phenyl tried in the 3-oxy series had been deleterious. Whereas the 3-oxy series had required 2- or 4-substitution on the pyrrolidine ring, the *meta*-oxy series suffers slight to complete loss of activity on ring substitution additional to 1,3-, in the order 5-, 2-, 4-. There are interesting relationships in the *meta*-oxygen series between heaviness of 2-alkylation, gradation in zwitterionic character, and loss of activity. *meta* Etherification seemingly muzzles considerably these interactions of 2-alkylation.

Finally, effects of alterations in N-substitution are much sharper in the *meta*-oxygen series than in the older series. Replacing methyl is, in most instances, clearly deleterious.

Acknowledgment.—The authors thank Dr. R. E. Bowman and Dr. H. M. Crooks, Jr., for helpful advice and consultation, Mr. F. H. Oliver for the microanalyses, Miss E. M. Tanner for the physical measurements, Mr. K. E. Richards for help in the resolution of the parent compound, and Miss L. Scotti, Miss J. Wax, and Mrs. S. Stanat for important participation in the pharmacological work.

Bicyclic Homologs of Piperazine. VII.[1] Synthesis and Analgesic Activity of 3-Aralkenyl-8-propionyl-3,8-diazabicyclo[3.2.1]octanes

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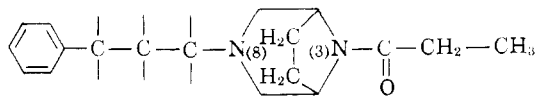
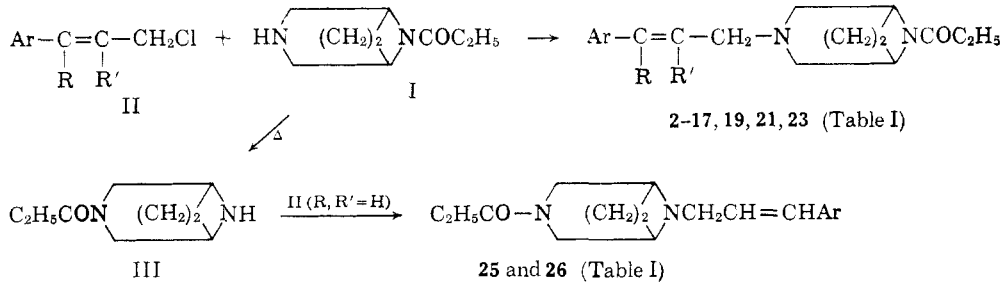
With the aim of enhancing the analgesic activity of 3-cinnamyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane (**1**), 25 derivatives were synthesized in which the 3-aralkenyl group was variously modified. Some of these compounds exhibited an analgesic potency comparable with that of **1**.

In the preceeding paper of this series,[1] the synthesis of analgesic 3-substituted 8-propionyl-3,8-diazabicyclo-[3.2.1]octanes was reported and the effect of the 3- and 8-substituent on the activity was discussed. It was observed that the greatest analgesic action is associated with the presence in the 8-position of a propionyl group and in position 3 of an aralkyl group whose aliphatic chain consisted of three carbon atoms.



Unsaturation of this chain markedly enhanced the analgesic potency, the 3-cinnamyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane (**1**, Table I) being the most active compound of the series, approximately 10 times more potent that morphine hydrochloride. It seemed, therefore, of interest to study the effects on the analgesic activity of the introduction of substituents in the cinnamyl group. We describe in this paper the syntheses and the properties of a number of 8-propionyl-3,8-diazabicyclo[3.2.1]octanes, in which the cinnamyl group of the model compound **1** was modified by substitutions on the aromatic ring (**2**–**12**) and on the ethylenic bond (**13**–**17**), replacement of the phenyl with α-naphthyl group (**18**) and with hydrogen (**21**), change in the unsaturation (**22**) and/or in the length of the aliphatic chain (**19**, **20**, and **23**), and replacement of the methylene group of the aliphatic chain with a carbonyl (**24**). In addition, two other derivatives (**25** and **26**) were synthesized in which the position of the propionyl and of the aralkenyl groups was reversed.

