Reaction of 4-Chloro-3-nitrocoumarin with Glycine and Alanine, and the Synthesis of 1-Benzopyrano[3,2-*c*]pyrimidine-3,5-dione

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A considerable improvement of the yields obtained in substitution of halogens in 4-chloro-3-nitrocoumarin by amino acid or amino acid ester residues was achieved over literature claims. Electrochemical reduction of the nitro group in these products brought about a ring closure leading to benzopyranopyrimidinones, which are obtained in excellent yields.

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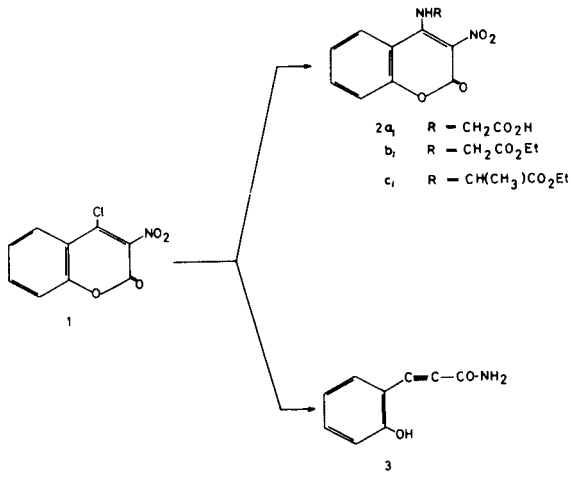
Introduction.

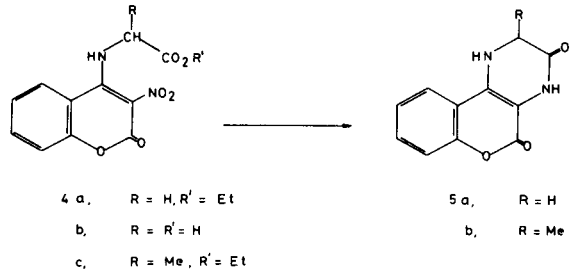
A group of authors (1) claimed that the halogen in 3-substituted 4-chlorocoumarins is easily replaced by an amino or alkylamino residue in reactions with ammonia and amines. The yields obtained may, however, be markedly lowered because of by-products and therefore greatly depend on the rection conditions. Solvent polarity, for example, may considerably facilitate an opening of the pyrone ring by nucleophilic on the 2-carbonyl group, which leads to the formation of an (*o*-hydroxyphenyl)unsaturated acid (*cf.* Chart 1). On the other hand, the yields of the amino derivative increased when an excess of amino reactant was used to serve as a hydrogen chloride acceptor.

Chart 1



We decided to examine the reaction of 3-substituted 4-chlorocoumarins with amino reactants which are less basic than ammonia and simple amines, especially with amino acids and their esters. To begin this study we selected the nitro group as the substituent in the 3-position because the expected 3-nitro products might possess biological activity (2). Further, the spatial disposition of the nitro group and the substituents introduced should enable the formation of a tricyclic ring system by reductive ring closure (*cf.* Chart 2), which may lead to novel compounds of chemical and possibly biological interest.

Chart 2



1. Reactions with Amino Acids.

To substitute the 4-chlorine atoms with an amino acid residue we applied the procedure of Otomasu and coworkers (3), who obtained *N*-(2,6-dinitrophen-1-yl)-α-amino acids by reacting the amino acid and 1-chloro-2,6-dinitrobenzene in an aqueous-alcoholic environment, with sodium hydrogen carbonate as a base catalyst. Our attempts with **1** as the starting compound led to many products, but none of these showed ir bands around 1700 (coumarinic CO) and 1610 cm^{-1} ($-\overset{3}{C}=\overset{4}{C}-$ coumarin) possibly because of pyrone ring destruction in the higher polar medium. As we tried to improve the reaction conditions by increasing the concentration of alcohol (using 96% ethanol) and by the addition of pyridine, as a base catalyst and a hydrogen chloride acceptor, we obtained only the pyridinium salt of 4-hydroxy-3-nitrocoumarin.

Satisfactory results were obtained, however, by using absolute ethanol as the solvent. Thus, *N*-(3-nitrocoumarin-4-yl)glycine was obtained in 80% yield when 4-chloro-3-nitrocoumarin was reacted with two equivalents of glycine; a practically quantitative yield was obtained (99.2%) by using triethylamine, instead of excess glycine, under the same conditions. Interestingly, the product *N*-(3-nitrocoumarin-4-yl)glycine was much less acidic than the

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amino acid itself. It was also much more acidic than its inner salt.

