Synthesis of a Novel Indolobenzodiazepine

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2-[(5-Methyl-1,3,4-oxadiazol-2-yl)methyl]benzenamine (**15**) was prepared in four steps from *o*-nitrophenylacetic acid, and treated with triethyl orthoformate in an attempt to prepare an oxadiazolobenzodiazepine. However, the resulting product was 13-(5-methyl-1,3,4-oxadiazol-2-yl)-5*H*-indolo[2,1-*b*][1,3]benzodiazepine monohydrate (**16**). Indolobenzodiazepine **16** is the first reported member of a novel ring system. Interesting features of the synthesis of **16** are discussed, including the mechanism of formation from **15**.

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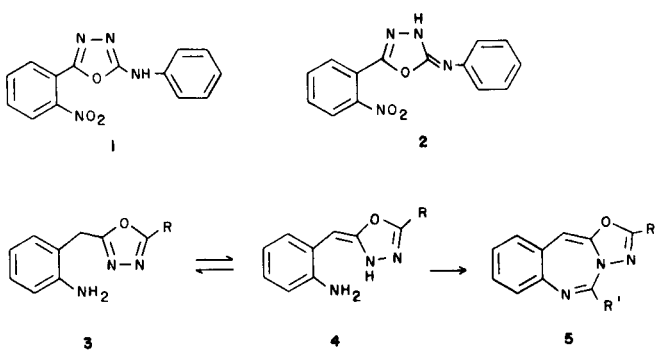
A recent report [1] from our laboratory described the preparation of 2-arylamino-5-(*o*-nitrophenyl)-1,3,4-oxadiazoles as synthetic intermediates. One of these compounds crystallized in different forms (from different solvents), which displayed distinctly different solid state infrared spectra. We surmised that these two crystalline forms may be tautomers **1** and **2** (Scheme I). If such tautomerism was occurring, we felt that a benzyl group in place of the phenylamino group might also undergo tautomerism. Thus, we planned to prepare an aminobenzyloxazoline of general structure **3**, which we envisioned might tautomerize to **4**, and subsequently be trapped by cyclization with an appropriate reagent to produce a 2,5-disubstituted 1,3,4-oxadiazolo[3,2-*c*][1,3]benzodiazepine (**5**).

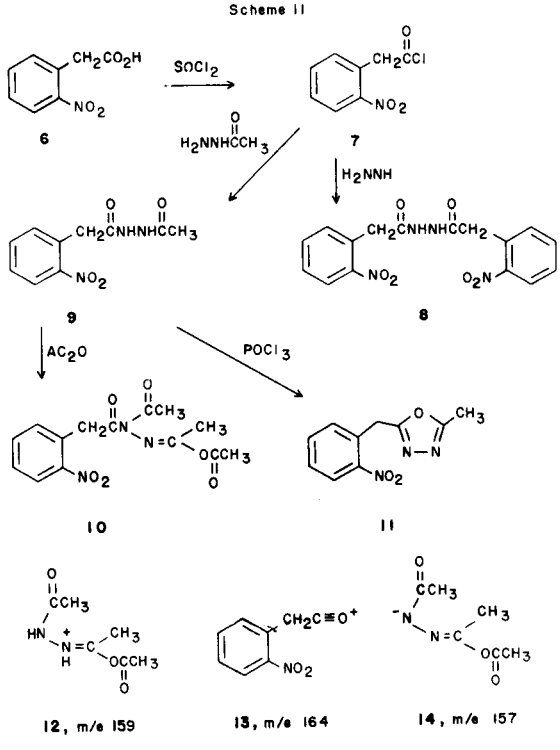
o-Nitrophenylacetic acid (**6**) was converted to its acid chloride (**7**) with thionyl chloride [2]. In an attempt to monoacylate hydrazine with **7**, we isolated bis compound **8** (Scheme II). Addition of **7** to a 5-fold excess of hydrazine (in methylene chloride) led to a mixture of two compounds containing methylene groups (by nmr), from which pure **8** was obtained after recrystallization (dimethylsulfoxide-water). When **7** was added to a 50-fold excess of hydrazine (neat), **8** was still isolated in a surprisingly high yield of 29%. Since our attempts at monoacylation, even under the latter conditions, were complicated by the formation of **8**, we decided to employ a protected hydrazine in the acylation with **7**.

