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

FRANK J. VILLANI, CLAIRE A. ELLIS, ROBERT F. TAVARES, AND CATHERINE BIGOS

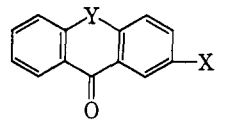
Medicinal Chemistry Department of the Schering Corporation, Bloomfield, New Jersey

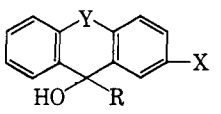
Received December 26, 1963

Further derivatives of 10,11-dihydro-5H-dibenzo[a,d]cycloheptene were prepared as potential antidepressant agents. 5H-Dibenzo[a,d]cyclohepten-5-one and the corresponding 10,11-dihydro ketone were allowed to react with a variety of organometallic reagents to give tertiary carbinols, from which additional compounds were prepared by dehydration and reduction procedures.

In the first paper of this series,[1] the synthesis and pharmacological properties of a series of dialkylaminoalkyl and dialkylaminoalkylidene derivatives of 5H-dibenzo[a,d]cycloheptene and the corresponding 10,11-dihydro derivatives were reported. We now describe some further derivatives of this tricyclic system, prepared as potential antidepressant agents.

The tertiary carbinols (II; Table I, **5–14**, **17–19**, **21**, and **22**) were prepared by the Grignard addition of a magnesium or lithium derivative to the tricyclic ketone I. In addition, sodium acetylide and the sodium derivative of 3-dimethyl-amino-1-propyne were added



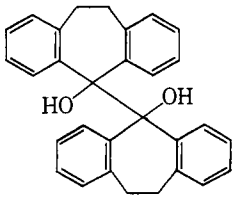


Ia, Y = CH_2CH_2; X = H
b, Y = CH=CH; X = H
c, Y = CH_2CH_2; X = Cl
d, Y = CH=CH; X = Cl

II

to Ia to give the expected tertiary carbinols in 89 and 64% yields, respectively.

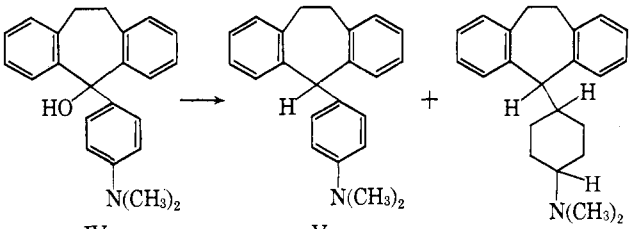
5H-Dibenzo[a,d]cyclohepten-5-one (Ib) and the 3-chloro derivative (Id) readily underwent a normal Reformatsky condensation with ethyl bromoacetate. However, in several attempts to effect this condensation with the saturated ketones Ia and Ic under similar reaction conditions, only starting ketones were recovered.[2] The attempted condensation of Ia with ethyl acetate and sodamide in liquid ammonia[3] gave the diol III in 33% yield. The same compound was isolated in an attempt to prepare N,N-dimethyl-2-(5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetamide by a similar alkylation reaction of Ia with N,N-dimethylacetamide.



III

The piperidylcarbinols listed in Table I were prepared by the catalytic hydrogenation of the corresponding pyridine carbinols. These reductions were carried out at room temperature in ethanol solution containing an equivalent amount of concentrated hydrochloric acid using platinum oxide catalyst. This procedure has been successful in our laboratory even when the hydrogenation of alcoholic solutions of substituted pyridine hydrochloride salts has failed.[4]

Catalytic hydrogenation of 5-hydroxy-5-(*p*-dimethylaminophenyl)-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (IV) under these conditions gave a mixture of 5-(*p*-dimethylaminophenyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (V) and 5-(4-dimethylaminocyclohexyl)-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (VI). Compound V codistilled with VI and the mixture formed a hydrochloride salt, m.p.



IV V VI

225–227°. The ultraviolet absorption spectrum showed a maximum of low intensity at 255 mμ (log ε 3.86). Chromatography on alumina resulted in the isolation of V and the separation of the two stereoisomers of VI, designated as isomers A and B. Nuclear magnetic resonance spectra[5] show that isomer B is the *cis* form and isomer A the *trans* form. Compound V isolated from the chromatogram was identical with an authentic sample prepared by the phosphorus-and-iodine reduction of IV. When the catalytic hydrogenation of IV was carried out at 50–60°, only VI was obtained as indicated by the absence of any absorption in the ultraviolet spectrum of the product. The hydrogenation of IV in acetic acid gave VI and a small amount of the deaminated compound, 5-cyclohexyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene.

