Bicyclic Homologs of Piperazine. VI.[1] Synthesis and Analgesic Activity of 3-Substituted 8-Propionyl-3,8-diazabicyclo[3.2.1]octanes

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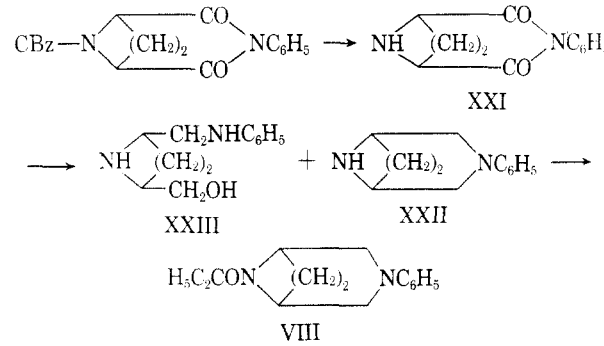
With the aim of enhancing the analgesic activity of 3-methyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane (I), the methyl group of I was substituted by a number of alkyl and aralkyl groups. 3-Cinnamyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane showed an analgesic potency approximately 25-fold that of I and 10-fold that of morphine hydrochloride.

The discovery of analgesic activity in 3-methyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane[1] (I) led us to synthesize a number of analogs with the aim of defining the structure–activity relationships in the series and possibly improving the activity of compound I. In a previous paper[1] we described a series of derivatives where the 8-propionyl group of I was replaced by other acyl or carbalkoxy groups. Preliminary pharmacological tests showed that all those analogs were less active as analgesics than I, thus suggesting that any modification on the propionyl group was unfavorable for the analgesic activity. In this paper we report the synthesis of a number of compounds where the modification concerns the 3-methyl group, together with preliminary pharmacological data. The choice of the 3-substituent was effected taking into account similar studies concerning the substitution of the methyl group bonded to the nitrogen in well known analgesics like morphine[2] and meperidine.[3]

Chemistry.—To obtain most of the compounds listed in Table I, 8-propionyl-3,8-diazabicyclo[3.2.1]octane (II) was employed as starting material. It was prepared by acylation with the propionic anhydride of 3-benzyl-3,8-diazabicyclo[3.2.1]octane[4] to 3-benzyl-8-propionyl-3,8-diazabicyclo[3.2.1] octane (IX) and by catalytic removal of the benzyl group. Treatment of II with various alkyl or aralkyl halides yielded compounds III–VII, IX, X, XII, and XIV by a general procedure described in the Experimental section. Compound VIII (R = C_6H_5) was obtained in the following way. Catalytic hydrogenolysis of 3-phenyl-8-carbobenzyloxy-3,8-diazabicyclo[3.2.1]octane-2,4-dione[5] gave 3-phenyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (XXI). Reduction of XXI with lithium aluminum hydride in ether yielded, besides 3-phenyl-3,8-diazabicyclo[3.2.1]octane (XXII), 2-hydroxymethyl-5-phenylaminomethylpyrrolidine (XXIII) by cleavage of the imidic ring. Acylation of XXII with propionic anhydride gave the desired VIII. Compound XI [R = $(CH_2)_3C_6H_5$] was prepared by catalytic reduction of XII (R = $CH_2CH{=}CHC_6H_5$). Condensation of II with ethylene oxide in methanol yielded the 3-(β-hydroxyethyl) derivative XV from which



XVI (R = $CH_2CH_2OCOC_6H_4NH_2$-*p*) was synthesized by condensation with *p*-nitrobenzoyl chloride, followed by catalytic reduction of the nitro group. Reaction of XV with thionyl chloride gave XVII (R = CH_2CH_2Cl) which was allowed to react with the appropriate amines to give compounds XVIII [R = $CH_2CH_2N(C_2H_5)_2$] and XIX (R = $CH_2CH_2NHC_6H_5$). Condensation of II with β-dimethylaminopropiophenone[6] by a described procedure[7] led to XIII (R = $CH_2CH_2COC_6H_5$). Finally, compound XX (R = COC_2H_5) was prepared by condensation of II with propionic anhydride.

