Bicyclic Homologs of Piperazine. V.[1,3] Synthesis and Analgesic Activity of 3-Methyl-3,8-diazabicyclooctane Derivatives

GIORGIO CIGNARELLA, EMILIO OCCELLI, GIULIO MAFFII, AND EMILIO TESTA

Research Laboratories, Lepetit S.p.A., Milano, Italy

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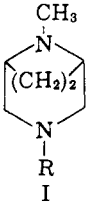
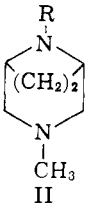
A number of 8-alkyl-8-aralkyl and 8-acyl substituted 3-methyl-3,8-diazabicyclo[3.2.1]octanes were synthesized for pharmacological screening. 3-Methyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane was found to possess high analgesic activity. Differences in chemical and biological behavior were also found between the 3-methyl-8-substituted diazabicyclooctanes and the corresponding isomeric 3-substituted 8-methyldiazabicyclooctanes.

In a previous paper of this series[1] we reported the synthesis of several 3-substituted 8-methyl-3,8-diazabicyclo[3.2.1]octanes (I) which have been tested for biological activity. We were also interested in synthesizing the isomeric 8-substituted 3-methyl-3,8-diazabicyclo[3.2.1]octanes (II) in order to observe the influence of the reversal of the substituents in the 3- and 8-position on the pharmacological activity. We wish to point out the different configuration of the N–R group at position 8 and of the N–R group at position 3. The difference is due to the presence of the endoethylenic bridge 1–5 which repels the 8-substituent toward the piperazine ring[2]; by contrast the 3-substituent is not deflected in any particular direction. It was therefore of interest to estimate the effect of this structural difference on the pharmacological behavior of such isomers. The compounds described were prepared by



I



II

conventional procedures starting from 3-methyl-3,8-diazabicyclo[3.2.1]octane[3] (III; II, R = H). The choice of the 8-substituent depended in part on the pharmacological properties of the related isomer I.

Chemistry.—A first group of products prepared is listed in Table I and concerns benzyl, cinnamyl, and benzhydryl derivatives and esters of 3-methyl-8-hydroxyethyl-3,8-diazabicyclo[3.2.1]octane (IV; II, R = CH_2CH_2OH) with representative aromatic acids. The compounds V–VIII (Table I) were obtained by refluxing in benzene the appropriate aralkyl chloride with 2 moles of III. The synthesis of compound IX (II, R = *p*-$O_2NC_6H_4COOCH_2CH_2$) and XI [II, R = $(C_6H_5)_2CHCOOCH_2CH_2$] started from IV which was prepared by refluxing III with ethylene oxide in methanol. The product obtained was finally condensed with *p*-nitrobenzoyl and diphenylacetyl chlorides in the presence of triethylamine yielding IX and XI, respectively. Compound X (II, R = *p*-$H_2NC_6H_4COOCH_2CH_2$) was easily obtained by catalytic reduction of IX.

A second group of compounds (XII–XVIII) consisted of 8-acyl derivatives of III (Table II). The synthesis of the compounds was carried out by condensing III with an excess of the appropriate acid anhydride (XII–XIV) without solvent or with an acid chloride in aqueous basic medium (XV–XVIII). The 8-N-methyl tropoyl derivative [XVIII; R = (±) $C_6H_5C(CH_3)CH_2OH$] was prepared by a previously described procedure.[1]

A group of miscellaneous 8-substituted 3-methyl-3,8-diazabicyclo[3.2.1]octanes (XIX–XXVII) is listed in Table III. 3-Methyl-8-guanidinoethyl-3,8-diazabicyclo[3.2.1]octane (XXI) was synthesized according to a described procedure[1] through the 8-cyanomethyl (XIX) and the 8-aminoethyl (XX) derivatives. Compound XXIII (II, R = NH_2) was prepared by lithium aluminum hydride reduction of XXII (II, R = NO) which was obtained by diazotization of III. The condensation between III and alkyl chlorocarbonates or diethylchloroformamide led to the isolation of compound XXIV (II, R = CH_3OCO), XXV (II, R = C_2H_5OCO), and XXVI [II, R = $(C_2H_5)_2NCO$]. Alternatively 3-methyl-8-phenylcarbamoyl-3,8-diazabicyclo-[3.2.1]octane (XXVII) was obtained by heating an equimolecular mixture of III and phenyl isocyanate.

