Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.7; H, 7.6; M, 424. Found: C, 69.7; H, 7.6; M (by mass spectrometry), 424.

Reduction of Brucidine to XIV.—Materials used were brucidine (4 g), Na (3.5 g), NH_3 (400 ml), methanol (4 ml), NH_4Cl (4.0 g). Time intervals were A, 30 min; B, 45 min. The product was recrystallized from acetone to give the 21ξ,22-dihydro-23,24-secobrucidine as a solvate (2 g); mp 192–196°; one major spot R_f 0.11, with a trace of a second, R_f 0.16. The desolvated substance, prepared by drying *in vacuo*, had mp 195–202°.

Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.8; H, 8.4. Found: C, 71.6; H, 8.4.

Acknowledgments.—We thank Dr. Larry Stein and his associates of the Psychopharmacology Section of these laboratories for the biological testing data, and Dr. D. DeJongh and Mr. J. Hribar, Wayne State University, Detroit, Mich., for the mass spectra.

New Psychotropic Agents. VIII.[1] Analogs of Amitriptyline Containing the Normeperidine Group

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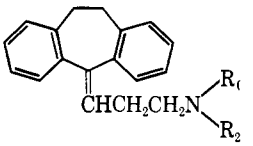
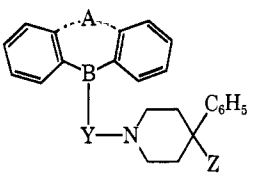
A series of compounds related to the previously reported 5-[3-(4-carbethoxy-4-phenylpiperidino)propylidene]-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene has been prepared. These include analogs in which the tricyclic ring and piperidino group were separated by one- to three-carbon side chains in differing states of oxidation. In several cases the corresponding reversed esters were also prepared. Related compounds were made in which the dibenzocycloheptene ring was replaced by an iminodibenzyl, a phenothiazinyl, or a benzhydryl grouping. The preparation of a number of novel intermediates is discussed including that of a dibenzocycloheptene 5-spiroepoxide. Analgetic testing showed that several of the compounds had activities in the range of morphine.

The preparation, in these laboratories, of a series of dibenzocycloheptenes possessing distinct psychotropic activities has been reported.[2] Two of the compounds, amitriptyline (Ia) and nortriptyline (Ib), have been used successfully in the treatment of depressive disorders.[3] One of the analogs which we had studied was Ic, in which the terminal amino function, NR_1R_2, formed part of the 4-carbethoxy-4-phenylpiperidine or normeperidine group. When the sparingly water-soluble hydrochloride salt of Ic was given intraperitoneally to mice and rats, it exhibited some of the pharmacological properties of the antidepressant drugs, but appeared to lack significant analgetic effects. The influence of the normeperidine group was seen, however, on subsequent oral administration. Due, possibly, to better absorption from the gastrointestinal tract (at large doses a portion of the unchanged compound had been found in the intraperitoneal cavity), it exhibited an analgetic action in the range between morphine and meperidine.

It is well known that replacement of the N-methyl moiety of meperidine by appropriate groups can lead to compounds with markedly enhanced analgetic activities.[4] On occasion it has been possible to dissociate the morphine-like effects of the parent drug to obtain agents which possess antiperistaltic[4] or antitussive[5] actions together with minimal or no narcotic properties. Accordingly, a series of compounds related to Ic was prepared having the common structural features shown in II. Those derived from the dibenzocycloheptene ring (A = CH_2CH_2 or CH=CH; B = carbon) carrying

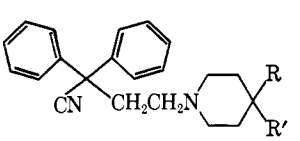




Ia, $R_1 = R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$
c, NR_1R_2 = 4-carbethoxy-4-phenylpiperidino

II

a one- to three-carbon side chain, Y, in differing states of oxidation are listed in Table I. As well as the usual normeperidine group (Z = $CO_2C_2H_5$), we have also prepared some of the compounds in the form of their reversed esters (Z = $OCOC_2H_5$) in the hope of increasing the analgetic potency. Table II lists compounds where the dibenzocycloheptene ring has been replaced by a heterocycle, *viz.*, 5-iminodibenzyl or 10-phenothiazinyl. A series of related compounds derived from iminodibenzyl has been claimed to possess antipsychotic properties,[6] while 2-substituted 10-phenothiazinyl analogs of Ic exhibited antihypertensive activity.[7] Several compounds were prepared in which the bridging group, A, is absent; these benzhydryl analogs are listed in Table III. They are related to 2,2-diphenylbutyronitrile derivatives having antidiarrheal (IIIa)[8a] and



IIIa, R = C_6H_5; R′ = $CO_2C_2H_5$ (diphenoxylate)
b, R = piperidino; R′ = $CONH_2$ (pirinitramide)

(1) Part VII: M. A. Davis, G. Beaulieu, J. R. Watson, and M.-P. Charest, *J. Med. Chem.*, **9**, 860 (1966).

(2) (a) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. A. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962); (b) J. Stewart, M.-P. Charest, and F. Herr, *J. Med. Chem.*, **6**, 338 (1963).

(3) F. Häfliger and V. Burckhardt in "Psychopharmacological Agents," Vol. 4-I, M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, p 35.

(4) R. A. Hardy, Jr., and M. G. Howell in "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 1965, p 179.

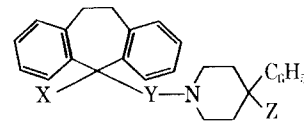
(5) M. A. Davis, U. S. Patent, 3,094,528 (1963).

(6) Yoshitomi Pharmaceutical Industries, Ltd., British Patent 1,017,986 (1966); *Chem. Abstr.*, **64**, 17559 (1966).

(7) H. S. Lowrie, U. S. Patent 3,112,308 (1963).

