present (1), moderate (2), and marked (3) for each mouse. All three mice showing maximum effect for the seven parameters at all three time intervals would have led to a total score of $3 \times 7 \times 3$ or 63. In each assay, animals treated with (a) saline followed by dopa and (b) drug followed by saline served as controls. Although the injection of 200 mg/kg of dopa was occasionally followed by some stimulation, yielding a score of 10 for a group of three mice in a single reading, the 100-mg/kg dose rarely caused stimulation. In a series of 18 consecutive control runs of saline followed by 100 mg/kg of dopa, the mean cumulative score for the three readings of three mice was 9.4 with a standard deviation of 4.6. In our drug experiments, a score of 30 was considered as evidence of unequivocal dopa potentiation. The dose of test compound causing this score, determined by interpolation, was called the effective dose. The negative logarithm of this dose in moles per kilogram was defined as a pD_{dopa}.

In Vitro **Enzyme Assay.**—Inhibition of the oxidation of kynuramine by isolated mitochondria from rat liver was determined by the method of Weissbach, *et al.*,[3] in a Gilford multiple-sample absorbance recorder as described by Fuller and Walters.[4] The negative logarithm of the molar concentration producing 50% inhibition (pI_{50}) was calculated.

Compounds.—Pheniprazine[5a] was obtained from Lakeside Laboratories, tranylcypromine[5b] from Smith Kline and French Laboratories, and pargyline[5b] from Abbott Laboratories. Other compounds were synthesized in the Lilly Research Laboratories,[6] and their chemical structures were verified by physicochemical methods. The compounds were used as soluble salts, either hydrochlorides or hydrobromides.

Acknowledgments.—We wish to thank for their help in chemical synthesis, Wilma E. McCarthy, W. Pfeiffer, and R. Simon; MAO assays, Emily Rosing; and dopa potentiation, C. E. Keller and H. Snoddy.

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Synthesis and Pharmacological Properties of N-Derivatives of 5,6-Dihydro-7H,12H-dibenz[*c*,*f*]azocine, a New Tricyclic System

Silvano Casadio, Gianfranco Pala, Elda Crescenzi, Ernesta Marazzi-Uberti, Germano Coppi, and Carla Turba

Research Laboratories of Istituto De Angeli S.p.A., Milan, Italy

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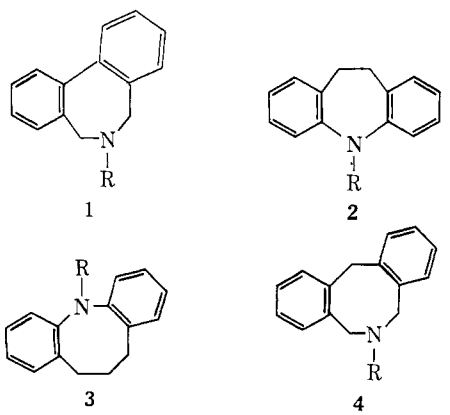
Several N-derivatives of 5,6-dihydro-7H,12H-dibenz[*c*,*f*]azocine were synthesized for extensive pharmacological screening. The test for antagonism of reserpine effects was negative for the whole series, whereas nearly all of the substances proved to possess interesting depressant properties. This effect was more pronounced for the N-aminopropyl derivatives. A number of the compounds displayed marked peripheral vasodilator and hypotensive action, particularly noteworthy for the N-alkyl derivatives (maximum potency with a C_2–C_3 chain). The series showed other numerous activities, among which the antitussive and anthelmintic actions seemed to be highly promising.

We have recently synthesized 5,6-dihydro-7H,12H-dibenz[*c*,*f*]azocine, a new tricyclic system.[1] This, together with the interesting pharmacological properties well known for the structurally similar N-substituted 6,7-dihydro-5H-dibenz[*c*,*e*]azepines (**1**),[2] 10,11-dihydro-5H-dibenz[*b*,*f*]azepines (**2**),[3] and 5,10,11,12-tetrahydrodibenz[*b*,*g*]azocines (**3**),[4] has led us to synthesize and pharmacologically screen several 5,6-dihydro-7H,12H-dibenz[*c*,*f*]azocines variously substituted on the nitrogen atom (**4**).