Chemistry.—Preparation of compounds listed in Table I was effected by condensing 8-propionyl-3,8-diazabicyclo[3.2.1]octane[1] (I) with aralkenyl chlorides II (**2**–**18**, **20**, and **23**), allyl bromide (**21**), phenylpropargyl bromide (**22**), and cinnamoyl chloride (**24**). Condensation of I with phenylacetaldehyde according to the method of Mannich[2] led to **19**. Compounds **25** and **26** were prepared by condensing 3-propionyl-3,8-diazabicyclo[3.2.1]octane[3] (III) with cinnamyl- and *p*-ethoxycinnamyl chloride, respectively. It is to be noted that **26** was first isolated during attempts to condense I with *p*-ethoxycinnamyl chloride; in this case the reaction conditions (refluxing in benzene for 15 hr.) clearly favored an $N_8 \rightarrow N_3$ acyl migration[3] of I to the

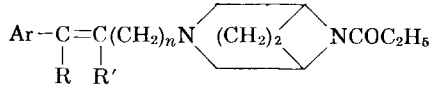
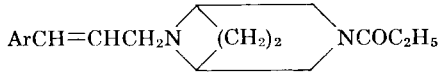


(1) Paper VI: G. Cignarella, E. Occelli, G. F. Cristiani, L. Paduano, and E. Testa, *J. Med. Chem.*, **6**, 764 (1963).

(2) C. Mannich and H. Davidsen, *Ber.*, **69B**, 2106 (1936).

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

TABLE I

No.	Ar	R	R′	n	M.p. or b.p. (mm.), °C.	Crystn. solvent[a]	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% Cl Calcd.	% Cl Found
																
1	C_6H_5	H	H	1	170–175 (0.2)			$C_{18}H_{24}N_2O$[1]								
2	*o*-ClC_6H_4	H	H	1	201–204	I	80	$C_{18}H_{23}ClN_2O \cdot HCl$					7.88	8.04	19.95	19.50
3	*m*-ClC_6H_4	H	H	1	203–205	I	80	$C_{18}H_{23}ClN_2O \cdot HCl$					7.88	7.92	19.95	19.86
4	*p*-ClC_6H_4	H	H	1	220–223	I	80	$C_{18}H_{23}ClN_2O \cdot HCl$					7.88	7.96	19.95	20.09
5	*o*-$O_2NC_6H_4$	H	H	1	182–185	E–Et	51	$C_{18}H_{23}N_3O_3 \cdot HCl$					11.48	11.02	9.69	9.08
6	*m*-$O_2NC_6H_4$	H	H	1	166–169	I	45	$C_{18}H_{23}N_3O_3 \cdot HCl$					11.48	11.84	9.69	10.00
7	*p*-$O_2NC_6H_4$	H	H	1	220	I	60	$C_{18}H_{23}N_3O_3 \cdot HCl$					11.48	11.50	9.69	9.67
8	*p*-MeC_6H_4	H	H	1	66–68	Et–P	66	$C_{19}H_{26}N_2O$	76.47	75.80	8.78	9.01	9.39	8.97		
9	*o*-$MeOC_6H_4$	H	H	1	150 (0.1)		50	$C_{19}H_{26}N_2O_2$	72.58	72.34	8.34	8.53	8.91	9.91		
10	2,4-$Cl_2C_6H_3$	H	H	1	195–198	I	50	$C_{18}H_{22}Cl_2N_2O$					7.18	7.27	27.29	27.30
11	2,6-$Cl_2C_6H_3$	H	H	1	115–120	I	50	$C_{18}H_{12}Cl_2N_2O \cdot HCl$					7.18	7.89	27.29	26.59
12	3,4,5-$(MeO)_3C_6H_3$	H	H	1	105–110	I	81	$C_{21}H_{30}N_2O_4 \cdot HCl$					6.81	6.57	8.62	8.45
13	C_6H_5	H	CH_3	1	180 (0.5)		84	$C_{19}H_{26}N_2O$	76.47	76.42	8.78	8.91	9.39	9.41		
14	C_6H_5	CH_3	H	1	170 (0.4)		85	$C_{19}H_{26}N_2O$	76.47	76.91	8.78	8.91	9.39	9.42		
15	C_6H_5	H	Br	1	180 (0.4)		50	$C_{18}H_{23}BrN_2O$	59.50	59.25	6.38	6.58	7.71	7.51	21.99[b]	21.89[b]
16	C_6H_5	Br	H	1	185 (0.4)		86	$C_{18}H_{23}BrN_2O$	59.50	59.36	6.38	6.56	7.71	7.50	21.99[b]	22.29[b]
17	C_6H_5	H	C_6H_5	1	195 (0.4)		74	$C_{24}H_{28}N_2O$	79.96	79.21	7.83	7.93	7.77	8.30		
18	α-Naphtyl	H	H	1	160–165	I	70	$C_{22}H_{26}N_2O \cdot 2HCl$					6.87	7.28	17.40	17.63
19	C_6H_5	H	H	0	98–99	Et	67	$C_{17}H_{22}N_2O$	75.52	76.30	8.20	8.80	10.36	10.14		
20	C_6H_5	H	H	2	118–121	E–Et	30	$C_{19}H_{26}N_2O \cdot HCl$					8.36	8.46	10.58	10.57
	Miscellaneous															
	3-Substituent															
21	$CH_2{=}CHCH_2{-}$				95–98 (0.2)		68	$C_{12}H_{20}N_2O$	69.18	70.27	9.68	10.03	13.45	13.79		
22	$C_6H_5C{\equiv}CCH_2{-}$				175 (0.4)		74	$C_{18}H_{22}N_2O$	76.56	74.50	7.85	8.05	9.92	9.96		
23	$C_6H_5CH{=}CHCH{=}CHCH_2{-}$				200–210 (0.5)		32	$C_{20}H_{26}N_2O$	77.38	77.38	8.44	8.46	9.03	8.72		
24	$C_6H_5CH{=}CHCO{-}$				136–137	B–L	88	$C_{18}H_{22}N_2O_2$	72.45	73.07	7.43	8.25	9.39	9.45		
																
