Novel Heterocycles. 13 [1]. Synthesis of 5,6-Dihydro-1*H*-3*H*-pyrrolo[3,2,1-*ij*][3,1]benzoxazine-1,3-dione

Gary M. Coppola* and Stephen Palermo

Sandoz Research Institute, Chemistry Research Department, Sandoz Pharmaceuticals Corporation, Route 10, East Hanover, NJ 07936

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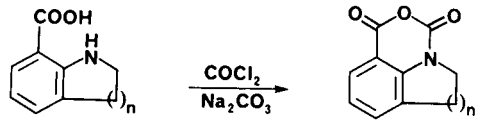
The synthesis of 5,6-dihydro-1*H*,3*H*-pyrrolo[3,2,1-*ij*][3,1]benzoxazine-1,3-dione (**2a**), a new ring system, from *N*-acetylindoline is described.

J. Heterocyclic Chem., **23**, 971 (1986).

Isatoic anhydrides have been shown to be valuable intermediates in organic synthesis [2-5]. The nature of the hetero portion of the molecule makes it behave like an activated, internally protected anthranilic acid where the C-4 carbonyl becomes extremely susceptible to nucleophilic attack.

In 1978 the synthesis of the tricyclic anhydride **2b** (a bridged isatoic anhydride) was accomplished in this laboratory and its reactivity with a variety of nucleophiles was investigated [6].



1 **a**, n = 1 **b**, n = 2 **2**

It was of interest to us to prepare the five-membered ring analog **2a** due to the fact that it represents a new ring system. Also, as a two carbon bridged isatoic anhydride derivative, it can be used as an intermediate for the potential generation of new ring systems.

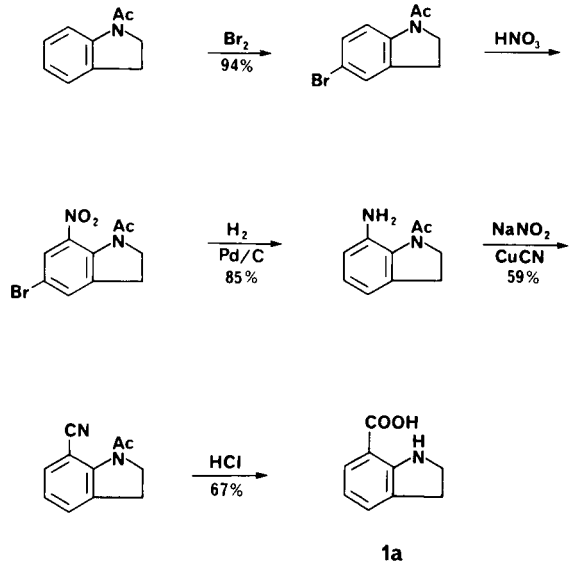
Since isatoic anhydrides are generally prepared by the cyclization of 2-aminobenzoic acid derivatives with phosgene, our synthetic strategy for the preparation of **2a** required the synthesis of indoline-7-carboxylic acid (**1a**) as the penultimate intermediate. Since compound **1a** is known in the literature, we chose a combination of two procedures [7,8] for its preparation. Although the route shown in the following scheme was rather laborious, we were able to prepare over 100 gm of **1a**.

The treatment of **1a** with phosgene according to the procedure described by us for the preparation of **2b** furnishes the tricycle **2a** in 35% yield. This result is in sharp contrast to that of **2b** where the conversion is essentially quantitative. A plausible explanation for this disparity is that the ring strain inherent in the 5-membered ring of the indoline **1a** places the nitrogen slightly farther from the carboxyl group, thus allowing intermolecular reactions as well as neutralization of the carboxylate anion to enter competitively with the desired intramolecular cyclization.

Although **2a** and **2b** only differ by one bridging methylene unit, their physical properties differ markedly. Compound **2b** is highly soluble in chlorinated solvents such as methylene chloride and chloroform, whereas **2a** is virtually insoluble in these solvents. In fact, **2a** is only sparingly soluble in DMSO and heating is required to effect solution. In addition, the melting point for **2a** is nearly 50° higher than that of **2b**.

