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Reactions of 3,4-Benzopyrrolidinones with β-Keto Esters

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Received October 15, 1974

As part of a synthetic study directed toward camptothecin and camptothecin analogs,[1,2] we had occasion to synthesize the tricyclic lactam **1** and to investigate its utility as a starting material for various annelation schemes.[3] Our route to lactam **1**, which we believe to be simpler than the three[4-6] which have been described in the interim, is set forth below.

The required 2-carbomethoxy-3-methylquinoline (**2**) was prepared by the Friedlander condensation of 2-oxobutyric acid with *o*-aminobenzaldehyde followed by esterification of the intermediate acid[7] with methanolic HCl. Compound **2** (87%) was treated with *N*-bromosuccinimide and dibenzoyl peroxide in carbon tetrachloride. The intermediate 2-carbomethoxy-3-bromomethylquinoline (**3**), assumed to be present but not characterized, was treated with ammonia to give an 86% yield of **1**. This method[8] was extended to the preparation of phthalimidine (**5**). Treatment of methyl *o*-toluate with *N*-bromosuccinimide gave methyl-2-bromomethylbenzoate (**4**). Reaction of **4** with ammonia gave **5** in 60% yield.

Sugasawa had reported that heating of **1** with diethyl acetone-1,3-dicarboxylate (**6**) gave the acylated product **7**[9] in 95% yield. Before the experimental procedure became available, we attempted to achieve this result, based on our reading of the preliminary report,[9] by heating **1** + **6** at 160–165° at atmospheric pressure. No product corresponding to **7** was isolated. In fact, the starting material, **1**, was recovered largely unchanged.[10] However, when the actual experimental conditions of Sugasawa[6,11] (**1** + **6** (excess), 160–165° (15–20 mm)) were employed, a 94% yield of **7** was obtained. The reason for the dramatic effect achieved by conducting the reacton under vacuum is not clearly understood.

When the reactants **5** + **6** were heated neat at 160–165° for 2 hr at atmospheric pressure, a 77% yield of a crystalline product, mp 138–139°, was obtained. Both its mass spectrum and combustion analysis indicated it to be a product corresponding to **5** + **6** − H_2O. This information, in addition to that obtained from its nmr spectrum, defines its structure as the enamide **8**,[12] rather than the expected **9**.

When the reaction of **5** + **6** was carried out under the Sugasawa conditions (15–20 mm, 160–165°, 0.5 hr), a mixture of **8** (24%) and another crystalline product, mp 94–95° (59%), was obtained. The mass spectrum and combustion analysis of the compound melting from 94 to 95° establish it to be the product of **5** + **6** − C_2H_6O. These data plus its nmr spectrum define its structure to be imide **9**, *i.e.* the analog of **7**.

Similarly, reaction of **5** with methyl acetoacetate at 200° for 18 hr gave a 46% yield of the crystalline enamide **10**,[11] mp 120–121°, whereas comparable conditions involving heating **1** with methyl acetoacetate up to 200–210° for 24 hr gave essentially recovered starting material and decomposition products. Also, Sugasawa had reported that cyclodehydration of **7** (formation of **11**) could be achieved (89%) using piperidine in acetonitrile. We were able to achieve the same result for compund **7**. However, attempts to extend the reaction to imide **9**, in the phthalimidine series (attempted formation of **12**), led to recovered starting material.

The greater nucleophilicity of the lactam nitrogen of **5** relative to **1** (enamide formation from β-keto esters *vs.* no reaction at atmospheric pressure) correlates logically with the greater electrophilicity of the carbonyl group of **7** relative to **9** with respect to internal aldolization (*cf.* **7** → **11**; **9** → **12**). Both presumably arise from the electron-withdrawing effect of the quinoline (inductive effect plus formal α-azomethine linkage) ring. The effect of the vacuum conditions in promoting imide relative to enamine formations is not understood.

The results of further studies involving annelations of **1** will be described shortly.

