Synthesis of Some Basic 3-(1-Acylaminobenzyl)-2*H*-1-benzopyran-2-ones

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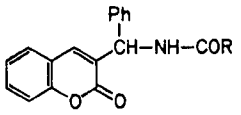
The reaction of 3-(1-propanoyloxybenzyl)-2*H*-1-benzopyran-2-one (**2**) with the nitriles of 4-dimethylaminobenzoic, 4-diethylaminobenzoic, nicotinic, isonicotinic, and 3-dimethylaminopropionic acid in conc. H_2SO_4 yields the amides **3a-e**. **3a-d** were converted into hydrochlorides.

Synthese einiger basischer 3-(1-Acylaminobenzyl)-2*H*-1-benzopyran-2-one

Die Umsetzung von 3-(1-Propanoyloxybenzyl)-2*H*-1-benzopyran-2-on (**2**) mit Nitrilen der 4-Dimethylaminobenzoe-, 4-Diethylaminobenzoe-, Nicotin-, Isonicotin- und 3-Dimethylaminopropionsäure in konz. H_2SO_4 lieferte die Amide **3a-e**. **3a-d** wurden in die Hydrochloride umgewandelt.

The preparation of N-substituted amides by *Ritter* reaction is often applied because of its easy accessibility and simplicity of realization.

Easily prepared 3-(1-acyloxybenzyl)-2*H*-1-benzopyran-2-ones react in sulfuric acid with nitriles at room temp. to yield the corresponding amides **1** in high yields[1].



1

R = CH_3, $CH{=}CH_2$, $H_2C{-}CO{-}OC_2H_5$, $CH_2C_6H_5$, CH_2Cl, C_6H_5

Coumarin derivatives have various physiological activities. In this context attention was drawn to amides like **1**. However, compounds **1** are not appropriate for biological screening because of their insufficient solubility.

Therefore, derivatives of amides **1** with better solubility should be prepared. A possibility in this respect is to include a basic N-atom in the substituent R of amides **1**, which affords an opportunity to prepare the corresponding hydrochlorides.

Along with various examples in lit. concerning the *Ritter* reaction there are only two cases leading to amides containing a basic atom in the acyl part[2,3]. These compounds show local anesthetic, analgesic, convulsant, spasmolytic or hypertensive properties.

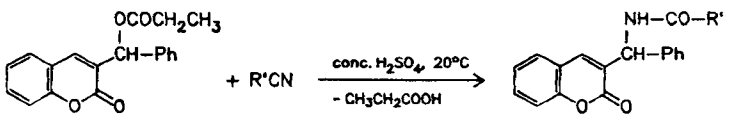
In this connection we checked the behaviour of 3-(1-propanoyloxybenzyl)-2*H*-1-benzopyran-2-one (**2**) towards nitriles containing such basic center, *e.g.* nitriles of 4-dimethylaminobenzoic, 4-diethylaminobenzoic, nicotinic, isonicotinic, and 3-dimethylaminopropionic acid.

With the exception of the nitrile of 3-dimethylaminopropionic acid the reaction proceeded smoothly and in good yields (50-65%, Table). The lower yield of amide **3e** (34%) in H_2SO_4 is due to its tendency to eliminate dimethylamine leading to the amide of acrylic acid (**1**, R = $CH{=}CH_2$). When the reaction was carried out in a mixture of acetic and sulfuric acid, after purification by column chromatography (CC) the yield of the amide **3e** increased to 66% and in addition the amide of the acrylic acid was isolated (3%). The presence of acetic acid, however, leads also to the formation of 3-(1-acetyloxybenzyl)-2*H*-1-benzopyran-2-one (7%), which is obviously the product of reacylation of the starting ester **2**.

Table: Yields of the amids **3a-e**

Comp.	R^1	Yield (%)[a]	
		H_2SO_4	H_2SO_4/CH_3COOH
a	$(CH_3)_2N$–C$_6$H$_4$–	50	87
b	$(C_2H_5)_2N$–C$_6$H$_4$–	52	94
c		65	92
d		53	90
e	$(CH_3)_2NCH\ CH_2$-	34	66

[a] Yield of isolated product.



