Dialkylaminoalkyl Derivatives of 10,11-Dihydro-5H-dibenzo[a,d]cycloheptene and Related Compounds

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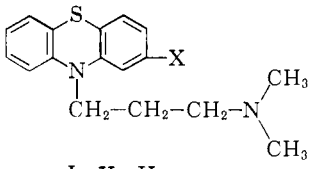
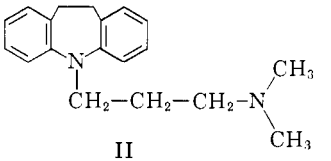
Dialkylaminoalkyl and dialkylaminopropylidene derivatives of 10,11-dihydro-5H-dibenzo[a,d]cycloheptene and 5H-dibenzo[a,d]cycloheptene were prepared as isosteric analogs of the clinically effective phenothiazine tranquilizers. Several syntheses of 5H-dibenzo[a,d]cycloheptene were investigated.

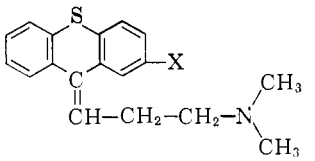
The replacement of one or more atoms in a pharmacologically active compound by an isosteric group or atom may give rise to compounds possessing similar or antagonistic biological properties.[1] For example, the substitution of the sulfur atom in the phenothiazine derivative (Ia), a central nervous system depressant, by the ethylene (CH_2–CH_2) group gives rise to compound II (imipramine) reported[2] to have an antidepressant effect on the central nervous system. Also, the nitrogen of the phenothiazine ring has been replaced by the



Ia, X = H
Ib, X = Cl



II

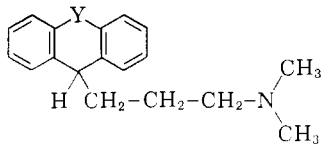


IIIa, X = H
IIIb, X = Cl

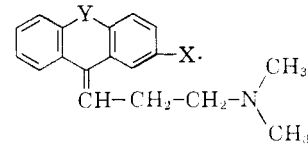
(1) For an excellent review of this subject see V. B. Schatz in "Medicinal Chemistry," A. Burger, ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 72.

(2) W. Schindler and F. Hafliger, *Helv. Chim. Acta*, **37**, 472 (1954).

isosterically similar methylene carbon (C=) to give compounds of Formula III[3] possessing biological activity comparable to I. Our interest in this field prompted the synthesis of compounds in which both the sulfur and nitrogen atoms of I are replaced by their respective carbon equivalents to give compounds represented by structures IV and V.[4]



IVa, Y = CH=CH
IVb, Y = CH_2—CH_2



Va, X = H; Y = CH=CH
Vb, X = H; Y = CH_2—CH_2
Vc, X = Cl; Y = CH=CH
Vd, X = Cl; Y = CH_2—CH_2

The synthetic approach to IVa involved the alkylation of the potassium derivative of 5H-dibenzo[a,d]cycloheptene (VI) with γ-dimethylaminopropyl chloride.[5] Compound IVa was isolated in a yield of 57% and the method was extended to the alkylation of VI with β-dimethylaminoethyl chloride and 1-(3-chloropropyl)-4-methylpiperazine to give the desired compounds in 46% and 12% yields respectively.

Several synthetic routes were studied for the preparation of VI. These are summarized in Scheme 1.

The sulfur dehydrogenation of 1,2,3,4,12,13-hexahydro-5H-dibenzo[a,d]cycloheptene (VII) resulted in a 30% yield of VI. Compound VII was prepared from 2-benzylcyclohexanone.[6] The direct Wolff-Kishner[8] reduction of 5H-dibenzo[a,d]cycloheptene-5-one[7] (VIII) did not lend itself in our laboratory to the preparation of sufficient quantities of VI. In several experiments using this procedure, small quantities of the hydrocarbon were obtained. The conversion of VIII to 5-hydroxy-5H-dibenzo[a,d]cycloheptene (IX) was effected

(3) P. E. Feldman, *Am. J. Psych.*, **116**, 929 (1960). Compound IIIb is used under the name chlorprothixene.