	Ar															
25	C_6H_5				185 (0.3)		77	$C_{18}H_{24}N_2O$					9.85	9.90		
26	*p*-$EtOC_6H_4$				125	E–Et	65	$C_{20}H_{28}N_2O_2 \cdot HCl$					7.67	8.01	9.71	10.48

[a] E = ethanol, Et = ethyl ether, I = isopropyl alcohol, P = petroleum ether, B = benzene, L = ligroin. [b] Br.

TABLE II

No.[a]	M.p. or b.p. (mm.), °C.	Yield, %	Formula ArC(R)=CCH$_2$Cl(R′) II	Cl %, Calcd.	Cl %, Found	
1	90 (0.6)	68	$C_9H_8Cl_2$	37.90	37.69	
2	90 (0.1)	67	$C_9H_8Cl_2$	37.90	38.21	
3	95 (0.6)	80	$C_9H_8Cl_2$	37.90	36.38	
4	105 (0.2)	81	$C_9H_8ClNO_2$	17.94	17.08	
5	78[b]	73	$C_9H_8ClNO_2$	17.94	17.84	
6	58.5–59.5[c]	78	$C_9H_8ClNO_2$[d]	17.94	17.44	
7	90–95 (0.6)	67	$C_{10}H_{11}Cl$[e]	21.27	22.10	
8	100 (0.5)	37	$C_{10}H_{11}ClO$	19.41	21.23	
9	Undist. oil	87	$C_{11}H_{13}ClO$	18.02	19.00	
10	95–100 (0.4)	82	$C_9H_7Cl_3$	48.01	47.81	
11	135 (0.8)	82	$C_9H_7Cl_3$	48.01	47.63	
12	Undist. oil	83	$C_{12}H_{15}BrO_3$	27.83	26.54	(Br)
13	75 (1)	96	$C_{10}H_{11}Cl$	21.27	21.20	
14	75 (0.5)	92	$C_{10}H_{11}Cl$[f]	21.27	22.38	
15	83–85 (0.5)	79	C_9H_8BrCl	15.31	15.08	
16	85 (0.4)	64	C_9H_8BrCl	15.31	15.46	
17	125–130 (0.5)	93	$C_{15}H_{13}Cl$	15.50	15.22	
18	95–100 (0.3)	83	$C_{12}H_{11}Cl$	17.49	18.10	
		Miscellaneous				
19	92–95 (0.5)	72	C_9H_7Br[g]	40.13	40.59	(Br)
20	80 (0.8)	82	$C_{10}H_{11}Cl$	21.27	20.44	
21	105 (0.8)	23	$C_{11}H_{11}Cl$[h]	19.84	19.01	

[a] The compound's numbering system utilized in Table V is used in this table. Specification of Ar, R, and R′ groups are therefore omitted. [b] From petroleum ether. [c] From ether–petroleum ether. [d] G. Cignarella, *Tetrahedron*, **20,** 1057 (1964). [e] H. Martin, *Compt. Rend.*, **232**, 1762 (1950). [f] E. G. E. Hawkins and R. D. Thompson, *J. Chem. Soc.*, 370 (1961). [g] J. von Braun and L. Tauber, *Ann.*, **458,** 105 (1927). [h] See ref. *m*, Table V.