Representative tertiary carbinols (Table I) on heating with a mixture of glacial acetic acid and hydrochloric

(1) F. J. Villani, C. A. Ellis, C. Teichman, and C. Bigos, *J. Med. Pharm. Chem.*, **5**, 373 (1962).

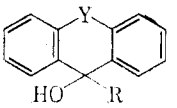
(2) S. G. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas, and R. Barber [*J. Org. Chem.*, **27**, 230 (1962)] reported the preparation of ethyl (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yliden)acetate under rigorous reaction conditions and of the corresponding 5-hydroxy compound by the procedure of K. Sisido, H. Nozaki, and O. Kurihara [*J. Am. Chem. Soc.*, **74**, 6254 (1952)].

(3) C. R. Hauser and W. R. Dunnavant, *J. Org. Chem.*, **25**, 1296 (1960).

(4) The reason for this apparent anomaly is not known. For further examples of this procedure see F. J. Villani, M. S. King, and F. J. Villani, *J. Med. Chem.*, **6**, 142 (1963).

(5) We are indebted to Dr. Leon Mandell of the Department of Chemistry, Emory University, for the n.m.r. data and interpretation. The spectra of these compounds differ only in the region of δ 2.65. Isomer A shows a complex multiplet centered at δ 2.68. Isomer B shows a sharp doublet ($J \sim 1$ c.p.s.) at δ 2.63. These are assigned to the axial and equatorial protons, respectively.

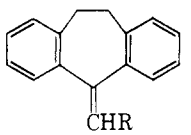
TABLE I



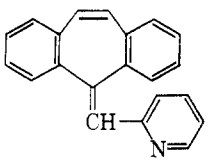
No.	Y	R	Method[a]	Yield, %	M.p., °C.	Solvent[b]	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	CH_2—CH_2	C≡CH	*b*	89	69–70	A	$C_{17}H_{14}O$	87.15	6.02	86.99	6.12
2	CH_2—CH_2	$COCH_3$	*c, d*	43	169–170	B	$C_{17}H_{16}O_2$	80.92	6.39	80.80	6.57
3	CH=CH	$CH_2COOC_2H_5$	A	75	105–106	C	$C_{19}H_{18}O_3$	77.53	6.16	77.43	6.28
4	CH_2—CH_2	$C{\equiv}CCH_2N(CH_3)_2$	B	64	154–156	D	$C_{20}H_{21}NO^c$	82.44	7.26	82.77	7.71
5	CH_2—CH_2	C_6H_{11}	*f*	66	*g*		$C_{23}H_{24}O$	86.25	8.27	86.65	7.96
6	CH=CH	C_6H_5	*f*	64	150–151[h]	A					
7	CH_2—CH_2	*p*-$OCH_3C_6H_4$	*f*	54	120–121	A	$C_{22}H_{20}O$	83.51	6.37	83.48	6.63
8	CH_2—CH_2	*p*-$N(CH_3)_2C_6H_4$	C	67	146–147[i]	D	$C_{23}H_{23}NO^j$	83.85	7.04	84.02	7.19
9	CH=CH	*p*-$N(CH_3)_2C_6H_4$	C	57	168–170	D	$C_{23}H_{21}NO^k$	84.37	6.47	84.60	6.83
10	CH_2—CH_2	*p*-$ClC_6H_4CH_2$	*f*	69	104–105	A	$C_{22}H_{19}ClO$	78.91	5.72	78.85	6.00
11	CH_2—CH_2	2-C_5H_4N	*l*	32	205–206[m,n]	D	$C_{26}H_{17}NO$	83.59	5.96	83.26	6.08
12	CH=CH	2-C_5H_4N	*l*	18	187–189[o]	E	$C_{26}H_{15}NO$	84.18	5.30	84.44	5.72
13	CH_2—CH_2	3-C_5H_4N	*l*	75	170–171	F	$C_{26}H_{17}NO$	83.59	5.96	83.97	5.93
14	CH=CH	3-C_5H_4N	*l*	20	203–204	G	$C_{26}H_{15}NO^n$	84.18	5.30	84.16	5.44
15	CH_2—CH_2	2-$C_5H_{10}N$	D[p]								
16	CH_2—CH_2	3-$C_5H_{10}N$	D	36	118–125	A	$C_{20}H_{23}NO$	81.87	7.90	82.08	7.55
17	CH_2—CH_2	2-$C_5H_4NCH_2$	*p*	65	117–118[q]	A	$C_{21}H_{19}NO$	83.69	6.35	83.89	6.59
18	CH_2—CH_2	4-$C_5H_4NCH_2$	*p*	42	176–178	C	$C_{21}H_{19}NO$	83.69	6.35	83.38	6.19
19	CH=CH	2-$C_5H_4NCH_2$	*p*	64	103–104	C	$C_{21}H_{17}NO$	84.25	5.72	84.13	5.72
20	CH_2—CH_2	2-$C_5H_{10}NCH_2$	D	51	114–115	D	$C_{21}H_{25}NO$	82.04	8.20	82.26	8.18
21	CH_2—CH_2	CH(2-C_5H_4N)(C_2H_5)	E	21	120–122	A	$C_{23}H_{23}NO^r$	83.85	7.04	84.01	7.05
22	CH_2—CH_2	CH(2-C_5H_4N)(C_6H_5)	E	27	116–119	A	$C_{27}H_{23}NO^s$	85.91	6.14	85.39	6.27

