Synthesis of some *N*-Substituted Isonicotinamides

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A one-pot transformation of some cyclic 1,3-dicarbonyls **1** with *N*-(isonicotinoyl)glycine **2** and one-carbon synthons in acetic anhydride to the corresponding *N*-substituted isonicotinamides (pyridine-4-carboxamides) **7-9** containing a fused pyran-2-one ring is described. Compound **8** was further converted with some nitrogen-containing nucleophiles either to the corresponding quinoline-2,5-diones **10-11** or 5-hydrazonobenzopyran-2-ones **14-15**. Under more severe conditions the compound **8** gave with hydrazine 5-hydrazonoquinoline derivative **12** or even **13**. Hydrazoic acid transformed compound **8** to the pyrano-[3,2-*c*]azepine system **16**. Diazotization of 1-amino derivative **10** gave deaminated product **11**.

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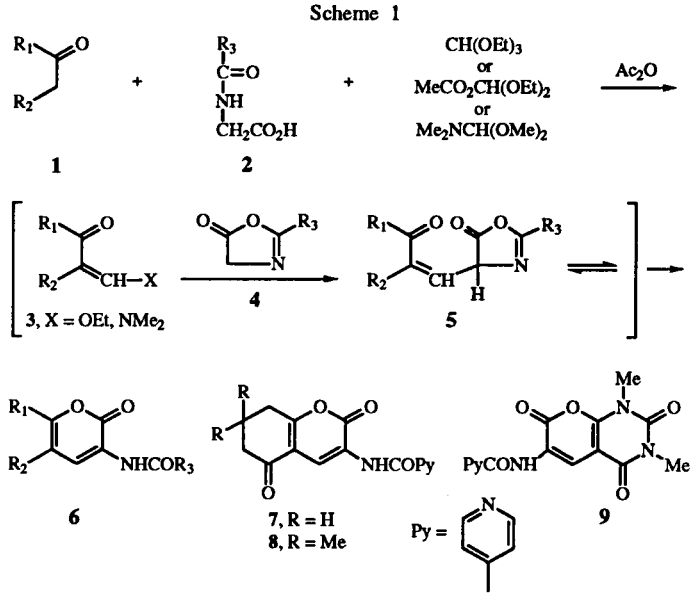
Fused pyran-2-ones are important biologically active compounds and synthons for organic synthesis [1]. 5,6,7,8-Tetrahydro-2*H*-1-benzopyran-2-ones possess wide variety of activities, such as antiarrhytmic, antiinflamatory, anesthetic, analgesic and platelet antiaggregating, *etc.* [2]. Derivatives of pyridine-4-carboxylic acid (isonicotinic acid) are also very important for biological reasons and have been thoroughly investigated for a longer period of time, among others as antibacterials [3]. The most effective drug for the chemotherapy of tuberculosis has proven to be isonicotinic hydrazide (isoniazid). Its mechanism of action in biological systems has been under detailed investigation during the last years [3c-d].