Pharmacology. Analgesic Action and Toxicity (Table II).—CF 1 Mice, weighing 22–25 g., and male CF Wistar rats, weighing 180–200 g., were used. The analgesic activity was evaluated through the changes in pain threshold according to the method of Randall and Selitto.[8] The average duration of action is also indicated. Compound XII (R = $C_6H_5CH{=}CHCH_2$) is the most active of this series and shows an analgesic potency approximately tenfold that of morphine. Slightly less active appear compounds XIII (R = $C_6H_5COCH_2CH_2$) and XI (R = $C_6H_5CH_2CH_2CH_2$) which, conversely, show a lower acute toxicity than XII. All the other derivatives of this group do not show a significant analgesic action. In the compounds tested the rapid onset and the short duration of action are noteworthy. Acute toxicity was evaluated in mice by intraperitoneal administration. It may be noted that the LD_{50} of XII is at least 200 times higher than the dose able to increase the pain threshold by 100%. In analogy to the known narcotic analgesics, sublethal doses of the active compounds produce excitation, sterotyped movements, and Straub-trail in mice.

Discussion.—Previously we demonstrated that analgesic activity of 3-alkyl-3,8-diazabicyclo[3.2.1]octanes

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TABLE I

3-SUBSTITUTED 8-PROPIONYL-3,8-DIAZABICYCLO[3.2.1]OCTANES R—N(CH$_2$)$_2$N—COC$_2$H$_5$

Compd.	R	M.p. or b.p. (mm.), °C.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
II	H	109–110 (0.4)	$C_9H_{16}N_2O$	64.25	64.35	9.58	9.82	16.65	16.62	...	...
III	C_2H_5	83–85 (0.2)	$C_{11}H_{20}N_2O$	67.30	67.27	10.27	10.40	14.27	14.30	...	...
IV	*i*-C_3H_7	100–101 (0.2)	$C_{12}H_{22}N_2O$	68.52	68.38	10.54	10.80	13.32	13.63	...	...
V	*n*-C_4H_9	103–105 (0.2)	$C_{13}H_{24}N_2O$	69.59	69.23	10.78	10.60	12.48	12.41	...	...
VI	$C_5H_9CH_2$[a]	135–138 (0.3)	$C_{15}H_{26}N_2O$	71.95	71.77	10.46	10.52	11.18	10.96	...	...
VII	$C_5H_9CH_2CH_2$[b]	145–148 (0.3)	$C_{16}H_{28}N_2O$	72.67	72.94	10.67	10.68	10.59	10.76	...	...
		236–240[c]	$C_{16}H_{28}N_2O \cdot HCl$	...	...	...	...	9.31	9.07	11.78	11.64
VIII	C_6H_5	85–86[d]	$C_{18}H_{20}N_2O$	73.73	73.77	8.25	8.32	11.46	11.61	...	...
IX	$C_6H_5CH_2$	153–155 (0.4)	$C_{19}H_{22}N_2O$	74.37	74.19	8.58	8.92	10.84	10.95	...	...
X	$C_6H_5CH_2CH_2$	150–152 (0.3)	$C_{17}H_{24}N_2O$	74.95	75.09	8.88	9.06	10.28	10.17	...	...
		227–229[e]	$C_{17}H_{24}N_2O \cdot HCl$	...	...	...	...	9.07	8.98	11.48	11.77
XI	$C_6H_5CH_2CH_2CH_2$	170–172[f] (0.4)	$C_{18}H_{26}N_2O$	75.48	75.73	9.15	9.36	9.77	9.64	...	...
XII	C_6H_5CH=CH—CH_2	170–175[f] (0.2)	$C_{18}H_{24}N_2O$	76.01	76.05	8.50	8.60	9.85	9.98	...	...
XIII	$C_6H_5COCH_2CH_2$	185–186[e]	$C_{18}H_{24}N_2O_2 \cdot HCl$	...	...	...	...	8.31	8.17	10.52	10.75
XIV	$(C_6H_5)_2CH$	143–146[g]	$C_{32}H_{32}N_2O \cdot HCl$	...	...	...	...	7.55	7.75	9.55	9.38
XV	$HOCH_2CH_2$[c]	161–162 (0.4)	$C_{11}H_{20}N_2O_2$	62.23	62.60	9.49	9.42	13.19	12.93	...	...
XVI	*p*-$H_2NC_6H_4COOCH_2CH_2$	154–157[e,h]	$C_{18}H_{27}N_3O_3 \cdot HCl$	...	...	...	...	11.42	11.18	9.63	9.43
XVII	$ClCH_2CH_2$	134–136 (0.4)	$C_{11}H_{19}ClN_2O$	57.25	57.09	8.30	8.28	12.14	12.25	15.39	15.30
		214–216[e]	$C_{11}H_{19}ClN_2O \cdot HCl$	...	...	...	...	10.48	10.31	26.53	27.01
XVIII	$(C_2H_5)_2NCH_2CH_2$	216–218[g]	$C_{15}H_{29}N_3O \cdot 2HCl$	...	...	...	...	12.34	12.55	20.83	20.59
XIX	$C_6H_5NHCH_2CH_2$	191–193[e]	$C_{17}H_{25}N_3O \cdot HCl$	...	...	...	...	12.97	12.79	10.94	11.20
XX	C_2H_5CO	143–145 (0.6)	$C_{12}H_{20}N_2O_2$	64.25	64.02	8.98	9.03	12.49	12.49	...	...