(4) After this work was completed, the clinical application of compound Vb (amitriptyline) was reported by H. Freed, *ibid.*, **117**, 455 (1960). A number of compounds described herein have been reported recently: see M. Protiva, V. Hněvsová-Seidlová, Z. J. Vejdělek, I. Jirkovský, Z. Votava, and J. Metyšová, *J. Med. Pharm. Chem.*, **4**, 411 (1961).

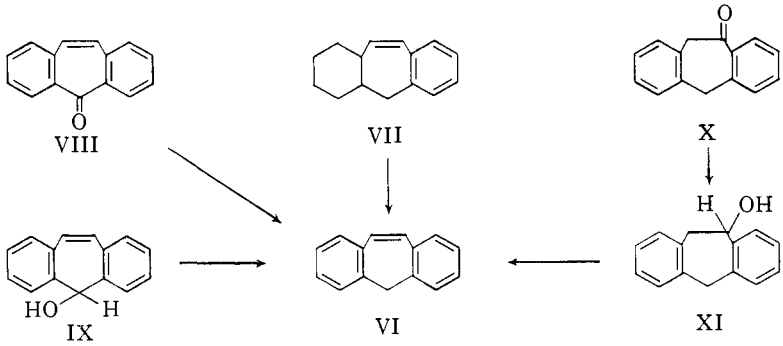
(5) R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 2326 (1947).

(6) J. Colonge and J. Sibeud, *Compt. rend.*, **234**, 530 (1952).

(7) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **63**, 1673 (1951).

(8) T. W. Campbell, R. Ginsig, and H. Schmid, *Helv. Chim. Acta*, **36**, 1489 (1953).

SCHEME 1



by reduction with zinc and ammonium hydroxide and by lithium aluminum hydride. This compound was treated with thionyl chloride and the resulting chloride was reduced with zinc and acetic acid to give VI in 40–45% yield. Alternatively, carbinol IX was reduced to VI with phosphorus and iodine in very poor yield.

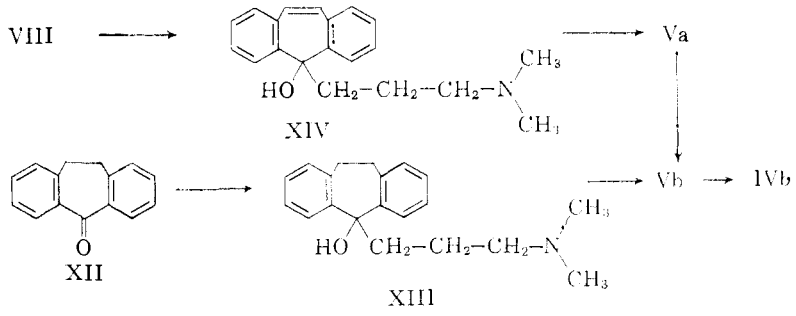
10,11-Dihydro-5H-dibenzo[a,d]cycloheptene-10-one (X) was prepared from *o*-benzylphenylacetic acid by cyclization with polyphosphoric acid[9] and from *o*-benzylphenylacetyl chloride and aluminum chloride.[10] This compound was reduced catalytically to the corresponding carbinol (XI) which was dehydrated in excellent yield to VI by heating with phosphoric acid. This sequence proved to be the method of choice for the synthesis of large amounts of VI.

The exocyclic double bonded compound *N,N*-dimethyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-$\Delta^{5,\gamma}$-propylamine (Vb), isomeric with IVa, was prepared by the elimination of water from the tertiary carbinol (XIII). The carbinol was synthesized by the Grignard addition of γ-dimethylaminopropylmagnesium chloride[11] to 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-one (XII). These reactions are summarized in Scheme 2. An analogous reaction sequence from ketone VIII yielded the completely unsaturated compound (Va).