(8) (a) P. A. J. Janssen, A. H. Jageneau, and J. Huygens, *J. Med. Pharm. Chem.*, **1**, 299 (1959); (b) C. van de Westeringh, P. Van Daele, B. Hermans, C. Van der Eycken, J. Boey, and P. A. J. Janssen, *ibid.*, **7**, 619 (1964).

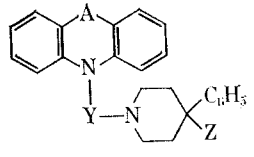
TABLE I: DIBENZOCYCLOHEPTENE DERIVATIVES



No.	X	Y	Z	Salt	Mp, °C	Recrystn solvent	Method	Yield, %	Formula	Calcd, % C	H	N	Halogen	Found, % C	H	N	Halogen
1	H	CH_2	$CO_2C_2H_5$	HBr	237–238	*j, k*	B	1	$C_{30}H_{31}BrNO_2$	69.23	6.58		15.35	69.50	6.66		15.60
2[a]	OH	CH_2	$CO_2C_2H_5$	...	117–119	*l*	F	32	$C_{30}H_{31}NO_3$	79.44	6.89	3.09		79.25	7.03	3.12	
3	H	$(CH_2)_2$	$CO_2C_2H_5$	HCl	222–223[b] dec	*k, m*	D	20	$C_{31}H_{36}ClNO_2$	75.97	7.41		7.23	75.73	7.44		7.10
4	H	$(CH_2)_2$	OH	...	132–133	*m*	A	84	$C_{28}H_{31}NO$	84.59	7.86	3.52		84.33	7.63	3.54	
5	H	$(CH_2)_2$	$OCOC_2H_5$	HBr	182–184[c] dec	*j, k*	E	37	$C_{31}H_{36}BrNO_2$	69.66	6.79		14.95	68.90	6.83		14.68
6	OH	$(CH_2)_2$	$CO_2C_2H_5$	HCl	233–234	*k, o*	B	32	$C_{31}H_{36}ClNO_3$	73.41	7.16		7.00	73.26	7.41		7.17
7		$=CHCH_2$	$CO_2C_2H_5$	HCl	175–176	*k, m*	A	90[d]	$C_{31}H_{34}ClNO_2$	76.27	7.02		7.26	75.93	7.02		7.20
8A		$=CHCH_2$	OH	...	159–160	*m, o*	A	56	$C_{28}H_{29}NO$	85.02	7.39	3.54		84.89	7.31	3.76	
8B		$=CHCH_2$	OH	HBr[e]	185–186	*j, k*			$C_{28}H_{30}BrNO \cdot 2H_2O$	65.63	6.69		15.60	65.30	7.07		16.14
9		$=CHCH_2$	$OCOC_2H_5$	HBr	200–201	*j, k*	E	45	$C_{31}H_{34}BrNO_2$	69.90	6.44		15.01	70.34	6.69		15.28
10		$=CHCH_2$	*b*	HBr[e]	244–246	*j, k, a*	A	27	$C_{28}H_{28}BrN$	73.35	6.15		17.43	73.11	6.33		17.27
11	OH	$C=C(CH_2)_2$	$CO_2C_2H_5$	HCl	180–181 dec	*k, m*	G	46[f]	$C_{32}H_{34}ClNO_3$	74.46	6.64	2.71	6.87	74.39	6.71	2.59	6.91
12A		$=CH(CH_2)_2$	$CO_2C_2H_5$	...	89–90	*o*	A	92	$C_{32}H_{35}NO_2$	82.54	7.58	3.01		82.19	7.60	3.07	
12B		$=CH(CH_2)_2$	$CO_2C_2H_5$	HCl[g]	207–208	*j, p*			$C_{32}H_{36}ClNO_2$	76.54	7.23		7.06	76.45	7.44		7.17
13		$=CH(CH_2)_2$	OH	...	118–119	*ot, o*	A	53	$C_{29}H_{31}NO$	85.04	7.63	3.42		84.86	7.58	3.48	
14		$=CH(CH_2)_2$	$OCOC_2H_5$	HCl	219–221	*j, k, u*	E	55	$C_{32}H_{36}ClNO_2$	76.54	7.23		7.06	75.89	7.50		7.19
15A	H	$CO(CH_2)_2$	$CO_2C_2H_5$	...	109–110	*o*			$C_{32}H_{35}NO_3$	79.80	7.33	2.91		79.66	7.23	2.75	
15B	H	$CO(CH_2)_2$	$CO_2C_2H_5$	HBr	192–193[c]	*k, n*	H	46	$C_{32}H_{36}BrNO_3$	68.33	6.45		14.21	68.28	6.56		14.27
15C	H	$CO(CH_2)_2$	$CO_2C_2H_5$	HCl	181–182	*k, n*			$C_{32}H_{36}ClNO_3$	74.15	7.00		6.84	74.25	7.21		6.95
16	H	$CO(CH_2)_2$	OH	HCl	185–187 dec	*k, n*	I	43	$C_{29}H_{32}ClNO_2$	75.38	6.98		7.68	75.17	7.04		7.74
17		$=CHCH_2$	$CONH_2$[h]	...[i]	169–170	*o, q*	A	87	$C_{28}H_{35}N_3O$	78.28	8.21	9.78		78.02	8.43	9.74	

[a] 5H-Dibenzo[*a,d*]cycloheptene ring. [b] 1,2,5,6-Tetrahydropyridine. [c] C_6H_5 replaced by piperidino; the 4-carbamyl-4-piperidinopiperidine was obtained from Aldrich Chemical Co., Inc. [d] Hygroscopic. [e] λ_{max}^{EtOH} 245 mμ (ε 27,300). [f] Reference 2a. [g] Dihydrobromide, mp 263–264° dec (from ethanol–nitromethane–ether), was used for biological testing; it could not be completely freed from solvent. [h] Dried 16 hr at 100° (0.1 mm). [i] Dried 5 hr at 45° (0.1 mm). [j] Acetonitrile. [k] Ether. [l] Methanol–cyclohexane was also used. [m] 2-Propanol. [n] Ethanol. [o] Hexane. [p] Solvates with alcohols or nitromethane. [q] Ethyl acetate. [r] A yield of 46% was obtained by method C. [s] Yield of free base.

