can find successful use in the approach to many pharmacological problems which involve competitive mechanisms. It will still remain open to question how far the chosen protein can be compared to the physiological receptor. Nevertheless, so little is known about physiological receptors that their protein nature is the only positive fact on this subject to date that can be put to use in hopes of gaining some insight on how to proceed in the infinitely more complex physiological system.

Bicyclic Homologs of Piperazine. IX.[1,2] Synthesis and Pharmacological Properties of Phenothiazine and of 10,11-Dihydrodibenzocycloheptene Derivatives of 3,8-Diazabicyclo[3.2.1]octanes

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All the psychotropic phenothiazines contain a basic substituent connected to the N of the tricyclic system, through a $(CH_2)_3$ chain. Since the basic group of many representative phenothiazines is a piperazine derivative,[3] we introduced, instead of this nucleus, that of 3,8-diazabicyclo[3.2.1]octane, in which a piperazine ring is embodied. The two nonequivalent basic nitrogens of 3,8-diazabicyclo[3.2.1]octane allow the synthesis of isomeric compounds; in fact, the three-carbon side chain may be attached to N-8 or to N-3. We have also synthesized two 10,11-dihydrodibenzocycloheptene derivatives of 3,8-diazabicyclo[3.2.1]octane, structurally related to the drug amitriptyline.[4] The psychotropic activity of the new compounds was evaluated.

Chemistry.—The phenothiazines synthesized (I-1–6, II-1–4) are summarized in Table I. The 10,11-dihydrobenzocycloheptene derivatives (III, IV) are reported in the Experimental Section. As indicated in Scheme I, the synthesis of I and II was carried out by condensing the appropriate 10-(γ-chloropropyl)phenothiazines[4,5] (V) with 3- or 8-substituted 3,8-diazabicyclo[3.2.1]-octanes (VI–IX)[6,7] in the presence of powdered NaOH in refluxing PhMe (method A), or NEt_3 in refluxing AcPr (method B). Alternatively I-1 and II-1 were synthesized by condensing VI and VIII with 1-bromo-3-chloropropane to give the corresponding γ-chloropropyl derivatives X and XI which were allowed to react with 2-chlorophenothiazine (method C). Compound VII was obtained by addition of ethylene oxide to 8-propionyl-3,8-diazabicyclo[3.2.1]octane[8] followed by the removal of the 8-propionyl group by acid hydrolysis. The isomer IX was synthesized either by addition of ethylene oxide to 3-benzyl-3,8-diazabicyclo-[3.2.1]octane,[9,10] followed by catalytic debenzylation of the intermediate, or by addition of ethylene oxide to 3,8-diazabicyclo[3.2.1]octane.[9]

Finally, III and the isomer IV were synthesized by treating dibenzosuberone with the Grignard reagent of X and XI to give the tertiary alcohols XIV and XV, which were eventually dehydrated with *p*-toluenesulfonic acid in refluxing toluene.

(1) Paper VIII of this series: E. Testa, G. Cignarella, L. Fontanella, and E. Occelli, *Farmaco, Ed. Sci.*, **24**, 418 (1969).

(2) Paper VII: G. Cignarella, E. Occelli, and E. Testa, *J. Med. Chem.*, **8**, 326 (1965).

(3) For a review see E. Jucker, *Angew. Chem. Intern. Ed. Engl.*, **2**, 493 (1963).

(4) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 888 (1944).

(5) H. L. Yale and F. Sowinsky, *J. Am. Chem. Soc.*, **82**, 2039 (1960).

(6) G. Cignarella, E. Occelli, and E. Testa, *Ann. Chim.* (Rome), **53**, 944 (1963).

(7) G. Cignarella and G. G. Nathansohn, *J. Org. Chem.*, **26**, 1500 (1961).

(8) G. Cignarella, E. Testa, and C. R. Pasqualucci, *Tetrahedron*, **19**, 113 (1963).