Pharmacology.—The methods used for the estimation of the activities of these compounds have been described in our earlier paper.[1]

Analgesic Activity (Table IV).—Preliminary results obtained by the method of Randall and Selitto[4] showed a significant analgesic activity in 3-methyl-8-acyl-3,8-diazabicyclo[3.2.1]octanes. Compound XIII (II, R = C_2H_5CO) when injected intraperitoneally in rats is the most active of this series. Further experiments showed that its analgesic activity was retained by oral administration. It is interesting to note that the replacement of the propionyl group of XIII by other acyl groups (XII, XIV, XVII) resulted in a sharp decrease of activity; the replacement also with the carbomethoxy (XXIV), carbethoxy (XXV), and phenylcarbamoyl group (XXVII) gave products which were scarcely active. By comparison, all the tested 3-acyl-8-methyl isomers (I, R = acyl) were inactive as analgesics.[1] Experiments to enhance the analgesic activity of compound XIII by modification of the group on the 3-nitrogen atom are in progress.

Other Activities.—No other significant activity is present in the tested compounds with the exception of

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

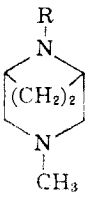
(2) G. Cignarella, E. Testa, and C. R. Pasqualucci, *Tetrahedron*, **19**, 143 (1963).

(3) G. Cignarella and E. Testa, *Gazz. Chim. Ital.*, to be published.

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

TABLE I

3-METHYL-8-ARALKYL-3-8-DIAZABICYCLO[3.2.1]OCTANES

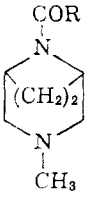


Cmpd.	R	B.p. or m.p.[a] °C	mm.	Yield, %	Formula	Calcd. C	H	N	Cl	Found C	H	N	Cl
IV	$HOClH_2CH_2$	105	0.6	88	$C_9H_{18}N_2O$	63.48	10.65	16.45		63.42	10.80	16.15	
		238–241			$C_9H_{18}N_2O \cdot 2HCl$			11.52	29.15			11.34	29.46
V	$C_6H_5ClI_2$	104–105	.5	94	$C_{14}H_{20}N_2$	77.71	9.31	12.94		77.49	9.47	12.84	
VI	$C_6H_5CH{=}CHCH_2$	138–140	.8	62.5	$C_{16}H_{22}N_2$	79.28	9.14	11.55		79.23	9.34	11.45	
		77–80			$C_{16}H_{22}N_2 \cdot 2C_6H_8O_7$[b]	53.63	6.10	4.46		53.90	6.10	4.47	
VII	o-$ClC_6H_4CHC_6H_5$	240–243		40	$C_{20}H_{23}ClN_2 \cdot 2HCl$			7.00	26.60			7.13	26.65
VIII	p-$ClC_6H_4CHC_6H_5$	260–263		48.5	$C_{20}H_{23}ClN_2 \cdot 2HCl$			7.00	26.60			7.28	26.78
IX	p-$O_2NC_6H_4COOCH_2CH_2$	203–207		77	$C_{16}H_{21}N_3O_4 \cdot 2HCl$			10.71	18.07			10.54	17.82
X	p-$H_2NC_6H_4COOCH_2CH_2$	223–225		70[c]	$C_{16}H_{23}N_3O_2 \cdot 3HCl$			10.55	26.66			10.26	26.81
XI	$(C_6H_5)_2CHCOOCH_2CH_2$	221–223		80	$C_{23}H_{23}N_2O_2 \cdot 2HCl$			6.40	16.21			6.52	16.40

[a] All solid compounds were crystallized from EtOH. [b] Citric acid. [c] From IX.