Treatment of **7** with acetylhydrazine produced 2-nitrobenzeneacetic acid 2-acetylhydrazide (**9**) in 75% overall yield from **6**. An initial attempt to dehydrate **9** with acetic anhydride led to diacetylation rather than oxadiazole formation.

Scheme I



Scheme II



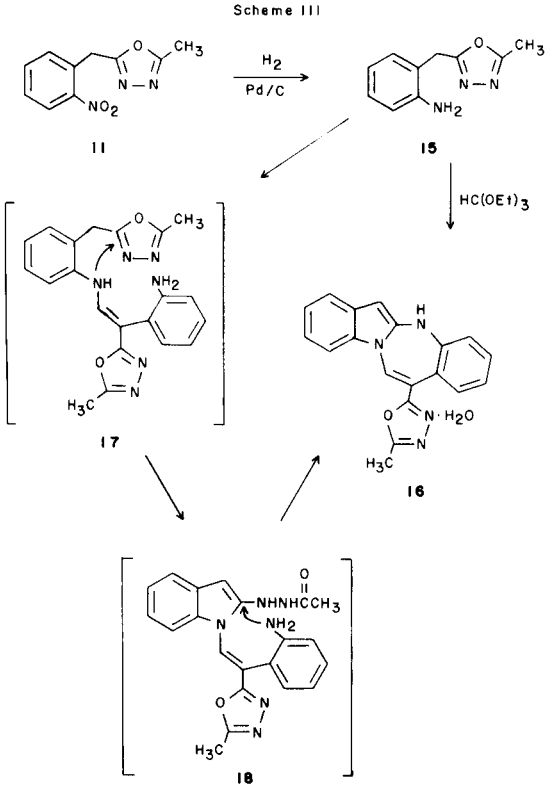
The structure of this diacetylated product was assigned as *N,O*-diacyl compound **10**, rather than one of the other three possible diacetylated species, on the basis of spectral evidence. The nmr (deuteriochloroform) spectrum of the diacylated material showed methyl signals at δ 2.39, 2.37 and 2.34. The presence of three methyl signals argued against an *N,N*-diacetyl compound. The infrared (potassium bromide) spectrum showed a broad carbonyl band at 1730 cm^{-1}, and unmistakable carbon-oxygen stretching at 1200 cm^{-1} which demonstrated that *O*-acetylation had occurred. The presence of ions at m/e 159 and 164 in the mass spectrum (positive chemical ionization), to which we assigned ion structures **12** and **13**, respectively, confirmed

that *O*-acetylation had not occurred on the phenylacetyl oxygen. In addition, the base peak in the negative chemical ionization mass spectrum was m/e 157, to which we assigned ion structure **14**. Thus, the spectral data taken together provided good evidence for assignment of structure **10** as the diacylated material.

Phosphorus oxychloride proved to be a good reagent for the preparation of 2-methyl-5-[(2-nitrophenyl)methyl]-1,3,4-oxadiazole (**11**). Treatment of **9** with excess phosphorus oxychloride gave an 84% yield of oxadiazole **11**.

Catalytic hydrogenation of **11** gave 2-methyl-5-[(2-aminophenyl)methyl]-1,3,4-oxadiazole (**15**) as shown in Scheme III. The nmr (dimethylsulfoxide-d_6) spectrum of **15** showed signals at δ 3.72 and δ 5.40. We interpreted these signals as corresponding to the methylene group and the vinyl proton of tautomeric forms **3** and **4** (R = CH_3), respectively, which were present in approximately equimolar amounts. Tautomeric forms were not seen with the corresponding nitro compound **11**. In the nmr (dimethylsulfoxide-d_6) spectrum of **11**, the methylene group appeared as a singlet at δ 4.56.