2. Reactions with Amino Acid Esters.

In addition to the procedures usable with amino acids as reactants, the amino acid esters offered the possibility of using non-polar solvents in which pyrone-ring cleavage should be extremely difficult. This promised good yields of type **2** products. Our choice of a non-polar solvent was benzene, in accordance with that of Savel'ev and coworkers (4). Previous workers (5) reported 70-100% yields with similarly conducted reactions in which ammonia and amines were the reactants. We were able to achieve yields of the same order. We found, for instance, that equimolar amounts of glycine ethyl ester and 4-chloro-3-nitrocoumarin, with triethylamine as a catalyst and a hydrogen chloride acceptor, react at room temperature and give a 79% yield of the desired product.

In a modification developed during this study we have released the glycine ester from its chloride in a preliminary step carried out in water-saturated benzene. The benzenic solution was thereupon freed of water and a volume of the resulting dry mixture corresponding to an about six-fold molar excess in ester (6) was allowed to react with 4-chloro-3-nitrocoumarin at room temperature. The yield of *N*-(3-nitrocoumarin-4-yl)glycine ethyl ester was 97.7%.

An attempt to generate the ester after having achieved the substitution with free amino acid in boiling absolute ethanol, by saturating the reaction mixture with dry hydrogen chloride gave only 49.7% of the theoretical amount of ester. This means that an equilibrium was reached when one-half of the nitrocoumarinyl-amino acid was esterified.

3. Reductive Ring Closure.

Compounds 4a-c were found to be polarographically active in an acid-containing ethanolic medium (7). These compounds exhibited typical S-shaped dependences of both limiting current and half-wave potential on *p*H. A preparative electrochemical reduction procedure for the type **4** compounds was based on polarographic data. Thus, the nitro group was reduced at a controlled potential, and the resulting amino group functioned as a convenient target for nucleophilic attack from the favorably placed carboxy or carbalkoxy group, which produced a new ring. The type **5** compounds thus obtained were easily soluble in 1*N* potassium hydroxide and 1*N* sodium carbonate, which suggests a predominance in enolic forms.

EXPERIMENTAL

All melting points are uncorrected (Koffler heating stage). Spectra were recorded with the following instruments: uv spectrophotometer, Beckman DU-2 (samples were dissolved in 96% ethanol); ir spectrophotometer, Perkin Elmer 377 (potassium bromide pellets); nmr spectrometer, Varian A-60 (samples in DMSO-d_6; internal standard, TMS); mass spectrometer, Varian MAT CH-7 (ionization potential 70 eV). 4-Chloro-3-nitrocoumarin (**1**) was prepared from the 4-hydroxy analogue and by a published procedure (8).

N-(3-nitrocoumarin-4-yl)glycine (**4a**).

A.

Glycine (2.0 g., 26.7 mmoles) was suspended in a hot solution of **1** (3.0 g., 13.3 mmoles) in absolute ethanol (20 ml.), and the suspension was refluxed for 2 hours. After cooling, the reaction mixture was brought to dryness (reduced pressure) and the greenish-yellow residue was washed with water and air-dried, yield 2.80 g. (80%). Purification by repeated crystallisations from 50% ethanol gave greenish-yellow platelets, m.p. 201-210°, pK_a 4.6; ir: cm^{-1} 3322 (NH), 1785 (carboxyl-CO), 1727 (coumarinic CO); nmr: ppm 10.73 (broad s, 1H, COOH), 9.78-9.94 (m, 1H, NH), 8.81-9.45 (m, 4H, aromatic), 4.88-4.96 (d, 2H, CH_2).

Anal. Calcd. for $C_{11}H_8N_2O_6$: C, 49.98; H, 3.05; N, 10.61. Found: C, 50.38; H, 3.22; N, 10.74.

B.

Glycine (1.0 g., 13.3 mmoles) and **1** (3.0 g., 13.3 mmoles) were suspended in absolute ethanol (about 250 ml.); one ml. of triethylamine was added and the mixture was stirred for 6 hours at room temperature. The solvent was removed (reduced pressure), the residue was washed with water and dried, yield 3.5 g. (99.2%), m.p. 146-170°. Several crystallizations from 50% ethanol raised the m.p. to 201-210° and the product gave an ir spectrum coincident with that of the product obtained by procedure A.