[a] Solvents used in recrystallization: A, hexane; B, toluene; C, methanol; D, benzene–petroleum ether (b.p. 30–60°); E, petroleum ether; F, isopropyl ether; G, benzene. [b] Sodium acetylide addition to ketone; see D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.*, **76,** 4446 (1954). [c] Boron trifluoride etherate method; see D. Papa, H. F. Ginsberg, and F. J. Villani, *ibid.*, **76,** 4441 (1954). [d] Oxime, m.p. 217–218°. *Anal.* Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.20; H, 6.80. [e] Hydrochloride salt, m.p. 162–164°. *Anal.* Calcd. for $C_{20}H_{21}NO \cdot HCl$: C, 73.27; H, 6.77. Found: C, 73.58; H, 6.98. [f] Usual Grignard addition to ketone. [g] B.p. 210–217° (3 mm.). [h] W. Treibs and H. Klinkhammer, *Ber.*, **84,** 671 (1951). [i] Log $\epsilon_{265\ m\mu}$ 4.30. [j] Calcd.: N, 4.25. Found: N, 4.51. [k] Calcd.: N, 4.28. Found: N, 4.45. [l] Usual pyridyllithium addition to ketone. [m] Reference 2, m.p. 203–205°. [n] *Anal.* Calcd.: N, 4.91. Found: N, 5.07. [o] Isolated as the hydrochloride salt; see Experimental section. [p] Addition of picolyllithium to the ketone. [q] Ref. 2, m.p. 114–115°. [r] *Anal.* Calcd.: N, 4.25. Found: N, 4.28. [s] *Anal.* Calcd.: N, 3.71. Found: N, 3.76. [t] Capital letters refer to Experimental Section.

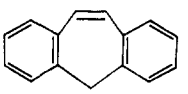
acid were converted into the unsaturated compounds VII and VIII.



VIIa, R = 2-piperidyl
b, R = *p*-chlorophenyl
c, R = 2-pyridyl



VIII



IX

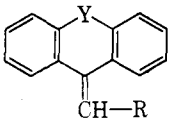
In agreement with data previously reported for compounds in this series,[1] 2-(10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-ylidenemethyl)piperidine (VIIa) shows an ultraviolet absorption maximum at 240 mμ. Compounds VIIb and VIIc show maxima at 280 and 295 mμ, respectively. The exocyclic double bond in these compounds is conjugated with two aromatic rings as is the double bond in 5H-dibenzo[*a,d*]-cycloheptene (IX) (λ_{max} 285 mμ),[1] *cis*-stilbene (λ_{max} 280 mμ),[6a] and in 2-stilbazole (λ_{max} 310 mμ).[6b] 2-(5H-Dibenzo[*a,d*]cyclohepten-5-ylidenemethyl)-pyridine (VIII) shows absorption maxima at 225, 235, and 290 mμ.