Scheme III



In spite of the tautomeric behavior displayed by **15**, treatment of **15** with triethyl orthoformate did not lead to oxadiazolobenzodiazepine **5** (R = CH_3). However, the interesting product isolated from this reaction was a benzodiazepine, namely, 13-(5-methyl-1,3,4-oxadiazol-2-yl)-5*H*-indolo[2,1-*b*][1,3]benzodiazepine monohydrate (**16**). Compound **16** is the first reported member of a novel indolobenzodiazepine ring system [4]. The structure of **16** was deduced from combustion analysis and spectral data. The mass spectra of **16** indicated a molecular weight of 314, by electron impact and by both positive and negative chemical ionization. In all three cases, the base peak corresponded to the loss of CH_3CON from the parent ion. The nmr spectrum (dimethylsulfoxide-d_6) was also consistent with the structure. The proton at the 12-position, deshielded by its environment, appeared as a sharp singlet at δ 9.42 [8].

Our postulated reaction mechanism for the formation of **16** from **15** is shown in Scheme III. Condensation of two molecules of **15** with one molecule of triethyl orthoformate would produce enamine intermediate **17**. Cyclization of **17** as shown, in 5-*exo*-trigonal fashion, with concomitant opening of the oxadiazole ring would lead to intrmediate **18**. A 7-*exo*-trigonal closure of **18**, with loss of acetylhydrazine, would subsequently yield indolobenzodiazepine **16**.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Beckman Model 4240 spectrophotometers, nmr spectra with Varian EM-360A and Perkin-Elmer R-32 (90 MHz) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Dow Analytical Laboratories, Midland, MI.

2-Nitrobenzeneacetic Acid 2-[(2-Nitrophenyl)acetyl]hydrazide (**8**).

A 25.0-g (0.138 mole) quantity of *o*-nitrophenylacetic acid (Aldrich) and 52.0 g (0.437 mole) of thionyl chloride were heated at reflux for 90 minutes. The solution was concentrated under *low* heat [2], and the resulting red oil was twice reconstituted in methylene chloride and concentrated to leave 27.0 g (98%) of **7**; ir (neat): 1800 (C=O) cm^{-1}. A solution of 27.0 g (0.135 mole) of **7** in 150 ml of methylene chloride was added dropwise to a solution of 21.0 g (0.655 mole) of 95% hydrazine (Eastman) in 150 ml of methylene chloride, with icebath cooling. After 30 minutes of stirring the solvent was evaporated and the residue was treated with water. The resulting solid was collected and air-dried to yield 20.5 g of crude **8**, whose nmr (dimethylsulfoxide-d_6) spectrum displayed methylene singlets at δ 3.92 and 3.80. Recrystallization from dimethylsulfoxide-water afforded pure **8**, mp 285-286°; ir (Nujol): 3175 (NH), 1695 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 10.08 (s, 2H, both NH protons, deuterium oxide-exchangeable), 8.16-7.90 (m, 2H, protons *ortho* to NO_2 group), 7.82-7.40 (m, 6H, remaining aromatic), 4.92 (s, 4H, both CH_2 groups); ms: (70 eV, chemical ionization, methane) 359 ($M^+ + 1$), 387 ($M^+ + 29$), 399 ($M^+ + 41$).

Anal. Calcd. for $C_{16}H_{14}N_4O_6$: C, 53.53; H, 4.06; N, 15.62. Found: C, 53.63; H, 3.94; N, 15.64.

When 26.1 g (0.131 mole) of **7** was added to 208 g (6.49 moles) of 95% hydrazine, dropwise with icebath cooling, quenching with ice after 30 minutes of stirring gave a white solid. Collection and air drying afforded 13.5 g (29%) of **8**, which was pure as indicated by nmr spectroscopy.

2-Nitrobenzeneacetic Acid 2-Acetylhydrazide (**9**).

