

SYNTHESIS OF UNSUBSTITUTED α -PIPERAZINO KETONES AND DIKETONES

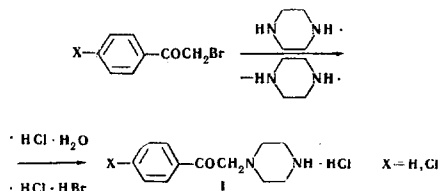
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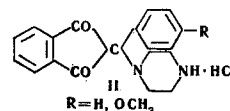
The reaction of halo ketones with piperazine hydrate hydrochloride gives N-phenyl- and N-[2-arylindan-1,3-dion-2-yl]piperazines.

Several derivatives of N-phenacyl-N'-substituted piperazines show antitussive activity greater than codeine, with less toxicity [1,2]. Also these compounds are used as starting materials in the synthesis of other physiologically active materials with a wide variety of other pharmacological effects. Several of these have found application in medical practice [3]. N-Phenacyl-N'-substituted piperazines are obtained by the reaction between ω -chloroacetophenones and N-substituted piperazines. By boiling a toluene solution of ω -chloroacetophenone with an excess of piperazine, the N-unsubstituted α -piperidino ketone α -phenacylpiperazine is likewise obtained [4]. However, in the reaction between 2-halo-2-arylindan-1,3-diones with piperazine, only the N,N'-bis derivatives are formed [3-8]. N-Unsubstituted piperazino diketones have not as yet been reported in the literature. By the introduction of different substituents (by alkylation or arylation) into the N-unsubstituted α -piperazino ketones, a variety of piperazino ketone derivatives may be obtained which are inaccessible or obtainable only with difficulty by other means. We have developed a method for obtaining unsubstituted α -piperazino ketones and diketones by the reaction between halo ketones and piperazine hydrate hydrochloride in methanol solution. ω -Bromoacetophenone and ω -bromo-p-chloroacetophenone react with piperazine hydrate hydrochloride [9] even at room temperature:



Monohydrochlorides of phenacylpiperazine (I, X = H) and p-chlorophenacylpiperazine (I, X = Cl) formed in this way are colorless crystalline substances, soluble in water and polar organic solvents. With acetyl chloride and acetic anhydride, the N'-acetyl derivatives were formed. The latter were isolated as the hydrochlorides—colorless crystals soluble in water and alcohol. They crystallized with one molecule of alcohol.

2-Piperazino-2-phenylindan-1,3-dione (II, R = H) and 2-piperazino-2-anisylindan-1,3-dione (II, R = OCH₃) were obtained in the same way as I from the corresponding 2-bromo-2-arylidane-1,3-diones and piperazine hydrate monohydrochloride.



By saturating ethereal solutions of the free bases II with dry HCl, the colorless dihydrochlorides are formed, which, however, lose one molecule of HCl on recrystallization from alcohol, due to the reduced basicity of the nitrogen attached to the carbon in position 2 of the indandione ring.

Monohydrochlorides of the bases II are yellow, crystalline materials soluble in water and alcohol and insoluble in ether. On boiling II in dioxane with p-nitrobenzoyl chloride, the N'-acylation of II takes place. The resulting N'-p-nitrobenzoyl derivatives are yellow crystalline substances soluble in organic solvents and insoluble in water.

The characteristics of the α -piperazino ketones and their N'-acyl derivatives are given in the table.

Phenacylpiperazines are characterized in their IR spectra by an absorption frequency at 1696-1687 cm⁻¹, due to the carbonyl group, and the N-[2-aryl-1,3-indandion-2-yl]piperazines by a doublet due to the diketone groups at 1742-1734 and 1710-1701 which is characteristic of the indandione system. In the N'-acyl derivatives, there is an additional absorption in the interval 1653-1625 cm⁻¹, corresponding to the absorption of the amide carbonyl. The IR spectra were recorded on a suspension of the solids in mineral oil on an IKS-14 instrument.

EXPERIMENTAL

Phenacylpiperazine Hydrochloride (I, X = H). To a solution of 2.81 g (0.02 mole) of piperazine hydrate hydrochloride in methanol was added 1.99 g (0.01 mole) of ω -bromoacetophenone and the mixture was allowed to stand at room temperature. The next day, the precipitated piperazine salt was filtered off and the filtrate was evaporated in a vacuum. After twice recrystallizing the residue from a mixture of ethanol and ether, 1.9 g (79%) of colorless crystals melting at 192-193° C (decomp.) was obtained.

