Synthesis of Unsymmetrical Methylene Derivatives of Benzopyran-4-ones from Mannich Bases

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The formation of methylene-bis derivatives of benzopyran-4-ones from their Mannich bases was studied. On these grounds, unsymmetrical methylene derivatives have been synthesized by reacting Mannich bases of benzopyran-4-ones with structurally related compounds lacking the dialkylaminomethyl group.

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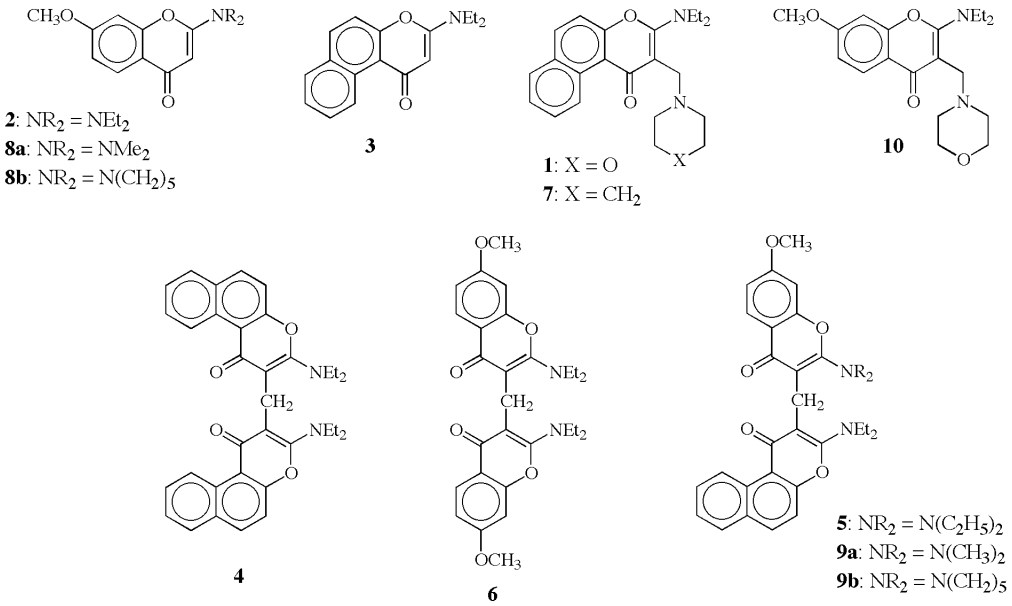
Introduction.

One of the simplest ways to obtain methylene-bis derivatives is through the reaction of compounds bearing an acidic hydrogen with formaldehyde. For instance, some benzopyrans may easily react with formaldehyde to yield the corresponding methylene-bis derivatives [1]. In particular, *N*'-(chromon-2-yl)-1-piperidine-1-carboxamide gave the methylene-bis derivative in good yield [2], whereas 2-(dialkylamino)chromones do not react efficiently with formaldehyde [3]. Mannich bases, which are well known as reactive substances for many interesting reactions [4], generate methylene-bis derivatives as by-products in their preparation. By treating Mannich bases with acetic anhydride it is possible to obtain their acetoxy derivatives as the main product [5]. However, by treating some Mannich bases of 3-hydroxycoumarin with acetic anhydride, it has been reported that a methylene-bis derivative was formed as a by-product along with the acetoxy derivatives [6]. When Mannich bases of 2-(dialkylamino)chromones were treated with acetic anhydride under similar conditions, the opposite result was observed. In these cases, the methylene-bis derivatives were obtained as the main products and the acetoxy derivative was isolated only in one case [7-9]. In this study, we focused our attention on the formation of unsymmetrical methylene derivatives through the treatment of certain Mannich bases with acetic anhydride.

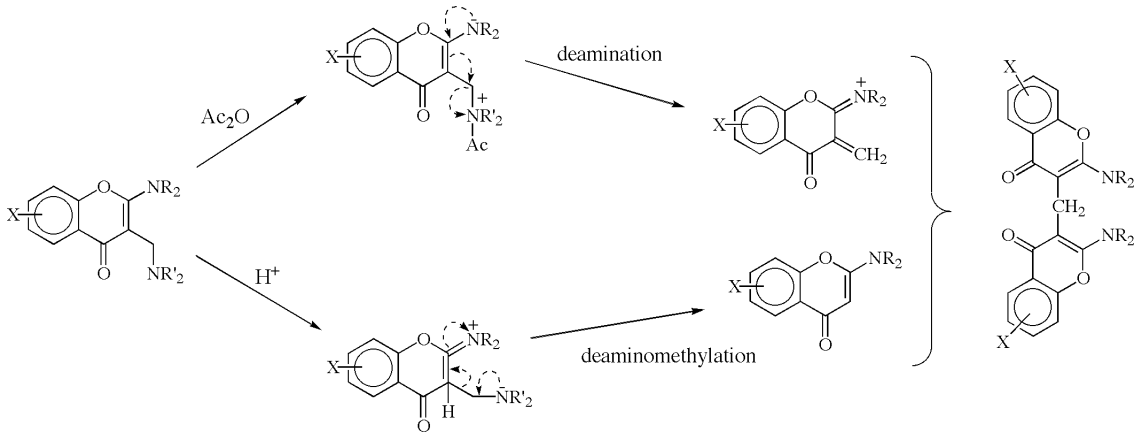
Results and Discussion.