Alkyl, hydroxyalkyl, aralkyl, and terpenyl derivatives were prepared by reaction (in a suitable solvent) of 2,2′-bis(bromomethyl)diphenylmethane with the proper amine (methods A, B, and C). Chloroalkyl derivatives were obtained by reaction of thionyl chloride with corresponding hydroxyalkyl compounds (method D), while aminoalkyl derivatives were synthesized by making the above chloroalkyl compounds react with the proper amines (method E). As shown in Table I, the great majority of the new substances were obtained in good yields.

Pharmacological screening included studies of acute toxicity, behavioral effects, action on the central nervous system and on arterial pressure, and analgetic, antiinflammatory, antireserpine, diuretic, antitussive, hypoglycemic, antispasmodic, local anesthetic, peripheral vasodilator, anthelmintic, antibacterial, and antifungal actions.

Experimental Section[5]

Chemistry. Intermediates.—4-Chlorobenzhydrylamine was prepared according to Najer, *et al.*[6] 1-Methyl-3-aminomethyl-

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(2) L. O. Randall and T. H. Smith, *J. Pharmacol. Exptl. Therap.*, **103**, 10 (1951).

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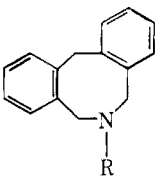
TABLE I

