2,6-Dialkylpiperazines. IV.[1] 1-Propionyl-4-substituted *cis*-2,6-Dimethylpiperazines Structurally Related to the Analgetic 8-Acyl-3,8-diazabicyclo[3.2.1]octanes[2]

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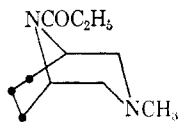
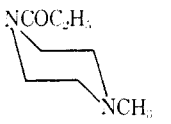
The high analgetic activity of 3-methyl- and 3-propionyl-3,8-diazabicyclo[3.2.1]octanes has been previously reported. The present paper deals with the synthesis of some piperazines structurally related to the analgetic diazabicyclooctanes but lacking their endoethylenic bridge. The most active analgetics in the piperazine series, namely, 2,6-dimethyl- and 2,2,6-trimethyl-1-propionyl-4-cinnamylpiperazines, are greatly inferior to the corresponding diazabicyclooctanes; the break of the endoethylenic bridge is unfavorable to the analgetic activity.

The analgetic potency of 8-propionyl-3,8-diazabicyclo[3.2.1]octane derivatives[3] (I) appears connected with the presence of the endoethylenic bridge which confers rigidity to the bicyclic system and also crowds the nitrogen bearing the propionyl group.[4] In fact, modifications of I, concerning the carbon atoms bridge or the position of the propionyl group, resulted in a marked decrease of the pharmacological activity. Thus, 3-methyl-9-propionyl-3,9-diazabicyclo[3.3.1]-nonane (A) (enlargement of the carbon bridge) exhibited one-half of the analgetic potency[4] of the corresponding diazabicyclooctane derivative (Ia, R = CH_3), while 1-methyl-4-propionylpiperazine[4] (B) (lacking the bridge) and 3-propionyl-8-methyl-3,8-diazabicyclo[3.2.1]octane[4,5] (C) (propionyl group on the unhindered nitrogen) showed a marked decrease in analgetic activity.

I



A



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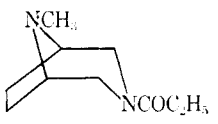
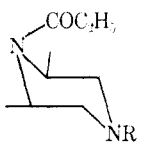


C

In persuing our researches in this field, we synthesized 1-propionyl-*cis*-2,6-dimethylpiperazines (II), structurally related to I, in order to evaluate their analgetic activity. In II, the steric hindrance on the nitrogen bearing the propionyl group is maintained by the *cis*-2,6-methyls,[6] while the rigidity of the system I is lost because of the breaking of the endoethylenic bridge.



II

The starting compound for the synthesis of the *cis*-2,6-dimethylpiperazines (Table I and Chart I) was 4-benzyl-*cis*-2,6-dimethylpiperazine (III) whose synthesis has been described recently.[7] Propionylation of III with propionic anhydride yielded the 1-propionyl-4-benzyl derivative (IV) which was debenzylated catalytically to 1-propionyl-*cis*-2,6-dimethylpiperazine (V). Compound V was then transformed by standard methods into 1-propionyl-4-methyl-*cis*-2,6-dimethyl- (VI) and 1-propionyl-4-cinnamyl-*cis*-2,6-dimethylpiperazine (VII), which were synthesized, taking into account the N-substituents of the diazabicyclooctanes most active as analgetics.

With the aim of increasing the steric hindrance at the nitrogen bearing the propionyl group, 1-propionyl-2,2,4,6-tetramethyl- (XI) and 1-propionyl-4-cinnamyl-2,2,6-trimethylpiperazines (XII) were also synthesized. The starting compound for XI and XII was 4-benzyl-2,2,6-trimethylpiperazine[8] (VIII) and the route followed was similar to that employed for VI and VII. Attempts to synthesize 4-benzyl-2,2,6,6-tetramethylpiperazine as an intermediate for 1-propionyl-2,2,6,6-tetramethylpiperazines were unsuccessful.[8]

Finally, the synthesis of 1-methyl-4-propionyl-2,6-dimethyl- (XVII) and 1-cinnamyl-4-propionyl-2,6-dimethylpiperazines (XVIII) was carried out. In this case the position of the N^1- and N^4-substituents of VI and VII was reversed. 1-Benzoyl-*cis*-2,6-dimethylpiperazine (XIII), obtained from III by a two-step synthesis,[7] was reduced with $LiAlH_4$ to the 1-benzyl derivative (XIV). Propionylation of XIV to XV followed by catalytical debenzylation led to 4-propionyl-2,6-dimethylpiperazine (XVI) which was transformed by standard procedures to the desired XVII and XVIII. This compound (XVII) can also be prepared by an alternative route involving methylation of III with formic acid and formaldehyde and debenzylation of the obtained XIX to 1-methyl-2,6-dimethylpiperazine (XX), which was propionylated to XVII.

