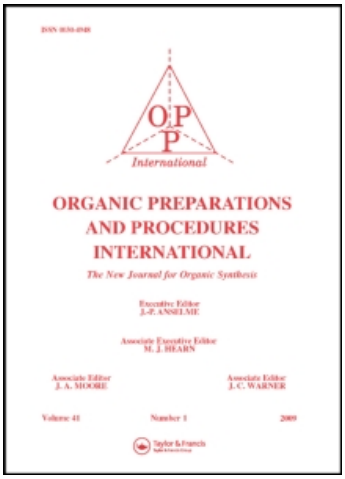

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THE SYNTHESIS OF 1-AMIDINO-4-AROYLPIPERAZINES

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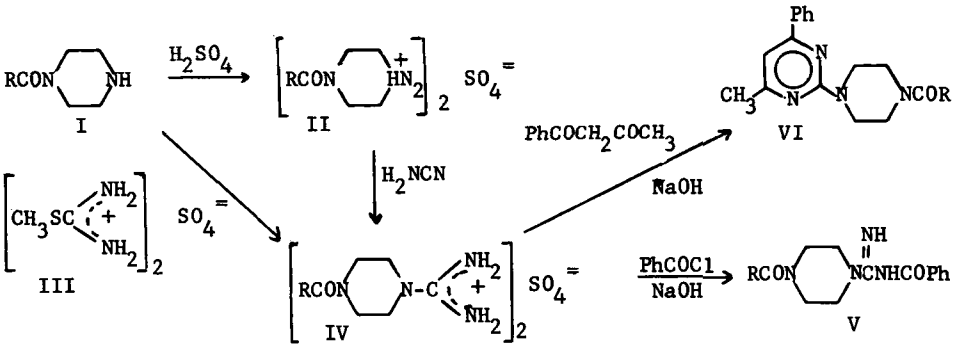
The preparation of a group of 1-amidino-4-aroyl derivatives of piperazine was undertaken in the course of a search for compounds with antiparasitic activity.[1] Although 1-amidinopiperazine derivatives with alkyl, aryl, aralkyl and heteroaryl substituents in the 4-position have been described,[2-7] 4-aroyl derivatives do not appear to have been prepared previously. Conversion of readily available 1-aroylpiperazine hydrochlorides[8] into sulfates of the 1-amidino-4-aroyl derivatives (IV) by liberation of the free bases I followed by treatment with methylisothiourea sulfate (III) in refluxing water or aqueous ethanol appeared promising in the light of the success of the procedure in the preparation of other amidinopiperazine derivatives.[4] However, when applied to 1-aroylpiperazines the method resulted in low yields and left much unchanged starting material. In the search for better methods, procedures leading directly to the sulfates of the desired products (IV) received most of the attention; the sulfates could be crystallized readily, but the free bases and



salts of other types were difficult to purify. Three procedures which were compared were the following: (1) fusion of the 1-aroylpiperazine with methylisothiourea sulfate at ca. 150-180° without solvent (procedure A), (2) distillation of water from an initial mixture of the 1-aroylpiperazine, methylisothiourea sulfate and water, followed by fusion at 180° (procedure B) and (3) distillation of water from an initial mixture of a 1-aroylpiperazine sulfate (III), cyanamide and water, followed by fusion at 160-180° (procedure C). Results are summarized in Table I. Contrary to a previous report on results in similar preparations in which these reagents were used at lower temperatures,[4] our cyanamide procedure was more successful than any of the procedures tried with methylisothiourea sulfate. When the latter reagent was used, the unchanged reagent proved difficult to remove from the product.

Because the desired products of type IV frequently crystallized well only as hydrates, additional characterization of these compounds was considered appropriate. They were readily converted into crystalline benzoyl derivatives (V) (Table II) by treatment with benzoyl chloride by the Schotten-Baumann procedure or into crystalline pyrimidine derivatives (VI) by condensation with benzoylacetone.