N-SUBSTITUTED 5,6-DIHYDRO-7H,12H-DIBENZ[*c,f*]AZOCINES



Compd	R	Method	Yield, %	Mp, °C	Crystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
I	*p*-[$(CH_3)_3C$]$C_6H_4CH_2$	A	62[b]	108–109	E	$C_{28}H_{29}N$	87.84	8.22	3.94	87.58	8.21	3.93
II	(*p*-ClC$_6$H$_4$)(C_6H_5)CH	A	52[b]	162–164	E	$C_{28}H_{24}ClN$	82.03	5.90	3.42	81.94	5.83	3.42
III	CH_3	B	80[c]	95	D	$C_{16}H_{17}N$	86.05	7.67	6.27	86.25	7.61	6.20
				132.5–134	A	·$C_4H_4O_4$[d]	70.78	6.24	4.13	71.11	6.31	4.18
IV	C_2H_5	B	74[c]	76–77	D	$C_{17}H_{19}N$	86.03	8.07	5.90	85.87	7.91	5.88
				185–185.5	B	·$C_4H_4O_4$[d]	71.37	6.56	3.96	71.00	6.50	3.91
V	*n*-C_3H_7	B	54[b]	88.5–89.5	D	$C_{18}H_{21}N$	86.01	8.42	5.57	86.61	8.53	5.61
				240–240.5 dec	P	·HBr	65.10	6.68	4.22	64.8	6.61	4.23
VI	*i*-C_3H_7	B	86[c]	32.5–35		$C_{18}H_{21}N$	86.01	8.42	5.57	86.31	8.38	5.66
				212.5–214	M	·$C_4H_4O_4$[d]	71.91	6.86	3.81	71.50	6.81	3.78
VII	CH_2=$CHCH_2$	B	50[b]	109–110.5	D	$C_{18}H_{19}N$	86.70	7.68	5.62	86.70	7.71	5.59
				216.5–219 dec	P	·HBr	65.50	6.11	4.21	65.45	6.10	4.21
VIII	*n*-C_4H_9	B	58[b]	209–211 dec	P	$C_{19}H_{23}N$·HBr	65.90	6.99	4.04	65.31	6.85	4.13
IX	$HO(CH_2)_2$	C	67[b]	140–142	D	$C_{17}H_{19}NO$	80.57	7.56	5.53	80.61	7.66	5.61
				231–232 dec	B	·HBr	61.07	6.03	4.19	61.24	6.00	4.17
X	$HO(CH_2)_3$	C	78[c]	148–149.5	D	$C_{18}H_{21}NO$	80.86	7.92	5.24	80.88	7.88	5.36
				206.5–209.5 dec	E	·HBr	62.06	6.37	4.02	61.90	6.21	4.13
XI	$CH_3CH(OH)CH_2$	C	74[c]	138–139	D	$C_{18}H_{21}NO$	80.86	7.92	5.24	80.51	7.90	5.20
				174.5–176	E	·$C_4H_4O_4$[d]	68.91	6.57	3.65	68.87	6.55	3.71
XII	$Cl(CH_2)_2$	D	80[c]	240–243.5 dec	B	$C_{17}H_{18}ClN$·HCl	66.25	6.21	4.54	66.33	6.16	4.53
XIII	$Cl(CH_2)_3$	D	88[c]	222–225 dec	P	$C_{18}H_{20}ClN$·HCl	67.10	6.57	4.34	67.30	6.61	4.30
XIV	$CH_3CH(Cl)CH_2$	D	93[c]	226–229.5 dec	B	$C_{18}H_{20}ClN$·HCl	67.10	6.57	4.34	67.00	6.61	4.31
XV	*e*	B	51[b]	182–183.5	B	$C_{22}H_{28}N_2$·($C_4H_4O_4$)$_2$[d]	65.20	6.57	5.07	65.44	6.69	5.07
XVI	*f*	B	78[c]	139.5–140.5	P	$C_{23}H_{30}N_2$·($C_4H_4O_4$)$_2$[d]	65.71	6.76	4.94	65.55	6.67	4.90
XVII	$(C_2H_5)_2N(CH_2)_2$	E	78[c]	46.5–49		$C_{21}H_{28}N_2$	81.77	9.15	9.08	81.47	9.18	9.08
				157.5–158.5	B	·($C_4H_4O_4$)$_2$[d]	70.72	7.60	6.60	70.41	7.57	6.56
XVIII	*g*	E[h]	78[c]	77–77.5		$C_{21}H_{26}N_2$	82.31	8.55	9.14	82.30	8.51	9.11
				184–185	B	·$C_4H_4O_4$	71.06	7.16	6.63	71.04	7.11	6.59
XIX	$(CH_3)_2N(CH_2)_3$	E	84[c]	43–44		$C_{20}H_{26}N_2$	81.58	8.90	9.52	81.62	8.87	9.50
				178–179.5	E	·($C_4H_4O_4$)$_2$[d]	63.86	6.51	5.32	64.10	6.61	5.38
XX	$CH_3CH[N(CH_3)_2]CH_2$	E	90[c]	64–66.5		$C_{20}H_{26}N_2$	81.58	8.90	9.52	81.80	8.90	9.48
				160–160.5	P	·$C_4H_4O_4$[d]	70.22	7.37	6.82	70.88	7.19	6.78
XXI	$CH_3NH(CH_2)_3$	E	64[c]	61–62.5		$C_{18}H_{24}N_2$	81.38	8.63	9.99	81.16	8.57	10.10
				150–151.5	P	·($C_4H_4O_4$)$_2$[d]	63.27	6.29	5.47	63.42	6.33	5.51
XXII	*i*	E[h]	67[c]	52–54	D	$C_{28}H_{31}N_3$	79.04	8.94	12.02	79.01	8.95	12.00
				175–177.5 dec	B	·($C_4H_4O_4$)$_3$[d]	60.27	6.22	6.03	60.27	6.19	6.08
XXIII	*j*	E[h]	48[c]	75–76	*k*	$C_{24}N_{30}N_2O$	75.95	8.76	11.07	76.50	8.91	11.27
				165–166	B	·($C_4H_4O_4$)$_3$[d]	59.40	6.23	5.78	59.63	6.26	5.81
XXIV	*l*	A[m]	48[c]	132–133	B	$C_{25}H_{35}N$	87.41	8.51	4.08	87.62	8.50	4.08
XXV	*n*	A[m]	80[c]	*o*		$C_{25}H_{35}N$	86.90	9.04	4.05	86.51	9.00	4.16