A cold solution of **7** made as previously described from 50.0 g (0.276 mole) of **6**, in 200 ml of methylene chloride was added to a cold solution of 44.0 g (0.594 mole) of acetylhydrazine in 200 ml of methylene chloride. After standing for 30 minutes the resulting precipitate was collected, washed with water and recrystallized from dimethylformamide-water to give 48.8 g (75%) of **9**, mp 220-222°; ir (Nujol): 3190 (NH), 1590 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 9.93 (s, 1H, NH, deuterium oxide-exchangeable), 9.75 (s, 1H, NH, deuterium oxide-exchangeable), 8.13-7.95 (m, 1H, proton *ortho* to NO_2 group), 7.85-7.45 (m, 3H, remaining

aromatic), 3.96 (s, 2H, CH_2), 1.86 (s, 3H, CH_3); ms: (70 eV, chemical ionization, methane) 238 ($M^+ + 1$), 266 ($M^+ + 29$), 278 ($M^+ + 41$).

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.72. Found: C, 50.24; H, 4.51; N, 17.74.

2-Nitrobenzeneacetic Acid 1-Acetyl-2-[1-(acetyloxy)ethylidene]hydrazide (**10**).

A solution of 10.0 g (42.2 mmoles) of **9** in 70 ml of acetic anhydride was heated at reflux for 4 hours. The solution was concentrated and the residue was treated with water. The resulting white solid was collected and air-dried to yield 11.6 g (86%) of **10**, mp 115-116°; mp 115.5-116.5° (2-propanol-hexane); ir (potassium bromide): 1730 (C=O), 1520, 1345 and 845 (NO_2) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.20-8.05 (m, 1H, aromatic), 7.84-7.45 (m, 3H, aromatic), 4.50 (s, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.34 (s, 3H, CH_3); ms (70 eV, positive chemical ionization, methane): 322 ($M^+ + 1$), 350 ($M^+ + 29$), 164 (22% of base peak), 159 (25% of base peak), 117 (base peak); ms (70 eV, negative chemical ionization, methane): 320 ($M^- - 1$), 157 (base peak).

Anal. Calcd. for $C_{14}H_{15}N_3O_6$: C, 52.33; H, 4.71; N, 13.08. Found: C, 52.31; H, 4.64; N, 12.97.

2-Methyl-5-[(2-nitrophenyl)methyl]-1,3,4-oxadiazole (**11**).

A solution of 36.9 g (0.156 mole) of **9** and 24.5 g (0.160 mole) of phosphorus oxychloride in 250 ml of acetonitrile was heated at reflux for 2 hours. The clear solution was concentrated and the residue was quenched with water. The resulting tan solid was collected and air-dried to yield 28.6 g (84%) of **11**, mp 87-88°; mp 88-89° (2-propanol-ether); ir (Nujol): 1610, 1595, 1560, 1520 (NO_2), 1345 (NO_2), 850 (NO_2) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.18-8.03 (m, 1H, H *ortho* to NO_2), 7.85-7.48 (m, 3H, remaining aromatic), 4.56 (s, 2H, CH_2), 2.43 (s, 3H, CH_3); ms: (70 eV, chemical ionization, methane) 220 ($M^+ + 1$), 248 ($M^+ + 29$), 260 ($M^+ + 41$).

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.70; H, 4.05; N, 19.07.

2-[(5-Methyl-1,3,4-oxadiazol-2-yl)methyl]benzenamine (**15**).

A solution of 10.0 g (45.6 mmoles) of **11** in 150 ml of methanol was treated with 500 mg of 10% Pd/C and hydrogenated in a Parr apparatus at 50 psi until hydrogen uptake ceased (1 hour). The catalyst was removed by filtration and the filtrate was evaporated to a small volume. The resulting solid was collected in two crops to yield 5.67 g (66%) of **15**, mp >210° (methanol); ir (Nujol): 3240 and 3160 (NH), 1665 (sh), 1640, 1615 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 7.30-6.98 (m, 2H, aromatic), 6.98-6.65 (m, 2H, aromatic), 5.40 [s, 0.5 H, vinyl H of tautomer **4** (R = CH_3)], 3.72 [broad signal, 1H, CH_2 of tautomer **3** (R = CH_3)], 2.10-1.80 (3 singlets, 3H, CH_3); ms: (70 eV, chemical ionization, methane) 190 ($M^+ + 1$), 218 ($M^+ + 29$), 230 ($M^+ + 41$).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.25; H, 5.89; N, 22.05.