TABLE II

3-METHYL-8-ACYL-3-8-DIAZOBICYCLO[3.2.1]OCTANES

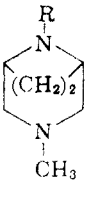


Cmpd.	R	B.p. or m.p. °C	mm.	Cryst. solvent	Yield, %	Formula	Calcd. C	H	N	Found C	H	N
XII	CH_3	90–95	0.9		76	$C_9H_{16}N_2O$	64.24	9.58	16.65	64.11	9.69	16.54
		40–43										
XIII	C_2H_5	92	.6		73.5	$C_{10}H_{18}N_2O$	65.88	9.95	15.36	66.02	10.15	15.21
XIV	n-C_3H_7	110	.4		67	$C_{11}H_{20}N_2O$	67.29	10.26	14.27	67.38	10.51	14.00
		120		EtOH/Et_2O		$C_{11}H_{20}N_2O \cdot HCl$	56.75	9.09	12.03	56.78	9.2	12.04
XV	C_6H_5	128–130	.4		88	$C_{14}H_{18}N_2O$	73.00	7.87	12.16	73.25	8.10	11.92
		182–184		EtOH		$C_{14}H_{18}N_2O \cdot C_6H_8O_7$[a]	56.85	6.20	6.63	56.98	6.24	6.64
XVI	$C_6H_5CH_2$	75			74	$C_{15}H_{20}N_2O$	73.70	8.25	11.46	73.98	7.93	11.21
XVII	$C_6H_5CH{=}CH$	92–94		Et_2O	84	$C_{16}H_{20}N_2O$	74.96	7.86	10.92	74.74	7.74	10.81
XVIII	(±) $C_6H_5C(CH_3)CH_2OH$	98–100		Et_2O	72	$C_{17}H_{24}N_2O_2 \cdot 0.5H_2O$	68.64	8.47	9.41	68.78	8.44	9.41

[a] Citric acid.

TABLE III

8-SUBSTITUTED-3-METHYL-3,8-DIAZABICYCLO[3.2.1]OCTANES



Cmpd.	R	B.p. or m.p. °C	mm.	Cryst. solvent	Yield, %	Formula	Calcd. C	H	N	Cl	Found C	H	N	Cl
XIX	$NCCH_2$	191 dec.		Sublimed	80	$C_9H_{15}N_3 \cdot HCl$			20.82	17.60			20.56	17.85
XX	$H_2NCH_2CH_2$	105	5		60.5[a]	$C_9H_{19}N_3$	63.84	11.24	24.82		64.00	11.55	24.63	
		142–144		dil. EtOH		$C_9H_{19}N_3 \cdot 2C_2H_2O_4$[b] $\cdot H_2O$	42.49	6.85	11.43		42.47	7.05	11.56	
XXI	$H_2NC(=NH)NHCH_2CH_2$	212–215		i-PrOH	45[c]	$C_{10}H_{21}N_5 \cdot 2HBr$			18.76	42.81			19.01	42.86
XXII	NO	98–100	5		96	$C_7H_{13}N_3O$	54.16	8.44	27.10		54.36	8.51	27.05	
		177–180		EtOH		$C_7H_{13}N_3O \cdot 2C_6H_8O_7$[d]	44.94	6.09	12.09		44.72	6.28	11.93	
XXIII	NH_2	94–95	5		80	$C_7H_{15}N_3$	59.52	10.70	29.78		59.30	10.85	29.42	
XXIV	$COOCH_3$	75	0.3		68.5	$C_9H_{16}N_2O_2$	58.66	8.75	15.20		58.80	9.00	14.91	
XXV	$COOC_2H_5$	91–93	1		63.5	$C_{10}H_{18}N_2O_2$	60.56	9.15	14.12		60.81	9.32	13.98	
XXVI	$(C_2H_5)_2NCO$	100–103	0.3		89.5	$C_{12}H_{23}N_3O$	63.94	10.28	18.64		63.63	10.08	18.58	
XXVII	C_6H_5NHCO	162–164		EtOH	80	$C_{14}H_{19}N_3O$	68.53	7.80	17.12		68.36	8.01	17.04	

[a] From XIX. [b] Oxalic acid. [c] From XX. [d] Citric acid.

the high local anesthetic action found in compound X (II, R = p-$H_2NC_6H_4COOCH_2CH_2$) comparable with that of the corresponding 8-methyl isomer and with that of procaine.[1] Compound XVIII [II, R = (±) $C_6H_5C(CH_3)CH_2OH$] showed poor spasmolytic action[5] in respect with that of the (±) 3-α-methyltropoyl isomer.[1]

(5) V. Scarselli, G. Cignarella, and G. Maffii, *J. Med. Chem.*, to be published.