[a] A = EtOAc, B = anhydrous EtOH, D = dilute EtOH, E = 95% EtOH, M = MeOH, P = *i*-PrOH. [b] Crystallized product. [c] Crude product. [d] Maleate. [e] 1-Methyl-3-piperidylmethyl. [f] 2-(1-Methyl-2-piperidyl)ethyl. [g] 2-Pyrrolidinoethyl. [h] XII and amine in a 1:5 molar ratio. [i] 3-(4-Methyl-1-piperazino)propyl. [j] 3-[4-(2-Hydroxyethyl)-1-piperazino]propyl. [k] Triturated with hexane. [l] 1-Adamantyl. [m] 2,2′-Bis(bromomethyl)diphenylmethane–adamantyl-1-amine–triethylamine in a 1:1:3 molar ratio. [n] Geranyl. [o] Very viscous oil.

piperidine was synthesized according to Sugasawa and Deguchi.[7] 1-(2-Hydroxyethyl)piperazine was obtained according to Hromatka and Engel,[8] geranylamine according to Kharasch, *et al.*,[9] and adamantyl-1-amine according to Stetter, *et al.*[10]

1-Methyl-2-(aminoethyl)piperidine.—A mixture of potassium phthalimide (51 g, 0.3 mole) and 2-(1-methyl-2-piperidyl)-1-chloroethane[11] (31 g, 0.2 mole) was heated for 45 min at 170–190° (stirring from time to time). The mixture was cooled to room temperature and extracted a few times with H_2O. The solid was filtered, dried, and recrystallized from Et_2O to give the desired phthalimido derivative (35 g). This was treated with 85% $NH_2NH_2 \cdot H_2O$ (8 ml) and EtOH (135 ml); the mixture was refluxed for 2 hr. Finally, the solution was acidified with concentrated HCl and diluted with EtOH (240 ml). The precipitated phthalhydrazide was filtered, and the acid solution was concentrated to a small volume under reduced pressure. The residue was dissolved in H_2O, decolorized with charcoal, and made strongly alkaline with 50% NaOH; the separated oil was extracted with Et_2O. The extract was dried (K_2CO_3), the solvent was evaporated, and the residue was distilled to give a colorless liquid, 14 g, bp 94–95° (15 mm).

Anal. Calcd for $C_7H_{18}N_2$: C, 67.55; H, 12.76; N, 19.70. Found: C, 67.58; H, 12.80; N, 19.61.

N-Substituted 5,6-dihydro-7H,12H-dibenz[*c,f*]azocines are listed in Table I, and their preparation is illustrated by the following methods.

Method A. 5,6-Dihydro-7H,12H-6-(*p-t*-butylbenzyl)dibenz[*c,f*]azocine (I).—*p-t*-Butylbenzylamine (6.4 g, 0.4 mole) in anhydrous C_6H_6 (25 ml) was dropped, at room temperature, into a solution of 2,2′-bis(bromomethyl)diphenylmethane[12] (4.34 g, 0.012 mole) in anhydrous C_6H_6 (25 ml). The solution was refluxed for 3 hr with stirring, cooled to room temperature, and filtered to remove *p-t*-butylbenzylamine hydrobromide. The C_6H_6 solution was washed with H_2O, dried (Na_2SO_4), and evaporated to dryness to yield a pasty residue which, on crystallization from EtOH, gave colorless crystals, mp 108–109°.

Method B. 5,6-Dihydro-7H,12H-6-methyldibenz[*c,f*]azocine (III).—A 33% ethanolic solution of $MeNH_2$ (28 ml, 0.3 mole) was added at room temperature to a suspension of 2,2′-bis(bromomethyl)diphenylmethane (30 g, 0.09 mole) in 1-hexanol (150 ml). The mixture was stirred for 4 hr at room temperature, slowly

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heated to boiling, and refluxed for 15 hr. The suspension was concentrated to a small volume under reduced pressure; the residue was dissolved in H_2O and made slightly acid by HBr, so that a complete solution was obtained. The acid solution was washed with Et_2O, then made alkaline with 10% NaOH. The precipitated solid was filtered, dried, and crystallized from dilute EtOH to give colorless crystals, mp 93°.