Pharmacology. Analgetic Activity and Toxicity (Table II).—The procedure of Randall and Selitto[9] was employed to measure analgetic activity in CF-Wistar rats. The approximate acute toxicity was investigated in CF-1 mice.

(1) Part III: G. G. Gallo and A. Vigevani, *J. Heterocyclic Chem.*, **2**, 418 (1965).

(2) Address inquiries to Dr. Mario Bellenghi.

(3) (a) G. Cignarella, E. Occelli, G. Maffii, and E. Testa, *J. Med. Chem.*, **6**, 385 (1963); (b) G. Cignarella, E. Occelli, G. F. Cristiani, L. Paduano, and E. Testa, *ibid.*, **6**, 764 (1963); (c) G. Cignarella, E. Occelli, and E. Testa, *ibid.*, **8**, 326 (1965).

(4) G. Cignarella, G. Maffii, and E. Testa, *Gazz. Chim. Ital.*, **93**, 226 (1963).

(5) G. Cignarella, E. Occelli, G. Madii, and E. Testa, *J. Med. Chem.*, **6**, 29 (1963).

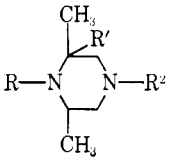
(6) 4-Methyl-*cis*-2,6-dimethylpiperazine does not react with 1-bromo-3-chloropropane to give 1-(γ-chloropropyl) derivative, in contrast to the isomer, 1-methyl-*cis*-2,6-dimethylpiperazine, in which the NH group is unhindered (G. Cignarella, unpublished work).

(7) G. Cignarella, *J. Med. Chem.*, **7**, 241 (1964).

(8) G. Cignarella, G. Maffii, and E. Testa, to be published.

(9) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn.*, **111**, 409 (1957).

TABLE I



Compd	R	R′	R²	Formula[a]	Bp (mm) or mp, °C	n_D
IV	COC_2H_5	H	$CH_2C_6H_5$	$C_{16}H_{24}N_2O$[7]	140 (0.5)	
V	COC_2H_5	H	H	$C_9H_{18}N_2O$[7]	90–92 (0.5)	1.5057
VI	COC_2H_5	H	CH_3	$C_{10}H_{20}N_2O$	73–75 (0.6)	1.4907
VII	COC_2H_5	H	$CH_2CH{=}CHC_6H_5$	$C_{18}H_{26}N_2O$	180–182 (0.6)	1.5609
IX	COC_2H_5	CH_3	$CH_2C_6H_5$	$C_{17}H_{26}N_2O$	122–125 (0.4)	
					63 (petr ether)	
X	COC_2H_5	CH_3	H	$C_{10}H_{20}N_2O$	90 (0.4)	1.5017
XI	COC_2H_5	CH_3	CH_3	$C_{11}H_{22}N_2O$	80 (1)	1.4881
XII	COC_2H_5	CH_3	$CH_2CH{=}CHC_6H_5$	$C_{19}H_{28}N_2O$	165–167 (0.5)	
XIV	$CH_2C_6H_5$	H	H	$C_{13}H_{20}N_2$	97–98 (0.6)	1.5473
XV	$CH_2C_6H_5$	H	COC_2H_5	$C_{16}H_{24}N_2O$	143–145 (0.4)	
XVI	H	H	COC_2H_5	$C_9H_{18}N_2O$	85 (0.5)	1.4941
XVII	CH_3	H	COC_2H_5	$C_{10}H_{20}N_2O$	98–100 (0.8)	1.4927
XVIII	$CH_2CH{=}CHC_6H_5$	H	COC_2H_5	$C_{18}H_{26}N_2O$	175–177 (0.2)	1.5703
XIX	CH_3	H	$CH_2C_6H_5$	$C_{14}H_{22}N_2$	95–96 (0.6)	
				$C_{14}H_{22}N_2 \cdot 2HCl$[b]	250–252 (EtOH–Et_2O)	
XX	CH_3	H	H	$C_7H_{16}N_2$	83–85 (50)	

[a] All compounds were analyzed for C, H, N unless otherwise noted. Analytical results were within ±0.4% of the calculated values. [b] N analysis only.

