol) of triethyl orthoformate (Aldrich) in 20 ml of EtOH were heated at reflux for 15 h. The yellow solution was concentrated and the resulting yellow oil was triturated with EtOH to afford 4.0 g (46%) of **5a**: mp 159–161 °C (yellow prisms from EtOH); ir (Nujol) 3300 (NH), 1675 cm^{-1} (C=O); uv λ_{max} (96% EtOH) 231 nm (log ϵ 5.32), 260 sh (4.33), 288 sh (4.47); NMR ($CDCl_3$) δ 7.93–7.74 (m, 1, H ortho to C=O), 7.37–7.05 (m, 1, H para to C=O), 7.05–6.74 (m, 3, H para to N and CH=NH), 6.67–6.47 (m, 1, H ortho to N), 3.33 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 175 (molecular ion).

Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.60; H, 5.11; N, 23.88.

Preparation of 3,4-Dihydro-2,4-dimethyl-5*H*-1,3,4-benzotriazepin-5-one (5b). An 8.26-g (50.0 mmol) quantity of 2[12] and 8.11 g (50.0 mmol) of triethyl orthoacetate (Aldrich) in 50 ml of EtOH were

heated at reflux for 12 h. The yellow solution was concentrated to a small volume. Trituration with ether afforded 5.35 g (57%) of **5b**: mp 132–133 °C (yellow prisms from EtOH–hexane); ir (Nujol) 3300 (NH), 1685 cm^{-1} (C=O); uv λ_{max} (95% EtOH) 228 nm (log ϵ 5.25), 252 sh (4.97), 288 sh (4.51); NMR ($CDCl_3$) δ 8.00–7.82 (m, 1, H ortho to C=O), 7.35–7.15 (m, 1, H para to C=O), 7.10–6.85 (m, 1, H para to N), 6.75–6.60 (m, 1, H ortho to N), 6.45 (broad s, 1, NH, D_2O exchangeable), 3.30 (s, 3, NCH_3), 2.07 (s, 3, CCH_3); mass spectrum (70 eV) *m/e* 189 (molecular ion).

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.60; H, 5.92; N, 21.93.

Preparation of 2-Ethyl-3,4-dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-one (5c). An 8.26-g (50.0 mmol) quantity of **2**[12] and 8.81 g (50.0 mmol) of triethyl orthopropionate (Aldrich) in 50 ml of EtOH were heated at reflux for 12 h. The light yellow solution was concentrated to a thick oil and crystallized from EtOH–hexane to afford 5.92 g (58%) of **5c** (yellow prisms): mp 103–104.5 °C; ir (Nujol) 3250 (NH), 1665 cm^{-1} (C=O); uv λ_{max} (95% EtOH) 229 nm (log ϵ 5.24), 251 sh (4.98), 285 sh (4.41); NMR ($CDCl_3$) δ 8.00–7.83 (m, 1, H ortho to C=O), 7.40–7.16 (m, 1, H para to C=O), 7.16–6.77 (m, 3, remaining aromatic plus NH), 3.37 (s, 3, NCH_3), 2.38 (q, J = 5 Hz, 2, CH_2), 1.17 (t, J = 5 Hz, 3, CH_2CH_3); mass spectrum (70 eV) *m/e* 203 (molecular ion).

Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.30; H, 6.49; N, 20.56.

Preparation of 3,4-Dihydro-4-methyl-2-phenyl-5*H*-1,3,4-benzotriazepin-5-one (5d). An 8.26-g (50.0 mmol) quantity of **2**[12] and 11.2 g (50.0 mmol) of triethyl orthobenzoate (ICN Pharmaceuticals, Inc.) in 40 ml of EtOH were heated at reflux for 12 h. The dark yellow solution was concentrated and the resulting solid was recrystallized from EtOH–ether to afford 7.90 g (63%) of **5d** (yellow prisms): mp 162–163.5 °C; ir (Nujol) 3260 (NH), 1610 cm^{-1} (C=O); uv λ_{max} (95% EtOH) 229 nm (log ϵ 5.34), 250 sh (4.25), 297 sh (4.81); NMR ($CDCl_3$) δ 8.03–7.85 (m, 1, H ortho to C=O), 7.85–7.65 (m, 2, aromatic), 7.55–7.26 (m, 4, aromatic), 7.15–6.82 (m, 2, aromatic), 6.79 (s, 1, NH, D_2O exchangeable), 3.43 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 251 (molecular ion).

Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.60; H, 5.23; N, 16.65.

Registry No.—**1**, 118-48-9; **2**, 59169-69-6; **3**, 59169-47-0; **5a**, 59169-76-5; **5b**, 59169-80-1; **5c**, 59187-60-9; **5d**, 59169-87-8; methyhydrazine, 60-34-4; triethyl orthoformate, 122-51-0; triethyl orthoacetate, 78-39-7; triethyl orthopropionate, 115-80-8; triethyl orthobenzoate, 1663-61-2.