These deviations originally led us to believe that we did not have the desired compound, however a detailed spectral examination (see Table and Experimental) of the product confirmed that the material is indeed **2a**. Investigation into the reactivity profile of this interesting tricycle is presently underway.

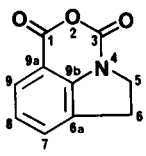
SCHEME

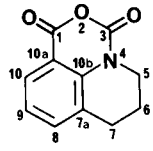


1a

Table

Carbon-13 Shifts for **2a** and **2b** [a]





Carbon No.	**2a** [b]	**2b** [c]
1	167.15	158.44
3	158.63	146.60
5	46.72	43.40
6	26.75	19.28
6a	129.89	—
7	131.38	25.45
7a	—	125.08
8	123.77 [d]	136.00
9	124.36 [d]	122.61
9a	107.26	—
9b	145.56	—
10	—	126.77
10a	—	110.51
10b	—	138.08

[a] Assignments are interchangeable. [b] In ppm from tetremethylsilane. [c] Spectrum taken in DMSO-d_6 at 120°. [d] Spectrum taken in DMSO-d_6 at 80°.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on either Perkin-Elmer Model 257 and 457, or Analect FX-6200 spectrophotomers. Absorption frequencies are quoted in reciprocal centimeters. The proton NMR spectra were recorded on EM-360 and Jeol FX-90-Q spectrometers using TMS as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Jeol FX-200 spectrometer system. The spectra were obtained at an observing frequence of 50.1 MHz. Sample concentrations were *ca.* 0.1 molar in 5 mm (od) sample tubes. General nmr spectral and instrumental parameters were employed were: Internal deuterium lock to the solvents; spectral width of 10000 Hz; a pulse width of 3μs corresponding to a 45° pulse angle, and a pulse repetition time of 1.8 seconds. For all spectra, 16K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to ± 0.05 ppm.

The mass spectra were determined on a Finnegan 4600 spectrometer either in EI or CI modes.

5,6-Dihydro-1*H*,3*H*-pyrrolo[3,2,1-*ij*][3,1]benzoxazine-1,3-dione (**2a**).

A mixture of 90.0 g of **1a** and 60.0 g of sodium carbonate in 2.5 l of water was stirred at room temperature for 1 hour after which any insoluble material was filtered off. To the filtrate was added dropwise 1.0 l of phosgene solution (12.5% in benzene) while maintaining a temperature of 25-30°. The mixture was stirred at room temperature for 3 hours then a current of air was blown through the vessel in order to drive off any excess phosgene and benzene. The resulting precipitate was filtered and washed with water. After drying under reduced pressure, the solid was triturated with ethyl acetate/methylene chloride (80:20) to give 37.0 g (35% yield) of **2a**. An analytical sample was crystallized from methanol/chloroform, mp 236-239° dec; ir (potassium bromide): 1780, 1728, 1610, 1520, 1380, 960 cm^{-1}; nmr (DMSO-d_6): 60°, δ 7.72-7.60 (m, 2H), 7.20 (t, 1H), 4.19 (t, 2H), 3.33 (t, 2H); ms: (70 eV) m/z 189 (M^+), 145 ($M-CO_2$).

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.5; H, 3.7; N, 7.4. Found: C, 63.6; H, 3.9; N, 7.5.

REFERENCES AND NOTES

[1] Part 12: G. M. Coppola, *Synth. Commun.*, **15**, 1013 (1985).

[2] G. M. Coppola, *Synthesis*, 505 (1980).

[3] T. Kappe and W. Stadlbauer, "Advances in Heterocyclic Chemistry", Vol 28, A. R. Katriksky and A. J. Boulton, eds, Academic Press, New York, 1981, pp 127-182.

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[8] W. G. Gall, B. D. Astill, and V. Boekelheid, *J. Org. Chem.*, **20**, 1538 (1955).

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Examples of Experimental Procedures.

The following typical experimental procedures illustrate the **required** format.

3-(3'-Thienyl)-2-cyclohexen-1-one (**15**).