TABLE III

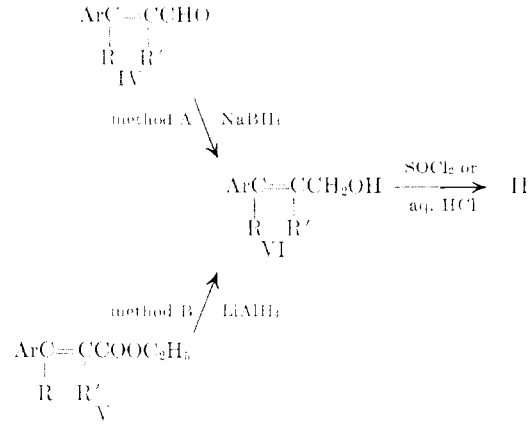
ArCH=CHCHO
IV

Ar	M.p. or b.p. (mm.), °C.	Crystn. solvent	Yield, %
o-ClC_6H_4[a]	60–62	Ether–petr. ether	64
m-ClC_6H_4[b]	40–42	Ether–petr. ether	67
p-ClC_6H_4[c]	63–65	Ether–petr. ether	66
o-$O_2NC_6H_4$[d]	126–128	Ethanol	64
m-$O_2NC_6H_4$[e]	117–119	Ethanol	67
p-$O_2NC_6H_4$[f]	140–143	Ethanol	80
p-$H_3CC_6H_4$[g]	85–90 (0.5)	...	35
o-$H_3COC_6H_4$[h]	128–130 (0.6)	...	40
α-Naphtyl[i]	115–116 (1)	...	38

[a] K. W. Rosemund and F. Zetzsche, *Ber.*, **56,** 1481 (1923). [b] *Anal.* Calcd. for C_9H_7ClO: C, 64.87; H, 4.23; Cl, 21.28. Found: C, 64.60; H, 4.37; Cl, 21.17. [c] H. Straus, *Ann.*, **393,** 311 (1912). [d] W. H. Mills and P. E. Evens, *J. Chem. Soc.*, **117,** 571 (1920). [e] C. F. Goehring, *Ber.*, **18,** 719 (1885). [f] S. G. Waley, *J. Chem. Soc.*, 2008 (1948). [g] M. Scholtz and A. Wiedemann, *Ber.*, **36,** 845 (1903). [h] O. L. Brandy and H. J. Grayson, *J. Chem. Soc.*, **125,** 1418 (1924). [i] S. Israelashirli, Y. H. Gottlieb, M. Imber, and A. Habas, *J. Org. Chem.*, **16,** 1519 (1951).

isomer III, which condensed with the poorly reactive halide.

A majority of the aralkenyl chlorides II (Table II) were unknown in the literature. Their synthesis involved the reduction of the aldehydes IV (Table III) with sodium borohydride (method A), or of the esters V (Table IV) with lithium aluminum hydride at low temperature (method B). The cinnamyl alcohols VI (Table V) thus obtained were eventually converted to II by reaction with thionyl chloride. Since the reaction of VI with thionyl chloride sometimes gave α-arylallyl chlorides as the main products,[3] the synthesis of II was accomplished in these cases by heating VI with concentrated hydrochloric acid.



Compounds IV and V, in which R, R′ = H, were synthesized by general methods involving alkaline condensation of the appropriate arylaldehyde with acetaldehyde and with monoethyl malonate, respectively. α-Bromocinnamaldehyde[4] and α(or β)-substituted ethyl cinnamates[5] were obtained according the procedures described in the literature.

Pharmacology. Analgesic Action and Toxicity (Table VI).—CF 1 mice ,weighing 22–25 g., and 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.[6] In Table II doses are reported which produce an approximate increase in pain threshold of about 80% and which was obtained from extrapolation of dose-response curves.

For each compound, at least three doses were used; animals were observed at half-hour intervals for 180 min. The average duration of analgesic activity was found not to exceed 60 min. for active compounds.

Discussion

The results listed in Table VI reveal that introduction of substituents in the cinnamyl group of **1** generally led to derivatives still possessing analgesic activity. This is especially true for **3**, **5**–**7**, and **14**, whose analgesic potency is comparable with that of **1**. With regard to substitution in the benzene ring, the high activity of the mononitro derivatives (**5**–**7**) and of the *m*-chloro derivative (**3**) is noteworthy. The toxicity of these compounds was lower than that of **1**, with the only exception of **7** which is also the most active compound of the series. However, the activity–toxicity ratio, being in every case higher than that of **1**, limited therapeutic interest in these derivatives.