N-Phenacyl-N'-acetyl piperazine Hydrochloride. 0.24 g (0.001 mole) of phenacylpiperazine hydrochloride (I, X = H) was covered with acetic anhydride 1 ml of acetyl chloride was added and the mixture was heated for 1 hr on a steam bath. After cooling, absolute ether saturated with dry HCl was added. The next day, the precipitated material was filtered off and recrystallized from alcohol. Yield, 0.25 g (76%) of colorless crystals, mp 225-226° C (decomp.).

2-Piperazino-2-phenylindan-1,3-dione Hydrochloride (II, R = H). A solution of 3.01 g (0.01 mole) of 2-bromo-2-phenylindane-1,3-dione in methanol was mixed with 2.81 g (0.02 mole) of piperazine hydrate hydrochloride and kept at room temperature. The next day, the mixture was heated 30 min on a steam bath, the precipitated piperazine salt was filtered off, and the filtrate was evaporated in a vacuum. The residue was treated with a 5% Na₂CO₃ solution and



R	R'	A	Mp · C	$\nu_{C=O}$, cm ⁻¹	Empirical formula	Found, %		Calc., %		Yield, %
						N	Cl	N	Cl	
C ₆ H ₅ COCH ₂	H	HCl	192—193 (decomp.)	1687	C ₁₂ H ₁₆ N ₂ O · HCl	11.55	14.67	11.64	14.72	79
<i>p</i> -C ₆ H ₄ COCH ₂	H	HCl	182 (decomp.)	1693	C ₁₂ H ₁₅ ClN ₂ O · HCl	10.23	25.81	10.18	25.80	73
C ₆ H ₅ COCH ₂	COCH ₃	HCl C ₂ H ₅ OH	225—226 (decomp.)	1694 1653	C ₁₄ H ₁₈ N ₂ O ₂ · HCl · C ₂ H ₅ OH	8.74	11.06	8.52	10.78	76
<i>p</i> -C ₆ H ₄ COCH ₂	COCH ₃	HCl C ₂ H ₅ OH	212—213 (decomp.)	1696 1646	C ₁₄ H ₁₇ ClN ₂ O ₂ · HCl · C ₂ H ₅ OH	7.56	19.75	7.71	19.52	70
C ₆ H ₄ (CO) ₂ CC ₆ H ₅	H	HCl	223—224 (decomp.)	1741 1710	C ₁₉ H ₁₈ N ₂ O ₂ · HCl	7.88	10.27	8.14	10.31	61
C ₆ H ₄ (CO) ₂ CC ₆ H ₄ OCH ₃ - <i>p</i>	H	HCl	224—245 (decomp.)	1741 1701	C ₂₀ H ₂₀ N ₂ O ₃ · HCl	7.71	9.92	7.74	9.80	55
C ₆ H ₄ (CO) ₂ CC ₆ H ₅	COC ₆ H ₄ NO ₂ - <i>p</i>	—	180	1742 1701 1626	C ₂₆ H ₂₁ N ₃ O ₅	9.19	—	9.23	—	75
C ₆ H ₄ (CO) ₂ CC ₆ H ₄ OCH ₃ - <i>p</i>	COC ₆ H ₄ NO ₂ - <i>p</i>	—	209	1734 1703 1637	C ₂₇ H ₂₃ N ₃ O ₆	8.98	—	8.66	—	80

extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and saturated with dry HCl. Recrystallization of the precipitated solid from alcohol yielded 2.12 g (61%) of 2-piperazino-2-phenylindan-1,3-dione, yellow crystals melting at 223–224° C (decomp.).

2-(N'-p-Nitrobenzoyl-N-piperazino)-2-phenylindan-1,3-dione.
0.17 g (0.5 mM) of II (R = H) was covered with dioxane and treated with 0.93 g (5 mM) of p-nitrobenzoyl chloride, and the mixture was heated for 1 hr under reflux. The solution was cooled and poured into water and the next day the precipitated material was recrystallized from alcohol. A yield of 0.17 g (75%) yellow crystals melting at 180° C was obtained.

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