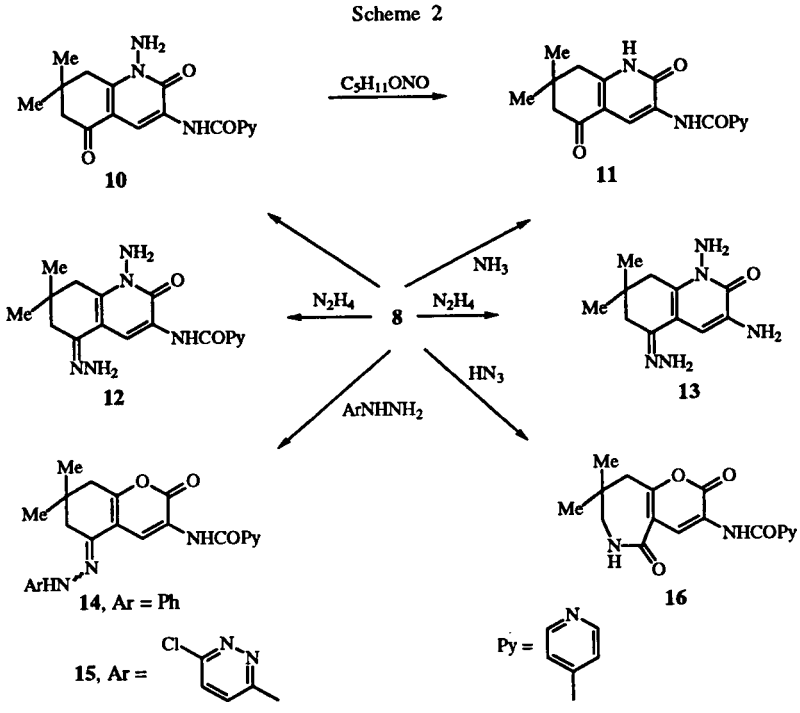
Recently, we investigated the synthesis and the reactivity of some 2*H*-pyran-2-ones and fused pyran-2-ones [4-13]. We have shown that such systems can be easily formed by the one-pot synthesis in one of its modification [4,5] or by the previously described Behringer-Falkenberg's method [7,14]. We have also shown, that 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones react with nitrogen-containing nucleophiles either with the lactone ring or with the 5-oxo group. By the action of ammonia, hydroxylamine, aniline, amino acids, hydrazine and *N,N*-dimethylhydrazine they were converted to the corresponding quinoline derivatives [6,8,9]. On the other hand, hydrazides, phenylhydrazines and heterocyclic hydrazines reacted with benzopyran-2,5-diones in absolute ethanol under the influence of acidic catalysts to afford 5-hydrazonobenzopyrans [10-13]. The latter, when treated with a mixture of ethanol, water and triethylamine, were selectively converted to the corresponding quinoline-2,5-diones *via* an open-ring intermediate [10]. Calculated heats of formation of some hydrazone or imine/fused pyridinone product pairs have shown that the products we isolated, are generally thermodynamically more stable isomers [9-12]. 5,6,7,8-Tetrahydro-2*H*-1-benzopyran-2,5-diones have also been useful intermediates for the synthesis of a novel heterocyclic system, pyrano[3,2-*c*]azepine, and for the related pyrido[3,2-*c*]azepine derivatives [6]. Interesting activity of isonicotinic acid derivatives [3] stimulated us in the preparation of *N*-(isonicotinoyl)-glycine (**2**, R_3 = 4-pyridinyl) [3b] and its further use for the preparation of *N*-substituted isonicotinamides, where the substituent on nitrogen represents a fused pyran-2-one or a pyridine derivative.

We report here the synthesis of *N*-substituted isonicotinamides containing a benzopyran-2-one or pyrano-[2,3-*d*]pyrimidine residue as a part of the molecule. For the preparation of the compounds **7-9** (Scheme 1) we used our one-pot method [4,5] starting from 1,3-cyclohexadiones or 1,3-dimethylbarbituric acid (type **1**), *N*-(isonicotinoyl)glycine (**2**, R_3 = 4-pyridinyl) and a one-carbon synthon (triethyl orthoformate, diethoxymethyl acetate or *N,N*-dimethylformamide dimethyl acetal) in the presence of a large excess of acetic anhydride. The corresponding products were isolated in rather poor yields (13-41%).

Scheme 1



Scheme 2



The dimethyl derivative **8** was chosen for some further studies. We investigated its transformations with some nitrogen-containing nucleophiles: ammonia, hydrazine hydrate, substituted hydrazines and hydrazoic acid (Scheme 2). Compound **8** was transformed with an equimolar amount of hydrazine hydrate in absolute ethanol after an hour of heating to the 1-aminoquinoline derivative **10** in 64% yield. Similarly, with ammonia in ethanolic solution we obtained the corresponding derivative **11**, which can also be obtained by diazotization from compound **10** and isoamyl nitrite in acetic acid in 38% yield. When heating compound **8** with an excess of 99% hydrazine hydrate in ethanolic solution hydrazonoquinoline derivative **12** was obtained in 56% yield, but on heating compound **8** with an excess of hydrazine hydrate, which was also used as a solvent, the deacylated product **13** was obtained. Compound **13** has already been previously prepared from *N*-(5,6,7,8-tetrahydro-7,7-dimethyl-2-oxo-2*H*-1-benzopyran-3-yl)benzamide and hydrazine hydrate [9].