Experimental

8-Aralkyl-3-methyl-3,8-diazabicyclo[3.2.1]octanes (V–VIII). General Procedure.—A mixture of 0.01 mole of the appropriate aralkyl chloride, 0.02 mole of 3-methyl-3,8-diazabicyclo[3.2.1]-octane (III),[3] and 15 ml. of benzene was refluxed for 10–24 hr. Sometimes during the heating, separation of the hydrochloride of III occurred. After cooling, the III hydrochloride was filtered and washed with benzene. The filtrate was collected and shaken in a separatory funnel with water until neutral. The organic layer was dried over sodium sulfate and evaporated. The oily

TABLE IV
ANALGESIC ACTION

Table	Compound	Dose, mg./kg.	Per cent increase of pain threshold in rats i.p.	Per cent increase of pain threshold in rats orally	Approximate LD_{50}, mg./kg. i.p., mouse
II	XII	50	58		500
		25	9		
II	XIII	25	327	235	282
		10	139	139	[229–347]
		5	25	22.6	
II	XIV	25	100		200
		15	52.8		
II	XVII	10	52		50
		5	19		
III	XXIV	25	10.4		200
III	XXV	25	48		200
		15	7		
III	XXVII	10	12		50
morphine HCl		5	186		410[a]
		3	90		

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

residue was purified by distillation at reduced pressure (V, VI) or through the corresponding hydrochloride (VII, VIII).

8-Hydroxyethyl-3-methyl-3,8-diazabicyclo[3.2.1]octane (IV).—To a stirred solution of 30 g. (0.238 mole) of III in 100 ml. of methanol, a solution of 22 g. (0.5 mole) of ethylene oxide in 100 ml. of methanol was added at room temperature. The reaction mixture was refluxed for 4 hr. on a steam bath, the solvent was evaporated and the oily residue was distilled.

Esters of 8-Hydroxyethyl-3-methyl-3,8-diazabicyclo[3.2.1]-octane (IX, XI).—To a stirred solution of 0.02 mole of IV and 0.022 mole of triethylamine in 50 ml. of ether, 0.022 mole of the acid chloride diluted with 50 ml. of ether was added dropwise. The reaction mixture was kept overnight at room temperature, 10% sodium bicarbonate was added, the organic layer was separated and dried over sodium sulfate. After removing of the solvent and triethylamine by distillation, the residue was purified through the dihydrochloride.

8-[β-Ethyl-3-methyl-3,8-diazabicyclo[3.2.1]octane] *p*-Aminobenzoate Trihydrochloride (X).—Five grams of IX was dissolved in 100 ml. ethanol and hydrogenated at normal pressure in the presence of 2 g. of 10% palladium on charcoal. When the gas absorption had ceased, the catalyst was removed and the alcoholic solution was evaporated. The oily residue was dissolved in ether and added to ether saturated with dry hydrogen chloride. The precipitate, after decanting of the ether solution, was crystallized from ethanol.

8-Acyl-3-methyl-3,8-diazabicyclo[3.2.1]octanes (XII–XVIII). Method A (from the Acid Anhydride); Preparation of XII.—To 7.05 g. (0.069 mole) of acetic anhydride cooled at 0°, 2.9 g. (0.023 mole) of III was added and the mixture was heated 1 hr. at 80–100°. After cooling, 20 ml. of 5% sodium hydroxide was added to decompose excess acetic anhydride, the mixture was stirred for 1 hr. at room temperature and extracted with ether. The organic layer was separated and dried over sodium sulfate, the solvent was evaporated, and the oily residue was distilled at reduced pressure. Compounds XIII and XIV were prepared in similar manner.

Method B (from the Acid Chloride). Preparation of 8-Benzoyl-3-methyl-3,8-diazabicyclo[3.2.1]octane (XV).—To a solution of 2.52 g. (0.02 mole) of III in 15 ml. of 2 *N* sodium hydroxide, cooled to 0°, 3.5 g. (0.025 mole) of benzoyl chloride was added with stirring. The mixture was then stirred for 3 hr. at room temperature and the oily suspension was extracted with ether; the extract was dried and evaporated and the residue was distilled at reduced pressure. By the same procedure, XVI and XVII were obtained. Similarly the reaction between III and (±) β-acetoxy-α-methyl-α-phenylpropionyl chloride[6] yielded the O-acetoxy-α-methyltropyl derivative. This product was saponified with 5% aqueous–ethanolic sodium hydroxide at room temperature, the mixture was adjusted at pH 7.5–8, concentrated, and extracted with chloroform. The extract was dried, the solvent was evaporated, and the solid residue was crystallized from ether to yield 72% of XVIII whose analysis agreed with the formula $C_{17}H_{24}N_2O_2 \cdot 0.5H_2O$.

(6) G. Melone, A. Vecchi, G. Pagani, and E. Testa, *J. Org. Chem.*, **25**, 859 (1960).