A moderate activity was also present in the *o*- and *p*-chloro isomers (**2** and **4**), while the other phenyl-substituted compounds are scarsely active or inactive. On the basis of these data monosubstitution of the aroma-

(4) C. F. H. Allen and C. D. Edens, Jr., "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 731.

(5) See footnotes of Table IV.

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

TABLE IV

ArC(R)=C(R′)COOC$_2$H$_5$

V

Ar	R	R′	Formula	M.p. or b.p. (mm.), °C.	Crystn. solvent	Yield, %
p-H$_5$C$_2$OC$_6$H$_4$	H	H	C$_{13}$H$_{16}$O$_3$[a]	126 (0.5) 36–37	Ether–petr. ether	82
2,4-Cl$_2$C$_6$H$_3$	H	H	C$_{11}$H$_{10}$Cl$_2$O$_2$[b]	53–54	Ethanol	78
2,6-Cl$_2$C$_6$H$_3$	H	H	C$_{11}$H$_{10}$Cl$_2$O$_2$[c]	124–126 (0.3) 67–68	Ether–petr. ether	29
3,4,5-(OCH$_3$)$_3$C$_6$H$_2$	H	H	C$_{14}$H$_{18}$O$_5$[d]	68–70	Ethanol	75
C$_6$H$_5$	Br	H	C$_{11}$H$_{11}$BrO$_2$[e]	145–150 (12)	...	90[f]
C$_6$H$_5$	H	CH$_3$	C$_{12}$H$_{14}$O$_2$[g]	130 (8)	...	93[f]
C$_6$H$_5$	CH$_3$	H	C$_{12}$H$_{14}$O$_2$[h]	130 (10)	...	44[f]
C$_6$H$_5$	H	C$_6$H$_5$	C$_{17}$H$_{16}$O$_2$[i]	192 (13)	...	70[f]

[a] R. Stoermer and F. Wodarg, *Ber.*, **61**, 2323 (1928). [b] B. Jones and J. G. Watkinson, *J. Chem. Soc.*, 4064 (1958). [c] *Anal.* Calcd. for C$_{11}$H$_{10}$Cl$_2$O$_2$: C, 53.89; H, 4.11; Cl, 28.93. Found: C, 53.67; H, 4.21; Cl, 29.10. [d] Ref. 8. [e] K. Auwers and E. Schmellenkamp [*Ber.*, **54**, 624 (1921)] report that this is the *trans* form [the synthesis of the corresponding acid is reported by A. Michael and G. M. Browne, *ibid.*, **19**, 1378 (1886)]. [f] By esterification of the corresponding acid. [g] J. B. Cohen and C. E. Whiteley [*J. Chem. Soc.*, **79**, 1305 (1903)] report that this is the *trans* form. [h] H. Rupe and E. Busolt [*Ber.*, **40**, 4537 (1907)] report that this is the *trans* form. [i] J. von Braun and G. Manz [*Ann.*, **468**, 258 (1928)] report that this is the *cis* form [the synthesis of the corresponding acid is reported by R. E. Buckles and K. Bremer, *Org. Syn.*, **33**, 70 (1953)].

tic ring seemed more favorable for the analgesic activity than polysubstitution.

With regard to substitution in the aliphatic chain, γ-substituted derivatives (**14** and **16**) were found more active than the corresponding β-isomers (**13** and **15**). Compound **14** also exhibited, beyond a high analgesic potency, a low toxicity; its favorable activity–toxicity ratio (0.002), comparable to that of **1** (~0.0025), suggested further pharmacological studies, now in progress.

Replacement of the phenyl with the α-naphthyl group (**18**) or with hydrogen (**21**) led to scarcely active compounds; moreover, the 3-allyl derivatives (**21**) did not antagonize nor-**1** or normorphine hydrochloride.[7]

Any variation of the length (**19–20**) or of the unsaturation (**22–23**) of the aliphatic chain markedly decreased the analgesic action, as did the replacement of the cinnamyl with a cinnamoyl group (**24**). Finally, compound **25**, in which the 3- and 8-substituent of **1** are reversed, was about 0.2 as active as **1**, while the *p*-ethoxy analog **26** showed a further decrease in activity. These results agreed with our previous observation[1] about the low analgesic action of 8-substituted 3-propionyl-3,8-diazabicyclo[3.2.1]octanes in comparison with that of the 8-propionyl isomers.