TABLE II: HETEROCYCLIC DERIVATIVES



No.	A	Y	Z	Salt	Mp, °C	Recrystn solvent	Method	Yield, %	Formula	Calcd, % C	H	N	Halogen	Found, % C	H	N	Halogen
18	$(CH_2)_2$	$(CH_2)_2$	OH	...	135–136	*h, c*	A	62	$C_{29}H_{30}N_2O$	81.37	7.59	7.03		81.27	7.68	7.00	
19	$(CH_2)_2$	$(CH_2)_2$	$OCOC_2H_5$	HBr	185–187	*d, e*	E	24	$C_{30}H_{33}BrN_2O_2$	67.28	6.59		14.92	67.04	6.79		15.55
20	$(CH_2)_2$	$(CH_2)_3$	$CO_2C_2H_5$	HCl	193–194	*d, e*	A	32	$C_{31}H_{37}ClN_2O_2$	73.70	7.38		7.02	74.31	7.44		7.46
21A	S	$(CH_2)_3$	$CO_2C_2H_5$	...	82–85	*f*	A	41	$C_{29}H_{32}N_2O_2S$	73.70	6.83	6.77[a]		73.45	6.97	6.70[a]	
21B	S	$(CH_2)_3$	$CO_2C_2H_5$	HBr[a]	173–174	*h, e*			$C_{29}H_{33}BrN_2O_2S$	62.91	6.01		14.44	62.87	6.02		14.60

[a] The following salts (melting point) were prepared for solubility determinations: maleate (152–154°), sulfate (188–192°), oxalate (196–197°), phosphate (223–227°), hydroiodide (225–226°); the hydrobromide was the most water soluble (0.1%). [b] 2-Propanol. [c] Hexane. [d] Acetonitrile. [e] Ether. [f] Pentane. [g] Sulfur.

TABLE III: BENZHYDRYL DERIVATIVES $(C_6H_5)_2CY—N$ (X, C_6H_5, Z)

No.	X	Y	Z	Salt	Mp, °C	Recrystn solvent	Method	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Halogen	Found, % C	Found, % H	Found, % N	Found, % Halogen
22	OH	$(CH_2)_2$	$CO_2C_2H_5$	HBr	242–243 dec	*c*	B	14	$C_{29}H_{34}BrNO_3$	66.40	6.53		15.25	66.64	6.79		14.91
23	OH	$(CH_2)_2$	OH	HCl	267–268	*c, d*	J	15	$C_{26}H_{30}ClNO_2$	73.64	7.13		8.36	73.43	7.20		8.40
24A		$=CHCH_2$	OH	...	147–148	*e*	A	44	$C_{26}H_{27}NO$	84.51	7.37	3.79		84.26	7.24	3.27	
24B		$=ClCH_2$	OH	HCl	201–202	*f, g*			$C_{26}H_{25}ClNO$	76.91	6.95		8.73	77.21	7.00		8.96
25		$=CHCH_2$	$OCOC_2H_5$	Oxalate	188–190[b] dec	*d, h*	E	28	$C_{31}H_{33}NO_6$	72.21	6.45	2.72		71.94	6.51	2.80	
26	H	$COCH_2$	$CO_2C_2H_5$	HCl	217–219 dec	*g, i*	A	73	$C_{29}H_{32}ClNO_3$	72.86	6.75	2.93	7.42	72.63	6.89	3.01	7.46
27	H	$COCH_2$	OH	HCl	195–196	*f, g*	A	13	$C_{24}H_{28}ClNO_2$	74.00	6.69	3.32	8.40	73.75	6.81	3.26	8.43
28	H	ClH_2CO	OH	...	191–192	*j*	A	14[t]	$C_{26}H_{27}NO_2$	81.01	7.06	3.63		81.16	6.91	3.55	
29A		$=CH(CH_2)_2$	$CO_2C_2H_5$	...	100–102	*k*	A	51	$C_{30}H_{33}NO_3$	81.97	7.57	3.19		82.19	7.53	3.30	
29B		$=CH(CH_2)_2$	$CO_2C_2H_5$	HCl	150–151	*f, g*			$C_{30}H_{34}ClNO_2$[o]	74.29	7.06		7.31	74.49	6.97		7.31
30A	H	$CO(CH_2)_2$	$CO_2C_2H_5$	HBr	193–195 dec	*c, g*	H	82[m]	$C_{30}H_{34}BrNO_3$	67.10	6.39	2.61	14.90	67.25	6.65	2.55	14.92
30B	H	$CO(CH_2)_2$	$CO_2C_2H_5$	HCl	169–171	*c, g*			$C_{30}H_{34}ClNO_3$	73.21	6.96	2.85	7.20	73.03	7.11	2.70	7.26
31	OH	$CO_2(CH_2)_2$	$CO_2C_2H_5$	HCl	199–200 dec	*c, d, g*	K	80	$C_{30}H_{34}ClNO_5$	68.76	6.56		6.77	68.58	6.60		6.79
32	OC_2H_5	$CO_2(CH_2)_2$	$CO_2C_2H_5$	...[n]	87–88	*c*	K	49	$C_{32}H_{37}NO_5$	74.51	7.23	2.72		74.71	7.34	2.71	
33A	SC_2H_5	$CO_2(CH_2)_2$	$CO_2C_2H_5$	...	98–99	*f*	K	65	$C_{32}H_{37}NO_4S$	72.29	7.02	6.06[n]		72.40	7.01	5.82[n]	
33B	SC_2H_5	$CO_2(CH_2)_2$	$CO_2C_2H_5$	HCl	147–148 dec	*g, h*			$C_{32}H_{38}ClNO_4S$	67.64	6.74	5.64[n]	6.24	67.75	6.68	5.70[n]	6.46