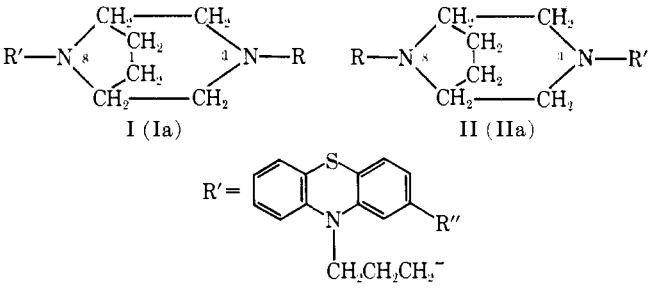
(9) G. Cignarella, G. G. Nathansohn, and E. Occelli, *J. Org. Chem.*, **26**, 2747 (1961).

(10) G. Cignarella and E. Testa, *Gazz. Chim. Ital.*, **92**, 1093 (1962).

Results and Discussion

The results of pharmacological studies are briefly summarized in Table II. Many 3,8-diazabicyclo[3.2.1]-octane derivatives show an effect on animal behavior (decrease of spontaneous motor activity and inhibition of conditioned response) in doses relatively low, even compared with chlorpromazine. Moreover, no compound produces side effects, such as α-adrenergic blocking and antihistaminic action, which are seen with chlorpromazine and other phenothiazine derivatives, to a higher extent than chloropromazine itself. Particularly good results were obtained with 3-(β-hydroxyethyl)-8-(2-trifluoromethyl-10-phenothiazinylpropyl)-3,8-diazabicyclo[3.2.1]octane (I-6), which is three to six times more active than chlorpromazine on behavior, and equally or less active in blocking the pressor response to epinephrine and antagonizing the action of histamine. The activity of I-6 seems worthy of further evaluation in view of a practical interest in the compound as a possible major tranquilizer. Relationships between structure and activity suggest that better results are obtained when the three-carbon side chain of phenothiazine is attached to N-8 of 3,8-diazabicyclo-[3.2.1]octanes instead of N-3. The β-hydroxyethyl group on N-3 of 3,8-diazabicyclo[3.2.1]octane nucleus is also more favorable for tranquilizing activity than Me. As in other phenothiazine derivatives, activity increases when substitutions are made in the 2 position of the phenothiazine ring with Cl or F_3C. Although the results need a more extended analysis, it may be pointed out that, generally, the basic side chain of psychotropic phenothiazine derivatives may be substituted with 3,8-diazabicyclo[3.2.1]octane at N-8, without substantial decrease of the pharmacological effectiveness and, perhaps with an advantage, at least in some cases, in the specificity of action. The 3,8-diazabicyclo[3.2.1]octane derivatives, structurally related to amitriptyline (III and IV), showed little or no