(6) (a) "Organic Electronic Spectral Data," Vol. I, H. E. Ungnade, Ed., Interscience Publishers Inc., New York, N. Y., 1960, p. 558; (b) *ibid.*, Vol. 2, p. 394.

Pharmacology.—The compounds were screened for their effects on the autonomic and central nervous systems. Compounds having a tertiary hydroxyl group at C-5 (Table I) showed a very low order of pharmacological activity. In the mouse activity screen[7] the most active compound in this series was VI with maximum activity found in isomer B. Isomer A showed slight activity whereas IV and V were inactive. Isomer B in the cat at an oral dose of 0.25 mg./kg. elicited the same behavioral effects as 1 mg./kg. of compound VI and 2 mg./kg. of amitriptyline. In the unanesthetized dog, isomer B at an oral dose of 50 mg./kg. showed a transient slight increase in mean blood pressure followed in 1 hr. by a slight decrease, and a prolonged slight increase in heart rate. No ECG abnormalities were noted and the animal showed a marked general stimulation from the compound. The oral LD_{50} in mice of isomer B is 175 mg./kg., and of VI, 541 mg./kg. Isomer B showed moderately potent anticholinergic activity in the *in vitro* guinea pig ileum preparation. The potency of this compound was 0.35 times the activity of atropine and 2.9 times the potency of VI. The complete biological and clinical data on isomer B will be published elsewhere.

(7) S. Irwin in "Clinical Pharmacological Techniques," J. H. Nodine and P. S. Siegler, Ed., Yearbook Medical Publishers, Inc., Chicago, Ill., 1954, Chapter 4, in press.

Table II



Y	R	Yield, %	M.p. or b.p. (mm.), °C.	Formula	Calcd., % C	H	N	Found, % C	H	N	Ultraviolet λ_{max} mμ	log ε
CH_2—CH_2	*p*-Cl-C_6H_4	81	225–226 (1)	$C_{22}H_{17}Cl$	83.39	5.41		83.11	5.39		285	4.34
CH_2—CH_2	2-C_5H_4N	66	89–90[a]	$C_{21}H_{17}N$	89.01	6.05	4.94	88.78	6.12	5.02	295	4.24
CH_2—CH_2	2-$C_5H_{10}N$	53	208–210 (1)	$C_{21}H_{23}N$	87.15	8.01	4.84	86.55	8.65	4.81	240	4.01
CH=CH	2-C_5H_4N[b]	42	250–251[c]	$C_{21}H_{15}N \cdot HCl \cdot H_2O$	75.08	5.40	4.17	75.49	5.21	4.52	225 235 290	4.41 4.40 4.28

[a] Recrystallized from hexane. [b] Isolated as hydrochloride salt. [c] Recrystallized from absolute ethanol–ether.

Experimental[8]

The ketones required for this work were prepared as described previously.[1,9]

A. Ethyl (3-Chloro-5-hydroxy-5H-dibenzo[a,d]cyclohepten-5-yl)acetate.—To 24.4 g. (0.1 mole) of Id in 300 ml. of anhydrous benzene and 10 g. of zinc (20 mesh) a solution of 16.7 g. (0.1 mole) of ethyl bromoacetate in 200 ml. each of anhydrous benzene and toluene was added portionwise. An additional 10-g. portion of zinc was added after one-half of the bromoester was added, again after the completion of the addition of the bromoester and a final portion after 1 hr. on the steam bath. The mixture was heated under reflux with stirring for 4 hr. and allowed to cool to room temperature. Dilute acetic acid was added and the mixture was extracted with benzene and finally with chloroform. The combined extracts were washed with water and with dilute sodium carbonate (10%) solution and concentrated to dryness. The product was recrystallized from methanol, yielding 20 g. (63%); m.p. 104–105°.

Anal. Calcd. for $C_{19}H_{17}ClO_3$: C, 69.22; H, 5.18; Cl, 10.76. Found: C, 68.59; H, 5.29; Cl, 10.66.

