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Some Condensations of Methyl 4-Acetylphenylcarbamate

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Abstract—Condensation of methyl 4-acetylphenylcarbamate with isatin in the presence of diethylamine afforded methyl 4-[(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]phenylcarbamate which was converted into the corresponding chalcone on heating in glacial acetic acid in the presence of hydrochloric acid. 1,3-Dipolar cycloaddition to that chalcone of azomethine ylide generated from 2-phenacylisoquinolinium bromide by the action of triethylamine gave methyl 4-(3′-benzoyl-2-oxo-1′,2,2′,3,3′,10b′-hexahydro-1*H*-spiro-[indole-3,1′-pyrrolo[1,2-*a*]isoquinolin]-2′-ylcarbonyl)phenylcarbamate. Condensation of 2-hydroxy- and 2,4-dihydroxybenzaldehydes with methyl 4-acetylphenylcarbamate in the presence of gaseous hydrogen chloride resulted in the formation of chromenium salts with a methoxycarbonylaminophenyl fragment on the C^2 atom in the heteroring.

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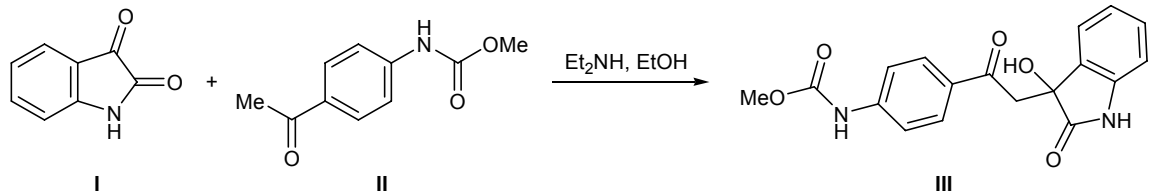
Acetophenone and its derivatives are convenient starting materials for the synthesis of various compounds, including chalcones which can be converted into various heterocycles [1–5]. Chalcones and flavonoids generally exhibit versatile biological activity, in particular antituberculous [6]. The ability of chalcones to inhibit leukocyte aggregation is completely lost upon hydrogenation of the double bond [7]. Taking into account the above stated, it seemed to be important to examine condensations of new acetophenone derivatives, specifically of those containing a carbamate moiety, with various carbonyl compounds.

In order to obtain carbamate derivatives of chalcones, isatin (**I**) was reacted with methyl 4-acetylphenylcarbamate (**II**) in anhydrous ethanol in the presence of diethylamine. The reaction mixture was heated for 1 h at 95°C, and the product was isolated after keeping the mixture for 4 days at 20°C. According to the IR and ^{1}H NMR data, the product was assigned the structure of methyl 4-[(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]phenylcarbamate (**III**, yield 85%; Scheme 1). Compound **III** underwent dehydration with formation of 79% of chalcone **IV** on heating in glacial acetic acid in the presence of concentrated hydrochloric acid (Scheme 2). The structure of methyl 4-[(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetyl]-phenylcarbamate (**IV**) was confirmed by IR and ^{1}H NMR spectroscopy.

1,3-Dipolar cycloaddition to carbamate **IV** of azomethine ylide generated from 2-phenacylisoquinolinium bromide by the action of triethylamine was regio- and stereoselective, and the product was spiro-compound **V** (yield 73%) which was identified as methyl 4-(3′-benzoyl-2-oxo-1′,2,2′,3,3′,10b′-hexahydro-1*H*-spiro[indole-3,1′-pyrrolo[1,2-*a*]isoquinolin]-2′-ylcarbonyl)phenylcarbamate on the basis of the IR and ^{1}H NMR data (Scheme 3).

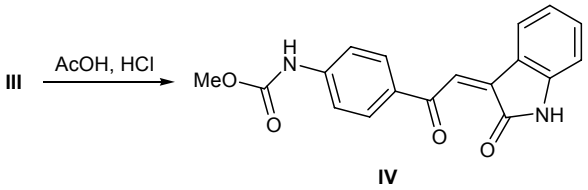
Derivatives of salicylaldehyde are widely used in the synthesis of 2-phenylchromenium salts which exhibit biological activity and are also used in laser technologies [8]. We examined condensation of methyl 4-acetylphenylcarbamate (**II**) with salicylaldehyde and

Scheme 1.