2 **3**

R': see Table

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The significant increase of the yield of amide **3e** by carrying out the reaction in a mixture of acetic and sulfuric acid prompted us to check the influence of the reaction conditions on the yields of amides **3a-d**. These reactions and isolation of the products by CC actually lead to **3a-d** in 87-94% yields.

Except for amide **3e**, amides **3** were converted into their hydrochlorides. By reason of elimination of dimethylamine under the action of HCl it was impossible to obtain the hydrochloride of **3e**. The reaction leads to the amide of acrylic acid (detected by TLC).

Experimental Part

Melting points (uncorrected): Carl Zeiss melting point microscope.- IR: Specord IR 71.- ^{1}H-NMR ($CDCl_3$ or DMSO-d_6, TMS as int. standard): Bruker WM 250 (250 MHz).- Elemental analyses: Laboratory of elemental analysis at the dep. of organic chemistry.- Column chromatography: silica gel (70-230 mesh) Merck.- TLC: silica gel ($60F_{254}$, Merck) glass plates.

Reaction of 3-(1-propanoyloxybenzyl)-2H-1-benzopyran-2-one with nitriles Method A, General Procedure

Conc. H_2SO_4 (2 ml) is added dropwise with cooling and stirring to a mixture of benzopyran **2** (1.54 g, 5 mmol) and the corresponding nitrile (5 mmol). After 2 h at room temp. the mixture is poured into ice/water (about 200 ml). The precipitate is filtered, washed with water, $NaHCO_3$-solution, again with water, and dried. The crude product is recrystallized several times from ethyl acetate or ethanol.

Method B, General Procedure

Glacial acetic acid (2 ml) and then conc. H_2SO_4 (4 ml) are added to a mixture of **2** (1.54 g, 5 mmol) and the appropriate nitrile (5 mmol). The mixture is stirred for 4 h at room temp. and worked up as above. The crude product is purified on a silica gel column ($CHCl_3$ as eluent).

3-[1-(4-Dimethylaminobenzoyl)aminobenzyl]-2H-1-benzopyran-2-one(**3a**)

From ethyl acetate, mp. 212-213°C.- IR ($CHCl_3$): 1650 (C=O, amide), 1715 (C=O, lactone), 3450 (NH) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.01 (s, 6H, CH_3), 6.45 (d, 1H, CHPh, $J_{CH,NH}$ = 8.8 Hz), 6.66 (d, J = 9 Hz, 2H, arom.), 7.26-7.53 (m, 9H, arom.), 7.68 (d, 1H, NH, J = 8.8 Hz), 7.78 (d, J = 9 Hz, 2H, arom.), 7.89 (s, 1H, H-4).- $C_{25}H_{22}N_2O_3$ (398.4) calc. C 75.4 H 5.57 N 7.0 found C 75.4 H 5.84 N 6.7.

3-[1-(4-Diethylaminobenzoyl)aminobenzyl]-2H-1-benzopyran-2-one(**3b**)

From ethanol, mp. 186-187°C.- IR (nujol): 1615; 1725; 3310 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.16 (t, J = 7 Hz, 6H, CH_3), 3.37 (q, J = 7 Hz, 4H, CH_2), 6.45 (d, 1H, CHPh, $J_{CH,NH}$ = 8.8 Hz), 6.62 (d, J = 8.7 Hz, 2H, arom.), 7.21-7.52 (m, 9H, arom.), 7.65 (d, 1H, NH, J = 8.8 Hz), 7.76 (d, J = 8.7 Hz, 2H, arom.), 7.86 (s, 1H, H-4).- $C_{27}H_{26}N_2O_3$ (426.5) calc. C 76.0 H 6.15 N 6.6 found C 76.1 H 6.42 N 6.2.