N-(3-nitrocoumarin-4-yl)glycine Ethyl Ester (**4b**).

A.

Glycine ethyl ester chloride (11.9 g., 107 mmoles) was suspended in water-saturated benzene (130 ml.) and gaseous ammonia was passed through the mixture for 3 hours with stirring and heating. After removal of the solid, excess ammonia was dispelled by a stream of air. The residual liquid was pre-dried with calcium chloride then thoroughly dried over metallic sodium for 24 hours. An aliquot volume (32 ml.), (corresponding to 26.5 mmoles of ester) was added dropwise with stirring during a half hour period at room temperature to a solution of **1** (3.0 g., 13.3 mmoles) in dry benzene (100 ml.). After further stirring for 30 minutes, the yellow crystalline product was collected, washed with 1% aqueous hydrochloric acid and dried, yield 3.82 g. (97.7%), m.p. 179-189°; uv: (38.6 mg./ml.) nm (log A) 255 (5.80), 280 (5.09), 345 (4.46); ir: cm^{-1} 3330 (NH), 1743 (coumarin CO), 1685 (ester CO); nmr: pmr 8.94 (t, 1H, NH), 8.25-7.30 (m, 4H, aromatic), 4.02 (q, 4H, CH_2); ms: (relative intensity) 293 (6.2, $M^+ + 1$), 292 (18.5, M^+), 276 (4.6), 246 (52.3), 218 (15.4), 201 (15.4), 172 (15), 173 (9), 147 (100), 129 (9), 116 (52), 76 (25).

Anal. Calcd. for $C_{13}H_{12}N_2O_6$: C, 53.52; H, 4.14; N, 9.59. Found: C, 53.52; H, 4.54; N, 9.54.

B.

Glycine (1.26 g., 9 mmoles) was suspended in a hot solution of **1** (1.0 g., 4.4 mmoles) in absolute ethanol (50 ml.) and the suspension was refluxed for 3 hours. Heating was thereupon discontinued and dry hydrogen chloride was passed through the hot mixture for the next half hour. Spontaneous cooling was subsequently allowed, and the yellow needles that deposited during this period were collected, washed with hydrochloric acid and dried. An additional crop was obtained by adding water (80 ml.) to the mother liquor, total yield 641 mg. (49%), m.p. 181-189°. Repeated crystallizations from 96% ethanol gave fine yellow needles, m.p. 178-187°, the ir spectrum of which coincided with that of the product obtained by procedure A.

C.

Compound **1** (1.0 g., 4.4 mmoles) was dissolved in dry benzene (35 ml.).

An equimolar amount of glycine ethyl ester chloride (620 mg., 0.23 mmole) was dissolved in a few drops of water, mixed with triethyl amine (1.25 ml., 8.8 mmoles), and the mixture was added to the benzene ester chloride solution with thorough shaking. The yellow crystalline product which separated immediately was collected, washed with 1% hydrochloric acid, and dried, yield 1.02 g.(79%), m.p. 162-180°, which rose to 178-187° after several crystallizations from 96% ethanol. The final product gave an ir spectrum coincident with those of the products obtained by procedures A and B.

N-(3-nitrocoumarin-4-yl)-DL-α-alanine Ethyl Ester (**4c**).

A.

The procedure described under A in the preceding section was used with 5.8 mmoles of DL-α-alanine ethyl ester (generated from the chloride by neutralization with ammonia) in dry benzene (9 ml.), which was added to an equimolar amount of **1** in dry benzene (20 ml.) over a 30 minute period. The product which was collected after another 30 minutes was washed with 1% hydrochloric acid and dried, yield 1.2 g. (55.4%), m.p. 146-158°. Recrystallization from 96% ethanol gave fine yellow needles, m.p. 165-168°; uv: (1 g. 1 mg./ml.) nm (log A) 255 (5.70), 280 (5.00), 346 (4.46); ir: cm^{-1} 3318 (NH), 1720 (coumarin CO), 1680 (ester CO), 1600; nmr: ppm 8.10-8.65 (m, 3H, NH and aromatic), 7.32-8.03 (m, 2H, aromatic), 4.07 (q, 2H, CH_2 ester) 2.81 (m, 1H), 2.50 (d, 3H, CH_3 ester) ms: 307 (7, M^+ + 1), 306 (37, M^+), 272 (6), 261 (5), 245 (12), 217 (16), 200 (10), 199 (37), 187 (7), 175 (10), 171 (100), 160 (10), 147 (85), 146 (16), 120 (17), 119 (39), 116 (26), 103 (22), 102 (37).