[a] Cyclopentylmethyl. [b] β-Cyclopentylethyl. [c] Recrystallized from 2-propanol. [d] Recrystallized from petroleum ether. [e] Recrystallized from ethanol. [f] Distilled by Ronco technique.[13] [g] Recrystallized from ethanol–ether. [h] Dried at 100° *in vacuo*. [i] Hydrogen sulfate, m.p. 146–148°. *Anal.* Calcd. for $C_{11}H_{22}N_2O_6S$: N, 9.02; S, 10.33. Found: N, 8.87; S, 10.44.

depends on the nature of the 8-substituent, the propionyl group being the most favorable one. Among the 8-propionyl-3,8-diazabicyclo[3.2.1]octanes described in this paper high analgesic activity is present in 3-phenylpropyl XI, 3-cinnamyl XII, and 3-benzoylethyl XIII derivatives, suggesting that the greatest analgesic activity may be related to the presence in the 3-position of an aralkyl group, the aliphatic chain of which consists of three unbranched carbon atoms. Unsaturation of the chain enhances the activity. Further investigations of pharmacological modifications induced by substitutions both on the aliphatic chain and on the phenyl group are now in progress.

Experimental[9]

3-Benzyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane (IX).—3-Benzyl-3,8-diazabicyclo[3.2.1]octane[4] (35 g., 0.173 mole) was cautiously added to propionic anhydride (65 g., 0.5 mole) with stirring and cooling. The mixture was kept at 100° for 1 hr., cooled, and poured into iced 20% NaOH. After stirring for 30 min. at room temperature, the oily suspension was extracted with ether. The extract was dried over Na_2SO_4, the solvent evaporated, and the residue distilled *in vacuo* to yield 90% of IX.

8-Propionyl-3,8-diazabicyclo[3.2.1]octane (II) was prepared by dissolving IX (23.2 g., 0.09 mole) in ethanol (250 ml.) and hydrogenating at 60° and 30 atm. (30.9 kg./cm.^{2}) of initial hydrogen pressure using 10% palladium-on-charcoal as catalyst. The catalyst was removed by filtration, and the filtrate was fractionally distilled *in vacuo*. The yield was 83%.

3-Alkyl-(or aralkyl)-8-propionyl-3,8-diazabicyclo[3.2.1]octanes (III–VII, IX, X, XII, and XIV). Intermediates.—Ethyl bromide, isopropyl iodide, *n*-butyl iodide, cinnamyl chloride, and benzhydryl chloride were commercially available. Cyclopentylmethyl bromide,[10] 2-cyclopentylethyl bromide,[11] and phenylethyl bromide[12] were prepared by known procedures.

General Method.—8-Propionyl-3,8-diazabicyclo[3.2.1]octane (II) (0.1 mole), the required halide (0.12 mole), anhydrous potassium carbonate (0.12 mole), and acetone (150 ml.) were placed in a flask, equipped with a mechanical stirrer and a reflux condenser protected with a drying tube, and refluxed for 7–10 hr. with vigorous stirring. The reaction mixture was cooled, filtered, and the filtrate evaporated. The residue was suspended in an excess of 10% HCl, the unreacted halide was extracted with ether, the aqueous layer was made alkaline with 50% NaOH, and the separated oil was extracted with ether. The extract was dried, the solvent was evaporated to dryness, and the residue was fractionally distilled or crystallized; yields, 45–88%. The low yields obtained in the case of poorly reactive halides (VI, VII) may be enhanced by refluxing II (2 moles) and the required halide (1 mole) in benzene for 15 hr. and working up the reaction mixture as described above. The physico-chemical properties and analysis of the compounds obtained are summarized in Table I.

