SYNTHESIS OF N-SUBSTITUTED 3-NITROPHTHALIMIDES

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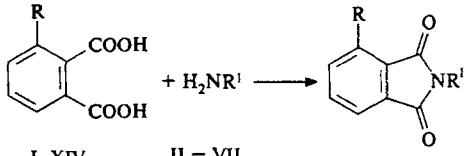
The N-substituted 3-nitrophthalimides are known to possess antibacterial [1], analgesic [2], and vasodilative [3] activity.

These compounds can be synthesized by heating 3-nitrophthalic anhydride with amines either without solvent [4] or in acetic acid [5].

Below we will show that N-substituted 3-Mitrophthalimides are conveniently obtained by cyclocondensation of 3-nitrophthalic acid (I) with amines in the presence of a two-component reagent system $ClSiMe_3$ – DMF. For example, the reaction of compound I with glycine (II), δ-aminovaleric acid (III), 4-aminobenzoic acids (IV), methyl ester of 4-aminobenzoic acid (V), aniline (VI), and *p*-toluidine (VII) lead to a high yield of the corresponding products (VIII – XIII). By the same token, the cyclocondensation of phthalic acid (XIV) with compounds II and III yield the N-substituted phthalimides XV and XVI:

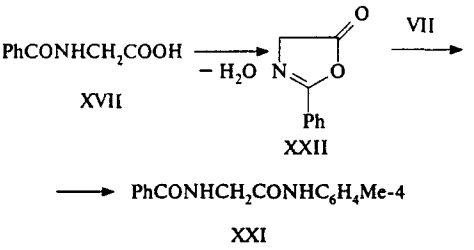


I, XIV II – VII VIII – XIII, XV, XVI

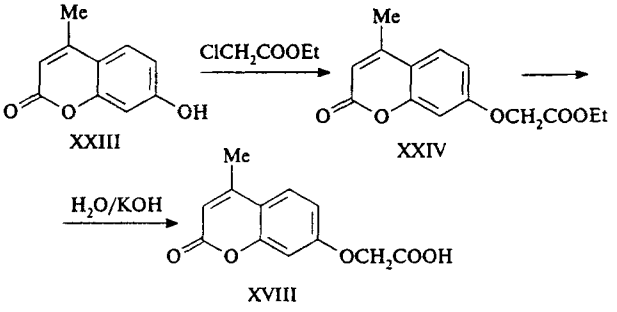
R = NO_2 (I, VIII – XIII), H (XIV – XVI); R^1 = CH_2COOH (II, VIII, XV), $(CH_2)_4COOH$ (III, IX, XVI), C_6H_4COOH-4 (IV, X), C_6H_4COOMe-4 (V, XI), Ph (VI, XII), C_6H_4Me-4 (VII, XIII).

In order to extend the known boundaries of applicability of the proposed method, we have attempted to conduct the reaction of N-acylation of *p*-toluidine by various monocarboxylic acids, including hippuric (XVII) and 4-nitrobenzoic acids, 7-(carboxymethoxy)-4-methylcoumarin (XVIII), 2-(carboxymethylthio)pyrimidine (XIX), and 5-(carboxymethylthiomethyl)uracil (XX).

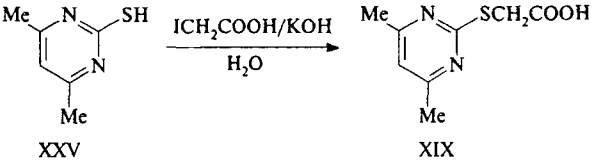
However, it was only compound XVII that entered into the desired N-acylation reaction, leading to a rather low yield of *p*-toluidide (XXI). The latter product was identified by comparing with the known compound synthesized by cyclization of compound XVII, followed by condensation of the intermediate 2-phenyl-2-oxazolin-5-one (XXII) with compound VII [6]:



Acid XVIII was obtained by alkylation of 7-hydroxy-4-methylcoumarin (XXIII) with chloroacetic acid ethyl ester, followed by saponification of the intermediate ester XXIV.



Acid XIX was obtained by alkylating 4,6-dimethyl-32-mercaptopyrimidine (XXV) with iodoacetic acid in an aqueous solution in the presence of KOH.