All formulas presented in this work are depicted in Scheme 1. To explain the formation of the methylene-bis derivatives, we propose the mechanism shown in Scheme 2, where the carbocation derived through

Scheme 1



Scheme 2

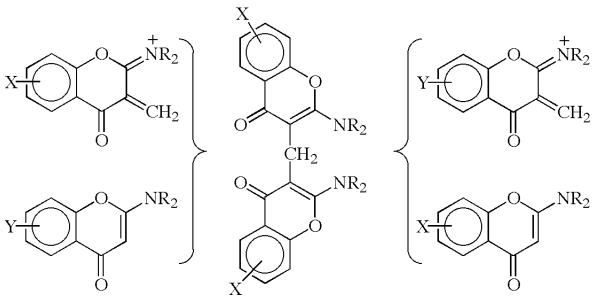


deamination of the Mannich base reacts with the amino-chromone derived through deaminomethylation of the Mannich base.

The mechanism shown in Scheme 2 indicates that the yield of the methylene-bis derivatives might be increased by addition of the chromone (formed by deamino-methylation) to the Mannich base in acetic anhydride, as shown in Scheme 3 (X = Y).

In fact, the addition of 3-(diethylamino)-2-morpholi-nomethyl-1*H*-naphtho[2,1-*b*]pyran-1-one **1** to a solution of 3-(diethylamino)-1*H*-naphtho[2,1-*b*]pyran-1-one **3** in acetic anhydride gave the corresponding methylene-bis derivative **4** in almost doubled yield (data not shown). This observation supports our proposed mechanism. If deaminomethylation of the Mannich base to form the corresponding chromone is the rate-determining step in this reaction, then the addition of a different chromone may allow one to produce an unsymmetrically di-substituted methylene derivative (Scheme 3, X different from Y).

Scheme 3



To test this hypothesis, the Mannich base **1** was added to a solution of 2-(diethylamino)-7-methoxychromone **2** in acetic anhydride. Analysis of the crude products by hplc produced a chromatogram showing four peaks. The main product (71%), isolated by crystallization, showed signals for the methoxy at 3.88 ppm and H-10 at 10.25 ppm in the ^{1}H nmr. The structure was determined to be the unsymmetrical di-substituted methylene derivative **5**. By comparing the retention times of authentic samples, the other three minor products were assigned to the symmetrical methylene-bis derivative **4** (17%), the symmetrical methylene-bis derivative **6** (10%) and the naphtho[2,1-*b*]pyran-1-one **3** (2%), respectively.

It is interesting to note that the Mannich base **1** is not present at the end of the reaction. The formation of the symmetrical derivative **6** might indicate that a retro reaction takes place, where the unsymmetrical product **5** decomposes to give the chromone **3** and the carbocation corresponding to **2**. The presence of a residual amount of chromone **3** in the final mixture supports this hypothesis.

Use of another Mannich base **7**, having the piperidinomethyl group, instead of Mannich base **1**, showed a similar pattern for the reaction. Moreover, the reaction of the chromone, 2-(dimethylamino)- or 2-(1-piperidinyl)-7-methoxychromone (**8a** or **8b**), with Mannich base **1** similarly gave the corresponding unsymmetrical derivative **9a** and **9b** in good yields.

To verify our results, the reaction of the bicyclic Mannich base **10** with the tricyclic chromone, naphtho[2,1-*b*]pyran-1-one **3** in acetic anhydride was similarly studied. Analysis of the crude products by hplc produced a chromatogram with three peaks, identical with the unsymmetrical methylene-bis derivative **5** (52%), the symmetrical derivative **4** (32%) and **6** (16%), respectively. The low yield of **5** may be due to low stability of the corresponding carbocation intermediate.

Conclusion.

Some Mannich bases, derived from various chromones, were reacted with other chromones in the presence of acetic anhydride to give the corresponding unsymmetrical

di-substituted methylene derivatives. In these reactions, it appears convenient to use the Mannich base that upon deamination will derive the more stable carbocation.

EXPERIMENTAL

Melting points were determined using an Electrothermal apparatus and are uncorrected. Microanalyses were carried out on a Carlo Erba 1106 elemental analyzer. ^{1}H nmr spectra were performed on a Hitachi Perkin-Elmer R 600 (60 MHz) spectrometer using tetramethylsilane as the internal standard (δ = 0). Infrared spectra were recorded on a Perkin-Elmer 398 spectrophotometer. The hplc analyses were carried out at room temperature on a Perkin-Elmer Series 4 equipped with a Rheodine 7125 injector valve with a 20-µl loop. The uv detector is a Perkin-Elmer LC-85B set at 254 nm. The eluent consisted of acetonitrile/water (85:15). The flow-rate was 1.0 ml/minute. Retention times and peak areas were recorded on Perkin-Elmer LCI-100 integrator.