References and Notes

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(2) (a) R. H. Clark and E. C. Wagner, *J. Org. Chem.*, **9**, 61 (1944). (b) The product of the reaction of isatoic anhydride with phenylhydrazine is 2-(*o*-aminobenzoyl)-1-phenylhydrazine.
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(7) E. H. Wolf and B. J. Duffy, Abstracts, 170th National Meeting of the American Chemical Society, Chicago, Ill., Aug 25–29, 1975, No. ORGN-97.
(8) A. L. Langis and M. P. Charest, *Chim. Ther.*, 349 (1967).
(9) (a) M. Takahashi, S. Onizawa, and T. Satoh, *Bull. Chem. Soc. Jpn.*, **47**, 2724 (1974). (b) The product of the reaction of isatoic anhydride with 2-pyridylamidrazone is 2-aminobenzoic acid 2-[(imino-2-pyridyl)methyl]hydrazide.
(10) The isatoic anhydride (mp 243–247 °C dec, colorless prisms) used in this reaction was prepared as described by N. P. Peet and S. Sunder, *J. Org. Chem.*, **39**, 1931 (1974), from methyl anthranilate.
(11) We are indebted to Dr. R. L. Jacobs of Sherwin-Williams Chemicals for suggesting these reaction conditions in a private communication.
(12) The mixture of hydrazides **2** and **3** (85:15, respectively) was used in this reaction. Yield is based on the total weight of the starting mixture.
(13) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", 2d ed, Wiley, New York, N.Y., 1967, p 162.
(14) Melting points are uncorrected. Ir spectra were recorded with a Perkin-Elmer 727B instrument; NMR spectra with Varian T-60 and Perkin-Elmer R32 (90 MHz) spectrometers; uv spectra with a Cary 15 spectrophotometer; mass spectra with a Hitachi RMU-6D mass spectrometer. Combustion analyses were performed by Dow Analytical Laboratories.
(15) The position of the NCH_3 group assigned to **3** was identical with that found for an authentic sample of **3**, whose synthesis will be described in a future report.[3c] The 85:15 mixture of hydrazides **2** and **3** was also substantiated by VPC analysis (5 ft × 0.125 in. 5% SE-30, 225 °C, 30 ml/min of He) where **2** eluted at 1.7 min and **3** at 2.3 min. Coinjection of this mixture with authentic **3** enhanced the peak at 2.3 min.
(16) Another paper by R. W. Leiby and N. D. Heindel, describing compounds **5a, b,** and **d**, appears in this issue.

Preparation and Utility of 1-Acetyl-1-methylhydrazine

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Received October 6, 1975

An efficient, simple synthesis of 1-acetyl-1-methylhydrazine (**1**) from acetyl chloride and methylhydrazine is reported. The utility of this protected methylhydrazine unit is demonstrated by the preparation of 1-methyl-4-phenylsemicarbazide (**5**) and 2-(*o*-nitrobenzoyl)-1-methylhydrazine (**14**). 2-(*o*-Aminobenzoyl)-1-acetyl-1-methylhydrazine (**9**), which was prepared either from **1** and isatoic anhydride (**10**) or from **1** and *o*-nitrobenzoyl chloride (**7**) followed by reduction, was cyclized to 2-methyl-3-(methylamino)-4(3*H*)-quinazolinone (**11**) with 10% sulfuric acid. The mechanism of this transformation, which demonstrates the utility of **1** in heterocyclic synthesis, is discussed.

1-Acetyl-1-methylhydrazine has been prepared from the monoacetylhydrazone of 2,3-butanedione by methylation of the potassium salt with methyl iodide and subsequent hydrolysis.[1] (An earlier report,[2] describing 1-acetyl-1-methylhydrazine as a solid, mp 98 °C, as the product from this same synthetic procedure is in error.) This three-step synthesis is cumbersome and the overall yield is poor.

A more recent procedure[3] describes the preparation of 1-acetyl-1-methylhydrazine from methylhydrazine and acetic anhydride in acetic acid (99% purity in 46% yield) or pyridine (96% purity in 76% yield). These procedures suffer the disadvantages of requiring specialized equipment, specific temperature monitoring, a long reaction time, a neutralization step which produces troublesome sodium acetate trihydrate, and extractions with a toxic solvent (pyridine). Distillation of the crude product is also troubled by the presence of pyridine, water, methylhydrazine, and a significant amount of unidentified white solid. These drawbacks are obviated by the following procedure, which is exceedingly simple.

A methylene chloride solution of acetyl chloride was added to a rapidly stirring solution of 3 equiv of methylhydrazine in methylene chloride. The methylhydrazine hydrochloride was