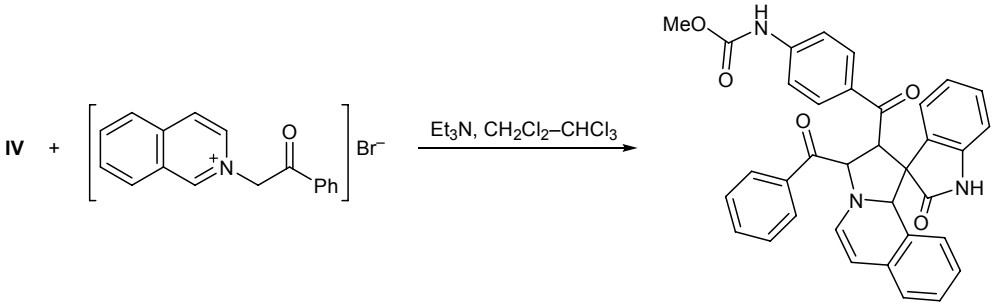
I II III

Scheme 2.



IV

Scheme 3.



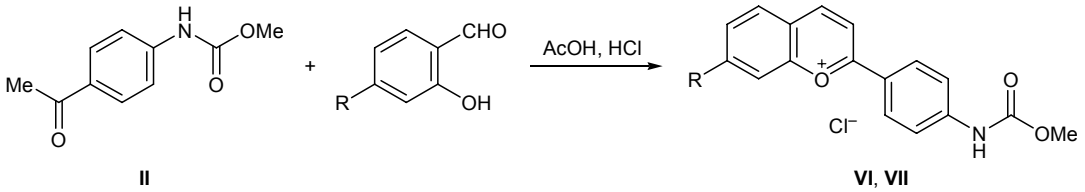
V

2,4-dihydroxybenzaldehyde in glacial acetic acid saturated with dry hydrogen chloride. As a result, we obtained 2-phenylchromenium salts **VI** and **VII** having a methoxycarbonylaminophenyl group attached to the C^2 atom (Scheme 4). The structure of 2-(4-methoxycarbonylaminophenyl)chromenium chlorides **VI** and **VII** was confirmed by elemental analyses and IR, electronic absorption, and mass spectra. The mass spectra of salts **VI** and **VII** contained no molecular ion peaks, presumably due to their low stability, but ion peaks with *m*/*z* 280 (**VI**) and 296 (**VII**) were present.

It is known that phenylchromenium salts are π-isoelectronic analogs of 2-phenylnaphthalene. Studies on the electronic structure of such compounds showed that all molecular orbitals therein are localized on the bicyclic chromene fragment or phenyl ring. Therefore, the electronic absorption spectra of phenylchromenium salts should display three types of transitions corresponding to three chromophores: chromenium, phenyl, and entire molecule. In fact, three absorption maxima were observed in the electronic spectra of compounds **VI** and **VII**. As shown in [9], the transition involving the whole molecule corresponds to the long-wave absorption band in the electronic spectra of 2-phenylnaphthopyrylium salts. Introduction of electron-donating groups into molecules of phenylchromenium salts weakens negative inductive and mesomeric effects of the chromenium fragment as a result of charge delocalization. However, as shown in [10], due to high degree of conjugation in the molecule mesomeric effect of a substituent introduced into any fragment is extended over both fragments (chromene and phenyl) and affects the energy of both lowest unoccupied orbital on the chromenium fragment and highest occupied molecular orbital on the phenyl group.

With a view to elucidate the effect of substituents on the position of absorption maximum in the electronic spectrum we performed quantum-chemical calculations of charge distribution in the molecules of 2-(4′-methoxycarbonylaminophenyl)chromenium chlorides **VI** and **VII**. The geometric parameters were optimized, and the charges on atoms in the ground state were calculated, in terms of AM1 valence approximation [11]. The results are collected in table; the data

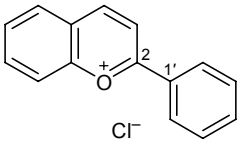
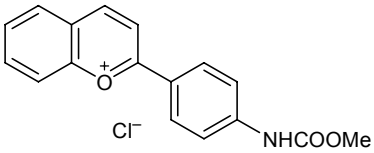
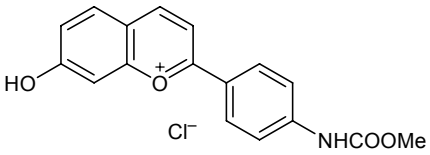
Scheme 4.



II **VI**, **VII**

VI, R = H; **VII**, R = HO.

Absorption maxima in the electronic spectra and charges on some atoms in 2-(4-methoxycarbonylaminophenyl)chromenium chlorides **VI** and **VII** and 2-phenylchromenium chloride

Compound	λ_{max}, nm	Charges on atoms in the ground state, *e*		
		C^2	$C^{1'}$	Δq
	450 [9]	0.286	–0.153	0.439
 (**VI**)	455	0.289	–0.203	0.494
 (**VII**)	490	0.283	–0.198	0.481

for 2-phenylchromenium chloride are also given for comparison. As follows from the calculated charge distribution, the main electronic interactions in phenylchromenium cations are: mesomeric effect of the chromenium fragment on the phenyl substituent, inductive effect of the charged bicyclic fragment on the phenyl ring, and mesomeric substituent effects.