TABLE I

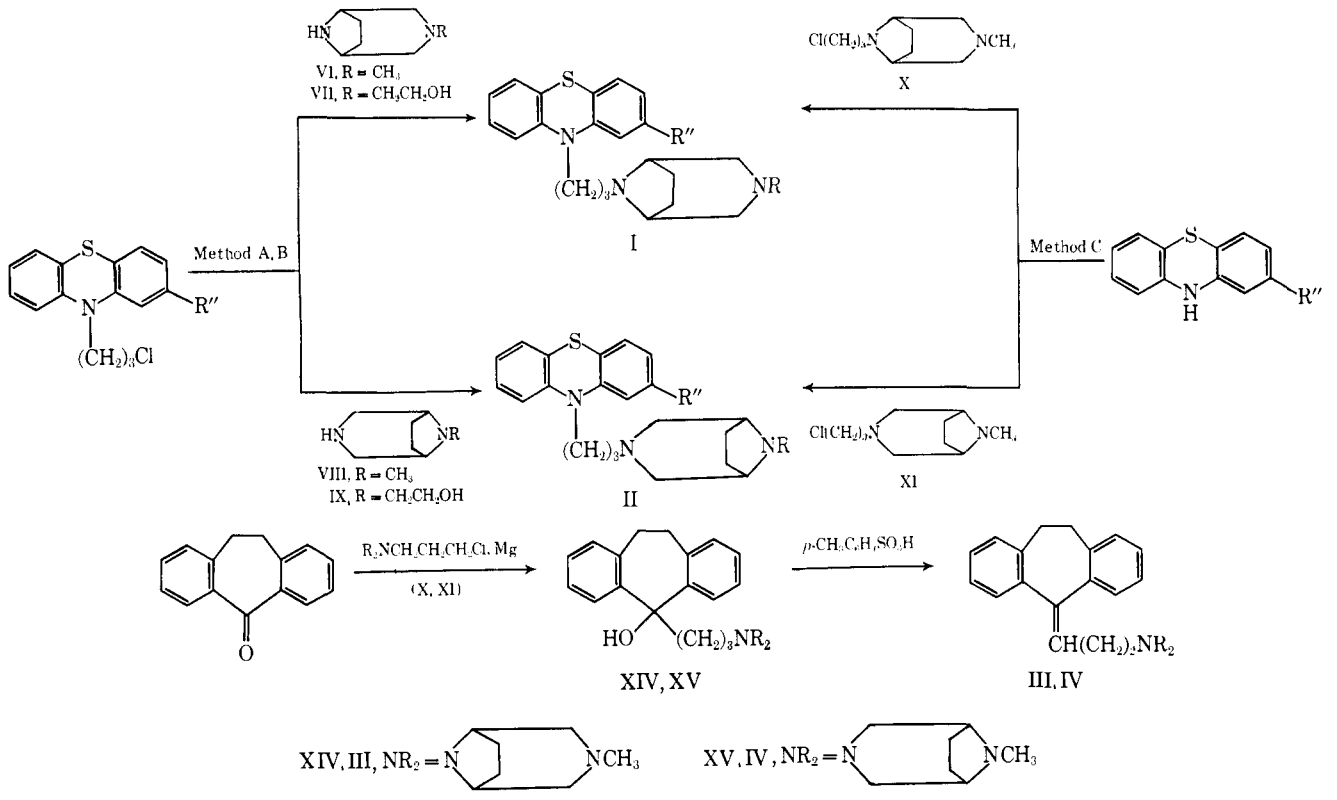


I (Ia) II (IIa)

Compd	R	R''	Method[a]	Yield, %	Mp, °C	Formula[c]
I-1	CH_3	Cl	C	63.5	232–234[b]	$C_{22}H_{26}ClN_3S \cdot 2HCl$
I-2	CH_3	OCH_3	A	62	214–216[c]	$C_{23}H_{29}N_3OS \cdot 2HCl$
I-3	CH_3	CF_3	A	46.5	240–243[c]	$C_{23}H_{26}F_3N_3S \cdot 2HCl$
I-4	CH_2CH_2OH	H	A	62	235–238[c]	$C_{23}H_{29}N_3OS \cdot 2HCl$
I-5	CH_2CH_2OH	Cl	A	25	205–208[c]	$C_{23}H_{28}ClN_3OS \cdot 2HCl$
I-6	CH_2CH_2OH	CF_3	B	64	222–224[b]	$C_{24}H_{28}F_3N_3OS \cdot 2HCl$
II-1	CH_3	Cl	C	63	189–192[b]	$C_{22}H_{26}ClN_3S \cdot 2HCl$
II-2	CH_3	OCH_3	A	58	225–227[c]	$C_{23}H_{29}N_3OS \cdot 2HCl$
II-3	CH_2CH_2OH	Cl	B	88	225–228[d]	$C_{23}H_{28}ClN_3OS \cdot 2HCl$
II-4	CH_2CH_2OH	CF_3	B	73.5	215–218[c]	$C_{24}H_{28}F_3N_3OS \cdot 2HCl$

[a] Experiments were not carried out to synthesize each compound with the various procedures. Therefore, the method reported does not exclude other procedures. [b] From EtOH–Et_2O. [c] From EtOH. [d] From aqueous EtOH. [e] All compounds analyzed satisfactorily for Cl, N, S.

SCHEME I



activity on either reserpine-induced ptosis of mice or on tetrabenazine-induced depression.

Experimental Section

Pharmacology.—The approximate acute toxicity and the effects on spontaneous motor activity were studied in CF1 mice after intraperitoneal administration of 10, 30, 60, 100, 300, and 1000 mg/kg to three animals per dose. The effective doses (ED_{50}) reported in Table II are those able to reduce to 50% the spontaneous motor activity (average of three mice). The LD_{50} was estimated by the method of Litchfield and Wilcoxon.[11] The inhibiting action on the conditioned avoidance response (CR) was evaluated in CF Wistar rats trained to escape painful electric shocks in the pole climbing test as described by Maffii.[12] The drugs were given intraperitoneally to ten rats per dose. The effective doses (ED_{50}) are those able to block the CR in 50% of the animals. Local anesthetic activity was tested in rabbits by the cornea method of Régnier.[13] The drugs were instilled into

(11) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).
(12) G. Maffii, *J. Pharm. Pharmacol.*, **11**, 129 (1959).
(13) J. Régnier, *Compt. Rend.*, **177**, 558 (1923).