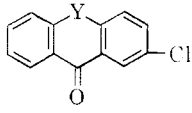
The synthesis of compounds in this series isosterically related to the clinically effective drug, chlorpromazine (1b), required the prepara-

(9) N. J. Leonard, A. J. Kresge, and M. Oki, *J. Am. Chem. Soc.*, **77**, 5078 (1955).
(10) J. Rigaudy and L. Nedelec, *Bull. soc. chim. France*, 641 (1959).
(11) K. Miescher and A. Marxer, U. S. Patent 2,411,664 (1946); A. Marxer, *Helv. Chim. Acta*, **24**, 217E (1941).

SCHEME 2



tion of 3-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-one (XIVa) and 3-chloro-5H-dibenzo[a,d]cycloheptene (XIVb).



XIVa, Y = CH_2-CH_2
XIVb, Y = CH=CH

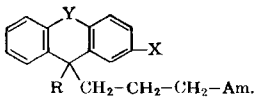
Compound XIVa was prepared by the polyphosphoric acid cyclization of *o*-(*p*-chlorophenethyl)-benzoic acid. Compound XIVa was converted to XIVb by bromination with N-bromosuccinimide and subsequent dehalogenation using excess triethylamine.[7] The dimethylaminopropyl carbinols, obtained by the Grignard reaction with ketones XIVa and XIVb, were converted to the corresponding propylidene derivatives Vc and Vd. The physical properties of these compounds and their hydrochloride salts are summarized in Table I.

Catalytic reduction of Va in the presence of palladium-on-carbon or Raney nickel catalyst resulted in the reduction of the endocyclic double bond and the isolation of Vb. Further reduction of Vb gave the saturated compound IVb. The structures of compounds Vb and IVb from the hydrogenation experiments were established by mixture melting points of the hydrochloride salts of authentic samples prepared as shown in Reaction Scheme 2 and were confirmed by their ultraviolet spectra.

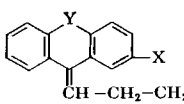
The ultraviolet absorption spectra of compounds possessing an exocyclic double bond show an intense absorption maximum in the 235–240 mμ region whereas compounds having an endocyclic double bond exhibit a shoulder at 220–225 mμ and a peak at 280–290 mμ. The spectra of compounds containing both an exo- and endocyclic

Table I

Compounds of Formula



Y	R	Am	X	Method	Yield, %	B.p., °C.	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
CH_2—CH_2	H	$N(CH_3)_2$	H	[a]	71		183–185	$C_{20}H_{25}N \cdot HCl$	76.04	8.30	76.47	8.37
CH=CH	H	$N(CH_3)_2$	H	A	57	173–175 (1 mm.)		$C_{20}H_{23}N$	86.59	8.36	86.63	8.33
							191–193	$C_{20}H_{23}N \cdot HCl$	76.56	7.76	76.24	7.72
CH=CH	H	$N_2C_5H_{11}$[b]	H	A	12	224–228 (1 mm.)	253–255	$C_{23}H_{26}N_2 \cdot 2HCl \cdot 2H_2O$	62.72	7.72	62.40	7.53
CH_2—CH_2	OH	$N(CH_3)_2$	H	B	70		116–118	$C_{20}H_{25}NO$	81.31	8.53	81.14	8.42
							217–218	$C_{20}H_{25}NO \cdot HCl$	72.38	7.89	72.53	7.95
CH=CH	OH	$N(CH_3)_2$	H	B	73		130–131	$C_{20}H_{23}NO$	81.87	7.90	81.80	7.92
							214–215	$C_{20}H_{23}NO \cdot HCl$	72.82	7.34	73.25	7.35
CH=CH	OH	NC_5H_{10}[c]	H	B	52		194–195	$C_{23}H_{27}NO$	82.83	8.16	83.13	8.99
							249–250	$C_{23}H_{27}NO \cdot HCl$	74.67	7.63	74.75	7.25
CH=CH	OH	$N(CH_3)_2$	Cl	B	75		129–130	$C_{20}H_{22}ClNO$	73.22	6.77	73.52	7.31
CH_2—CH_2	OH	$N(CH_3)_2$	Cl	B	60		123–124	$C_{20}H_{24}ClNO$	72.86	7.33	72.72	7.33