In contrast, treatment of compound **8** with phenylhydrazine or 3-chloro-6-hydrazinopyridazine gave 5-hydrazonobenzopyran-2-one derivatives **14** or **15**, which were isolated in 66 and 57% yield. We differentiated between the structures of the hydrazone type and the quinoline type on the basis of infrared spectroscopic data. The starting compounds **8** show in the infrared spectrum a slightly broadened lactone signal at 1725 cm^{-1}. Similarly, products **14** and **15** show in their infrared spectra the lactone signals with the maximum absorption at 1705 cm^{-1}, while for the quinoline derivatives there are no carbonyl signals above 1668 cm^{-1}. These data are in agreement with our previous observations [9,10,12,13].

When the Schmidt reaction [15] was applied to benzopyran derivative **8**, the corresponding pyrano[3,2-*c*]-azepine derivative **16** was isolated as the only product, and its structure was determined on the basis of the ^1H nmr spectrum.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. The nmr spectra were obtained on a Varian EM360L spectrometer in dimethyl sulfoxide-d_6 with tetramethylsilane as an internal standard. Infrared spectra were recorded with a Perkin Elmer 727B or 1310 spectrophotometer. Mass spectra were obtained with a VG-Analytical AutospecQ instrument. Elemental analysis (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. *N*-(Isonicotinoyl)glycine [3b] and 3-chloro-6-hydrazinopyridazine [16] were prepared as described in the literature. All other compounds were used without purification as obtained from the commercial sources.

N-(5,6,7,8-Tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl)nicotinamide (**7**).

A.

A mixture of 349 mg (2.28 mmoles) of 97% triethyl orthoformate, 252 mg (2.18 mmoles) of 97% 1,3-cyclohexanedione and 360 mg (2 mmoles) of *N*-(isonicotinoyl)glycine in 5 ml of acetic anhydride was heated at 70-80° (oil bath temperature) for 4 hours with occasional shaking. The reaction mixture was evaporated *in*

vacuo and the residue was treated with ethanol (2 ml). Upon cooling, the solid was filtered and washed with a small amount of ethanol to give 108 mg (19%) of compound **7**, mp 242-244° (from methanol/*N,N*-dimethylformamide); ^{1}H nmr: δ 2.15 (m, 2H, 7'-CH_2), 2.55 (m, 2H) and 2.90 (m, 2H) (6'-CH_2, 8'-CH_2), 7.86 (deg dd, 2H, 3-H, 5-H), 8.38 (s, 1H, 4'-H), 8.83 (deg dd, 2H, 2-H, 6-H), 10.17 (br s, 1H, NH); ir: ν 1680 br, 1705 cm^{-1}.

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.73; H, 3.91; N, 9.92.

B.

Compound **7** was also obtained from 335 mg (2.0 mmoles) of 97% diethoxymethyl acetate, 230 mg (2.0 mmoles) of 1,3-cyclohexanedione, 360 mg (2.0 mmoles) of *N*-(isonicotinoyl)glycine and 3 ml of acetic anhydride after 4 hours of heating at 70-80°. In this case, the crude product was thoroughly washed with ethanol and methanol and finally crystallized to give 75 mg (13%) of the product **7**.

N-(5,6,7,8-Tetrahydro-7,7-dimethyl-2-oxo-2*H*-1-benzopyran-3-yl)nicotinamide (**8**).

A.