TABLE II
ANALGETIC ACTIVITY IN THE RAT AND ACUTE TOXICITY IN THE MOUSE

Compd	Dose, mg/kg	% increase of pain threshold	Av duration of act., min	Approx LD_{50}, mg/kg ip
VI	50 ip	4	...	500
VII	2 ip	131	30–60	300
	1 ip	50	15–30	
	5 *po*	114	20–60	
	3 *po*	39	15–30	
XI	50 ip	0	...	500
XII	2 ip	195	30	>1000
	1 ip	156	30	
	0.5 ip	83	30	
	0.3 ip	28	15	
	3 *po*	52	30	
	1 *po*	45	30	
XVII	50 ip	4	...	500
XVIII	10 ip	17	...	80
3-Methyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane	10 ip	139	90	282
	5 ip	25	90	
	10 *po*	139	90	
	5 *po*	22.6	...	
3-Cinnamyl-8-propionyl-3,8-diazabicyclo[3.2.1]-octane	0.4 ip	143	45–60	73
	0.2 ip	75.8	45–60	
	0.1 ip	46.5	45–60	
3-Propionyl-8-methyl-3,8-diazabicyclo[3.2.1]octane	25 ip	8	...	200
3-Propionyl-8-cinnamyl-3,8-diazabicyclo[3.2.1]-octane	2 ip	156	30	100
	1 ip	82	30	
	0.5 ip	41	45	
Morphine·HCl	5 ip	>170	120	410[a]
	3 ip	91	90	
	1.5 ip	31.5	60	

[a] See A. Pinto Corrado and V. G. Longo, *Arch. Intern. Pharmacodyn.*, **132**, 255 (1961).

In Table II some pharmacological data concerning analgetic activity and acute toxicity of six compounds are reported. The data previously obtained on four analogs of the diazabicyclooctane series are also listed for comparison.

The 1-propionyl-4-cinnamylpiperazines, both 2,6-dimethyl- (VII) and 2,2,6-trimethyl- (XII), are the most active compounds of the piperazine series and show relatively low toxicity, especially XII. The 1- (or 4-) methyl-substituted derivatives VI, XI, and XVII appear devoid of any activity. The analgetic action of 1-cinnamyl-4-propionyl (XVIII) is very low. Comparison of these piperazine derivatives with the analogous diazabicyclooctanes shows that analgetic activity either decreases in the corresponding methylpiperazines or is completely abolished.

Consequently the endoethylenic bridge present in diazabicyclooctanes cannot be broken without either loss or decrease of the analgetic activity.