CH_2—CH_2		$N(CH_3)_2$	H	C	99	164–166 (1 mm.)		$C_{20}H_{23}N$	86.59	8.36	86.11	8.06
							199–200	$C_{20}H_{23}N \cdot HCl$	76.53	7.71	77.09	7.63
CH=CH		$N(CH_3)_2$	H	C	80	175–180 (1 mm.)		$C_{20}H_{21}N$	87.22	7.69	87.52	7.83
							216–218	$C_{20}H_{21}N \cdot HCl$	77.52	7.16	77.27	7.26
CH=CH		$N(CH_3)_2$	Cl	C	76	204–206 (2 mm.)		$C_{20}H_{20}ClN$	77.53	6.51	77.25	6.40
CH_2—CH_2		$N(CH_3)_2$	Cl	C	75	184–185 (1 mm.)		$C_{20}H_{22}ClN$	77.03	7.23	76.81	6.79
							210–212	$C_{20}H_{22}ClN \cdot HCl$	68.96	6.66	68.64	6.42

[a] See reduction experiments in Experimental Section. This compound was isolated as the hydrochloride salt. [b] $N_2C_5H_{11}$ is *N*-methylpiperazinyl. The required intermediate, 1-(3-chloropropyl)-4-methylpiperazine, was prepared from 1-(3-hydroxypropyl)-4-methylpiperazine and thionyl chloride; b.p. 76–80° (2 mm.), $n^{25}D$ 1.4710. *Anal.* Calcd. for $C_8H_{17}ClN_2$: C, 54.37; H, 9.69. Found: C, 54.45; H, 10.64. [c] NC_5H_{10} is piperidino. The required intermediate, 1-(3-chloropropyl)piperidine, was prepared by the method of Marxer.[11]

TABLE II

ULTRAVIOLET ABSORPTION DATA (s = shoulder)

Compound	λ mμ	Log ε	λ mμ	Log ε	λ mμ	Log
Vb			238	4.07		
Vd			239	4.13		
VI	220[s]	4.43			284	4.14
IX	220[s]	4.42			283	4.16
XIX	225[s]	4.34			290	4.15
IVa	225[s]	4.30			292	4.06
Va	224	4.57	240[s]	4.34	289	4.02
Vc	225	4.56	242[s]	4.36	290	4.04

double bond are a summation of these absorptions and show maxima at 224 and 289 mμ and a shoulder at 240 mμ. These data are summarized in Table II.

The compounds were screened for their effects on the central nervous system and for their behavioral effects in laboratory animals.[12] In general, these compounds elicited the same over-all behavioral pattern shown by compound II, namely, the depression of locomotor activity and sociability and a reduction in skeletal muscle tone. Maximum activity was found in compounds containing the exocyclic unsaturation at C-5 of the ring, and compounds containing the hydroxyl group at this position were the least active. Compound Vb, the most active in this series, appeared to be three times as potent as compound II when administered intraperitoneally to mice. For example, 30 mg./kg. of Vb elicited the same behavioral effects in mice as 100 mg./kg. of II, but the compound was twice as toxic. The intraperitoneal LD_{50} of this compound in mice was 70 mg./kg. On oral administration, however, both compounds had comparable toxicity. The oral LD_{50} in mice was 220 mg./kg.

Of great interest is the multiplicity of autonomic blocking activities shown by these compounds as a group and particularly compound Vb. The most prominent of these are potent antihistaminic, anticholinergic and moderate antiadrenergic and antiserotonin activities. Table III lists the relative potencies of the more active compounds in various *in vitro* test procedures.

Intravenous injection of compound Vb (1–4 mg./kg.) in anesthetized dogs produced slight transient falls in blood pressure, slight

(12) S. Irwin, Communication to the Gordon Research Conference on Medicinal Chemistry Colby Junior College, New London, New Hampshire, August 3–7, 1959.