Method C. 5,6-Dihydro-7H,12H-6-(2-hydroxypropyl)dibenz[c,f]azocine (XI).—1-Amino-2-hydroxypropane (68 g, 0.9 mole) in anhydrous EtOH (200 ml) was added to a solution of 2,2′-bis(bromomethyl)diphenylmethane (100 g, 0.3 mole) in anhydrous EtOH (1100 ml). The solution was refluxed for 10 hr with stirring, cooled to room temperature, acidified with 48% HBr, and concentrated to a small volume under reduced pressure. The separated XI hydrobromide was filtered and dissolved in H_2O, and the aqueous solution was filtered (charcoal) and made alkaline with 10% NaOH. The precipitated solid was filtered, dried, and crystallized from dilute EtOH to give colorless crystals, mp 138–139°.

Method D. 5,6-Dihydro-7H,12H-6-(2-chloropropyl)dibenz[c,f]azocine Hydrochloride (XIV).—$SOCl_2$ (28.1 g, 0.24 mole) was dropped (at room temperature) into a solution of XI (21.3 g, 0.08 mole) in anhydrous C_6H_6 (100 ml); the suspension was refluxed for 5 hr. Excess $SOCl_2$ was removed on distilling under reduced pressure, with the simultaneous addition of fresh C_6H_6. The suspension was then cooled to room temperature, and the solid was filtered, dried, and crystallized from anhydrous EtOH to give colorless crystals, mp 226–229.5° dec.

Method E. 5,6-Dihydro-7H,12H-6-(2-dimethylaminopropyl)dibenz[c,f]azocine (XX).—A 33% ethanolic solution of Me_2NH (180 ml, 1.3 moles) was added at room temperature to a suspension of XIV (20.9 g, 0.07 mole) in 1-hexanol (350 ml). After addition, the clear solution was refluxed for 20 hr, then concentrated to a small volume under reduced pressure. The pasty residue was taken up with Et_2O and 10% HCl; the two layers were shaken, and the acid solution was filtered (charcoal) and made alkaline with 10% NaOH. The precipitated oil was extracted with $CHCl_3$, and the extract was washed with H_2O until neutral. After drying (Na_2SO_4), removal of the solvent yielded XX as a waxy solid, which was characterized as the **maleate** (from *i*-PrOH), mp 160–160.5°.

Pharmacology.—The acute toxicity, behavioral effects, and analgetic, antiinflammatory, antispasmodic, diuretic, antitussive, hypoglycemic, antibacterial, and antifungal activities were investigated by the techniques previously described.[13,14] The action on spontaneous motility was studied in mice by the test of Dews,[15] while the activity on hypothermia by reserpine was tested in rats as described by Garattini, *et al.*[16] The local anesthetic action was studied in guinea pigs by the corneal method of Chance and Lobstein.[17] The action on isolated vessels was measured on the hind part of rats according to Burn,[18] and the action on arterial pressure was determined in urethan-narcotized rabbits. Pressure was recorded at the carotid by a mercury manometer using a 1% heparinized sodium citrate solution as anticoagulant. The *in vivo* antihistaminic action was studied in guinea pigs by aerosol of histamine according to Herxheimer,[19] and the anthelmintic action was investigated in mice using the method described by Roth, *et al.*[20]

The highest dosage level which did not provoke an obvious toxic symptomatology in experimental animals was used for each test. Meprobamate, phenylbutazone, cocaine, atropine, diphenhydramine, hexamethonium, chlorpromazine, hydrochlorothiazide, α-isopropyl-α-(2-dimethylaminopropyl)phenylacetonitrile citrate (peracon), azapetine, chlorpropamide, and piperazine were used as standards for comparison of the action on spontaneous motility and of the analgetic, antiinflammatory, local anesthetic, antispasmodic, antihistaminic, diuretic, antitussive, hypotensive, peripheral vasodilator, hypoglycemic, and anthelmintic activities.