TABLE II

Compd	Inhib of oxotilicity, approx ED_{50}, mg/kg ip	Inhib of CR, approx ED_{50}, mg/kg ip	Local anesthetic act., effective concn, %	*In vitro* antihistaminic act., EC_{50}, μg/ml	Adrenolytic act., ED_{50}, mg/kg iv	Approx LD_{50}, mg/kg ip
I-1	3	3.7	>1	0.5	≤0.1	84 (59–119)
I-2	3.5	10	>0.5	0.1	1	200
I-3	1	2.5	>0.5	2	5	200
I-4	18		0.1	0.07	<1	200
I-5	2	1.5	0.5	0.3	0.2	80
I-6	0.5	0.6	0.2	0.2	0.5	80
II-1	50		>1	5	>20	80
II-2	60	>10	0.25	0.07	10	80
II-3	30			0.3	10	60
II-4	30			0.5	5	100
Chlorpromazine	2.5	3.7	0.2	0.02	0.1	112 (95–132)

the conjunctival sac at different concentrations and pH 6–7. The evaluation was based on the number of mechanical stimuli necessary to provoke the wink reflex. A maximum of 30 stimuli was fixed. Antihistaminic and antispasmodic activities were studied *in vitro* on histamine- and $BaCl_2$-induced spasms of isolated strips of guinea pig and rat ileum, respectively. The effective concentrations (EC_{50}) are those able to reduce to 50% the contractile responses to histamine and $BaCl_2$. Adrenolytic activity was studied in anesthetized mongrel dogs (chloralose 75 mg/kg + urethan 750 mg/kg iv). The drugs were given intravenously and changes in arterial blood pressure (recorded from the carotid artery by a Hg manometer) and respiratory frequency (recorded by a pneumometer attached to the thorax) were measured, as well as those of the vascular responses to temporary occlusion of the carotid artery (performed manually with a hemostat) and intravenous administration of epinephrine.

Chemistry.[14] **2-Substituted 10-(γ-chloropropyl)phenothiazines (Va–d)** are known in the literature. Their syntheses were accomplished by a general procedure based on the method reported[15] for Vb (R'' = Cl). Therefore the other references to V do not indicate that the compounds were prepared according to the literature method.

To freshly prepared $NaNH_2$ in liquid NH_3 (from 0.11 g-atom of Na and 300 ml of liquid NH_3), 0.1 mole of the appropriate phenothiazine was added and the mixture was stirred for 2.5 hr at −35°. A solution of 0.15 mole of 1-bromo-3-chloropropane in 150 ml of PhMe was added and the whole was stirred overnight at room temperature, then refluxed for 2 hr. After cooling, the reaction mixture was filtered and the filtrate was evaporated *in vacuo* to give crude V which was purified by distillation by the Ronco technique and/or by trituration with petroleum ether: Va (R'' = H), mp 95–96° (lit.[4] 96–97°), yield 66%; Vb (R'' = Cl), 190–200° (0.5 mm) (lit.[15] 212–217° (1–1.5 mm)), yield 90%; Vc (R'' = OCH_3),[16] bp 190–195° (0.4 mm), yield 72% [*Anal.* ($C_{16}H_{16}ClNOS$) N, Cl, S]; Vd (R'' = CF_3), bp 180–190° (0.8 mm), mp 71–73° (lit.[5] mp 70–71°), yield 67% (lit.[5] 32%) [*Anal.* ($C_{16}H_{13}ClF_3NS$) N, Cl, S].

3,8-Diazabicyclo[3.2.1]octanes.—3-Methyl-[6] (VI) and 8-methyl-3,8-diazabicyclo[3.2.1]octanes[7] (VIII) were prepared by known methods.