[a] Biological testing done on HCl salt, mp 137–138° (acetone–ether), which could not be obtained analytically pure; regeneration of the base gave material mp 87–88°. [b] A sample of the oxalate, mp 161–162° dec (acetone–nitromethane), was obtained in 36% yield by keeping a $CHCl_3$ solution of the carbinol and propionyl chloride overnight at room temperature followed by heating under reflux for 20 min with subsequent conversion to the free base. *Anal.* Found: C, 72.06; H, 6.43; N, 2.81. The ultraviolet spectra of the two samples were similar: λ_{max}^{EtOH} 252 mμ (ε 16,700 and 19,350, respectively). [c] Ethanol. [d] Nitromethane. [e] Cyclohexane. [f] 2-Propanol. [g] Ether. [h] Acetone. [i] Ethyl acetate. [j] Acetonitrile. [k] Hexane. [l] Rearrangement by-product from preparation of **27** (see Experimental Section). [m] Yield of crude hydrochloride obtained directly from the reaction mixture. [n] Sulfur. [o] ·0.5 H_2O.

analgetic (IIIb)[8b] activities. A recent patent[9] claims long-acting analgetic activity and low toxicity for analogs of IIIa in which the α-cyano group is replaced by hydrogen.

A variety of methods was employed to prepare the dibenzocycloheptene derivatives listed in Table I. The most general one involved treatment of an appropriate 5-(ω-haloalkylene or -alkylidene)dibenzocycloheptene with secondary amines (method A). With normeperidine, it was preferred to carry out the reactions in boiling benzene or toluene containing triethylamine, while the condensations with 4-phenyl-4-piperidinol were best effected in boiling 1-butanol and Na_2CO_3. For certain compounds, especially those carrying a hydroxy group on the 5 position of the tricyclic ring, a *p*-toluenesulfonate was used in place of the halogen compound (method B). Yields were fair to poor, but it was shown that little or no dehydration of the carbinols to the corresponding alkylidenes had occurred. These alkylidenes could, however, be obtained by heating the 5-hydroxy compounds with mineral acid (method C) and could in turn be reduced catalytically to the corresponding saturated side chains (method D). Both of these latter approaches were less satisfactory than method A. The reversed esters were obtained from the appropriate piperidinols by heating with propionic anhydride containing a little H_2SO_4 (about 90°) (method E). The products, as their hydrohalide salts, tenaciously retained water or solvent of crystallization and required careful drying. Some difficulties were incurred in finding suitable conditions for the acylations. Treatment of the piperidinol, **8A**, for example, with propionyl chloride in $CHCl_3$ either at room temperature[10] or at the boiling point of the solvent gave either incomplete reaction or concomitant dehydration of the 4-hydroxyl group to form **10**. Prior treatment of the piperidinol with ethereal methylmagnesium bromide[11] or with NaH in benzene followed by the acid chloride was unsatisfactory, while the action of propionic anhydride in pyridine at 50° gave only unchanged carbinol. Other workers[12] were unable to esterify a related compound (IV), attributing this to steric hindrance caused by the benzhydryl group.

IV

V

VI

VIIa, R=H
b, R=$CH_2N(CH_3)_2$

Three other syntheses were employed for the normeperidine derivatives. Interaction of the piperidine with the spiroepoxide V (method F) gave compound

(9) Farbwerke Hoechst A.-G., Belgian Patent 673,267 (1966).

(10) P. M. Carabateas and L. Grumbach, *J. Med. Pharm. Chem.*, **5**, 913 (1962).

(11) R. T. Major and F. Dürsch, *J. Org. Chem.*, **26**, 1867 (1961).

(12) B. G. Boggiano, V. Petrow, O. Stephenson, and A. M. Wild, *J. Chem. Soc.*, 1143 (1959).

2 in which the dibenzocycloheptene ring, bearing a 5-hydroxyl group, is joined to the heterocycle by a methylene chain. The 10,11-dihydro analog could not be obtained due to the inaccessibility of the corresponding epoxide (see below). Compound **11**, an acetylenic alcohol, was prepared by condensation of the tricyclic ketone with 1-propargylnormeperidine (VI), using sodamide in liquid ammonia–ether mixture (method G). Others have condensed basic alkynes with diaryl ketones using sodamide either in liquid ammonia[13] or in benzene,[14] or KOH in ether.[13,15,16] These conditions were unsuccessful in our hands as was the use of lithium amide in ammonia.[17] To prepare compounds in which an oxygenated function was located in the alkylene side chain, Mannich reactions were carried out with 5-acetyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene (VIIa) (method H). This ketone has been converted to Mannich bases with primary and secondary amines;[18] with normeperidine in boiling 1,2-dimethoxyethane,[19] we obtained the product (**15A**) in moderate yield. The reaction failed, however, with 4-phenyl-4-piperidinol, but the desired product (**16**) could be obtained by an amine-exchange reaction[16,20] between the carbinol and methiodide of the 5-(3-dimethylaminopropionyl) compound (VIIb)[18] (method I). The resulting Mannich base decomposed on attempted propionylation.

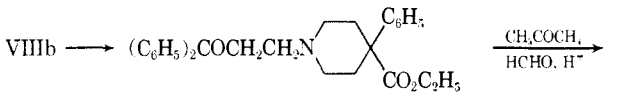
The interaction of an ω-haloalkyl dibenzazepine or phenothiazine with the appropriate piperidine following method A gave the compounds listed in Table II.