Experimental

Unless otherwise specified, the synthesis of the intermediates listed in Tables II–V was accomplished according the general methods described below. Therefore, references to Tables II–V do not necessarily indicate that the known compounds were prepared according to the literature method.

Cinnamaldehydes IV (R, R′ = H) (Table III). General Method.—To 150 g. of freshly distilled acetaldehyde, 0.3 mole of the appropriate arylaldehyde was added with stirring, in small portions, keeping the temperature under 15°. At the end of the addition, 8 ml. of 25% methanolic KOH was dropped into the reaction mixture at 5°, at such a rate that the inner temperature did not exceed 30°. The resulting solution was cooled at 0°, 150 ml. of acetic anhydride was added, and the whole was heated 20 min. at 100° by an oil bath kept at 120°. After cooling at 30°, 460 ml. of water and 40 ml. of concentrated HCl was added, the mixture was refluxed 30 min., then allowed to stand overnight at room temperature. The resulting IV was filtered or extracted with ether and was purified by crystallization or distillation.

α-Bromocinnamaldehyde was prepared according to a literature procedure[4] which involves addition of bromine to the double bond of the cinnamaldehyde, followed by dehydrohalogenation with K_2CO_3.

Unsubstituted Ethyl Cinnamates V (R, R′ = H) (Table IV). General Method.—The following procedure is based on that reported by Freudenberg and Schraube.[8] To a solution of 0.1 mole of arylaldehyde and 0.2 mole of ethyl hydrogen malonate in 70 ml. of anhydrous pyridine, 2 ml. of piperidine was added, the stirred mixture was heated 4–5 hr. on a steam bath and 0.5 hr. at reflux temperature until CO_2 evolution ceased (for the synthesis of ethyl 3,4,5-trimethoxycinnamate, better results were obtained by allowing the reaction mixture to stand 5 days at room temperature). After cooling, the mixture was poured into ice–water, the whole was acidified with HCl, and the separated oil was extracted with ether. The organic layer was washed with 10% $NaHCO_3$ and with water then was dried (Na_2SO_4), and the solvent was evaporated to give crude V which was purified by distillation or crystallization.

α(or β)-Substituted Ethyl Cinnamates V (R, R′ = H, Br, CH$_3$, or C$_6$H$_5$) (Table IV).—These compounds were prepared according the methods described in the literature. References are reported at the foot of Table IV.

Cinnamyl Alcohols VI (Table V). Method A.—To a solution of 0.1 mole of the appropriate aldehyde IV in 500 ml. of ethanol heated at 50°, a solution of 0.033 mole of sodium borohydride in 50 ml. of ethanol was added, the reaction mixture was stirred for 3 hr. at room temperature, then acidified to congo red with dilute HCl, the impurities were filtered off, and the alcoholic filtrate was evaporated *in vacuo*. The residue was treated with 50 ml. of water and the insoluble material was extracted with ether. The extract was decolorized with charcoal and dried, the solvent was evaporated, and the crude VI was purified by crystallization or distillation.

Method B.—To a suspension cooled to −20° of 0.11 mole of $LiAlH_4$ in 400 ml. of anhydrous ether, a solution of 0.1 mole of the appropriate ester V in 100 ml. of anhydrous ether was added dropwise with stirring. At the end of the addition, the reaction mixture was stirred for 0.5 hr. at −20°, then for 6 hr. without cooling, and was eventually decomposed at −20° with 20 ml. of water. To the mixture, 200 ml. of 10% H_2SO_4 was added, the organic layer was separated, and the aqueous acid solution was extracted with 100 ml. of ether. The extracts were collected and dried, and the solvent was evaporated to give crude VI which was purified by distillation or crystallization.

Cinnamyl Chlorides II (Table II).—With the exception of derivatives **2** and **4–6**, the chlorides II were prepared by adding

(7) G. Maffii, private communication.

(8) K. Freudenberg and H. Schraube, *Ber.*, **88**, 16 (1955).