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: C, 54.88; H, 4.61; N, 9.15. Found: C, 54.94; H, 4.52; N, 9.18.

B.

Procedure B from the section on compound **4b** was applied to a solution of 1.33 mmoles of **1**, 2.7 mmoles of DL-α-alanine ethyl ester, and 10 mmoles of triethylamine in absolute ethanol (50 ml.), yield 330 mg. (81%), crude m.p. 132-141°, purified (by crystallization from 96% ethanol), m.p. 165-167°. The ir spectrum of the pure product coincided with that of the product obtained by procedure A.

1,2-Dihydro-3*H*,5*H*-1-benzopyrano[3,2-*c*]pyrimidine-3,5-dione (**5a**).

A.

Compound **4b** (740 mg., 2.54 mmoles) was suspended in a catholyte [96% ethanol and 0.1*N* hydrochloric acid 3:1 (v/v)]. The suspension was placed into the cathodal compartment of an electrolysis cell (7), the anode compartment provided with 0.1*N* hydrochloric acid, and an electrochemical reduction was run at controlled potential (-900 mV *vs.* S.C.E.) until the current had dropped to its base value (90 mA). Five and forty hundredths electrons were transferred by this time (coulometric determination, theory requires transfer of six electrons per molecule of reactant). The solid product was collected, washed with water, and dried, yield 368 mg. (55.2%) of grayish crystals which did not melt at the endpoint temperature of the thermometer (330°); uv (17.2 $\mu g./cm^{-3}$) nm (log A) 235 (5.143), 250 (5.187), 435 (5.057); ir: cm^{-1} 3295, 1700, 1665, 1616; nmr: ppm 9.75 (t, 2H, NH), 8.10-7.20 (m, 4H, aromatic), 4.07 (m, 2H, CH_2); ms: 216 (15, M^+ + 1), 215 (52, M^+), 201 (6.2), 200 (38.2), 186 (7), 173 (100), 121 (8) 120 (7).

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.10; H, 5.73; N, 12.95. Found: C, 60.99; H, 4.50; N, 12.77.

B.

Compound **4a** (310 mg., 1.21 mmoles) was treated in the same manner as **4b** and yielded 530 mg. (58.3%) of product after a transfer of 5.83 electrons per molecule of reactant (by coulometry). Several recrystallizations from glacial acetic acid gave grayish crystals, no m.p. up to 330°; the ir spectrum was coincident with that of the product obtained by procedure A.

1,2-Dihydro-2-methyl-3*H*,5*H*-1-benzopyrano[3,2-*c*]pyrimidine-3,5-dione (**5b**).

Compound **4c** (612 mg., 2.2 mmoles) was treated in the same manner as **4b** (see preceding section). The electrochemical reduction involved a transfer of 5.88 electrons per molecule of reactant (by coulometry) and the current remained slightly above base value (90 mA) at the end of electrolysis. The product separated in the form of white needles, and a second crop was obtained by concentrating the mother liquor (reduced pressure), total yield, 470 mg. (93%); crude m.p. 290-299°, purified (crystallization from 96% ethanol) m.p. 294-302°; uv (20 $\mu g./cm^{13}$) nm (log A) 234 (5.12), 248 (5.16), 345 (5.10); ir: cm^{-1} 3268 (NH), 1667 (coumarin CO), 1667; nmr: ppm 8.34-8.17 (m, 1H, NH), 7.67-7.20 (m, 4H, aromatic), 2.57 (d, 3H, CH_3); ms: 231 (12, M^+ + 1), 230 (66, M^+), 216 (7), 215 (44), 201 (10), 188 (13), 187 (100), 121 (8), 120 (6).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.95; H, 4.91; N, 11.98.

REFERENCES AND NOTES

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(5) V. A. Zagorevskii and N. V. Dudikina, *Zh. Org. Khim.*, **32**, 238 (1962).

(6) In subsequent experiments we found that only a two-fold excess gives the same yield.

(7) Data from the doctoral Thesis of one of us (Z. S.) submitted to the University of Zagreb in partial fulfillment of requirements for a D. Sc. degree (1978).