3-Phenyl-8-propionyl-3,8-diazabicyclo[3.2.1.]octane (VIII). Step 1. 3-Phenyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (XXI).—In a 3-l. flask equipped with a mechanical stirrer, an inlet and an outlet gas tube, 3-phenyl-8-carbobenzyloxy-3,8-diazabicyclo-[3.2.1]octane-2,4-dione[5] (40 g., 0.114 mole) was dissolved in 1 l. of 95% ethanol, and the stirred mixture was hydrogenated in the presence of 20 g. 10% Pd-on-charcoal at room temperature until CO_2 evolution ceased (barium hydroxide test). Uptake of hydrogen was essentially complete after 3 hr. The catalyst which contained white crystals of the reaction product, was collected by filtration, extracted with 200 ml. of boiling ethanol, and filtered. The ethanolic solution was added to the initial filtrate and the whole was concentrated to a small volume. On cooling, 18.9 g. (77%) of XXI was obtained as white crystals, m.p. 183–184°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.98. Found: C, 66.54; H, 5.54; N, 13.00.

Step 2. 3-Phenyl-3,8-diazabicyclo[3.2.1]octane (XXII).—A suspension of 6.2 g. (0.0287 mole) of XXI in ether (200 ml.) was added to a stirred suspension of lithium aluminum hydride (3.27 g., 0.861 mole) in 100 ml. of ether. The reaction mixture was refluxed for 7 hr., cooled, and cautiously decomposed with 10 ml. of water. After stirring for 1 hr. at room temperature the inorganic salts were filtered and washed with ether, the filtrates were collected and dried over sodium sulfate, and the solvent was evaporated. The residue after trituration with ether gave 2 g. of a white product, m.p. 105–107°, which was identified by microanalysis and functional analysis as 2-hydroxymethyl-5-phenylaminomethylpyrrolidine (XXIII). The analytical sample was recrystallized from ether, m.p. 107–108°.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.85; H, 8.79; N, 13.58. Found: C, 69.57; H, 8.91; N, 13.72.

(9) Melting points and boiling points are uncorrected. Melting points were obtained with a Büchi capillary melting point apparatus.

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TABLE II

ANALGESIC ACTIVITY OF DIAZABICYCLO[3.2.1]OCTANES IN THE RAT, AND ACUTE TOXICITY IN THE MOUSE

Compd.	Dose, mg./kg. (i.p.)	% increase of pain threshold	Average duration of action (min.)	Approximate LD_{50}, mg./kg., i.p. (mouse)
II	25	10		300
III	25	24	90	300
IV	25	32	60	200
V	10	36	60	300
	25	47.7	60	
	50	46.5	60	
VI	25	26		200
VII	5	23		200
	10	60	45	
VIII	25	36.9		
IX	25	32	60	200
X	3	32	90	600
	5	41.5	45	
XI	0.5	28	45	400
	1	99	45	
	2	142	60	
XII	0.1	46.5	60	73.01
	0.2	75.8	60	
	0.4	143	45	
XIII	0.1	11		185
	0.3	76	60	
	0.5	81	30	
	1	330	30	
XIV	10	14.2		200
XV	50	20.5		1000
XVI	50	25	30	600
XVII	1	36	45	20
XVIII	10	19	30	200
XIX	1	48	45	400
	2	46	60	
XX	50	20		600
Morphine HCl	1.5	31.5	60	410[a]
	3	91	90	
	5	>170	120	
3-Methyl-8-propionyl-3,8-diazabicyclo[3.2.1]-octane[b]	25	327	180	282
	10	139	90	
	5	25	90	

[a] See ref. 14. [b] See ref. 1.

The ether-soluble fraction was distilled to yield 1.95 g. of XXII, b.p. 120–122° (0.5 mm.) which solidified on standing, m.p. 57–60° (ether).

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.53; H, 8.56; N, 14.87. Found: C, 76.21; H, 8.72; N, 14.89.

Step 3.—Compound XXII (1.5 g.) was added to propionic anhydride (2 g.), and the mixture was heated at 100° for 1 hr., cooled, and worked up as described for IX; yield of VIII, 1.4 g. (72%).

3-[3-Phenylpropyl]-8-propionyl-3,8-diazabicyclo[3.2.1]octane (XI) was obtained in 85% yield by hydrogenating at room temperature 4 g. of XII in 40 ml. of ethanol with 1 g. of 10% Pd-on-charcoal as catalyst at a hydrogen pressure of 1.5 atm. The theoretical amount of hydrogen (320 ml.) was absorbed in 50 min. The catalyst was filtered off, and the alcohol was removed by concentration *in vacuo* on the steam bath. The residue was purified by distillation.