TABLE V

No.	Ar	R	R′	Method	B.p. (mm.) or m.p., °C. from ether–petr. ether	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Other elements, % Calcd.	Other elements, % Found
					$ArC(R)=CCH_2OH$ (R′) VI								
1	*o*-ClC_6H_4	H	H	A	105–107 (0.5)	82	C_9H_9ClO	64.10	64.22	5.38	5.33	21.02	21.10 (Cl)
2	*m*-ClC_6H_4	H	H	A	125–130 (0.4)	63	C_9H_9ClO	64.10	64.04	5.38	5.28	21.02	21.33 (Cl)
3	*p*-ClC_6H_4	H	H	A	110 (0.4)	77	C_9H_9ClO[a]	64.10	64.31	5.38	5.26	21.02	20.93 (Cl)
4	*o*-$O_2NC_6H_4$	H	H	A	62–63	42	$C_9H_9NO_3$	60.32	60.20	5.06	5.27	7.81	7.58 (N)
5	*m*-$O_2NC_6H_4$	H	H	A	49–50	59	$C_9H_9NO_3$[b]	60.32	60.02	5.06	5.55	7.81	7.54 (N)
6	*p*-$O_2NC_6H_4$	H	H	A	128–129	86	$C_9H_9NO_3$[c]	60.32	60.32	5.06	5.21	7.81	7.94 (N)
7	*p*-MeC_6H_4	H	H	A	51	50	$C_{10}H_{12}O$[d]	81.04	81.13	8.16	8.36	...	...
8	*o*-$MeOC_6H_4$	H	H	A	95–100 (0.4)	44	$C_{10}H_{12}O_2$	73.14	72.89	7.36	7.58	...	...
9	*p*-$EtOC_6H_4$	H	H	B	90–91	79	$C_{11}H_{14}O_2$	74.13	74.80	7.92	7.90	...	...
10	2,4-$Cl_2C_6H_3$	H	H	B	130 (0.7)	30	$C_9H_8Cl_2O$	53.22	53.05	3.97	4.15	34.92	34.68 (Cl)
11	2,6-$Cl_2C_6H_3$	H	H	B	130 (0.8)	69	$C_9H_8Cl_2O$	53.22	53.24	3.97	4.29	34.92	34.80 (Cl)
12	3,4,5-$C_6H_2(MeO)_3$	H	H	B	145 (0.2)	65	$C_{12}H_{16}O_4$[e]	64.26	64.40	7.19	7.45	...	...
13	C_6H_5	H	CH_3	B	85–88 (0.6)	92	$C_{10}H_{12}O$[f]	81.04	81.22	8.16	8.84	...	...
14	C_6H_5	CH_3	H	B	90–95 (0.2)	91	$C_{10}H_{12}O$[g]	81.04	81.30	8.16	8.34	...	...
15	C_6H_5	H	Br	B	125 (0.6)	85	C_9H_8BrO[h]	50.72	51.18	4.25	4.65	37.50	37.01 (Br)
16	C_6H_5	Br	H	A	90–92 (0.5)	40	C_9H_9BrO	50.72	51.05	4.25	4.40	37.50	36.60 (Br)
17	C_6H_5	H	C_6H_5	B	67–69	78	$C_{15}H_{14}O$[i]	85.68	85.84	6.71	7.02	...	...
18	α-Naph(yl	H	H	A	125 (0.9)	46	$C_{13}H_{12}O$	84.75	84.59	6.57	6.65	...	...
					Miscellaneous								
	Compd.												
19	$C_6H_5C{\equiv}CCH_2OH$			B	100–105 (1)	50	C_9H_8O[j]	81.79	81.68	6.10	6.25	...	...
20	$C_6H_5CH{=}CHCH_2CH_2OH$			B	100–105 (1)	73	$C_{10}H_{12}O$	81.04	80.07	8.16	8.17	...	...
21	$C_6H_5CH{=}CHCH{=}CHCH_2OH$				130–135 (3)	50	$C_{11}H_{12}O$[k]	82.46	82.06	7.55	7.68	...	...

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TABLE VI

ANALGESIC ACTIVITY OF 3,8-DIAZABICYCLO[3.2.1]OCTANES IN THE RAT AND ACUTE TOXICITY IN THE MOUSE

No.[a]	Approx. equieffective dose (rat), mg./kg. i.p.	Approx. LD_{50} (mouse), mg./kg. i.p.
1	0.2	73
2	1.5	200
3	0.7	200
4	3	200
5	0.7	200
6	0.5	100
7	0.3	25
8	6	300
9	$\gg 5$	200
10	7.5	200
11	4	200
12	$\gg 25$	500
13	>1	100
14	0.4	200
15	7	500
16	3	500
17	10	150
18	>10	500
19	$\gg 25$	100
20	2	50
21	50	300
22	2	80
23	3	200
24	$\gg 25$	500
25	1	100
26	7.5	200

[a] Numbers from Table I.

a 100% excess of thionyl chloride to a solution of VI in chloroform, and allowing the reaction mixture to stand for 1 hr. at room temperature and for 3–4 hr. at 50–60°. Removal of the solvent and of excess of thionyl chloride *in vacuo* and distillation of the residue gave pure II, the structure of which was established by the ultraviolet spectra which exhibited the characteristic absorption of aryl-conjugated double bonds.