5-Hydroxy-5-(5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (III).—To a suspension of sodamide prepared from 2.4 g. of sodium in 400 ml. of anhydrous ammonia in the presence of ferric nitrate was added 8.8 g. (0.1 mole) of ethyl acetate followed immediately by 20.8 g. of Ia in 40 ml. of ether. The red solution was stirred for 1 hr. and poured into a slurry of ammonium chloride. The ammonia was allowed to evaporate, ice-water was added to the residue, and the product was extracted with chloroform. The product, after removal of the solvent, was recrystallized from ethanol, yielding 14 g. (33%); m.p. 206–208°.

Anal. Calcd. for $C_{30}H_{26}O_2$: C, 86.09; H, 6.26. Found: C, 86.25; H, 6.03.

B. 5-Hydroxy-5-(3-dimethylamino-1-propynyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene.—To a suspension of sodamide, from 5.3 g. (0.23 g.-atom) of sodium in 1 l. of anhydrous ammonia, a solution of 16.4 g. (0.1 mole) of 2-bromo-3-dimethylamino-1-propene[10] in an equal volume of ether was added dropwise and the mixture was stirred for 1.5 hr. A solution of 21 g. of Ia in an equal volume of ether was added dropwise and the mixture was stirred for 2 hr. Ether (500 ml.) was added and the mixture was allowed to stand overnight. After addition of water the organic material was extracted with chloroform.

C. 5-Hydroxy-5-(*p*-dimethylaminophenyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (IV).—To 2.75 g. (0.4 mole) of lithium and 150 ml. of anhydrous ether was added a solution of 40.0 g. (0.2 mole) of *p*-bromodimethylaniline in 200 ml. of ether. The mixture was refluxed with stirring for about 4 hr. until the lithium had reacted. To the hot solution 20.8 g. (0.1 mole) of Ia was added and the mixture was stirred and heated for an additional 4 hr. The mixture was decomposed with ice-water and extracted with ether. The ether extracts were taken through dilute (10%) hydrochloric acid and the acid solution was made basic with ammonium hydroxide and extracted with chloroform. The solvent was removed and the residue was triturated with petroleum ether (b.p. 30–60°) and recrystallized.

D. 2-(5-Hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperidine Hydrochloride.—Five grams of 2-(5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)pyridine in 100 ml. of anhydrous ethanol containing 3 ml. of concentrated hydrochloric acid was hydrogenated in a Parr hydrogenator at room temperature in the presence of 0.5 g. of platinum oxide catalyst at 4.2 kg./cm.^{2} pressure. The reaction was permitted to run overnight, the catalyst was filtered, and the solvent was removed *in vacuo* on a steam bath. The residue was recrystallized several times from a mixture of absolute ethanol and absolute ether, yielding 2.5 g., m.p. 297–298°.

Anal. Calcd. for $C_{20}H_{23}NO \cdot HCl$: C, 72.94; H, 7.29. Found: C, 73.17; H, 7.54.

If the hydrochloride salt did not crystallize readily, it was dissolved in water, neutralized with ammonium hydroxide, the free base was extracted with chloroform, the solvent was removed, and the residue was recrystallized.

E. 2[α-(5-Hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)benzyl]pyridine.—To a refluxing ethereal solution of phenyllithium prepared from 2.8 g. of lithium and 31.4 g. of bromobenzene was added 33.8 g. (0.2 mole) of 2-benzylpyridine. After an additional 0.5-hr. reflux, 20.8 g. of Ia was added and heating was continued for 2 hr. The mixture was decomposed with water and the product was isolated in the usual manner.

F. General Dehydration Procedure.—A solution of 10 g. of carbinol, 20 ml. of concentrated hydrochloric acid, and 60 ml. of glacial acetic acid was heated under reflux for 4 hr. After removal of the solvents *in vacuo*, the residue was dissolved in water, neutralized with ammonium hydroxide, and extracted with chloroform. These compounds are listed in Table II.

5-(*p*-Dimethylaminophenyl)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene (V).—A mixture of 25 g. (0.076 mole) of IV, 78 g. of iodine, 39 g. of red phosphorus, 280 ml. of acetic acid, and 280 ml. of water was heated under reflux for 3 hr. with stirring. The hot solution was filtered through a sintered glass funnel and poured onto ice. The yellow precipitate was filtered, suspended in water, made strongly basic with sodium hydroxide solution, and extracted with chloroform. The chloroform was removed and the solid was recrystallized from petroleum ether, yielding 18 g. (76%), m.p. 100–102°, λ_{max} 260 mμ (log ε 4.23).