Table III

Relative Potency in *in vitro* Tests. Standard = 1

Test→ standard	Antihistamine[a] chlorprophen-pyridamine maleate	Anticholinergic[b] atropine	Antiserotonin[c] bromolysergic acid	Antiadrenergic[d] phentolamine
Vb	0.67	0.12	0.06	0.2
IVb	0.35	0.14	...	0.0
Vd	0.10	0.026	0.25	0.3
II	0.29	0.02	0.022	0.01

[a] Guinea pig ileum (histamine dose 200 γ/l.). ED_{50} standard 1.6 γ/l. [b] Guinea pig ileum (acetylcholine dose 20 γ/l.). ED_{50} standard 2 γ/l. [c] Rat aorta (serotonin dose 10 γ/ml.). ED_{50} standard 13 γ/l. [d] Rat aorta (norepinephrine dose 0.2 γ/ml.). ED_{50} standard 150 γ/l.

mydriasis, moderate transient tachycardia and increased respiratory rate. On blood pressure responses, antihistaminic and antiadrenergic actions were slight to marked in this dose range. The response to epinephrine was never reversed and that to *l*-norepinephrine was unaffected or slightly potentiated. Anticholinergic activity was variable on blood pressure, being most evident at 2–4 mg./kg. There was no ganglion-blocking action.

The authors are indebted to Drs. Samuel Irwin and Franklin Roth for the pharmacological information. We also wish to express our appreciation to Miss Dorothy Kender and Mr. Walter Boraczek for their invaluable technical assistance, to Mr. Edwin Connor for the microanalyses reported herein, and to the Physical and Analytical Chemical Research Department of the Schering Corporation for the ultraviolet absorption spectra determinations.

Experimental

Preparation of 5H-Dibenzo[a,d]cycloheptene (VI). 1. From 1,2,3,4,12,13-Hexahydro-5H-dibenzo[a,d]cycloheptene (VII). 2-Benzylcyclohexanone.—This simplified method is an improvement over the published procedures. To a refluxing mixture of 126.6 g. (1 mole) of benzyl chloride and 147.2 g. (1.5 moles) of cyclohexanone in 1 l. of anhydrous benzene was added, with stirring, a suspension of 39 g. (1 mole) of commercial sodamide in 500 ml. of benzene. The mixture was refluxed overnight and was hydrolyzed by the addition of ice water. The water layer was extracted twice with chloroform and the combined organic solution was washed with water and distilled; yield, 123 g. (65%), b.p. 157–166° (12 mm.), $n^{25}D$ 1.5330; semicarbazone, m.p. 168–170°, after recrystallization from dilute methanol (lit.[13] m.p. 168–169°).

(13) J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 69 (1936).

Ethyl 1-Hydroxy-2-benzylcyclohexylacetate.—Our modified procedure (*cf.* ref. 6) employs ethyl bromoacetate and zinc instead of ethyl chloroacetate, magnesium and ethyl bromide. To 32 g. of zinc metal (20 mesh), 200 ml. of dry ether, 400 ml. of dry benzene, and a small crystal of iodine, a solution of 94 g. (0.5 mole) of 2-benzylcyclohexanone and 84 g. (0.5 mole) of ethyl bromoacetate in 200 ml. of ether was added dropwise with stirring under reflux on the steam bath. Additional zinc (10 g.) and a crystal of iodine were added after the first, second and fourth hr. and heating was continued overnight. The mixture was decomposed by the addition of 10% acetic acid and extracted with chloroform. The combined extracts were washed with water and after removal of the solvents the residue was distilled; yield 119 g. (86%), b.p. 170–186° (2 mm.), n^{28}_D 1.5152; lit.[6] b.p. 150–180° (2 mm.).

1,2,3,4,12,13-Hexahydro-5H-dibenzo[a,d]cycloheptene (VII) was prepared from ethyl 1-hydroxy-2-benzylcyclohexylacetate,[6] b.p. 132–139° (4 mm.), n^{30}_D 1.5782 (lit.[6] b.p. 129.5–131° (3 mm.), n^{23}_D 1.5808). A mixture of 45.5 g. (0.23 mole) of VII and 20 g. of sulfur was heated at 190–220° for 3 hr. and at 230–240° for an additional hr. The mixture was distilled *in vacuo;* b.p. 182–195° (20 mm). The product was recrystallized from methanol; yield 13.5 g. (30.7%), m.p. 130–132° (lit.[6] m.p. 127–129°).