For the synthesis of compounds **2** and **4–6**, the reaction of the corresponding VI with thionyl chloride led to the α-arylallyl chlorides as main product. Therefore, the following procedure was employed to obtain the desired derivatives.

A mixture of 0.1 mole of the appropriate cinnamyl alcohol (VI, **2**, **4–6**) and 150 ml. of concentrated HCl was stirred for 3 hr. at 70–80°, then the dark suspension was cooled and extracted with ether, and the extract was washed with ice–water, decolorized with charcoal, and dried (Na_2SO_4). After evaporation of the solvent, the crude II was distilled (**2** and **4**) or crystallized (**5** and **6**).

3-Aralkenyl-8-propionyl-3,8-diazabicyclo[3.2.1]octanes (Table I, 2–18, 20, 22, and 23) were prepared according the general method described in the preceding paper[1] which involves condensation in refluxing acetone of I (1 mole) with the required halide (1 mole) in the presence of equimolar amounts of anhydrous K_2CO_3. In the case of **20** the reaction was accomplished by refluxing in benzene a mixture of halide (1 mole) and I (2 mole) for 15 hr.

This general method was also employed to obtain **21** and **24** starting from allyl bromide and cinnamoyl chloride, respectively.

The structure of each compound was confirmed through the infrared spectrum (the lack of the band near 1240 cm.$^{-1}$, characteristic of 3-propionyl-3,8-diazabicyclo[3.2.1]octane, excluded any $N_8 \rightarrow N_3$ acyl migration[3] in the course of the synthesis) and the ultraviolet spectrum (characteristic absorption of aryl-conjugated double bonds).

3-Styryl-8-propionyl-3,8-diazabicyclo[3.2.1]octane (Table I, 19).—A mixture of I (5.04 g., 0.03 mole) and phenylacetaldehyde (1.8 g., 0.015 mole) was heated at 120° for 3 hr., and the residue was fractionally distilled by the Ronco technique[9] collecting 2.7 g. (67.5%) of the desired compound, b.p. 205° (0.8 mm.), which on standing solidified and was crystallized from ether. The product was unstable in an acidic medium.

3-Propionyl-8-aralkenyl-3,8-diazabicyclo[3.2.1]octanes (Table I, 25 and 26) were prepared from 3-propionyl-3,8-diazabicyclo-[3.2.1]octane[3] and the required halide, according the procedure described for the 8-propionyl derivatives (see above); the reflux period was 6 hr. for **25** and 24 hr. for **26**. The infrared spectra of **25** and **26** showed a strong band near 1240 cm.$^{-1}$, characteristic of 3-acyl-3,8-diazabicyclooctanes.[3]

Condensation of I with *p*-Ethoxycinnamyl Chloride (26).—A solution of 3.36 g. (0.02 mole) of I and 1.96 g. (0.01 mole) of *p*-ethoxycinnamyl chloride in 30 ml. of benzene was refluxed for 20 hr. After cooling, the reaction mixture was diluted with 50 ml. of ether, and the viscous oil that separated was dissolved by adding 20 ml. of water. The organic layer (a) was separated and the aqueous solution was cooled to 0°, covered with 50 ml. of ether, and made basic with 50% NaOH. The ether extract was dried (Na_2SO_4), and the solvent was evaporated to give 1.5 g. of crude 3-propionyl-3,8-diazabicyclo[3.2.1]octane which was identified by infrared spectral comparison with an authentic sample. The organic layer (a) was extracted twice with 10 ml. of 10% HCl, the acid solution was made alkaline with 50% NaOH, and the oil was extracted with ether. The extract was dried, then was treated with dry HCl, and the precipitated hydrochloride was crystallized from ethanol–ether to give 1.5 g. of a product, m.p. 125°, identical (mixture melting point and infrared spectral comparison) with the sample prepared by condensing III with *p*-ethoxycinnamyl chloride.

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