The benzhydryl analogs in Table III were prepared by procedures similar to those described above with two additional approaches being used. Thus **23**, a benzhydrol, was prepared in low yield by the interaction of 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-piperidinol with phenyllithium (method J); phenylmagnesium bromide was used unsuccessfully. The poor yields of tertiary alcohols frequently incurred on treatment of Mannich bases with Grignard reagents has been attributed, in part, to enolization.[21] The three carboxylic acid esters (**31–33**) were readily obtained by Horenstein-Pählicke condensation[22] of 1-(2-chloroethyl)normeperidine with the appropriate 2,2-diphenyl-2-substituted acetic acids (method K). These compounds are related to a series of substituted benzilates prepared by Klosa which have been reported to possess good spasmolytic, analgetic, and psychotropic effects.[23] Similar compounds were also reported as antitussives.[24] The application of method A to 3-bromo-1,1-diphenylacetone (VIIIa) gave the normal displacement product (**26**) with normeperidine but with 4-phenyl-4-piperidinol both the displacement (**27**) and rearrangement (**28**) products were obtained in low yields. A similar rearrangement has been reported for the interaction of the bromo ketone and diethylamine to give the diethylamide (X) in small amounts.[25]

$$(C_6H_5)_2COCH_2R \xrightarrow{HNR'_2} (C_6H_5)_2C(O)CH_2NR'_2 + (C_6H_5)_2CH_2CONR'_2$$

VIIIa, R = Br; b, R = H — IX — X

Two interesting differences were noted between the stabilities of the Mannich bases derived from the interaction of 1,1-diphenylacetone (VIIIb) and its dibenzocycloheptene analog (VIIa) with normeperidine. An aqueous–alcoholic solution of the salt of the benzhydryl compound (**30**) gradually decomposed at room temperature in the same manner as that reported for the diethylamino analog.[26] It also underwent a reverse Mannich reaction in the presence of acetone and formaldehyde to give the acetone-derived product (XI). In both instances the dibenzocycloheptene analog (**15**) was unaffected.



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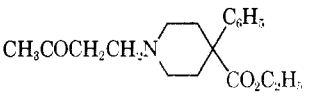


XI

Most of the required intermediates were obtained by conventional procedures and pertinent details are given in the Experimental Section. A desired precursor for 1, 5-bromomethyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene (XIIb) could not be prepared by the action of HBr or PBr_3 on the carbinol (XIIa); the corresponding *p*-toluenesulfonate (XIIc) was used for the amination. Tardieu[27] has converted the 10,11-dehydro analog of carbinol XIIa to its 5-chloromethyl derivative using hydrochloric acid or thionyl chloride.

The action of dimethylsulfonium methylide on 5H-dibenzo[*a*,*d*]cyclohepten-5-one gave the spiroepoxide (V) in good yield. The use of dimethylsulfoxonium methylide also gave the epoxide rather than the 10,11-methano ketone. It has been reported[28] that with certain unsaturated carbonyl systems the former ylide gives epoxides through carbonyl addition while the latter attacks the double bond to form cyclopropanes. Efforts to prepare the 10,11-dihydro analog of the spiroepoxide were unsuccessful. The 10,11-dihydro ketone formed a deep red color on treatment with the oxonium ylide but was recovered unchanged on dilution with water. It reacted similarly with the methylsul-

(13) W. J. Croxall and J. W. Dawson, U. S. Patent 2,584,429 (1952).
(14) J. H. Biel, U. S. Patent 3,192,112 (1965).
(15) H. P. W. Huggill and J. D. Rose, *J. Chem. Soc.*, 335 (1950).
(16) This reagent has been used for the condensation of propiolic esters with ketones; *cf.* E. K. Rando and L. P. Remsberg, Jr., *J. Org. Chem.*, **25**, 1436 (1960).
(17) H. D. Hartzler, *J. Am. Chem. Soc.*, **83**, 4990 (1961).
(18) T. Holm, U. S. Patent 3,215,739 (1965).
(19) S. Hirai, R. G. Harvey, and E. V. Jensen, *Tetrahedron Letters*, 1123 (1963).
(20) E. M. Fry and E. L. May, *J. Org. Chem.*, **24**, 116 (1959).
(21) R. Baltzly and J. W. Billinghurst, *ibid.*, **30**, 4330 (1965).
(22) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).
(23) J. Klosa, *Arch. Pharm.*, **286**, 218 (1953); **287**, 321 (1954); **288**, 42 (1955); *J. Prakt. Chem.*, **16**, 258 (1962); D. Kupke and S. Geissler, *Arzneimittel-Forsch.*, **13**, 312 (1963); H. Hüller, E. Schulz, and W. Scheler, *Acta Biol. Med. Ger.*, **10**, 357 (1963); H. Hüller and W. Scheler, *ibid.*, **11**, 220 (1963); P. C. Dandiya and S. S. Rungta, *Arch. Intern. Pharmacodyn.*, **149**, 493 (1964).
(24) F. P. Doyle, M. D. Mehta, R. Ward, J. Bainbridge, and D. M. Brown, *J. Med. Chem.*, **8**, 571 (1965).
(25) R. M. Dodson, E. F. Morello, and W. G. Dauben, *J. Am. Chem. Soc.*, **76**, 606 (1954); *cf.* R. E. Lutz and J. W. Wilson, *J. Org. Chem.*, **12**, 707 (1947).
(26) W. Wilson and Z.-Y. Kyi, *J. Chem. Soc.*, 1321 (1952).
(27) J. Rigaudy and P. Tardieu, *Compt. Rend.*, **248**, 1538 (1959); *Chem. Abstr.*, **53**, 17989 (1959); P. Tardieu, *Ann. Chim.* (Paris), **6**, 1415 (1961); *Chem. Abstr.*, **57**, 5857 (1962).
(28) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