A solution of 3.13 g (0.019 mole) of 3-bromothiophene (**12**) dissolved in 50 ml of dry ether was cooled to −78°. The 3-bromothiophene (**12**) was lithiated by slowly adding 12.4 ml of a 1.55 *M* solution of *n*-butyllithium in hexane. After the addition was complete, the solution was stirred at

−78° for 30 minutes. A solution of 3.0 g (0.019 mole) of 1,4-dioxaspiro-[4.5]decan-7-one in 25 ml of dry ether was added over a period of 20 minutes. The solution was allowed to warm to room temperature overnight. The solution was then neutralized with 10% aqueous ammonium chloride solution. The ether layer was separated, dried and the solvent was evaporated. The residue was then refluxed in aqueous 1.4 *M* hydrochloric acid for 1 hour. The organic product was isolated by extraction with ether. The ether was dried (sodium sulfate) and evaporated to yield an oil which was crystallized from benzene-hexane as yellow needles, 1.4 g (41%), mp 100-102°; nmr (deuteriochloroform): 2.0-3.0 (m, 6H), 6.3 (s, 1H), 7.3 (m, 2H), 7.5 (m, 1H); ms: 180 (3.0), 179 (6.4), 178 (54), 150 (95), 122 (100), 121 (84), 39 (86).

Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.06; H, 5.75; S, 17.69.

General Procedure for the Reaction of Tropone Hydrazones **1-3** with Phenylketene (**8**).

All of these reactions were carried out under a nitrogen atmosphere. To a stirred and cooled (0°) solution of tropone benzoylhydrazone (**11**) (1.12 g, 5 mmoles) and triethylamine (0.61 g, 6 mmoles) in dry THF (15 ml), a solution (5 ml) of phenacetyl chloride (0.77 g, 6 mmoles) was added drop by drop for ten minutes and the reaction mixture was allowed to stand at that temperature for an additional thirty minutes. After being warmed to room temperature gradually, the mixture was stirred overnight. The resultant triethylamine hydrochloride was filtered and the filtrate was evaporated *in vacuo* to give an oily residue. The residue was separated by column chromatography (silica gel-chloroform) to give **9a** and **10a** in 25 and 9% yield, respectively.

1-Benzamido-1,2,3,3a-tetrahydro-2-oxo-3-phenyl-1-azaazulene (**9a**).

This compound was obtained as colorless needles (isopropyl alcohol), mp 179-180°; ir: ν NH 3200, ν CO 1725, 1675 cm^{-1}; pmr: δ 3.12 (br, 1H, 3a-H), 3.86 (br d, 1H, 3-H, J = 5.7 Hz), 5.24 (dd, 1H, 4-H, J = 3.0, 9.0 Hz), 5.44 (d, 1H, 8-H, J = 6.3 Hz), 6.1-6.5 (m, 3H, 5-, 6-, and 7-H), 7.2-7.9 (m, 10H, phenyl protons), 9.3 ppm (br s, 1H, NH); ms: (m/e) 342 (M^+), 224 (M^+-PhCHCO), 119 ($PhNCO^+$), 105, 77.

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.16; H, 5.28; N, 8.35.

1,2,3,3a-Tetrahydro-2-oxo-1-phenylacetylbenzamido-3-phenyl-1-azaazulene (**10a**).

This compound was obtained as colorless prisms (isopropyl alcohol), mp 158-159°; ir: ν CO 1755, 1730, 1705 cm^{-1}; pmr: δ 2.86 (br, 1H, 3a-H), 3.82 (br d, 1H, 3-H, J = 5.4 Hz), 4.15, 4.37 (2d, each, 1H, $-CH_2-$, J = 15.3 Hz), 5.25 (dd, 1H, 4-H, J = 3.2, 9.6 Hz), 5.44 (d, 1H, 8-H, J = 6.3 Hz), 6.0-6.7 (m, 3H, 5-, 6-, and 7-H), 7.1-7.7 ppm (m, 15H, phenyl protons); ms: (m/e) 460 (M^+), 341 (M^+-$PhCH_2CO$), 224 (hydrazone 1^+), 119 ($PhNCO^+$), 105, 77.