A mixture of 480 mg (3.62 mmoles) of 90% *N,N*-dimethylformamide dimethyl acetal, 513 mg (3.62 mmoles) of 99% dimedone and 655 mg (3.64 mmoles) of *N*-(isonicotinoyl)glycine in 4 ml of acetic anhydride was heated at 90-100° for 4 hours with occasional shaking. The reaction mixture was evaporated *in vacuo* and the residue was treated with ethanol (1.8 ml). Upon cooling, the solid was filtered and washed with a small amount of ethanol to give 480 mg (41%) of compound **8**, mp 175-177° (twice crystallized: first from methanol, then from ethanol); ^{1}H nmr: δ 1.08 (s, 6H, two Me), 2.47 (s, 2H) and 2.82 (s, 2H) (6'-CH_2, 8'-CH_2), 7.84 (deg dd, 2H, 3-H, 5-H), 8.35 (s, 1H, 4'-H), 8.81 (deg dd, 2H, 2-H, 6-H), 10.12 (br s, 1H, NH); ir: ν 1665 br, 1725 cm^{-1}; ms: m/z 312 (M^+, 43%), 106 (100).

Anal. Calcd. for $C_{17}H_{16}N_2O_4 \cdot 0.5\ H_2O$: C, 63.54; H, 5.30; N, 8.72. Found: C, 63.57; H, 5.30; N, 8.91.

B.

Compound **8** was also obtained from 167 mg (1.0 mmole) of diethoxymethyl acetate, 141 mg (1.0 mmole) of 99% dimedone, 180 mg (1.0 mmole) of *N*-(isonicotinoyl)glycine and 1.25 ml of acetic anhydride after 4 hours of heating at 70-80°. After treatment with ethanol, cooling and washing with ethanol 118 mg (37%) of product **8** was isolated.

C.

This compound was also obtained from 153 mg (1.0 mmole) of triethyl orthoformate, 150 mg (1.06 mmoles) of 99% dimedone, 180 mg (1.0 mmole) of *N*-(isonicotinoyl)glycine and 1.25 ml of acetic anhydride after 4 hours of heating at 70-80° and 1 hour at 90-100°. After treatment with ethanol (0.8 ml), cooling and washing with a small amount of ethanol 76 mg (24%) of product **8** was isolated.

N-(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4,7-trioxo-7*H*-pyrano-[2,3-*d*]pyrimidin-6-yl)nicotinamide (**9**).

A.

A mixture of 289 mg (2.18 mmoles) of *N,N*-dimethylformamide dimethyl acetal, 316 mg (2.0 mmoles) of 99% 1,3-dimethylbarbituric acid and 360 mg (2.0 mmoles) of *N*-(isonicotinoyl)glycine in 2.5 ml of acetic anhydride was heated at 70-80° for 4 hours with occasional shaking. The reaction mixture was evaporated *in vacuo* and the residue was treated with ethanol (1.8 ml). Upon cooling, the solid was filtered and washed with ethanol and crystallized from a mixture of ethanol and *N,N*-dimethylformamide to give 95 mg (14%) of compound **9**, mp 244-245°; ^{1}H nmr: δ 3.25 (s, 3H, Me), 3.45 (s, 3H, Me), 7.88 (deg dd, 2H, 3-H, 5-H), 8.35 (s, 1H, 4'-H), 8.84 (deg dd, 2H, 2-H, 6-H), 10.30 (br s, 1H, NH); ir: ν 1655 br, 1703, 1755 cm^{-1}.

Anal. Calcd. for $C_{15}H_{12}N_4O_5$: C, 54.88; H, 3.68; N, 17.07. Found: C, 55.14; H, 3.56; N, 16.95.

N-(1-Amino-1,2,5,6,7,8-hexahydro-7,7-dimethyl-2,5-dioxo-3-quinolinyl)nicotinamide (**10**).

A mixture of compound **8** (290 mg, 0.93 mmole) and 47 mg (0.93 mmole) of 99% hydrazine hydrate in absolute ethanol (2 ml) was refluxed for 1 hour. Upon cooling, the separated product was filtered and washed with a small amount of ethanol to give 196 mg (65%) of product **10**, mp 200-202° (methanol); ^{1}H nmr: δ 1.08 (s, 6H, two Me), 2.43 (s, 2H) and 3.07 (s, 2H) (6'-CH_2, 8'-CH_2), 6.28 (br s, 2H, NH_2), 7.90 (deg dd, 2H, 3-H, 5-H), 8.62 (s, 1H, 4'-H), 8.86 (deg dd, 2H, 2-H, 6-H), 9.83 (br s, 1H, NH); ir: ν 1632, 1668 cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.60; H, 5.17; N, 16.86.