EXPERIMENTAL

Monoaroylpiperazines (I).- To a solution of sodium (0.01 g-atom) in absolute ethanol (40 ml), was added the monoaroylpiperazine hydrochloride (0.01 mole). The mixture was stirred for 30 min. and was filtered to remove sodium chloride. The filtrate was evaporated to dryness to obtain free monoaroylpiperazine. Benzoyl, p-chlorobenzoyl and o-chlorobenzoyl derivatives were obtained as white solids and were used in further steps without purification.

TABLE I.- 1-Amidino-4-aroylpiperazine Sulfates (IV)

Ar	MP (°C)	Yield, % Procedure	Formula	Analysis[a] C	Calcd. (Found) H	N
C_6H_5	284-285[b]	10.5(A)[c]	$C_{24}H_{34}N_8O_6S\cdot\frac{1}{2}H_2O$	50.42	6.17	19.60
		18.5(B)		(50.01)	(5.94)	(19.89)
		38.5(C)				
p-ClC_6H_4	284-285	18.5(A)[d]	$C_{24}H_{32}Cl_2N_8O_6S\cdot\frac{1}{2}H_2O$	43.77	5.36	17.01
		22 (B)		(44.23)	(5.06)	(16.68)
o-ClC_6H_4	282-284	55 (C)	$C_{24}H_{32}Cl_2N_8O_6S\cdot\frac{1}{2}H_2O$	45.00	5.19	17.49
				(44.93)	(5.11)	(17.38)

(a) Microanalyses are by M-H-W Laboratories, Garden City, Michigan.
(b) IR (μ) (Nujol mull): 6.03, 6.10, 6.16, 7.86, 8.88, 9.38 (broad), 10.13, 12.70, 14.10. Nmr (CF_3CO_2H): δ 3.6-4.4 (m, 8, piperazine methylenes), 7.6 (singlet, 5, aromatic ring).
(c) Mixture fused 75 min. at 160-180°.
(d) Mixture fused 45 min. at 150-170°.

TABLE II.- 4-Aroyl-1-(N-benzoylamidino)-piperazines (V)

Ar	MP (°C)	Yield, %	Formula	Analysis[a] C	Calcd. (Found) H	N
C_6H_5	235-236[b]	50	$C_{19}N_{20}N_4O_2$	67.84	5.99	16.16
				(67.58)	(5.94)	(16.39)
p-ClC_6H_4	220.5-222[c]	45	$C_{19}N_{19}ClN_4O_2$	61.54	5.13	15.11
				(61.66)	(5.15)	(15.22)

(a) Microanalyses by M-H-W Laboratories, Garden City, Michigan.
(b) IR (μ) (Nujol mull): 2.96, 3.13, 6.12, 6.25, 6.38, 7.40, 8.72, 9.90, 10.00, 10.26, 11.18, 13.04, 14.04. Nmr ($CDCl_3$-CF_3CO_2H): δ 3.51-4.17 (m, 8, piperazine methylenes), 7.20-7.95 (m, 10, aromatic rings).
(c) IR (μ) (Nujol mull): 2.94, 3.14, 3.20, 6.03, 6.25, 6.40, 6.48, 7.30, 7.36, 7.76, 7.90, 8.70, 9.18, 9.90, 10.25, 11.18, 11.78, 13.23, 14.00. Nmr ($CDCl_3$-CF_3CO_2H): δ 3.67-4.50 (m, 8, piperazine methylenes), 7.27-8.03 (m, 9, aromatic rings).

Preparation of 1-Amidino-4-aroylpiperazine Sulfates (IV). General Procedures.

Procedure A. Dry Fusion with 1-Methylisothiourea Sulfate.- A finely ground mixture of monoaroylpiperazine (0.005 mole) and methylisothiourea sulfate was heated at 150-180° under slightly reduced pressure (ca. 120 mm) in a side-arm test-tube for 45-75 min. The mixture was then cooled and extracted with boiling 95% ethanol (5 x 100 ml). The ethanol extract, after concentration to 100 ml and cooling, gave a white solid, mp. 225-236°. Several crystallizations from ethanol gave the pure products.