3-(β-Hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane (VII). 3-(β-Hydroxyethyl)-8-propionyl-3,8-diazabicyclo[3.2.1]octane (XII).—A solution of 20 g of 8-propionyl-3,8-diazabicyclo[3.2.1]-octane,[8] 10 g of $(CH_2)_2O$, and 150 ml of MeOH was refluxed for 3 hr. The solvent was evaporated and the residue was distilled to give 24 g (95%) of XII, bp 155–158° (0.4 mm). *Anal.* ($C_{11}H_{20}N_2O_2$) N.

Hydrolysis of XII.—A solution of 13 g of XII in 80 ml of 10% HCl was refluxed for 3 hr and concentrated to dryness *in vacuo*. The residue was treated on cooling with excess 30% NaOH and the oil that separated was extracted with ether to give 8.1 g (84.5%) of VII as an oil which solidified on standing; mp 78–80° (Et_2O–petroleum ether (bp 60–100°)). *Anal.* ($C_8H_{16}N_2O$) C, H, N.

The **dihydrochloride** of VII melted at 210–212° (EtOH–Et_2O). *Anal.* ($C_8H_{18}Cl_2N_2O$) N, Cl.

8-(β-Hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane (IX). 3-Benzyl-8-(β-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane (XIII).—A solution of 20.2 g (0.1 mole) of 3-benzyl-3,8-diazabicyclo-[3.2.1]octane,[8,16] 6.6 g (0.15 mole) of $(CH_2)_2O$, and 100 ml of MeOH was gently refluxed for 4 hr. After removing the solvent, the residue was distilled to give 22 g (89.5%) of XIII, bp 140–145° (0.2 mm), mp 68–69° (Et_2O–petroleum ether). *Anal.* ($C_{15}H_{22}N_2O$) C, H, N.

Debenzylation of XIII.—A solution of 20 g of XIII in 200 ml of anhydrous EtOH was hydrogenated at 50° and 50 atm in the presence of 5 g of 10% Pd–C, yield 10.8 g (85%) of IX, bp 115–120° (1 mm), mp 60–61° (ether–petroleum ether). *Anal.* ($C_8H_{16}N_2O$) C, H, N.

Compound IX can also be prepared, in 61% yield, by refluxing for 90 min an equimolar mixture of 3,8-diazabicyclo[3.2.1]-octane[8] and $(CH_2)_2O$ in MeOH. Besides IX, a small amount of 3,8-bis(β-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane, bp 120–125° (0.3 mm), was isolated. *Anal.* ($C_{10}H_{20}N_2O_2$) N.

8-(γ-Chloropropyl)-3-methyl-3,8-diazabicyclo[3.2.1]octane (X).—A solution of 12.6 g (0.1 mole) of 3-methyl-3,8-diazabicyclo-[3.2.1]octane (VI) and 7.9 g (0.05 mole) of 1-bromo-3-chloropropane in PhH (50 ml) was refluxed for 14 hr. The reaction mixture was extracted with 100 ml of 10% HCl, the aqueous layer was made alkaline with 50% NaOH, and the oil which separated was extracted (Et_2O). The extract was dried (Na_2SO_4), the solvent was evaporated, and the residue was distilled, yield 8.6 g (42.5%) of X, bp 75–78° (0.5 mm). *Anal.* ($C_{10}H_{19}ClN_2$) N, Cl.

3-(γ-Chloropropyl)-8-methyl-3,8-diazabicyclo[3.2.1]octane (XI) was prepared from 8-methyl-3,8-diazabicyclo[3.2.1]octane (VIII) according to the procedure followed for X; yield 45%, bp 84–86° (0.8 mm). *Anal.* ($C_{10}H_{19}ClN_2$) N, Cl.

Phenothiazine Derivatives of 3,8-Diazabicyclo[3.2.1]octanes (Table I). Method A.—To a stirred suspension of 4 g (0.0317 mole) of VI and 3.5 g of powdered NaOH in 40 ml of PhMe, 8.8 g (0.0284 mole) of Vb (R'' = Cl) was added and the mixture was refluxed for 15 hr with vigorous stirring. After cooling, the mixture was filtered and the filtrate was extracted with 50 ml of 10% HCl. The aqueous layer was made alkaline with 40% NaOH and was extracted (Et_2O). The extract was dried (Na_2SO_4) and the solvent was evaporated *in vacuo* to give the compound I-1 as an undistillable oil, which appeared pure on tlc. The oil was treated with excess dry HCl in ether to give 7.2 g (63.5%) of I-1 as a 2HCl salt, mp 232–234° (EtOH–Et_2O). Compounds I-5 and II-2 were purified by chromatography on Al_2O_3 eluting with MeOH–EtOAc (7:3).