According to [10], the parameter characterizing π-charge transfer is linearly related to the difference Δq in the total (σ+π) charges on the electrophilic (C^2) and nucleophilic ($C^{1'}$) centers in the ground state. This means that larger difference between the charges on the molecular fragments corresponds to stronger charge transfer upon excitation. Introduction of a carbamate group into the *para*-position of the benzene ring increases the negative charge on the C^2 atom in chromenium salt **VI**. The difference Δq becomes greater than that found for unsubstituted phenylchromenium salt. Introduction of a hydroxy group into position *7* (salt **VII**) leads to delocalization of positive charge over the chromenium fragment and reduction of Δq due to decrease of the charge on C^2 and (in part) on $C^{1'}$ as a result of weakening of inductive effect of the chromenium cation on the phenyl fragment (through the C^2–$C^{1'}$ bond).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR-400 spectrometer (400.13 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The IR spectra were measured in the range from 4000 to 400 cm^{-1} on an InfraLUM FT-02 spectrometer with Fourier transform from samples prepared as KBr pellets. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS 50 instrument. The electronic absorption spectra were recorded on an SF-103 spectrophotometer (cell path length 1 cm) from solutions in acetonitrile with a concentration of 3.6×10^{-4} or 1.3×10^{-4} M. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor.

Methyl 4-acetylphenylcarbamate (II). Methyl chloroformate, 7.7 ml (0.1 mol), was added dropwise over a period of 1.5 h under stirring and cooling to a solution of 13.5 g (0.1 mol) of *p*-aminoacetophenone in 46 ml of anhydrous pyridine. The mixture was stirred for 0.5 h, kept for 13 h at room temperature, poured onto ice, and carefully acidified with concentrated hydrochloric acid (according to Congo Red). The colorless crystals were filtered off and washed with water. Yield 1.76 g (91%), mp 167°C (from benzene); published data [12]: mp 167.5–168.0°C.

Methyl 4-[(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]phenylcarbamate (III). A mixture of 1.47 g (0.01 mol) of isatin, 1.93 g (0.01 mol) of methyl 4-acetylphenylcarbamate (**II**), and 0.5 ml of diethylamine in 30 ml of anhydrous ethanol was heated for 1 h under reflux and was then left to stand for 96 h at 20°C. The light yellow crystals were filtered off and

recrystallized from ethanol. Yield 2.2 g (85%), mp 210–211°C. IR spectrum, ν, cm^{-1}: 3340–3400, 3250 (NH, OH), 1710, 1685 (C=O), 1620, 1575, 1550 (C=C_{arom}). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.14 s (2H, CH_2), 3.71 s (3H, $NHCO_2$**Me**), 4.52 s (1H, NH), 7.15 d (2H, H_{arom}, J = 8.6 Hz), 7.28–7.38 m (3H, H_{arom}), 7.55 d (1H, H_{arom}, J = 7.8 Hz), 8.14 d (2H, H_{arom}, J = 8.6 Hz), 9.20 s (1H, OH), 9.54 br.s (1H, NH). Found, %: C 63.32; H 4.54; N 8.24. $C_{18}H_{16}N_2O_5$. Calculated, %: C 63.53; H 4.71; N 8.07.

Methyl 4-[(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetyl]phenylcarbamate (IV). A mixture of 1.7 g (5 mmol) of methyl 4-[(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]phenylcarbamate (**III**), 8 ml of glacial acetic acid, and 0.25 ml of concentrated hydrochloric acid was heated for 30 min at 95°C, 10 ml of ethanol was added, the mixture was cooled with an ice bath, and the orange crystals were filtered off, dried in air, and recrystallized from ethanol–dioxane (1:2 by volume). Yield 1.27 g (79%), mp 237–238°C. IR spectrum, ν, cm^{-1}: 3340–3400 (NH), 1710, 1675 (C=O), 1620, 1575, 1555 (C=C_{arom}). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.71 s (3H, CO_2Me), 7.20–7.14 m (3H, H_{arom}), 7.43 t (1H, H_{arom}, J = 7.5 Hz), 7.70 t (1H, H_{arom}, J = 7.5 Hz), 7.82 s (1H, CH), 8.16 d (2H, H_{arom}, J = 8.6 Hz), 8.30 d (1H, H_{arom}, J = 8.2 Hz), 8.42 s (1H, NH), 9.56 br.s (1H, NH). Found, %: C 66.85; H 4.27; N 8.53. $C_{18}H_{14}N_2O_4$. Calculated, %: C 67.08; H 4.35; N 8.70.