3-(Nicotinoylaminobenzyl)-2H-1-benzopyran-2-one(**3c**)

From ethyl acetate, mp. 219-221°C.- IR (nujol): 1635; 1715; 3300 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.46 (d, 1H, CHPh, $J_{CH,NH}$ = 8.9 Hz), 7.27-7.59 (m, 10 H, arom. + H-5 - pyridine), 7.91 (s, 1H, H-4), 8.06 (d, 1H, NH, J = 8.9 Hz), 8.15 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1H, H-4-pyridine) 8.74 (dd, J_1 = 4.8 Hz, J_2 = 1.5 Hz, 1H, H-6 - pyridine), 9.10 (d, J = 2 Hz, 1H, H-2 - pyridine).- $C_{22}H_{16}N_2O_3$ (356.4) calc. C 74.1 H 4.53 N 7.9 found C 74.1 H 4.59 N 7.6.

3-(Isonicotinoylaminobenzyl)-2H-1-benzopyran-2-one(**3d**)

From ethyl acetate, mp. 221-222°C.- IR ($CHCl_3$): 1665; 1710; 3410 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.44 (d, 1H, CHPh, $J_{CH,NH}$ = 9 Hz), 7.26-7.60 (m, 9H, arom.), 7.70 (d, J = 5.4 Hz, 2H, H-3 and H-5 - pyridine), 7.91 (s, 1H, H-4), 8.17 (d, 1H, NH, J = 9 Hz), 8.76 (d, J = 5.4 Hz, 2H, H-2 and H-6 - pyridine).- $C_{22}H_{16}N_2O_3$ (356.4) calc. C 74.1 H 4.53 N 7.9 found C 74.4 H 4.83 N 7.6.

3-[1-(3-Dimethylaminopropanoyl)aminobenzyl]-2H-1-benzopyran-2-one (**3e**)

From ethyl acetate, mp. 148-149°C.- IR (nujol): 1640; 1715; 3310 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.34 (s, 6H, CH_3), 2.47 (t, J = 6.5 Hz, 2H, CH_2), 2.66 (t, J = 6.5 Hz, 2H, CH_2), 6.22 (d, 1H, CHPh, $J_{CH,NH}$ = 8.6 Hz, with D_2O: s at 6.61), 7.21-7.52 (m, 9H, arom.), 7.81 (s, 1H, H-4), 9.71 (d, J = 8.6 Hz, 1H, NH, exchangeable with D_2O).- $C_{21}H_{22}N_2O_3$ (350.4) calc. C 72.0 H 6.33 N 8.0 found C 71.8 H 6.44 N 7.7.

Hydrochlorides, General Procedure

Conc. HCl is added dropwise under stirring to a suspension of the amide **3** in water (6 ml) until it dissolves. The water is removed *i. vac.* and the residue is crystallized from absol. ethanol. Yields are quantitative.

Hydrochloride of **3a**

From ethanol, mp. 147-157°C (decomp.).- IR (nujol): 1640; 1732; 2200-2700 ($^+$NH); 3280 (NH) cm^{-1}.- $C_{25}H_{22}N_2O_3$ · HCl (434.9) calc. C 69.0 H 5.33 found C 69.6 H 5.38.

Hydrochloride of **3b**

From ethanol, mp. 132-139°C (decomp.).- IR (nujol): 1655; 1715; 2200-2800 ($^+$NH); 3420; 3300 (NH) cm^{-1}.- $C_{27}H_{26}N_2O_3$ · HCl - monohydrate (481.0) calc. C 67.4 H 6.08 found C 67.1 H 6.30.

Hydrochloride of **3c**

From ethanol, mp. 144-149°C (decomp.).- IR (nujol): 1670; 1705; 2200-2800 ($^+$NH); 3430; 3300 (NH) cm^{-1}.- $C_{22}H_{16}N_2O_3$ · HCl - monohydrate (410.8) calc. C 64.3 H 4.66 found C 64.1 H 5.04.

Hydrochloride of **3d**

From ethanol, mp. 175-180°C (decomp.).- IR (nujol): 1665; 1705; 2200-2800 ($^+$NH); 3400 (NH) cm^{-1}.- $C_{22}H_{16}N_2O_3$ · HCl - monohydrate (410.8) calc. C 64.3 H 4.66 found C 64.2 H 4.86.

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