Procedure B. Methylisothiourea Sulfate with Water.- A mixture of monoaroylpiperazine (0.005 mole) and methylisothiourea sulfate (0.0035 mole) was dissolved in water (2.5 ml). The mixture was placed in a side-arm test-tube and heated to 180° in an oil bath over a period of one hour. After the water had evaporated leaving a white paste, the mixture was held at 180° for one additional hour under reduced pressure (120 mm). The mixture was next cooled and extracted with boiling 95% ethanol (2 x 100 ml). The concentrated extract on cooling deposited the products as white solids. The white solids were collected by filtration and purified by crystallization from 95% ethanol.

Procedure C. Cyanamide with Water.- For conversion to the sulfates, 1-aroylpiperazine hydrochlorides were treated with one equivalent of sodium ethoxide in absolute ethanol (0.25 molar solution). The mixtures were warmed for a few minutes, then filtered to remove NaCl. Following addition of an equivalent of 0.5 N ethanolic H_2SO_4 (concentrated H_2SO_4 in absolute ethanol) to the filtrate, the sulfate was collected by filtration, or, if soluble, was isolated by evaporation of the solvent. A mixture of monoaroylpiperazine sulfate (0.001 mole) and cyanamide (0.003 to 0.04 mole) was dissolved in water (2-3 ml). The mixture was heated to 160-180° in a side-arm test-tube over a period of one hour under reduced pressure

(120 mm) and then held at that temperature for two hours. The mixture was next cooled and then extracted with boiling 95% ethanol (2 x 100 ml). The ethanol extract on cooling deposited the product as a white solid. The 1-amidino-4-benzoylpiperazine sulfate was purified by crystallization from 95% ethanol while 1-amidino-4-o-chlorobenzoylpiperazine sulfate was crystallized from a mixture of ethanol, water and acetone.

4-Aroyl-1-(N-benzoylamidino)-piperazines (V).- The 1-amidino-4-aroylpiperazine sulfate (0.001 mole) was added to aqueous sodium hydroxide (0.4 g of NaOH in 10 ml of water). Benzoyl chloride (0.3 g; 0.002 mole) was then added dropwise while the mixture was stirred. After one hour of stirring the solid that precipitated was collected by filtration and purified by crystallization from a mixture of methylene chloride and petroleum ether (bp. 30-60°). Results with individual compounds are given in Table II.

2-(4-Benzoylpiperazino)-4-methyl-6-phenylpyrimidine (VI).- 1-Amidino-4-benzoylpiperazine sulfate (0.225 g; 0.0004 mole) was added to a solution of sodium ethoxide prepared from 0.0184 g (.0008 mole) of sodium in 10 ml of ethanol. After the mixture had been stirred for 30 min. benzoylacetone (0.162 g; 0.001 mole) was added and the mixture was heated to reflux for 5 hrs. After concentration to ca. 3 ml on a rotary evaporator 25 ml of water was added and the precipitate was collected by filtration. Recrystallization from aqueous ethanol yielded 0.145 g (51%) of white crystals, mp. 154.5-155.5°. IR (μ): 6.10 (>C=O), 6.22, 6.32, 6.42, 7.42, 7.84, 7.96, 8.20, 8.64, 9.92, 10.82, 11.50, 12.94, 13.54, 14.08, 14.34. Nmr ($CDCl_3$): δ 2.40 (s, 3, CH_3), 3.45-4.10 (m, 8, piperazine methylene), 6.87 (s, 1, H, at pyrimidine 5-position), 7.42 (s, 8, aromatic ring), 7.83-8.12 (m, 2, aromatic ring).

Anal. Calcd. for $C_{22}H_{22}N_4O$: C, 73.72; H, 6.19; N, 15.63. Found: C, 73.74;

H, 6.08; N, 15.61.

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