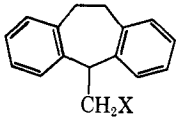
TABLE IV

PHARMACOLOGICAL PROFILE OF REPRESENTATIVE COMPOUNDS

Compd	Route of admin	LD_{50}, mg/kg	Analgesia (tail flick), mg/kg	ED_{50} (hot plate), mg/kg	Spontaneous motility Dose mg/kg	Spontaneous motility Effect, %	Mydriasis Dose, mg/kg	Mydriasis Effect, units[c]	Antispasmodic[a] Dose, mg	Antispasmodic[a] Effect, %
6	ip	600 ± 42	7 ± 0.7	19 ± 4	7	+32	7	1.7		
					15	+175				
	po	>1200	18 ± 3	81 ± 11			25	4.2	9	118
									18	146
7	ip	450	8 ± 0.2	13 ± 0.2	8	+241	7	1		
					15	+975				
	po	750	13 ± 1	32 ± 6			12	0	6	86
									12	238
9	ip	450	1.4 ± 0.2	1.1 ± 0.07	1.5	+22	1.4	3.8		
					3	+117				
	po	750	2.8 ± 0.3	2.8 ± 0.5			2.8	6.4	1.5	208
									3	350
10	ip	280	>150	>200	150	−68	100	0		
	po	>1200	>300	>300			225	0	1.5	70
									3	90
12B	ip	>1000	>100		14	+222	14	0		
					28	+990				
	po	>1200	14 ± 2	23 ± 4			14	0	7	150
									14	360
14	ip	125	1.6 ± 0.2	6 ± 0.5	1.5	+10	1.6	1.2		
					3	+44				
	po	175	2.6 ± 0.4	11 ± 2			2.6	0	1.3	220
									2.6	200
19	ip	>1200	140 ± 10	145 ± 17	145	−85	145	2		
	po		450	400			280	14		
20	ip	180	12 ± 0.6	14 ± 2	12	+52	12	0.6		
					24	+278				
	po	850	22 ± 4	36 ± 4			22	1.6	11	370
									22	310
21B	ip	550	20 ± 4	45 ± 14	20	−38	20	4.2		
					40	+195				
	po	600	42 ± 8	67 ± 10			40	4.6	21	146
									42	208
29B	ip	380	>160	118 ± 9	94	−71	120	4.2		
	po	>1200	58 ± 3				120	0		
Morphine sulfate	ip	275	4.3 ± 0.5	5 ± 2	3	+133	4.3	3.6		
					10	+78				
	po	1000	20 ± 2	13 ± 3			20	4	10	370
									20	360
Meperidine HCl	ip	145[b]	22 ± 2	67 ± 10	22	+167	22	5.4		
					44	+46				
	po	268[b]	81 ± 5	76 ± 4			81	18.6	40	250
									80	790

[a] In rats. The effect is the per cent increase in residual $BaSO_4$ on the stomachs of treated rats compared to untreated controls. [b] Values in agreement with the findings of C. M. Gruber, E. R. Hart, and C. M. Gruber, Jr., *J. Pharmacol. Exptl. Therap.*, **73**, 319 (1941). [c] Units of increase over pupil diameter in control groups; a score of 40 represents maximal dilatation.

finyl carbanion,[29] but efforts to trap any ring-derived anion by treatment with CO_2 also gave unchanged ketone. The observation that 1,1-diphenylethylene did not form the epoxide with perbenzoic acid[30] was paralleled in the case of 5-methylene-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene on treatment with 3-chloroperbenzoic acid.



XIIa, X = OH
b, X = Br
c, X = OTos

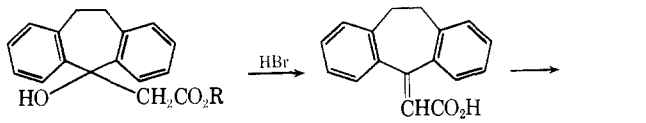
5-(2-Bromoethylene)-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene, required for the preparation of **3** and **4**, was prepared from the corresponding hydroxy compound. This was obtained from the unsaturated acid (XIV) which was first hydrogenated to XV and then reduced with $LiAlH_4$. The olefinic acid has been previously described,[2,31] but a preferred route involved the action of HBr on either the isopropyl (XIIIa) or the *t*-butyl ester (XIIIb) of the related 5-hydroxy acid. Decarboxylation became important if the reaction was carried out at elevated temperatures and an attempted one-step conversion of XIIIb to the saturated acid (XV) using hydriodic acid gave no acidic product.

(29) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962); *J. Org. Chem.*, **28**, 254 (1963); C. Walling and L. Bollyky, *ibid.*, **28**, 256 (1963); G. A. Russell, H. D. Becker, and J. Schoeb, *ibid.*, **28**, 3584 (1963).

(30) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 247 (1945).

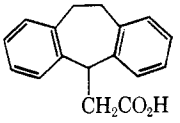
(31) C. van der Stelt, A. Haasjes, H. M. Tersteege, and W. Th. Nauta, *Rec. Trav. Chim.*, **84**, 1466 (1965).

Recently, a similar approach has been successfully applied for the conversion of the benzhydryl analog of XIIIb to 3,3-diphenylpropionic acid.[32] An attempted preparation of the ethyl ester of the olefinic acid XIV from 10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-one, triethyl phosphonoacetate,[33] and NaH was unsuccessful.



XIIIa, R = $CH(CH_3)_2$
b, R = $C(CH_3)_3$

XIV



XV

Pharmacology.—The pharmacological profile, in mice, of **12B** as an analgetic agent is compared to that of morphine and meperidine in Table IV. The data for several of its analogs are also included while more limited testing for the remaining members of the series is presented in Table V.