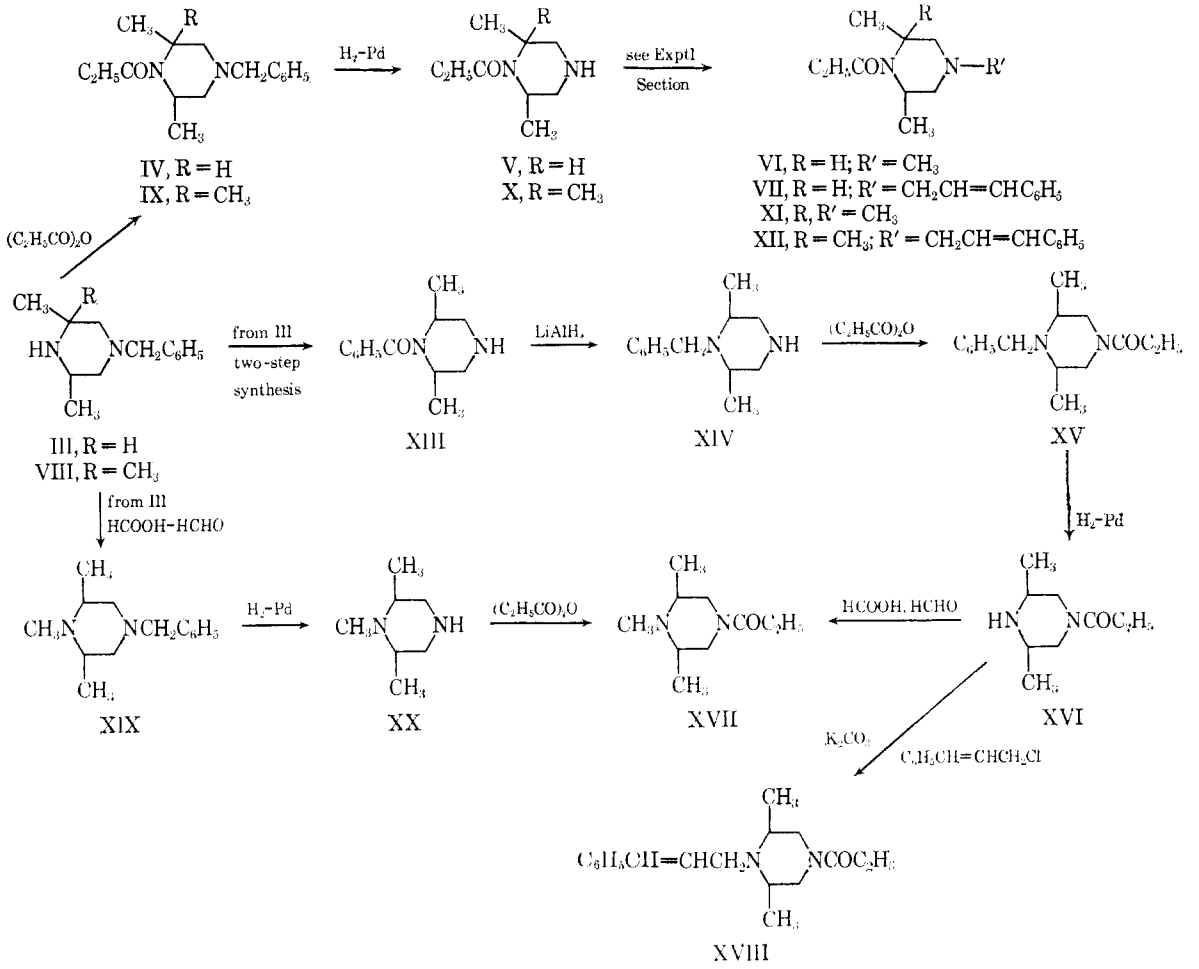
Experimental Section

Propionylation of N-Monosubstituted Piperazines (IV, IX, XV, XVII). General Procedure.—A mixture of 0.05 mole of the appropriate piperazine and excess (0.18 mole) propionic anhydride was heated 1.5 hr at 100°. After cooling, 30 ml of 10% HCl was added, the unreacted propionic anhydride was extracted with ether, and the acid layers were separated and made alkaline (Na_2CO_3). The N-propionyl-N′-substituted piperazine was extracted with ether and purified by distillation. The yields ranged from 83 to 95%.

Catalytical Debenzylation of N-Benzyl-N′-substituted Piperazines (V, X, XVI, XX). General Procedure.—A solution of 20 g of the appropriate N-benzyl derivative in 200 ml of absolute EtOH was hydrogenated in the presence of 10 g of 10% Pd–C at 50° and 50 atm of initial H_2 pressure. After the gas absorption ceased the catalyst was filtered off, the alcoholic filtrate was evaporated at room pressure, and the residue was purified by distillation; yields 88–96%.

N-Methyl-N′-propionylpiperazines (VI, XI, XVII). Method A. General Procedure.—A solution of 0.05 mole of the appropriate N-propionylpiperazine, 0.15 mole of 98% HCO_2H, and 0.15 mole of 40% aqueous CH_2O was refluxed 15 hr. To the solution, 10 ml of concentrated HCl was added and the whole was evaporated to dryness *in vacuo*. The residue was made

CHART I



alkaline by adding at 0° 20% NaOH and the oil that separated was extracted with ether and distilled; yields 50–65%.

Method B. Example.—To a suspension of 8 g (0.0435 mole) of X in 49 ml of 30% aqueous CH_2O (0.049 mole), 5.2 ml of AcOH was added, and the resulting solution was hydrogenated in the presence of 2 g of 10% Pd–C at room temperature and atmospheric pressure. After the gas absorption ceased (90% of the theoretical amount of H_2 absorbed) the catalyst was filtered off and the separated oil was extracted with ether. After removal of the solvent the residue was distilled to give 7 g (79.5%) of XI.

N-Cinnamyl-N′-propionylpiperazines (VII XII, XVIII). General Procedure.—A mixture of 0.02 mole of the appropriate N′-propionylpiperazine, 0.025 mole of cinnamyl chloride, 0.0025 mole of anhydrous K_2CO_3, and Me_2CO (50 ml) was refluxed 8 hr, then the inorganic salts were filtered off, the filtrate was evaporated, the residue was treated with 10 ml of 10% HCl, and the insoluble was extracted with ether. The acid layer was made alkaline (Na_2CO_3) and the separated oil was extracted and distilled.

1-Methyl-4-benzyl-2,6-dimethylpiperazine (XIX) was obtained in 87% yield by methylation of III with HCO_2H–CH_2O, following method A.

1-Benzyl-2,6-dimethylpiperazine (XIV).—To a stirred suspension at 0° of 30 g of $LiAlH_4$ in 300 ml of ether, a solution of 30 g of 1-benzoyl-2,6-dimethylpiperazine[7] in 300 ml of ether was added in 30 min. The mixture was refluxed for 6 hr then was cautiously decomposed on cooling at −5 to 0° with 90 ml of H_2O. After stirring 1 hr at room temperature, the inorganic salts were filtered off and were washed with ether. The filtrate was dried (Na_2SO_4), the solvent was evaporated, and the residue was distilled to yield 25.8 g (90%) of XIV, bp 97–98° (0.6 mm).

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