3-[3-Oxo-3-phenylpropyl]-8-propionyl-3,8-diazabicyclo[3.2.1]-octane (XIII) hydrochloride was prepared starting from II (0.01 mole) and 5-dimethylaminopropiophenone hydrochloride[14] (0.011 mole) in dimethylformamide (25 ml., according to the procedure described by Snyder and Brewster[7]; yield, 65%).

3-Hydroxyethyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane (XV).—A mixture of II (22.2 g., 0.132 mole), ethylene oxide (17.4 g., 0.396 mole), and 100 ml. of methanol was refluxed gently for 3 hr., the solvent was distilled, and the residue was fractionally distilled to yield 89% of XV.

3-[2-Chloroethyl]-8-propionyl-3,8-diazabicyclo[3.2.1]octane (XVII).—A solution of XV (6.1 g., 0.0288 mole) in ether (30 ml.) was saturated with hydrogen chloride. The ether was decanted, the solid residue was treated with 25 ml. of thionyl chloride, and the reaction mixture was refluxed gently for 3 hr. During the heating, dissolution of the XV hydrochloride occurred, followed by a slow separation of crystalline XVII hydrochloride. After cooling, the product was collected by filtration, thoroughly washed with dry ether, and recrystallized from absolute ethanol; yield, 90.5%. The corresponding base XVII may be isolated by adding a cold sodium carbonate solution to an ice-cold aqueous suspension of the hydrochloride, extracting the liberated oil immediately with ether, drying, and distilling under reduced pressure.

3-[2-Diethylaminoethyl]-8-propionyl-3,8-diazabicyclo[3.2.1]-octane Dihydrochloride (XVIII).—A solution of XVII (2.3 g., 0.01 mole), anhydrous diethylamine (1.6 g., 0.022 mole), and benzene (5 ml.) was heated at 120° in a sealed tube for 10 hr. After cooling, diethylamine hydrochloride was filtered, the filtrate was evaporated *in vacuo*, and the crude residue was added to an ether solution of hydrogen chloride. The crude XVIII was collected by filtration and recrystallized from ethanol–ether; yield, 52%.

3-[2-Anilinoethyl]-8-propionyl-3,8-diazabicyclo[3.2.1]octane Hydrochloride (XIX).—A mixture of XVII (2.3 g., 0.01 mole) and aniline (2.05 g., 0.022 mole) was heated at 100° for 7 hr., cooled, treated with 10 ml. 10% NaOH, and extracted with ether. The extract was dried over sodium sulfate, the solvent was evaporated, and the residue distilled by the Ronco technique[15] collecting the fraction (2.8 g.) boiling at 180–190° (0.1 mm.). The product was added to an ether solution of hydrogen chloride, and the precipitate was crystallized from isopropyl alcohol to yield 2.6 g. (80%) of XIX.

3-[2-(*p*-Aminobenzoxy)ethyl]-8-propionyl-3,8-diazabicyclo-[3.2.1 octane Hydrochloride (XVI).—To a cooled and stirred mixture of VI (2.12 g., 0.01 mole), triethylamine (1.3 g., 0.012 mole), and ether (70 ml.), *p*-nitrobenzoyl chloride (2.22 g., 0.012 mole) was added dropwise. The reaction mixture was stirred for 5 hr. at room temperature, triethylamine hydrochloride was filtered off, the filtrate was evaporated, and the oily residue without further purification, was hydrogenated in ethanol (30 ml.) with 0.5 g. of 10% Pd-on-charcoal, at room temperature and an initial hydrogen pressure of 5 atm. The catalyst was filtered and the filtrate evaporated. The viscous residue was found to be undistillable and unerystallizable. By adding it to an ether solution of hydrogen chloride, a precipitate was obtained which after recrystallization from isopropyl alcohol melted at 209–210°. The analysis of this compound agrees with the dihydrochloride; it was hygroscopic and rather unstable. On drying at 100° (0.1 mm.) it lost 1 mole of HCl to yield 2 g. (55%) of XVI.

3,8-Dipropionyl-3,8-diazabicyclo[3.2.1]octane (XX) was obtained by heating II at 100° for 2 hr. with a slight excess of propionic anhydride and working up the mixture as described for XII; yield, 78%.

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