8-Cyanomethyl-3-methyl-3,8-diazabicyclo[3.2.1]octane (XIX).—A mixture of 3 g. (0.0238 mole) of III, 2.25 g. (0.03 mole) of chloroacetonitrile, 4.1 g. (0.03 mole) of potassium carbonate, and 50 ml. acetone was stirred and refluxed for 5 hr. After cooling the inorganic salt was filtered off and the filtrate was evaporated. The oily residue was distilled twice at reduced pressure. The product was highly hygroscopic. A sample was transformed with 2 *N* ethanolic hydrochloric acid to the monohydrochloride, m.p. 186–190°, which was further purified by sublimation at 100° (1 mm.).

8-β-Aminoethyl-3-methyl-3,8-diazabicyclo[3.2.1]octane (XX).—To a stirred suspension of 1.83 g. (0.048 mole) of lithium aluminum hydride in 20 ml. of anhydrous tetrahydrofuran, 1.9 g. (0.015 mole) of XIX in 20 ml. of tetrahydrofuran was added at 0°. The reaction mixture was refluxed for 6 hr., then cooled to −5° and decomposed with 6 ml. of water. After stirring for 1 hr. at room temperature the inorganic material was filtered and thoroughly washed with tetrahydrofuran. The filtrate was dried over sodium sulfate, the solvent evaporated, the residue dissolved in ether and dried over solid potassium hydroxide. After evaporation of the solvent the residue was distilled. A sample was transformed to the corresponding **dioxalate** by adding the base to an ethereal solution of oxalic acid.

8-Guanidinoethyl-3-methyl-3,8-diazabicyclo[3.2.1]octane Dihydrobromide (XXI).—A mixture of 1.5 g. (0.0089 mole) of XX, 6.95 g. (0.0267 mole) of S-ethylisothiouronium bromide[7] and 30 ml. of chloroform was refluxed for 5 hr. under an efficient hood. A viscous oil separated and solidified on cooling. The product crystallized from isopropyl alcohol.

8-Nitroso-3-methyl-3,8-diazabicyclo[3.2.1]octane (XXII).—To a stirred solution of 3.3 g. (0.0262 mole) of III in 2 *N* hydrochloric acid was added, at 0°, dropwise a solution of 2.07 g. of sodium nitrite (0.03 mole) in 5 ml. of water. The mixture was stirred for 2 hr. at room temperature, then cooled, made alkaline with 50% sodium hydroxide, and extracted with ether. The extract was dried over sodium sulfate, the solvent evaporated, and the residue distilled. The **dicitrate** was obtained by adding the base to ethanolic citric acid.

8-Amino-3-methyl-3,8-diazabicyclo[3.2.1]octane (XXIII).—To a stirred suspension of 2.3 g. (0.0606 mole) of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran, 4.6 g. (0.0295 mole) of XXII in 20 ml. of tetrahydrofuran was added dropwise at such a rate that the temperature was kept at 40–45°. The mixture was then refluxed for 6 hr., cooled to −5°, and cautiously decomposed with 8 ml. of water. Stirring was continued for 2 hr. at room temperature; the inorganic salts were filtered and thoroughly washed with ether. The filtrates were collected, dried, and evaporated; the residue was dissolved in ether and dried over solid potassium hydroxide. After evaporation of the solvent the oily residue was distilled.

8-Carboalkoxy-3-methyl-3,8-diazabicyclo[3.2.1]octane (XXIV, XXV). General Procedure.—Alkyl chlorocarbonate (0.02 mole) was added dropwise to a stirred solution of 0.018 mole of III in 10 ml. of 2 *N* sodium hydroxide at 0°. The mixture was stirred for 2 hr. at room temperature, extracted with ether, and the extract was dried and distilled.

8-Diethylcarbamoyl-3-methyl-3,8-diazabicyclo[3.2.1]octane (XXVI).—This product was obtained according to the procedure described for XXIV and XXV starting from 3 g. of III, 3.25 g. of diethylchloroformamide,[8] and 12.2 ml. 2 *N* sodium hydroxide.

8-Phenylcarbamoyl-3-methyl-3,8-diazabicyclo[3.2.1]octane (XXVII).—Three grams of III was cautiously added to an equimolar amount of phenyl isocyanate. When the exothermic reaction subsided the white precipitated solid was triturated with ether, filtered, and crystallized from ethanol.

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(7) E. Brand and F. Brand, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, New York, N. Y., 1955, p. 440.

(8) A. Lumière and F. Perrin, *Bull. Soc. Chim. France*, **31**, 689 (1904).