13-(5-Methyl-1,3,4-oxadiazol-2-yl)-5*H*-indolo[2,1-*b*][1,3]benzodiazepine Monohydrate (**16**).

A mixture of 3.69 g (19.5 mmoles) of **15** in 75 ml of triethyl orthoformate was heated at reflux for 2 hours. The resulting red solution was concentrated and the residue (semisolid) was triturated with ether. The resulting red solid was collected to yield 2.60 g (42%) of **16**. The solid was washed with hot ethanol and recrystallized from dimethylformamide to yield pure **16**, mp >280°; ir (potassium bromide): 3550-2400 (broad stretching, NH and water), 1640, 1610, 1560, 1455, 1315, 1255, 1215, 1095, 760, 730 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 9.42 (s, 1H, H at 12-position), 8.35-8.05 (m, 2H, aromatic), 7.80-7.15 (m, 6H, remaining aromatic), 5.30 (very broad signal, NH and H_2O), 2.16 (s, 3H, CH_3); ms: (70 eV, electron impact) m/e 314 (molecular ion), 257 (base peak, $M^+ - CH_3CON$); ms: (70 eV, positive chemical ionization, methane) 315 ($M^+ + 1$), 343 ($M^+ + 29$), 258 (base peak, 315 − CH_3CON); ms: (70 eV, negative chemical ionization, methane) 313 ($M^- - 1$), 256 (base peak, 313 − CH_3CON).

Anal. Calcd. for $C_{19}H_{14}N_4O \cdot H_2O$: C, 68.65; H, 4.85; N, 16.86. Found: C, 68.25; H, 4.95; N, 16.87.

Acknowledgements.

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REFERENCES AND NOTES

[1] S. Sunder, N. P. Peet and R. J. Barbuch, *J. Heterocyclic Chem.*, **18**, 1601 (1981).

[2] Caution should be used in the preparation of *o*-nitophenylacetyl chloride (**7**), due to its explosive potential. We have prepared this material several times without incident, using methylene chloride as the reaction solvent and as a chaser solvent to remove excess thionyl chloride. In one preparation, however, we inadvertently used toluene as the chaser solvent. The higher temperature used in removing the toluene under reduced pressure led to an explosion. The thermal instability of *o*-nitrophenylacetyl chloride has been previously noted in the literature by other authors [3] who encountered a violent decomposition of **7** when it was heated at 83° (1-3 mm).

[3] C. W. Math, N. Abraham, M. L. Linfield, R. B. Wotring and E. A. Pacofsky, *J. Org. Chem.*, **25**, 736 (1960).

[4] Three indolobenzodiazepine ring systems have been previously reported. These are the 6*H*-indolo[2,1-*c*][1,4]benzodiazepine [5], the 5*H*-indolo[1,2-*d*][1,4]benzodiazepine [6], and the indolo[2,3-*b*][1,5]benzodiazepine [7] systems.

[5] E. E. Garcia, A. Arfaei and R. I. Fryer, *J. Heterocyclic Chem.*, **7**, 1161 (1970).

[6] R. L. Duncan and G. C. Helsley, German Offen. 2,051,230 (Apr 29, 1971); *Chem. Abstr.*, **75**, 36163t (1971).

[7] K. E. Schulte, J. Reisch and U. Stoess, *Arch. Pharm. (Weinheim)*, **305**, 523 (1972); *Chem. Abstr.*, **77**, 152131w (1972).

[8] We are unable to locate adequate model compounds in the literature bearing protons in a deshielding environment similar to that of the proton at the 12-position in **16**. The nmr spectra of *trans*-1-styrylpyrrole [9] and *trans*-1-styrylimidazole [10], both in deuteriochloroform, have been reported. The styryl protons adjacent to nitrogen in these compounds appear at δ 7.23 and 7.22, respectively.

[9] W. J. Irwin and D. L. Wheeler, *Tetrahedron*, **28**, 1113 (1971).

[10] G. Cooper and W. J. Irwin, *J. Chem. Soc., Perkin Trans. I*, 798 (1975).