TABLE V

INTRAPERITONEAL ANALGETIC ACTIVITIES

Compd	LD_{50}, mg/kg	Tail flick ED_{50}, mg/kg
2	>1200	>400
3	225	16 ± 0.7
5	225	1.4 + 0.2
8B	225	>60
15B	180	5.6 ± 2
17[a]	110	>20
25	90	2.1 ± 0.4
26	425	39 ± 9
30A	225	10 ± 2
31	450	85 ± 4
32	>1600	400 ± 55
33B	>1600	>400

[a] Dihydrochloride salt used; *cf.* Table I, footnote *g*.

Analgesia in mice was measured by the tail flick method of D'Amour and Smith[34] as modified by Witkin[35] and by the hot plate test.[36] The ED_{50}'s and their standard errors were calculated by the method of Miller and Tainter.[37] The effect of the compounds on the spontaneous activity of mice was measured by the method of Chappel, *et al.*[38] The mydriatic effect in mice at doses equivalent to the tail flick ED_{50} was determined as previously described.[21c] The antispasmodic activity was a measure of the effect on gastric motility or delay in emptying time.[39] The test compound was administered orally to starved rats at doses equal to the mouse analgesia ED_{50} and at half this value. After 1 hr the animals were given 2 ml of 40% $BaSO_4$ meal and 2 hr after the meal they were killed. The residual $BaSO_4$ in the stomachs of the treated animals was compared to that found in the controls and is expressed as per cent increase.

It was found that the original member of the series, **12B**, had good analgetic activity, being in the range of morphine when given orally. It differed from the latter in being more active in increasing motor activity and in being virtually inactive in the mydriasis test. Its effect on gastric motility was about the same as that of an equianalgetic dose of morphine, but both agents were less active in this respect than meperidine. The structural variations of **12**, summarized in formula II and listed in Tables I–III, have given a number of interesting results. In the series of dibenzocycloheptene analogs (Table I), shortening the alkylene chain to two carbon atoms (**3**, **6**, **7**) did not appreciably alter the analgetic potency but, in all cases, preparation of the reversed esters (**5**, **9**, **14**) led to the most active agents. Intraperitoneally in the tail flick assay, these were about three times more potent than morphine and orally, about seven times. The role of the 4-substituent on the piperidine ring was also seen in **8B** (4-OH), **10** ($\Delta^{3,4}$-double bond), and **17** (4-carboxamido-4-piperidino); these were all devoid of activity. Replacing the dibenzocycloheptene ring by an iminodibenzyl or a phenothiazine ring (**19**, **20**, **21B**, Table II) tended to lower the activity. Unlike the parent compound (**12B**) these last two normeperidine-containing compounds did exhibit analgetic activity when given intraperitoneally as indeed did most of the other active members cited above. In the benzhydryl series (Table III), the direct analog of **12B** (**29B**) was notably less active. The pair of reversed esters (**9**, **25**) were, however, about equally active, but the benzylhydryl compound was considerably more toxic. The Mannich bases in both series (**15B**, **30A**) were also effective compounds, the dibenzocycloheptene derivative being among the most active of the normal esters. The three diphenylacetic acid derivatives (**31**, **32**, **33B**) showed only weak activity.

Experimental Section

Melting points were read on a Thomas-Hoover Uni-Melt apparatus.

10,11-Dihydro-5H-dibenzo[*a,d*]cycloheptene-5-carboxylic Acid Methyl Ester.—A solution of the above acid[40] (29.6 g) in methanol (300 ml) was saturated with HCl and heated under reflux overnight. The solvent was removed *in vacuo*, and a $CHCl_3$ solution of the product was extracted with aqueous $NaHCO_3$ to give 30.0 g (95%) of ester, mp 93–95° (from hexane).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.58; H, 6.44.

10,11-Dihydro-5H-dibenzo[*a,d*]cycloheptene-5-methanol (XIIa).—The above methyl ester (38.0 g, 0.15 mole) was reduced with $LiAlH_4$ (5.7 g, 0.15 mole) in ether (800 ml) giving 29.4 g (88%) of the carbinol, mp 64–65° (from ethanol–hexane). For material prepared by a different method[41] the reported melting point was 56–59°.

The corresponding *p*-toluenesulfonate ester (XIIc), mp 107–108° (lit.[41] mp 101–103°), was prepared; λ_{max}^{EtOH} 262 mμ (ε 1170).

(32) T. Mukaiyama, *J. Org. Chem.*, **31**, 1933 (1966).

(33) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

(34) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(35) L. B. Witkin, M. Maggio, and W. E. Barrett, *Proc. Soc. Exptl. Biol. Med.*, **101**, 377 (1959).

(36) G. Woolfe and A. D. MacDonald, *J. Pharmacol. Exptl. Therap.*, **80**, 300 (1944).

(37) L. C. Miller and M. L. Tainter, *Proc. Soc. Exptl. Biol. Med.*, **57**, 261 (1944).

(38) C. I. Chappel, G. A. Grant, S. Archibald, and R. Paquette, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 497 (1957).

(39) M.-G. Siegen and C. I. Chappel, unpublished results.

(40) M. A. Davis, S. O. Windhorst, J. Stewart, F. A. Sunahara, and F. Herr, *J. Med. Chem.*, **6**, 251 (1963).

(41) E. Ciorănescu, A. Bueur, M. Elian, M. Bancu, M. Voica, and C. D. Neuitzescu, *Rev. Roumaine Chim.*, **10**, 161 (1965); *Chem. Abstr.*, **63**, 11458 (1965).