2. From VIII by Wolff–Kishner Reduction.—Seven g. of crude VI, m.p. 123–127°, was obtained from 40 g. of VIII[7] using the method of Campbell, *et al.*[8] After several recrystallizations from methanol the product melted at 129–131°.

3. From 5-Hydroxy-5H-dibenzo[a,d]cycloheptene (IX). 5-Hydroxy-5H-dibenzo[a,d]cycloheptene (IX).—To a mixture of 20.6 g. (0.1 mole) of the ketone VIII, 75 ml. of water and 150 ml. of ammonium hydroxide, 75 g. of zinc dust was added portionwise with cooling and stirring. The mixture was stirred for 1.5 hr. in an ice bath, 5 ml. of a saturated solution of cupric sulfate was added and the mixture was heated on the steam bath for 24 hr. The solids were filtered off and the precipitate was washed several times with warm benzene. The aqueous solution was extracted several times with benzene and the combined benzene extracts were concentrated to dryness. The residue was recrystallized from benzene–petroleum ether; yield 16.5 g. (80%), m.p. 114–117°. An analytical sample recrystallized three times from hexane, melted at 120–121°.

Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.91; H, 5.76.

Compound IX was also obtained from 20 g. of the ketone by reduction with 11.2 g. of lithium aluminum hydride in 500 ml. of ether; yield 12 g. (81%), m.p. 115–117°. This compound did not depress the melting point of the sample prepared above.

A mixture of 41.6 g. of the carbinol IX, and 200 ml. of thionyl chloride was refluxed for 1 hr. on the steam bath. The excess thionyl chloride was removed *in vacuo*, 100 ml. of dry benzene was added and the mixture was again evaporated to dryness. Glacial acetic acid (200 ml), 40 g. of potassium iodide and 100 ml. of water were added to the residue. The mixture was heated on the steam bath and 200 g. of zinc dust was added with stirring over a period of 2 hr. After 15–20 hr. on the steam bath, the hot solution was filtered and the filtrate was diluted with ice water. The product was extracted with chloroform and the extracts were washed with a dilute (5%) sodium hydroxide solution. The residue, after the

evaporation of the solvent, was triturated with ice-cold petroleum ether and recrystallized from methanol or a mixture of benzene–petroleum ether; yield 16 g. (42%), m.p. 129–131°.

From 12 g. of the carbinol IX in 150 ml. of glacial acetic acid, 3 g. of phosphorus and 19 g. of iodine was obtained 0.5 g. (4.5%) of product melting at 128–132°.

4. From 10,11-Dihydro-5H-dibenzo[a,d]cycloheptene-10-one (X). 10-Hydroxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XI).—A solution of 11.5 g. (0.055 mole) of the ketone X[9,10] in 200 ml. of ethanol was hydrogenated at 4.22 kg./cm.^{2} in the presence of Raney nickel catalyst at room temperature. After removal of the catalyst the solution was evaporated to dryness on the steam bath and the residue was distilled; yield 9.5 g. (82%), b.p. 145–153° (1 mm.), $n^{24}D$ 1.6110. An analytical sample was recrystallized from petroleum ether; m.p. 64–66°.

Anal. Calcd. for $C_{15}H_{13}O$: C, 86.00; H, 6.26. Found: C, 85.85; H, 6.75.

A mixture of 7.5 g. (0.03 mole) of XI and 4 ml. of 85% phosphoric acid was heated at 160° for 2 hr. Some of the product sublimed in the condenser and was washed into a beaker with chloroform. The mixture was dissolved in water and extracted with chloroform. After removal of the solvent, the residue was recrystallized from methanol; yield 5.5 g. (78%), m.p. 131–133°.