Anal. Calcd. for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 5.97. Found: C, 78.23; H, 5.25; N, 6.38.

Methyl 5-Cyanomethyl-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrazole-4-carboxylate (**14**).

To a solution of **9** (0.80 g, 1.54 mmoles) in dry methanol (25 ml) was added 1M sodium methoxide in methanol (1.25 ml) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was neutralized with Dowex-50 H^+ resin and filtered. The filtrate was evaporated to dryness. The residual semisolid was purified on a silica gel column (2.5 x 45 cm), prepacked in chloroform. Elution of the column with chloroform:methanol (19:1, v/v) gave a homogeneous residue, which was crystallized from aqueous ethanol to yield 0.17 g (37%), mp 118-120°; ir (potassium bromide): ν 1700 (C=O), 2260 (C≡N), 3400 (OH) cm^{-1}; uv: λ max (*p*H 1) 218 nm (ϵ 11,000); λ max (*p*H 7) 218 nm (ϵ 11,100); λ max (*p*H 11) 224 nm (ϵ 10,200); ^1H nmr (DMSO-d_6): δ 3.82 (s, 3, CO_2CH_3), 4.40 (s, 2, CH_2), 6.16 (t, 1, peak width 14.5 Hz, C_1H), 8.18 (s, 1, C_3H), and other sugar protons.

Anal. Calcd. for $C_{12}H_{15}N_3O_5$ (281.17): C, 51.24; H, 5.33; N, 14.94. Found: C, 50.99; H, 5.43; N, 14.80.

5-Amino-1-[4-(methylsulfonyl)phenyl]-1*H*-pyrazole-4-carbonitrile (**5b**).

A solution of 50.0 g (0.268 mole) of 4-(methylsulfonyl)phenylhydrazine (**3b**) and 34.3 g (0.281 mole) of ethoxymethylenemalononitrile (**4**) in 250 ml of ethanol was heated at reflux. A precipitate was observed after 15 minutes. After 15 hours, the mixture was cooled and the yellow solid was collected and air-dried to yield 51.4 g (73%) of **5b**, mp 236-238°; ir (Nujol): 3450, 3315 and 3170 (NH), 2225 (CN), 1635 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.11 (d, J = 8 Hz, 2H, phenyl), 7.89 (s, 1H, C3-H), 7.84 (d, J = 8 Hz, 2H, phenyl), 6.94 (broad s, 2H, NH_2, deuterium oxide-exchangeable), 3.25 (s, 3H, CH_3); ms: (70 eV, electron impact) m/e 262 (molecular ion).

Anal. Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.40; H, 3.87; N, 21.57.

3-Methoxy-4*H*-pyran-4-one-2-carboxaldehyde.

2-Hydroxymethyl-3-methoxy-4*H*-pyran-4-one (700 mg) was dissolved in 50 ml of methylene chloride. Barium manganate (7.5 g) was ground to a fine powder and added immediately to the methylene chloride solution. The mixture was stirred with the aid of a magnetic stirrer for two hours at room temperature. Inorganic by-products were removed by filtration of the reaction mixture through Celite. The Celite was washed with methylene chloride; the latter solution was added to the methylene chloride filtrate previously obtained. Evaporation of methylene chloride *in vacuo* gave a white residue, which was recrystallized from cyclohexane to give 635 mg (92%) of 2-methoxy-4*H*-pyran-4-one-2-carboxaldehyde, mp 85-86°; nmr (deuteriochloroform): δ 4.16 (s, 3H, OCH_3), 6.43 (d, 1H, H_5), 7.73 (d, 1H, H_6), 10.14 (s, 1H, CHO); ir (potassium bromide): 3100 (CH), 1695 (aldehyde CO), 1655 (pyrone CO), 1575, 1460, 1430, 1395, 1275, 1225, 1200, 1175, 1050, 950, 850, 830, 750, 640 cm^{-1}.

Anal. Calcd. for $C_7H_6O_4$: C, 54.55; H, 3.92. Found: C, 54.58; H, 3.91.

The above experimental procedures illustrate the following:

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2. The requirement of a sufficiently detailed experimental description to enable an experienced chemist to repeat the experiment successfully.

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