Anal. Calcd. for $C_{23}H_{23}N$: C, 88.13; H, 7.40. Found: C, 87.89; H, 7.18.

The hydrochloride salt after recrystallization from ethanol–ether melted at 247–248°.

Anal. Calcd. for $C_{23}H_{23}N \cdot HCl$: C, 78.84; H, 6.73. Found: C, 78.74; H, 7.02.

Reduction of IV in Ethanol.—A solution of 33 g. (0.1 mole) of IV in 350 ml. of ethanol containing 8 ml. of concentrated hydrochloric acid was hydrogenated at 4.2 kg./cm.^{2} pressure in the presence of 1 g. of platinum oxide catalyst for 20 hr. at room temperature. The catalyst was filtered and the solvent was removed. The residue was dissolved in water and made basic

(8) All melting points are corrected. Microanalyses were performed by Mr. Edwin Conner of these laboratories. The authors gratefully acknowledge the help of the Physical and Analytical Chemistry Department of Schering Corporation for the ultraviolet absorption spectra determinations. We also wish to express our gratitude to Drs. S. Irwin and F. Roth of the Biological Division of Schering Corporation for the biological data reported herein.

(9) Special care should be taken in the preparation of the phenethylbenzoic acids by the reduction of the benzalphthalides with phosphorus and iodine. During the processing of these reactions in our laboratory a violent explosion, the cause of which is not understood, occurred on two occasions.

(10) I. Marzak, J. P. Guermont, and P. Epsztein, *Mém. Serv. Chim. Etat* (Paris), **36**, 301 (1951); *Chem. Abstr.*, **48**, 8724 (1954).

with ammonium hydroxide. The product was extracted with chloroform and distilled, b.p. 220–225° (2 mm.), 25 g. (80%).

Anal. Calcd. for $C_{23}H_{29}N$: C, 86.47; H, 9.15; N, 4.38. Found: C, 86.17; H, 9.24; N, 4.36.

The hydrochloride, after recrystallization from ethanol–ether, melted at 225–227°.

Anal. Calcd. for $C_{23}H_{29}N \cdot HCl$: C, 77.61; H, 8.43. Found: C, 77.77; H, 7.63.

Chromatography of 10 g. of the free base in 75 ml. of pentane was carried out in a 25 × 900-mm. column packed with 300 g. of aluminum oxide. Fractions of approximately 200 ml. were collected (Table III).

TABLE III

Eluent	Fraction	Compd.	Yield, g.	M.p., °C.
Benzene(10%)–pentane	6–13	V	2.4	93–95
	14–20		Trace	
Ether(50%)–pentane	21–24	Isomer A	2.1	Oily solid
Ether(75%)–pentane	25–32	Isomer B	3.5	96–99

Compound V, after recrystallization from petroleum ether, melted at 100–102°. A mixture melting point with an authentic sample prepared above showed no depression.

The hydrochloride salt of isomer A was prepared, m.p. 274–275°.

Anal. Calcd. for $C_{23}H_{29}N \cdot HCl \cdot 0.5H_2O$: C, 75.68; H, 8.49; N, 3.83. Found: C, 75.22; H, 8.43; N, 4.32.

The salt was converted into the free base of isomer A, m.p. 90–91°, from hexane.

Anal. Calcd. for $C_{23}H_{29}N$: C, 86.47; H, 9.15; N, 4.38. Found: C, 86.76; H, 8.92; N, 4.29.

Isomer B was recrystallized from petroleum ether, m.p. 100–101°.

Anal. Calcd. for $C_{23}H_{29}N$: C, 86.47; H, 9.15; N, 4.38. Found: C, 86.80; H, 9.24; N, 4.09.

The hydrochloride salt was recrystallized from ethanol–ether, m.p. 272–273°.

Anal. Calcd. for $C_{23}H_{29}N \cdot HCl$: C, 77.60; H, 8.43; N, 3.90. Found: C, 77.35; H, 8.82; N, 4.06.