3-Chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XIVa). o-(p-Chlorophenethyl)benzoic Acid.[14]—To 768 g. of iodine and 670 ml. of water, 97 g. of red phosphorus was added over a period of 1 hr. maintaining the temperature below 40°. The mixture was stirred for an additional hr. *p*-Chlorobenzalphthalide[15] (180 g., 0.7 mole) was added and the mixture was refluxed with stirring for 3 hr. An additional quantity (40 g.) of red phosphorus was added and the mixture was heated under reflux for 8 hr. The warm liquid was poured on ice and filtered. The precipitate was washed thoroughly with water and heated under reflux for 1 hr. with 2 l. of ammonium hydroxide. The hot solution was filtered and acidified with hydrochloric acid. The product was recrystallized from chloroform–petroleum ether; yield 136 g. (83%), m.p. 129–131°.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.02. Found: C, 69.33; H, 5.12.

A mixture of 60 g. (0.2 mole) of *o*-(*p*-chlorophenethyl)benzoic acid and 440 g. of polyphosphoric acid was heated with stirring for 4 hr. at 170–175°. The mixture was poured into ice water and extracted several times with ether. The ether extracts were washed with sodium bicarbonate solution and dried over sodium sulfate. The residue, after removal of the ether, was distilled; b.p. 189–193° (2 mm.). The product was crystallized from petroleum ether; yield 41 g. (80%), m.p. 62–64°.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.14; H, 4.57. Found: C, 74.71; H, 4.21.

3-Chloro-5H-dibenzo[a,d]cycloheptene-5-one (XIVb).—From 42 g. (0.17 mole) of XIVa by the procedure of Cope,[7] there was obtained 27 g. (66%) of product; m.p. 99–100° (from ethanol).

(14) We wish to acknowledge the help of Mr. Irving Berger of our Process Development Department for the development of this procedure.

(15) H. G. Krey, *Pharm.*, **13**, 619 (1958); *Chem. Abstr.*, **53**, 10143 (1959).

Anal. Calcd. for $C_{15}H_{19}ClO$: C, 74.84; H, 3.77. Found: C, 74.71; H, 4.21.

Method A: 5-(β-N,N-Dimethylaminoethyl)-5H-dibenzo[a,d]cycloheptene.—Potassium amide was prepared in the usual manner from 4.2 g. (0.1 mole + 10% excess) of potassium and 400 ml. of anhydrous ammonia in the presence of ferric oxide catalyst. A solution of 19.2 g. (0.1 mole) of VI in 500 ml. of anhydrous ether was added dropwise over a period of 1 hr. The ammonia was allowed to evaporate and the ether solution was refluxed with stirring for 2 hr. on the steam bath. The mixture was cooled to room temperature and a solution of 11 g. of freshly distilled β-dimethylaminoethyl chloride in 50 ml. of dry ether was added dropwise. The mixture was heated on the steam bath for 8 hr. and allowed to stand overnight. Ice water was added and the organic layer was separated. The water solution was extracted with ether and the combined ether solutions were extracted several times with 10% hydrochloric acid. The acid extracts, after a preliminary ether wash, were made basic with ammonium hydroxide and extracted with chloroform. The product was distilled; yield 12 g. (46%), b.p. 170–175° (2 mm.), $n^{26}D$ 1.6146.[17]

Anal. Calcd. for $C_{19}H_{21}N$: C, 86.64; H, 8.04. Found: C, 86.29; H, 8.15.