Experimental Section[13]

Preparation of 2-Carbomethoxy-3-methylquinoline (2). A solution of 2-oxobutyric acid (7.5 g; 0.074 mol), *o*-aminobenzalde-

hyde (8.0 g; 0.066 mol), and sodium methoxide (6.32 g; 0.117 mol) in 300 ml of methanol was heated under reflux for 12 hr. After cooling, 11.96 g (0.12 mol) of concentrated H_2SO_4 was cautiously added. The resultant solution was heated under reflux for 24 hr. After neutralization with aqueous sodium bicarbonate, the mixture was extracted with chloroform. After removal of the volatiles at the water pump, the residue was distilled at 0.01 mm. A fraction of bp 138–140° consisting of 11.54 g (87%) was obtained: λ_{max} (CCl_4) 5.79 μ; δ (CCl_4) 2.35 (s, 3), 3.78 (s, 3), 7–8 (m, 5).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.69. Found: C, 71.40; H, 5.63; N, 6.86.

Preparation of 3-Oxo-1*H*-pyrrolo[3,4-*b*]quinoline (1). A solution of **2** (19.51 g; 0.097 mol) in 50 ml of carbon tetrachloride was added, with stirring, to a solution of *N*-bromosuccinimide (17.05 g; 0.096 mol) and dibenzoyl peroxide (1.09 g; 0.0045 mol) in 200 ml of the same solvent. The temperature was raised over 1 hr to the boiling point and heating under reflux was continued for an additional 18 hr. After removal of the succinimide (lighter than the solvent) by filtration, the volatiles were evaporated at the water pump. The residual bromomethyl compound, **3**, was dissolved in 500 ml of methanol. Gaseous ammonia was continuously bubbled through the solution as concentrated ammonium hydroxide (9 drops) was added. Heating under reflux was continued for 2.5 hr. A white solid separated and was collected by filtration. Additional solid was obtained by concentration of the methanolic solution. Recrystallization of the combined solids from 95% ethanol yielded 15.28 g (86%) of compound **1**: mp 295–302° dec (lit.[6] 280–283° dec; λ_{max} (nujol) 3.05, 5.91μ; δ (CF_3CO_2H) 5.17 (s, 2), 8.3–9.2 (m, 4), 9.96 (s, 1), 10.04 (s, 1).

Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.49; H, 4.39; N, 14.99.

Conversion of Methyl *o*-Toluate to Phthalimidine (5). A mixture prepared by adding *N*-bromosuccinimide (114 g; 0.64 mol) and dibenzoyl peroxide (1.29 g; 5 mmol) to a solution of methyl *o*-toluate (90 g; 0.66 mol) in 350 ml of carbon tetrachloride was heated under reflux for 4 hr. After cooling and filtration of the succinimide, the solvent was evaporated at the water pump. The residue (125 g) consisting of **4** was dissolved in 500 ml of methanol. To this was added 150 ml of concentrated ammonia and the system was brought to reflux. Anhydrous ammonia was bubbled through. After cooling, the volatiles were removed at the water pump. The solid residue was washed with water and then with ether. The phthalimidine (48 g, 60%) upon recrystallization from water had a melting point of 155–156° (lit.[14] 150–151°).

Condensation of Phthalimidine (5) with Diethyl Acetone-1,3-dicarboxylate (6). (i) At Atmospheric Pressure (Formation of 8). Compound **5** (500 mg; 4.2 mmol) was added to excess (6 ml) **6**. The system was heated at 160–165° for 2 hr. On cooling, white crystals separated and were collected. More product was recovered by chromatography of the mother liquor on 300 g of silica gel by elution with 1:1 ether–petroleum ether. The elution order was **6** > **8** > **5**. The combined solid, **8**, mp 138–139°, weighed 923 mg (77% conversion; 93% yield). In addition compound **5** (100 mg; 20%) was recovered: *m/e* 317 (parent); λ_{max} ($CHCl_3$) 5.80, 5.89 (sh), 6.18 (sh), 6.20 μ; δ ($CDCl_3$) 1.25 (t, J = 7 Hz, 6 H, overlapping triplets), 4.20, 4.22 (2 q, J = 7 Hz for each, 4 H), 4.68 + 4.70 (2 s, 4 H), 5.65 (s, 1 H), 7.2–8.0 (m, 4 H).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.35; H, 5.99; N, 4.44. Found: C, 64.36; H, 6.07; N, 4.40.