Results and Discussion

The great majority of the compounds showed CNS depression which appeared as a decrease of the spontaneous motility, more pronounced than that provoked by meprobamate, and as motor incoordination and decrease of body muscle tonus. Table II gives the most interesting results of the pharmacological screening. As for the hot plate analgetic test, most of the compounds markedly increased the pain threshold of mice, especially IV (N-ethyl), VI (N-isopropyl), XV (N-1-methyl-3-piperidylmethyl), XVI [N-2-(1-methyl-2-piperidyl)ethyl], and XIX (N-3-dimethylaminopropyl), and the activity of these was also superior to that of phenylbutazone. Regarding local anesthetic action, VI, XVI, XX (N-2-dimethylaminopropyl), and XXI (N-3-methylaminopropyl) were found to be of some interest. The whole series showed a significant antispasmodic activity *in vitro*, which was particularly noteworthy against spasm produced by histamine. In addition, compounds II (N-4-chlorobenzhydryl), III (N-methyl), V (N-propyl), and XXVI (R = H) displayed a marked antihistaminic action *in vivo*. Nearly all of the substances were found to inhibit formalin-induced edema more markedly than phenylbutazone. In addition to the tests mentioned in Table II, the compounds have been screened for antireserpine (rats), diuretic (rats), antitussive (guinea pigs), hypotensive (rabbits), and anthelmintic (mice) activities and for vasodilator (rat, hind paw), hypoglycemic (rats), antibacterial, and antifungal action. The results obtained have not been reported in the table since only a few of the compounds tested did show some effect. The *in vivo* antireserpine activity was negligible for all the substances. Some of the compounds produced increases in water excretion on oral administration. Of the substances tested for the antitussive activity, VI, VII (N-allyl), IX (N-2-hydroxyethyl), XIX, and XXIII (R = 3-[4-(2-hydroxyethyl)-1-piperazino]propyl) inhibited the experimental cough more than peracon. Compounds V, VIII (N-butyl), XII (N-2-chloroethyl), and XIX caused a fall of the arterial pressure. The *in vivo* anthelmintic action of XII and XXVI was close to that of piperazine. A number of the compounds displayed a peripheral vasodilator action, and this effect was pronounced for V and XII, and superior to that of azapetine. None of the substances showed hypoglycemic, antibacterial, and antifungal actions worthy of note. Due to scarce availability, XIII (N-3-chloropropyl) and XIV (N-2-chloropropyl) were not screened.

From the point of view of the general pharmacological picture, N-aminoalkyl derivatives of 5,6-dihydro-7H,12H-dibenz[c,f]azocine exert a general depressant action, in contrast to the antidepressant properties possessed by corresponding derivatives of 10,11-dihydro-5H-dibenz[b,f]azepine. The depressant activity seemed to be more pronounced for N-aminopropyl compounds, as was very often found for structurally similar sub-