General Procedure.

To a solution of 0.82 mmoles of chromone (**A**) in 5 ml of freshly distilled acetic anhydride, 0.82 mmoles of Mannich base (**B**) were added and the mixture was stirred at 90 °C for 1.5 hours [10]. The resulting brown solution was poured onto crushed ice and stirred. The solids were collected by filtration and washed well with water. For each crude product, approximately 5 mg of precipitate was dissolved in 20 ml of acetonitrile and an aliquot was subjected to hplc analysis. For the preparation of unsymmetrical derivative **5** by the route I (see below), the following retention times in minutes were found: 5.70 (**6**), 7.80 (**3**), 9.00 (**5**), 15.95 (**4**). Regardless of minor components, the other unsymmetrical derivatives **9a** and **9b** had retention times 6.55 and 10.10, respectively. After hplc analysis, the crude precipitates were crystallized from ethyl acetate to yield colorless crystals.

2-[2'-(Diethylamino)-7'-methoxychromon-3'-yl]methyl-3-(diethylamino)-1*H*-naphtho[2,1-*b*]pyran-1-one (**5**).

Compound **5** was obtained by three routes (I-III) using different starting materials: (I) **A**: 0.20 g of 2-(diethylamino)-7-methoxychromone **2** [3]; **B**: 0.30 g of 3-(diethylamino)-2-morpholinomethyl-1*H*-naphtho[2,1-*b*]pyran-1-one **1** [11]; 71% yield (hplc). (II) **A**: 0.20 g of 2-(diethylamino)-7-methoxychromone **2** [3]; **B**: 0.30 g of 3-(diethylamino)-2-piperidinomethyl-1*H*-naphtho[2,1-*b*]pyran-1-one **7** [11]; 64% yield (hplc). and (III) **A**: 0.22 g of 3-(diethylamino)-1*H*-naphtho[2,1-*b*]pyran-1-one **3** [12]; **B**: 0.28 g of 2-(diethylamino)-3-morpholinomethyl-7-methoxychromone **10** [3]; 52% yield (hplc); **5**: mp 182-183 °C; ir (potassium bromide): ν 1630, 1610 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.75-1.18 (m, 12H, CH_2-*CH_3*), 2.95-3.53 (m, 8H, *CH_2*-CH_3), 3.88 (s, 3H, OCH_3), 4.18 (s, 2H, CH_2), 6.67-8.20 (m, 8H, aromatic), 10.25 (d, 1H, H-10).

Anal. Calcd. for $C_{32}H_{34}N_2O_5$: C, 72.98; H, 6.51; N, 5.32; Found: C, 73.12; H, 6.55; N, 5.26.

2-[2'-(Dimethylamino)-7'-methoxychromon-3'-yl]methyl-3-(diethylamino)-1*H*-naphtho[2,1-*b*]pyran-1-one (**9a**).

Compound **9a** was prepared by mixing the following starting materials according to the general proceedure **A**: 0.18 g of 2-(dimethylamino)-7-methoxychromone **8a** [3]; **B**: 0.30 g of 3-(diethylamino)-2-morpholinomethyl-1H-naphtho[2,1-b]pyran-1-one **1** [11]; 68% yield (hplc); **9a**: mp 181-182 °C; ir (potassium bromide): ν 1630, 1610 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.00 (t, 6H, CH_2-*CH_3*), 2.85 (s, 6H, NCH_3), 3.25 (q, 4H, *CH_2*-CH_3), 3.87 (s, 3H, OCH_3), 4.21 (s, 2H, CH_2), 6.68-8.23 (m, 8H, aromatic), 10.26 (d, 1H, H-10).

Anal. Calcd. for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 72.07; H, 6.01; N, 5.61.

2-[2'-(1-Piperidinyl)-7'-methoxychromon-3'-yl]methyl-3-(diethylamino)-1*H*-naphtho[2,1-*b*]pyran-1-one (**9b**).

Compound **9b** was prepared by mixing the following starting materials according to the general proceedure **A**: 0.18 g of 2-(1-piperidinyl)-7-methoxychromone **8b** [3]; **B**: 0.30 g of 3-(diethylamino)-2-morpholinomethyl-1*H*-naphtho[2,1-*b*]pyran-1-one **1** [11]; 65% yield (hplc); **9b**: mp 189-190 °C; ir (potassium bromide): ν 1630, 1610 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.95 (t, 6H, CH_2-*CH_3*), 1.20-1.55 (m, 6H, β- and γ-piperidine), 2.85-3.43 (m, 8H, α-piperidine, *CH_2*-CH_3), 3.86 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 6.57-8.21 (m, 8H, aromatic), 10.23 (d, 1H, H-10).

Anal. Calcd. for $C_{33}H_{34}N_2O_5$: C, 73.59, H, 6.36, N, 5.20. Found: C, 73.68; H, 6.28; N, 5.25.

Acknowledgements.

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