Method B.—A solution of 3.12 g (0.02 mole) of IX, 6.85 g (0.22 mole) of Vb (R'' = Cl), and 2.22 g (0.022 mole) of Et_3N in 30 ml of AcPr was refluxed for 20 hr. After cooling, ether was added to precipitate Et_3N·HCl which was filtered off. The filtrate was evaporated to dryness *in vacuo* and the residue was treated with 50 ml of 10% HCl, extracting the insoluble residue with Et_2O. The aqueous layer was made alkaline with 50% NaOH and was extracted ($CHCl_3$). The extract was dried (Na_2SO_4) and the solvent was evaporated to give 7.6 g (88%) of II-3 as undistillable oil which exhibited a single spot on the tlc. The product was transformed into the dihydrochloride, mp 225–228° (dilute EtOH).

Method C.—To freshly prepared $NaNH_2$ (from 0.2 g of Na

(14) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(15) S. V. Zhuravlev and Z. J. Ermakova, *Med. Prom. SSSR*, **18** (7), 17 (1964); *Chem. Abstr.*, **61**, 14667g (1964).

(16) M. H. Sherlock, U. S. Patent 2,899,431 (Aug 11, 1959); *Chem. Abstr.*, **54**, 5857a (1960).

in 25 ml of liquid NH_3) suspended in 15 ml of PhMe, 1.96 g (0.0084 mole) of 2-chlorophenothiazine was added, the mixture was refluxed for 3 hr, then 1.7 g (0.0084 mole) of XI in 10 ml of PhMe was added, and the whole was refluxed with stirring for 6 hr. After cooling it was extracted with 30 ml of 10% HCl, the aqueous layer was made alkaline with 50% NaOH, and the oil that separated was extracted (Et_2O). The extract was dried (Na_2SO_4), the solvent was evaporated, and the oil residue was treated with dry HCl in ether to give 2.5 g (63%) of II-1·2HCl, mp 189–192° (Et_2O–EtOH).

10,11-Dihydrodibenzocycloheptene Derivatives of 3,8-Diazabicyclo[3.2.1]octanes (III, IV). Synthesis of 8-[5-(10,11-Dihydrodibenzocycloheptenyl)propylidene]-3-methyl-3,8-diazabicyclo[3.2.1]octane (III). (a) Reaction of the Grignard of X with Dibenzosuberone. 8-[5-Hydroxy-5-(10,11-dihydrodibenzocycloheptenyl)propyl]-3-methyl-3,8-diazabicyclo[3.2.1]octane (XIV).—To a suspension of 0.9 g (0.037 g-atom) of Mg turnings in 10 ml of anhydrous THF, a crystal of I_2 and a few drops of EtBr were added. As the reaction started, a solution of 7.5 g (0.037 mole) of X in 10 ml of THF was added within 0.5 hr. The mixture was refluxed for 1 hr, then 3.9 g (0.085 mole) of dibenzosuberone was added portionwise, and the whole was refluxed for 16 hr. After cooling the resulting solution was dropped into 200 ml of a stirred 10% solution of NH_4Cl at 0°. The oil separated was extracted ($CHCl_3$), the extract was dried, and the solvent was evaporated to give 5.6 g (79%) of XIV, mp 153–155° (Et_2O–petroleum ether). *Anal.* ($C_{25}H_{32}N_2O$) C, H, N.

(b) Dehydration of XIV to 8-[(10,11-Dihydrodibenzocycloheptenyl)propylidene]-3-methyl-3,8-diazabicyclo[3.2.1]octane (III).—A mixture of 5.4 g (0.014 mole) of XIV, 3.3 g (0.017 mole) of *p*-toluenesulfonic acid monohydrate, and 200 ml of PhMe was refluxed 1 hr, then 100 ml of the solvent was slowly distilled. After cooling, the solution was concentrated to a small volume and washed with two 20-ml portions of 10% NaOH. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was chromatographed on silica gel, eluting the impurities with EtOAc–cyclohexane (8:2), then eluting with MeOH to give 4 g (78%) of III as an undistillable oil which exhibited a single spot on tlc.