Methyl 4-(3′-benzoyl-2-oxo-1′,2,2′,3,3′,10b′-hexahydro-1*H*-spiro[indole-3,1′-pyrrolo[1,2-*a*]isoquinolin]-2′-ylcarbonyl)phenylcarbamate (V). A solution of 0.5 ml of triethylamine in 10 ml of chloroform was added dropwise under stirring over a period of 45 min to a suspension of 0.74 g (2.3 mmol) of chalcone **IV** and 0.66 g (2 mmol) of 2-phenacylisoquinolinium bromide in 20 ml of methylene chloride, and the mixture was stirred for 2 h more. The mixture was then washed with water (2×20 ml), the organic phase was dried over sodium sulfate, the solvent was removed under reduced pressure, and the residue crystallized. The product was purified by column chromatography on silica gel (60–100 mesh) using acetone as eluent, followed by recrystallization from chloroform–hexane (2:1 by volume). Yield 0.75 g (57%), light yellow crystals, mp 143–146°C. IR spectrum, ν, cm^{-1}: 3340–3410 (NH), 1710, 1680, 1675 (C=O), 1620, 1580, 1575 (C=C_{arom}). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.71 s (3H, $NHCO_2$**Me**), 4.12 d (1H, 4′-H, J = 7.5 Hz), 5.57 d (1H, 3′-H, J = 7.5 Hz), 5.85 s (1H, 1′-H), 6.34 d (2H, J = 8.0 Hz), 7.07 t (1H, H_{arom}, J = 7.7 Hz), 7.20–7.89 m (13H, H_{arom}), 7.97 d (1H, H_{arom}, J = 7.6 Hz), 8.31 d (2H, H_{arom}, J = 8.6 Hz), 8.42 s (1H, NH), 9.54 br.s (1H, NH). Found, %: C 73.59; H 4.57; N 7.16. $C_{35}H_{27}N_3O_5$. Calculated, %: C 73.73; H 4.74; N 7.37.

2-(4-Methoxycarbonylaminophenyl)chromenium chloride (VI). Dry hydrogen chloride was passed over a period of 1.5 h through a mixture of 1.93 g (0.01 mol) of methyl 4-acetylphenylcarbamate (**II**) and 1 ml (0.01 mol) of freshly distilled salicylaldehyde in 7 ml of glacial acetic acid. Carbamate **II** dissolved, the solution turned bright red, and red crystals separated. The mixture was left to stand for 8 h at 20°C, 10 ml of anhydrous diethyl ether was added, and the precipitate was filtered off, dried in air, and purified by reprecipitation from acetic acid with diethyl ether. Yield 2.72 g (86%), mp 128–129°C (decomp.). IR spectrum, ν, cm^{-1}: 3430 (NH), 1715 (C=O), 1610, 1575, 1545 (C=C_{arom}), 1075. Electronic absorption spectrum, λ_{max}, nm (ε, l mol^{-1} cm^{-1}): 224 (7577), 284 (11438), 455 (3846). Mass spectrum, m/z (I_{rel}, %): 280 (26), 279 (100), 248 (10), 131 (5), 118 (9), 89 (10), 76 (12). Found, %: C 64.49; H 4.12; N 4.28. $C_{17}H_{14}ClNO_3$. Calculated, %: C 64.60; H 4.43; N 4.43.

7-Hydroxy-2-(4-methoxycarbonylaminophenyl)-chromenium chloride (VII) was synthesized in a similar way by reaction of 1.93 g (0.01 mol) of methyl 4-acetylphenylcarbamate (**II**) with 1.38 g (0.01 mol) of 2,4-dihydroxybenzaldehyde. Yield 2.49 g (75%), red crystals (from glacial acetic acid), mp 189–191°C (decomp.). IR spectrum, ν, cm^{-1}: 3420–3510 (NH, OH), 1715 (C=O), 1610, 1565 (C=C_{arom}), 1095. Electronic absorption spectrum, λ_{max}, nm (ε, l mol^{-1} cm^{-1}): 229 (2000), 353 (530), 490 (614). Mass spectrum, m/z (I_{rel}, %): 296 (25), 295 (100), 264 (10), 263 (47), 235 (87), 206 (20), 165 (17), 153 (24), 152 (32), 131 (5), 118 (10), 89 (16), 77 (6). Found, %: C 61.37; H 4.25; N 3.92. $C_{17}H_{14}ClNO_4$. Calculated, %: C 61.54; H 4.22; N 4.22.

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