Method B: 5-Hydroxy-5-(γ-N,N-dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XIII).—To 7.2 g. (0.3 mole) of magnesium and 150 ml. of anhydrous ether, ethyl bromide (0.5 ml.) and a crystal of iodine were added. When the reaction started, a solution of 36.4 g. (0.3 mole) of γ-dimethylaminopropyl chloride in 100 ml. of ether was added with vigorous reflux and stirring over a period of 15–20 min. A second portion of ethyl bromide (0.5 ml.) was added and the reflux was continued for an additional 15 min. A solution of 21 g. (0.1 mole) of XII[7] in 150 ml. of ether was added dropwise with stirring and the mixture was heated on the steam bath for 6 hr. An aqueous solution of ammonium chloride (10%) was added and the product was extracted with chloroform. The chloroform extracts after washing with water were concentrated to dryness on the steam bath and the residue was triturated with petroleum ether (150–200 ml.). The product was filtered off and recrystallized from a mixture of benzene–petroleum ether.[16]

Method C: N,N-Dimethyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-$\Delta^{5,\gamma}$-propylamine (Vb).—A mixture of 13 g. (0.04 mole) of XIII, 40 ml. of concentrated hydrochloric acid and 135 ml. of glacial acetic acid was heated under reflux for 3 hr. The colorless solution was concentrated to dryness *in vacuo* and the residue was dissolved in water, made basic with ammonium hydroxide and extracted with chloroform. After removal of the chloroform, the residue was distilled.[17]

Reduction of Va to Vb.—A solution of 12 g. (0.043 mole) of Va in 200 ml. of ethanol was reduced at room temperature and 4.22 kg./cm.^{2} initial hydrogen pressure in the presence of 5 g. of 5% palladium-on-carbon. The reduction was completed within 2 hr., the catalyst was filtered off, the filtrate was concentrated to dryness and distilled; yield 9.5 g, b.p. 175–182° (2 mm.), $n^{26}D$ 1.5845; hydrochloride, m.p. 191–193°. The hydrochloride did not depress the melting point of the hydrochloride prepared by dehydration of carbinol XIII. A similar result

(16) See Table I for compounds prepared by this method.

was obtained with Raney nickel catalyst.

Reduction of Vb to IVb.—A solution of 6 g. (0.02 mole) of Vb in 200 ml. of ethanol was reduced in the Parr hydrogenerator in the presence of 5 g. of 5% palladium-on-carbon at room temperature and an initial hydrogen pressure of 4.22 kg./cm.^{2} for 18 hr. The catalyst was removed and the filtrate was concentrated to a residue, which was dissolved in 400 ml. of absolute ether and acidified with an alcoholic solution of hydrogen chloride. The white crystalline product was filtered and recrystallized from a mixture of absolute ethanol and absolute ether; m.p. 183–185°.

Anal. Calcd. for $C_{20}H_{26}ClN$: C, 76.04; H, 8.30. Found: C, 76.47; H, 8.37.

The Anticonvulsant Activity of 1,2,4-Triazoles

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A series of 1- and 4-substituted 1,2,4-triazoles has been studied for convulsant and anticonvulsant activity by both the maximal electroshock seizure and subcutaneous pentylenetetrazole seizure tests in rats. 1,2,4-Triazole and 1- and 4-lower alkyl-1,2,4-triazoles are inactive at 200 mg./kg. 1-Aryl, 4-*m*- and *p*-substituted phenyl-1,2,4-triazoles are anticonvulsants. 4-*o*-Chlorophenyl-1,2,4-triazole and 4-*o*-tolyl-1,2,4-triazole are convulsants, whereas 4-*o*-methoxyphenyl-1,2,4-triazole is an anticonvulsant orally but a convulsant when administered by I.P. injection. Qualitatively opposite effects were noted for several isomeric compounds. 1-(1,2,4-Triazolyl-1)-4-(4,1,4-triazolyl-4)benzene (Compound A) showed weak anti-electroshock activity.

Recently, Gibson, Swanson, and Meyers[1] reported the pharmacology of the structurally isomeric compounds 1-phenyl-1,2,4-triazole and 4-phenyl-1,2,4-triazole. They substantiated the earlier report of Pellizzari[2] which stated that 4-phenyl-1,2,4-triazole was a

(1) W. R. Gibson, E. E. Swanson, and D. B. Myers, *J. Am. Pharm. Assoc.*, **47**, 778 (1958).
(2) G. Pellizzari and C. Massa, *Atti Real. Acad. Lincei*, **10**, 363 (1901); *J. Chem. Soc.*, **80**, I. 488 (1901).