(ii) **At Reduced Pressure (Formation of 8 + 9).** Phthalimidine (**5**) (1.0 g; 7.55 mmol) was added to an excess 12 ml of **6**. The system was connected to an aspirator (15–20 mm). It was heated at 160–165° for 30 min. After cooling the total mixture was chromatographed on *ca.* 600 g of silica gel. Elution with 1:1 ether–petroleum ether first removed **6**. After this, 0.56 g (23%) of **8** was obtained. The final product eluted was compound **9**: 1.28 g (59% yield); mp 94–95°; *m/e* 289 (parent); λ_{max} ($CHCl_3$) 5.80 (sh) 5.85, 5.92 (sh), 6.20 μ; δ ($CDCl_3$)[15] 1.30 (t, J = 7 Hz, 3 H), 3.72 (s, 2 H), 4.05–4.40 (q, J = 7 Hz, + s δ = 4.3, total = 4 H), 4.83 (s, 2 H), 7.3–8.0 (m, 4 H).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19; N, 4.84. Found: C, 62.57; H, 5.15; N, 4.75.

Reaction of 5 with Methyl Acetoacetate. Formation of 10. Phthalimidine (500 mg; 3.7 mmol) and methyl acetoacetate (1 g; 8.5 mmol) were heated in a sealed tube at 200° for 18 hr. After cooling, the contents were dissolved in chloroform. Addition of petroleum ether gave a precipitate which was recrystallized from ethanol to give **10**: 410 mg; 46% yield; mp 120–122°; *m/e* 231 (parent); λ_{max} 5.80, 5.85, 6.20 μ; δ ($CDCl_3$) 2.76 (s, 3 H), 3.70 (s, 3 H), 4.55 (s, 2 H), 5.95 (s, 1 H), 7.2–8.0 (m, 4 H).

Acknowledgments. This research was supported by Public Health Service Grant No. CA-12107-05-10. Nmr spectra were obtained on facilities supported by Public Health Service Grant No. RR-00292-05. Preliminary studies in the phthalimidine series were conducted by Dr. Lantz Crawley.

Registry No.—**1**, 34535-42-7; **2**, 53821-46-8; **5**, 480-91-1; **6**, 105-50-0; **8**, 53821-47-9; **9**, 53821-48-0; **10**, 53821-49-1; 2-oxobutyric acid, 600-18-0; *o*-aminobenzaldehyde, 529-23-7; *N*-bromosuccinimide, 128-08-5; methyl *o*-toluate, 89-71-4; methyl acetoacetate, 105-45-3.

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(10) Although starting **1** was recovered in high yield (starting with 368 mg, 320 were recovered) the mass spectrum of the mother liquors exhibits a small peak at *m/e* 368 which corresponds to **1** + **6** − H_2O, *i.e.*, the enamide analog of **7**. Thus, there may be a slight amount of enamine formation even here.
(11) We thank Dr. Sugasawa for making the details of his excellent procedure available to us prior to publication.
(12) The double bond geometry is unspecified.
(13) Melting points are uncorrected. Nmr spectra were measured at 60 MHz on Varian Associates A60, A60D, and T60 spectrometers with tetramethylsilane as internal standard. Data are reported in parts per million (δ) from TMS. Infrared spectra were obtained from Perkin-Elmer 137 or 247 spectrophotometers. Mass spectra were measured on an LKB 9 combined glc–mass spectrometer by direct insertion. Analyses were conducted by Galbraith Inc., Knoxville, Tenn.
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(15) The nmr spectrum also indicates the presence of *ca.* 20% of enol tautomers.

Synthesis of Benziodathiazoles

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Received October 7, 1974

A number of heterocyclic compounds whose rings contain polyvalent iodine have been described. Recently we have reported on the synthesis and properties of *o*-iodosophenylphosphoric acid and its methyl ester to which we have assigned the six-membered cyclic structures 1,3-dihydroxy-1*H*-1,2,4,3-benziodadioxaphosphorin 3-oxide and 1-methoxy-3-hydroxy-1*H*-1,2,4,3-benziodadioxyphosphorin-3-oxide.[2]

The present note describes the synthesis of polyvalent iodine derivatives of *o*-iodobenzenesulfonamide to which we have assigned the five-membered benziodathiazole structures **1a–c**. Entry into the benziodathiazole system is achieved *via* 1-acetoxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1a**) (Scheme I) synthesized by peracetic acid oxidation of *o*-iodobenzenesulfonamide or *via* 1-chloro-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1b**) synthesized by hydrolysis of *o*-(dichlorido)iodosobenzenesulfonamide (**2**). The latter is synthesized by chlorination of *o*-iodobenzensulfonamide. Compound **1b** is also obtained by acidification of a NaOH solution of **1a** or **2** (Scheme I).