Reduction of IV in Ethanol at 60°.—The same procedure as above was used except that the reduction was carried out at 60–65°, b.p. 190–200° (2 mm.). The product did not show any absorption in the ultraviolet. Ten grams of this compound was chromatographed on 300 g. of alumina and fractions of approximately 180 ml. were collected (Table IV).

TABLE IV

Eluent	Fraction	Compd.	Yield, g.	M.p., °C.
Ether(10%)–pentane	13–28	Isomer A	2.8	81–87
	29–51	Mixture	2.1	Oily solid
Ether(15%)–pentane	52–57		Trace	Oil
Ether(20%)–pentane	67–69	Isomer B	2.4	HCl salt, 266–271
Ether	70–85	Isomer B	1.4	95–99

Reduction of IV in Acetic Acid.—Twenty-four grams (0.073 mole) of IV in 200 ml. of glacial acetic acid was hydrogenated in a Parr hydrogenator in the presence of 2 g. of platinum oxide catalyst at 4.2 kg./cm.² pressure at 55–60° for 20 hr. The catalyst was filtered and the solvent was removed on a steam bath *in vacuo*. Dilute (10%) hydrochloric acid (300 ml.) was added and the solution was extracted with ether. The acid solution was made basic with ammonium hydroxide, extracted with chloroform, and the residue after removal of the solvent was distilled, b.p. 185–200° (1 mm.), 18.6 g. (81%). Evaporation of the ether solution gave 2.1 g. (11%) of 5-cyclohexyl-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene, m.p. 76–79°, from petroleum ether.

Anal. Calcd. for $C_{21}H_{24}$: C, 91.25; H, 8.75. Found: C, 91.20; H, 8.90.

A Viscometric Study of Hydrogen-Bonding Properties of Carcinogenic Nitrosamines and Related Compounds[1]

MARY F. ARGUS, JOSEPH C. ARCOS, ASHRAFUL ALAM, AND JERRELL H. MATHISON

Seamen's Memorial Research Laboratory, U. S. Public Health Service Hospital, New Orleans, and Department of Medicine (Biochemistry), Tulane University, New Orleans, Louisiana

Received December 9, 1963

The viscosity of the hepatic carcinogens, dimethylnitrosamine and dioxane, in binary mixture with either water or propionic acid, shows a very large increase above the values of ideal mixing. No such increase is observed in the absence of a proton donor, as with mixtures of dimethylnitrosamine–dioxane, dimethylnitrosamine–propionic anhydride, or dimethylnitrosamine–benzene. The noncarcinogenic 1,1-dimethylhydrazine is considerably more potent in forming hydrogen bonds with water or propionic acid as measured by the extent of maximum viscosity increase. However, while the viscosity of dimethylnitrosamine–water is independent of the pH, neutralization of both basic groups in the hydrazine compound, as shown by its titration curve, causes considerable decrease in the viscosity of its water solutions. Hydrogen bonding with propionic acid approximately parallels carcinogenic activity of a small series of nitrosamines and dioxane. The carboxyl group of proteins appears to be the main participant in the hydrogen bonding of nitrosamines in the process of protein denaturation by these compounds. Hydrogen bonding with nitrosamines is through the nitroso oxygen and involves displacement of the amino electron doublet, resulting in lack of basicity of the amino nitrogen. Aryl substituents decrease hydrogen bonding by redirecting the displacement of the doublet.

Interaction with functional groups that partake in intramolecular hydrogen bonding is commonly assumed to be involved in the mechanism of denaturation of proteins and nucleic acids by chemical agents. The carcinogenic N-nitrosodialkylamines,[2–5] N-nitroso-

(1) This investigation was supported by the U. S. Public Health Service Research Grants CA-05793 and CA-05431.

(2) P. N. Magee and J. M. Barnes, *Brit. J. Cancer*, **10**, 142 (1956).

(3) M. F. Argus and C. Hoch-Ligeti, *J. Natl. Cancer Inst.*, **27**, 695 (1961); **30**, 533 (1963).

(4) H. Druckrey, R. Preussmann, D. Schmähl, and M. Müller, *Naunyn-Schmiedebergs Arch. Exptl. Pathol. Pharmakol.*, **248**, 134 (1961); **249**, 19 (1962).

(5) H. Druckrey and R. Preussmann, *ibid.*, **249**, 111 (1962).