The **dihydrochloride** melted at 271–273°. *Anal.* ($C_{25}X_{32}Cl_2N_2$) N, Cl.

3-[5-(10,11-Dihydrodibenzocycloheptenyl)propylidene-methyl-3,8-diazabicyclo[3.2.1]octane (IV) was prepared from XI according to the procedure described for III. The intermediate 3-[5-hydroxy-5-(10,11-dihydrodibenzocycloheptenyl)propyl]-8-methyl-3,8-diazabicyclo[3.2.1]octane (XV), mp 167–169° (ether), was isolated in 42% yield. *Anal.* ($C_{25}H_{32}N_2O$) C, H, N.

Dehydration of 2.1 g of XV led to 1.8 g of an oil which was chromatographed on Al_2O_3, eluting with EtOAc–cyclohexane (8:2) to give 1.2 g (60%) of pure IV as undistillable oil.

The dihydrochloride melted at 239–242° ($EtOH$–Et_2O). *Anal.* ($C_{25}H_{32}Cl_2N_2$) N, Cl.

Acknowledgment.—The authors wish to thank Dr. A. Vigevani for spectroscopic determinations and Mr. A. Campi for chemical analyses.

Stereochemical Studies on Medicinal Agents. VII.[1] Absolute Stereochemistry of Methadol Isomers and the Role of the 6-Methyl Group in Analgetic Activity[2,3]

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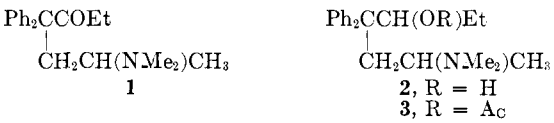
Received March 28, 1969

The stereochemistry of optically active α- and β-methadol has been deduced by the asymmetric synthetic procedure of Prelog. The apparent dissociation constants of the title compounds, when compared with those of methadone and 3-deoxymethadone, suggest the absence of substantial intramolecular H bonding in aqueous medium. Nmr and ir studies point to the presence of strong intramolecular H bonds in nonpolar media, with the β isomer being more strongly internally associated. Possible preferred conformations which are consistent with the spectral data are depicted. The (6*R*), (6*S*), and (6*R*) receptor stereoselectivities for methadone, α-methadol, and acetyl-α-methadol, respectively, have been rationalized in terms of differing modes of interaction.

It is generally believed that strong analgetics exert their effect by interacting with specific sites in the CNS, and that these sites possess asymmetric topographies which enable them to distinguish between enantiomorphs.[5]

The more active enantiomers of methadone (**1**) and certain related analgetics possessing a common asymmetric center have been determined to have the (*R*) configuration.[6] It subsequently was pointed out that there are also a number of strong analgetics whose configurations are in the (*S*) series, and that the reversal of stereoselectivity may be due to differing modes of drug–receptor interaction.[7]



1 **2**, R = H; **3**, R = Ac

One of the most dramatic and interesting examples of this phenomenon has been in the literature[8,9] for some time and is illustrated in Table I. The more potent α-methadol enantiomer [(−)-α-**2**] is derived from (6*S*)-methadone which has a low order of activity. Moreover, conversion of α-**2** to α-**3** again reverses the stereoselectivity so that the more potent enantiomer, (+)-α-**3**, now has the (6*R*) configuration. With the optically active β isomers there is no inversion of stereoselectivity and, consequently, the activity is found in the (6*R*) series [(−)-β-**2**, (−)-β-**3**].[9]

(1) Part VI of this series: P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968).

(2) We gratefully acknowledge support of this work by National Institutes of Health Grant NB 05192.

(3) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstract P-4. (b) For a preliminary report on this work, see P. S. Portoghese and D. A. Williams, *J. Pharm. Sci.*, **55**, 990 (1966).

(4) NIH Predoctoral Fellow 5-F1-GM-20515, 1963-1966.

(5) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966), and references cited therein.

(6) A. H. Beckett and A. F. Casy, *J. Chem. Soc.*, 900 (1955).

(7) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).

(8) A. Pohland, F. J. Marshall, and T. P. Carney, *J. Am. Chem. Soc.*, **71**, 460 (1949).

(9) N. B. Eddy and E. L. May, *J. Org. Chem.*, **17**, 321 (1952).