N-(1,2,5,6,7,8-Hexahydro-7,7-dimethyl-2,5-dioxo-3-quinolinyl)nicotinamide (**11**).

A.

A mixture of 170 g (0.52 mmole) of 1-amino derivative **10** in 7.5 ml of acetic acid and an excess (6 drops) of isoamyl nitrite was left at room temperature for 130 minutes. Upon evaporation *in vacuo*, the solid product was crystallized from the mixture of methanol and *N,N*-dimethylformamide to give 67 mg (40%) of the product **11**, mp 295-299°, dec; ^{1}H nmr: δ 1.02 (s, 6H, two Me), 2.38 (s, 2H) and 2.73 (s, 2H) (6'-CH_2, 8'-CH_2), 7.81 (deg dd, 2H, 3-H, 5-H), 8.55 (s, 1H, 4'-H), 8.78 (deg dd, 2H, 2-H, 6-H), 9.58 (br s, 1H, NH), 12.60 (br s, 1H, NH); ir: ν 1650 br cm^{-1}; ms: m/z 311 (M^+, 84), 106 (100).

Anal. Calcd. for $C_{17}H_{17}N_3O_3 \cdot 0.5\ H_2O$: C, 63.74; H, 5.66; N, 13.12. Found: C, 63.85; H, 5.55; N, 12.94.

B.

Gaseous ammonia was introduced for 20 minutes into a mixture of 100 mg (0.31 mmole) of the compound **8** in 3 ml of absolute ethanol, then the reaction mixture was allowed to stand at room temperature for 6 days. Upon evaporation *in vacuo*, the solid product was crystallized from a mixture of methanol and *N,N*-dimethylformamide to give 25 mg (25%) of the product **11**.

N-(1-Amino-5-hydrazono-1,2,5,6,7,8-hexahydro-7,7-dimethyl-2-oxo-3-quinolinyl)nicotinamide (**12**).

A mixture of compound **8** (200 mg, 0.62 mmole) and 140 mg (2.77 mmoles) of 99% hydrazine hydrate in absolute ethanol (5.5 ml) was refluxed for 6 hours. Upon cooling, the separated product was filtered and washed with a small amount of ethanol to give 123 mg (57%) of product **12**, mp 216-218° (methanol/*N,N*-dimethylformamide); ^{1}H nmr: δ 1.02 (s, 6H, two Me), 2.27 (s, 2H) and 2.81 (s, 2H) (6'-CH_2, 8'-CH_2), 6.15 (br s, 2H, NH_2), 6.26 (br s, 2H, NH_2), 7.91 (deg dd, 2H, 3-H, 5-H), 8.82 (s, 1H, 4'-H), 8.88 (deg dd, 2H, 2-H, 6-H), 9.65 (br s, 1H, NH); ir: ν 1630 br, 1662 cm^{-1}; ms: m/z 340 (M^+, 75), 106 (100).

Anal. Calcd. for $C_{17}H_{20}N_6O_2 \cdot 0.5\ H_2O$: C, 58.44; H, 6.06; N, 24.05. Found: C, 58.80; H, 6.07; N, 23.71.

1,3-Diamino-5-hydrazono-7,7-dimethyl-2-oxo-1,2,5,6,7,8-hexahydroquinoline (**13**) [9].

A mixture of compound **8** (225 mg, 0.72 mmole) and 1.5 ml (30.5 mmoles) of 99% hydrazine hydrate was heated at 110° for 3 hours. Upon cooling, the separated product was filtered and washed with water to give 79 mg (47%) of the product **132**, mp 250-253° (*N,N*-dimethylformamide) (lit [9] gives mp 250-253°).