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TABLE II

PHARMACOLOGICAL SCREENING RESULTS

Compd	LD_{50}[a] (mouse), mg/kg ip	Act on spontaneous motility (mouse) Decrease, %[b]	mg/kg ip	Analgetic act. (mouse) Increase of reaction time, %[c]	mg/kg ip	Surface local anesthetic act. (guinea pig), %[d]	Antispasmodic act. *in vitro*[e] —% inhib of spasm produced by— Acetylcholine 1×10^{-7} g/ml	Histamine 1×10^{-6} g/ml	Nicotine 2×10^{-8} g/ml	5-HT 1×10^{-6} g/ml	Antihistaminic act. *in vivo*[f] (guinea pig) Protection, %	mg/kg ip	Antiinflammatory act. (rat) Inhib of edema,[g] %	mg/kg ip
I	≃400[h]										Inactive	800	24	800
II	>1600[h]						Inactive	96	74	63	100	800	20	800
III	195[a]	92	100	Inactive	100	28	Inactive	93	85	72	100	100	24	100
IV	236[a]	71	100	74	100	47	27	97	25	18	Inactive	100	42	100
V	251[a]	79	100	44	100	29	17	100	Inactive	100	100	100	51	100
VI	560[a]	70	200	87	200	62	26	22	52	14			42	200
VII	645[a]	83	100	38	100	33	Inactive	46	36	26	67	100	60	100
VIII	100-150[a]	82	50	Inactive	50	11	28	53	Inactive	95	Inactive	50	75	50
IX	520[a]	50	100	48	100	11	25	94	24	36	Inactive	100	18	100
X	280–320[h]	66	100	57	100	38	31	100	31	33	Inactive	100	26	100
XI	275-325[h]	59	100	47	100	Inactive	Inactive	68	41	22	Inactive	100	26	100
XII	39[a]	53	10	27	10	15	54	99	45	19	33	10	18	10
XV	180–220[h]	82	100	79	100	38	18	69	70	100	67	100	21	100
XVI	150-180[h]	74	100	74	100	67	14	40	37	55	67	100	31	100
XVII	194[a]	64	50	32	50	32	29	44	47	34			35	100
XVIII	135–160[h]	67	25	Inactive	25	46	34	100	47	76	33	25	16	25
XIX	295–340[h]	81	100	94	100	Inactive	23	64	44	31	Inactive	50	50	100
XX	159[a]	28	50	55	50	59	Inactive	51	44	100	Inactive	50	36	100
XXI	294[a]	75	100	46	100	51	Inactive	53	16	43	33	100	46	200
XXII	385–420[h]	82	200	53	200	Inactive	26	Inactive	43	30			31	200
XXIII	505–590[h]	85	200	54	200	29	Inactive	100	46	52	33	200	47	200
XXIV	>1600[h]										67	800	20	800
XXV	270–350[h]						25	60	43	28	Inactive	50		
XXVI[i]	145–170[h]						16	94	52	46	100	100	Inactive	100
XXVII[j]	>1600[h]										67	800	21	800
Meprobamate		50	200											
Phenylbutazone				61	100								18	100
Diphenhydramine·HCl											100	25		

[a] Calculated according to Litchfield and Wilcoxon.[21] [b] Values referred to controls, 15 min after treatment. [c] Hot plate test, 1 hr after treatment. [d] All the compounds were tested at a concentration of 1 mg/ml. The ED_{50} value for the standard cocaine hydrochloride is 0.70 mg/ml. [e] All the compounds were tested at a concentration of 1 γ/ml. The ED_{50} values for the standards are atropine sulfate (antiacetylcholinic), 0.0035 γ/ml; diphenhydramine hydrochloride (antihistaminic), 0.0074 γ/ml; hexamethonium bitartrate (antinicotinic), 0.88 γ/ml; and chlorpromazine hydrochloride (anti-5HT), 0.055 γ/ml. [f] 0.25% aerosol by histamine, 15 min after treatment. [g] Formalin-induced edema, 2 hr after treatment. [h] Approximate LD_{50}. [i] 5,6-Dihydro-7H,12H-dibenz[*c,f*]azocine, to be published elsewhere. [j] 5,6-Dihydro-7H,12H-6-benzyldibenz[*c,f*]azocine, to be published elsewhere.

stances (*e.g.*, phenothiazines). N-Alkyl derivatives exhibited, on the contrary, a strict resemblance to the corresponding 6,7-dihydro-5H-dibenz[*c,e*]azepines as for the peripheral vasodilator and hypotensive action. In this respect, the present work has shown that in our series also a C_2–C_3 chain is the most promising for reaching the highest potency. Analgetic, antiinflammatory, antispasmodic, and local anesthetic activities, found for many of the compounds, do not appear to be peculiar characteristics of this class of substances, as they are frequently displayed by similar structures. The antitussive action shown by some of the compounds seems to be of particular interest. From this viewpoint, however, scarcity and incompleteness of available data will lead us, in the near future, to submit the most interesting compounds to a more detailed study, and to extend this investigation to other similar structures. The promising anthelmintic activity of XII and XXVI indicates that this study is worthy of extension.

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