Acid XX was synthesized by heating 5-(hydroxymethyl)uracil (XXVI) with mercaptoacetic acid. The proposed structure of compound XX was confirmed by its

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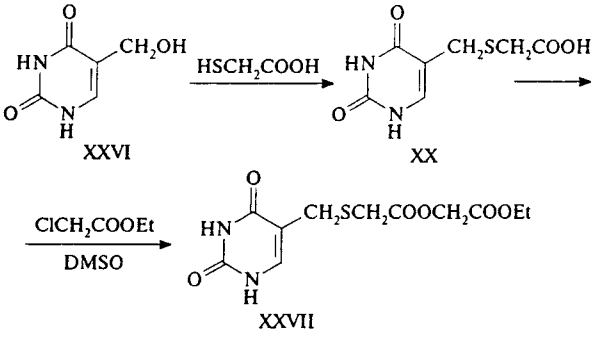
conversion into ester XXVII upon reaction with chloroacetic acid ethyl ester in DMSO in the presence of $NaHCO_3$.



The synthesized compounds were identified by comparison with known samples and by their ^1H NMR spectra (see experimental part below).

Because of high yields and simplicity of the experimental procedure, the proposed method of obtaining N-aryl derivatives of N-substituted 3-nitrophthalimides is quite competitive with those previously known [4, 5].

EXPERIMENTAL CHEMICAL PART

The ^1H NMR spectra were measured on a Bruker AM-300 spectrometer using samples dissolved in a $CDCl_3$–CF_3COOD mixture (6 : 1). The course of reactions was monitored and the purity of products was checked by TLC on Silufol UV-254 plates eluted in a benzene – ethyl acetate (1:1) system and visualized under UV illumination. The data of elemental analyses agree with the results of calculations according to empirical formulas.

N-(3-Naphthaloyl)glycine (VIII). A mixture of 1 g (4.5 mmole) of 3-nitrophthalic acid, 0.37 g (4.6 mmole) of glycine, 2 ml $ClSiMe_3$ and 2 ml of dry DMF was stirred for 90 min on a bath at 165 – 170°C, cooled to ~ 20°C, diluted with water, and allowed to stand for 12 h. The precipitate of compound VIII was separated by filtration, washed with water, and dried at 90 – 100°C in a vacuum of 20 Torr. Similar procedures were used to obtain the other N-substituted 3-nitrophthalimides and the N-phthaloyl derivatives of glycine and δ-aminovaleric acid XV and XVI (see Table 1).

Ester XI was purified by recrystallization from AcOH, while acid X was reprecipitated with diluted HCl from an aqueous K_2CO_3 solution.

The ^1H NMR spectrum of compound VIII (δ, ppm): 4.66 (s, 2H, CH_2), 8.15 (t, 1H, arom. protons, J 8.0 Hz), 8.28 (t, 2H, arom. protons, J 8.0 Hz).

The ^1H NMR spectrum of compound IX (δ, ppm): 1.77 (m, 4H, $2CH_2$), 2.51 (t, 2H, CH_2, J 7.1 Hz), 3.80 (t, 2H, CH_2, J 7.1 Hz), 7.96 (t, 1H, arom. proton, J 8.0 Hz), 8.18 (t, 2H, arom. proton, J 8.0 Hz).

The ^1H NMR spectrum of compound XV (δ, ppm): 4.66 (s, 2H, CH_2), 7.87 (m, 2H, arom. protons), 7.99 (m, 2H, arom. protons).

7-(Carboxymethoxy)-4-methylcoumarin (XVIII). A mixture of 1.4 g (8 mmole) of 7-hydroxy-4-methylcoumarin (XXIII), 1.4 g (11 mmole) of chloroacetic acid ethyl ester, 0.02 g KI, and 2 g of finely ground anhydrous Na_2CO_3 in 4 ml of dry DMF was kept with periodicall stirring for 96 h at 20 – 25°C and diluted with water. The precipitate was separated by filtration, washed with water, and dried in air to obtain 2 g (96%) of 4-methyl-7-(ethoxycarbonylmethoxy)coumarin (XXIV); m.p., 83 – 85°C; $C_{14}H_{14}O_5$. This product was saponified without additional purification as follows. To a solution of 1 g KOH in 10 ml water was added 1 g of ester XXIV and the mixture was stirred for 24 h at ~ 20°C and then acidified with concentrated HCl. The precipitate was filtered and dried at 80 – 90°C in a vacuum of 20 Torr to obtain 0.7 g (78%) of acid XVIII; m.p., 208 – 210°C; $C_{12}H_{10}O_5$; ^1H NMR spectrum (δ, ppm): 2.55 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 6.70 (d, 1H, 6-H, J 8.5 Hz), 7.27 (s, 1H, 8-H), 7.70 (d, 1H, 5-H, J 8.5 Hz).