N-[5,6,7,8-Tetrahydro-7,7-dimethyl-5-(phenylhydrazono)-2-oxo-2*H*-1-benzopyran-3-yl]nicotinamide (**14**).

A mixture of 200 mg (0.64 mmole) of compound **8** and 69 mg (0.64 mmole) of phenylhydrazine in absolute ethanol (3.2 ml) was refluxed for 9 hours. Upon cooling, the separated product was filtered to give 176 mg (68%) of compound **14**, mp 240-242° (twice crystallized: first from methanol/*N,N*-dimethylformamide and then from methanol); ^{1}H nmr: δ 1.1 (s, 6H, two Me), 2.52 (s, 2H) and 2.61 (s, 2H) (6'-CH_2, 8'-CH_2), 6.85 (m, 1H, Ph), 7.26 (m, 4H, Ph), 7.93 (deg dd, 2H, 3-H, 5-H), 8.78 (s, 1H, 4'-H), 8.87 (deg dd, 2H, 2-H, 6-H), 9.48 (br s, 1H, NH), 10.08 (br s, 1H, NH); ir: ν 1670, 1705 cm^{-1}.

Anal. Calcd. for $C_{23}H_{22}N_4O_3$: C, 68.64; H, 5.51; N, 13.92. Found: C, 68.94; H, 5.50; N, 13.72.

N-{5-[(6-Chloropyridazin-3-yl)hydrazono]-5,6,7,8-tetrahydro-7,7-dimethyl-2-oxo-2*H*-1-benzopyran-3-yl}nicotinamide (**15**).

A mixture of 100 mg (0.32 mmole) of compound **8** and 46 mg (0.32 mmole) of 3-chloro-6-hydrazinopyridazine in absolute ethanol (1.6 ml) was refluxed for 8 hours. Upon cooling, the separated product was filtered to give 80 mg (57%) of compound **15**, mp 263-265° dec (methanol/*N,N*-dimethylformamide); ^{1}H nmr: δ 1.1 (s, 6H, two Me), 2.56 (s, 2H) and 2.70 (s, 2H) (6'-CH_2, 8'-CH_2), 7.83 (deg dd, 2H, 4"-H, 5"-H), 8.05 (deg dd, 2H, 3-H, 5-H), 8.85 (s, 1H, 4'-H), 9.04 (deg dd, 2H, 2-H, 6-H), 10.25 (br s, 1H, NH), 10.95 (br s, 1H, NH); ir: ν 1660, 1705 cm^{-1}.

Anal. Calcd. for $C_{21}H_{19}ClN_6O_3$: C, 57.47; H, 4.36; N, 19.15. Found: C, 57.13; H, 4.32; N, 18.94.

N-(2,5,6,7,8,9-Hexahydro-8,8-dimethyl-2,5-dioxopyrano-[3,2-*c*]azepin-3-yl)nicotinamide (**16**).

Sodium azide (267 mg, 4.1 mmoles) was added over a period of 30 minutes to a stirred mixture of compound **8** (200 mg, 0.62 mmole) in chloroform (26.5 ml) and concentrated sulfuric acid (1 ml) at 0°. The reaction mixture was then stirred for 90 minutes at 0° and 90 minutes at room temperature. After the addition of ice and water (26.5 g) and neutralization of the mixture with solid sodium bicarbonate the layers were separated and the aqueous layer was extracted with chloroform (3 x 20 ml). The solid product (95 mg, 47%) was crystallized for analysis first from methanol and then from a mixture of methanol and *N,N*-dimethylformamide, mp 305-308° dec; ^{1}H nmr: δ 1.02 (s, 6H, two Me), 2.55 (s, 2H, 9'-CH_2), 2.85 (d, J = 5.6 Hz, 2H, 7'-CH_2), 7.86 (deg dd, 2H, 3-H, 5-H), 8.23 (s, 1H, 4'-H), 8.38 (t, J = 5.6 Hz, 1H, 6'-H), 8.82 (deg dd, 2H, 2-H, 6-H), 10.1 (br s, 1H, NH); ir: ν 1660, 1680, 1715 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.29; H, 4.95; N, 12.45.

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