4,6-Dimethyl-2-(carboxymethylthio)pyrimidine (XIX). To a solution of 0.6 g (10 mmole) KOH in 10 ml water were sequentially added with stirring 0.9 g (5 mmole) of 4,6-dimethyl-2-mercaptopyrimidine hydrochloride XXV [10] and 1 g (5.3 mmole) of iodoacetic acid and the mixture was allowed to stand for 1 h. The precipitate was separated by filtration and washed with water to obtain 0.8 g (80%) of compound XIX; m.p., 76 – 77°C; $C_8H_{10}N_2O_2S$; ^1H NMR spectrum in $CDCl_3$ (δ, ppm): 2.48 (s, 6H, $2CH_3$), 3.80 (s, 2H, CH_2), 6.87 (s, 1H, 5-H).

5-(Carboxymethylthiomethyl)uracil (XX). A mixture of 2 g 5-(hydroxymethyl)uracil (XXVI) [11] and 10 ml of 80% mercaptoacetic acid was stirred for 1 h on a bath at 120 – 130°C, cooled to ~ 20°C, and diluted with water. The precipitate was separated by filtration, washed with water, and dried in air to obtain 1.8 g (62%) of acid XX; m.p., 233 – 235°C; $C_7H_8N_2O_4S$; ^1H NMR spectrum (δ, ppm): 3.42 (s, 2H, CH_2), 3.77 (s, 2H, CH_2), 7.15 (s, 1H, 6-H).

5-(Carboxymethylthiomethyl)uracil ethoxycarbonylmethyl ester (XXVII). A mixture of 2 g (10 mmole) acid XX, 1.3 g (10 mmole) of chloroacetic acid ethyl ester, and 0.4 g of finely ground anhydrous $NaHCO_3$ in 2 ml of dry DMFSO was stirred for 48 h at ~ 20°C and diluted with water. The precipitate was separated by filtration, washed

TABLE 1. Characteristics of Newly Synthesized Phthalimide Derivatives

Compounds	Yield, %	M.p., °C	Empirical formula	Ref.
VIII	90	210 – 212	$C_{10}H_6N_2O_6$	[4]
IX	60	164 – 166	$C_{13}H_{12}N_2O_6$	–
X	81	> 300	$C_{15}H_8N_2O_6$	[8]
XI	96	215 – 218	$C_{16}H_{10}N_2O_6$	–
XII	85	137 – 138	$C_{14}H_8N_2O_4$	[5]
XIII	90	152 – 154	$C_{15}H_{10}N_2O_4$	[5]
XV	91	194 – 196	$C_{10}H_7NO_4$	[4]
XVI	80	134 – 135	$C_{13}H_{13}NO_4$	[9]

ROPHTHALIMIDES

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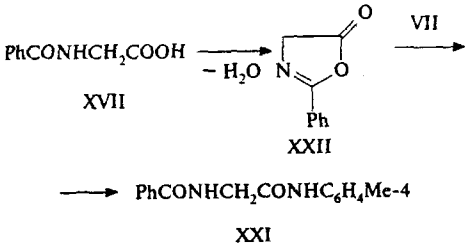

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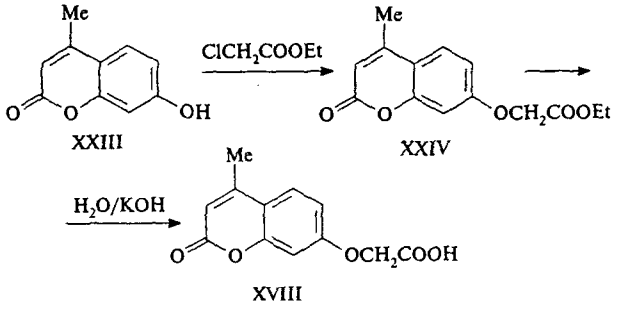

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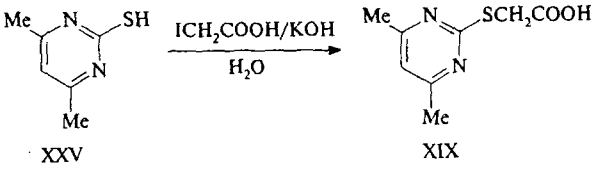

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