Spiro{5H-dibenzo[*a,d*]cycloheptene 5,2'-Epoxide} (V). A.—NaH (50% dispersion, 1.15 g, 0.024 mole) was freed of mineral oil and added to dry dimethyl sulfoxide (DMSO) (30 ml). The mixture was heated at 60–75° for 45 min, cooled to 0°, and diluted with dry tetrahydrofuran (THF) (30 ml). A solution of trimethylsulfonium iodide (4.9 g, 0.02 mole) in DMSO (25 ml) and THF (10 ml) was added followed by 5H-dibenzo[*a,d*]cyclohepten-5-one[42] (4.1 g, 0.02 mole) dissolved in THF (10 ml). The reaction mixture, which was a light red color, was kept at 0° for 30 min and allowed to warm to room temperature (1 hr). It was poured into cold water to give 4.0 g (91%) of material, mp 85–89°, which contained no residual ketone. Recrystallization from cyclohexane gave the pure epoxide: mp 91–93°; $\nu_{max}^{CHCl_3}$ 950, 800 cm^{-1} (epoxide); λ_{max}^{EtOH} 287 mμ (ε 15,500).

Anal. Calcd for $C_{16}H_{12}O$: C, 87.24; H, 5.49. Found: C, 87.28; H, 5.33.

B.—Dimethylsulfoxonium methylide was generated from trimethylsulfoxonium iodide (6.1 g, 0.03 mole) and NaH (50%, 1.32 g, 0.03 mole) in DMSO (25 ml) at room temperature. The preceding ketone (4.7 g, 0.02 mole) was added, and the mixture was stirred for 1 hr at 25° followed by 1 hr at 50–55°. The solid obtained by dilution with water contained the product plus a little ketone; one recrystallization from cyclohexane gave 2.1 g (42%) of the epoxide, mp 89–90°.

10,11-Dihydro-5-hydroxy-5H-dibenzo[*a,d*]cycloheptene-5-acetic Acid Isopropyl Ester (XIIIa).—Following a procedure of Sisido,[43] the Grignard reagent prepared from ethyl bromide (43.5 g, 0.4 mole) and Mg (9.8 g, 0.4 g-atom) in ether (200 ml) was cooled to 5° while diethylamine (29.4 g, 0.4 mole) in ether (100 ml) was added dropwise. The mixture was then heated under reflux for 0.5 hr, cooled again to 5°, and treated dropwise with a solution of 10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-one[42] (41.6 g, 0.2 mole) and isopropyl acetate (20.4 g, 0.2 mole) in ether (200 ml). After heating under reflux for an additional 2 hr the mixture was hydrolyzed with ice–water and NH_4Cl. The aqueous layer was separated and extracted with ethylene dichloride (emulsions were broken by the addition of dilute H_2SO_4 to pH 3). The extracts were combined with the ether layer, then dried and evaporated. There was obtained 36.0 g (58%) of product, mp 101–103° (from 2-propanol), λ_{max}^{EtOH} 264 mμ (ε 502).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 76.98; H, 7.32. Found: C, 77.39; H, 7.14.

10,11-Dihydro-5H-dibenzo[*a,d*]cyclohepten-5-ylideneacetic Acid (XIV). A.—A solution of XIIIb[2a] (108.0 g, 0.33 mole) in acetic acid (1 l.) was cooled in an ice bath and saturated with gaseous HBr. It was kept overnight, part of the solvent was removed *in vacuo*, and water (1 l.) was added. The precipitate was dissolved in $CHCl_3$ and extracted with dilute, aqueous NaOH. Acidification of the alkaline layer gave 77.0 g (93%) of product, mp 169–170° (from benzene–hexane); lit.[2a,31] 172–173°, 168–170°. If the reaction mixture was heated on the steam bath for 0.5 hr, the yield of carboxylic acid dropped to 44%, while heating for 5.5 hr gave only the decarboxylated product, 5-methylene-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene,[42] mp and mmp 63–65°.

B.—A solution of XIIIa (5.0 g) in $CHCl_3$ (25 ml) was kept at 10° and treated with HBr for 2 hr. It was then kept at room temperature overnight, poured into water (50 ml), and processed as above to give 2.6 g (66%) of the unsaturated acid, mp 168–170°.

The reaction was repeated at 0° for 15 min, and the mixture was processed at once. The only isolated product in this case was the isopropyl ester of XIV (3.5 g, 74%), mp 63–64° (from hexane), λ_{max}^{EtOH} 261 mμ (ε 12,750).[44]

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.43; H, 6.69.

10,11-Dihydro-5H-dibenzo[*a,d*]cycloheptene-5-ethanol.—A solution of 10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene-5-acetic acid (XV)[31,45] (31.7 g, 0.13 mole) in THF (200 ml) was added dropwise to $LiAlH_4$ (10.6 g, 0.28 mole) in the same solvent (300 ml). The mixture was heated under reflux for 1.5 hr, cooled, and treated successively with water (11 ml), 20% NaOH (8 ml), and water (37 ml). Removal of the precipitate and evaporation of the solvent gave 18.5 g (62%), mp 59–60° (from cyclohexane), λ_{max}^{EtOH} 266 mμ (ε 604).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.78; H, 7.40.

5-(2-Bromoethylene)-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene.—A solution of PBr_3 (11.9 g, 0.04 mole) in dry benzene (50 ml) was added dropwise and with cooling to a solution of the preceding carbinol (10.5 g, 0.04 mole) in benzene (50 ml) containing pyridine (0.1 ml). The mixture was stirred for 2 hr at room temperature and then heated under reflux for 0.5 hr. It was cooled and poured into water, and the organic layer was distilled to afford 6.4 g (48%) of the bromide, bp 154–158° (0.01 mm). The oil solidified on standing; mp 54–55°, unchanged on recrystallization from pentane, λ_{max}^{EtOH} 266 mμ (ε 545).

Anal. Calcd for $C_{17}H_{17}Br$: C, 67.93; H, 5.69; Br, 26.53. Found: C, 67.69; H, 5.50; Br, 26.54.

5-(2-Bromoethylidene)-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene.—The interaction of 10,11-dihydro-5-hydroxy-5H-dibenzo[*a,d*]cycloheptene-5-ethanol[2a] (10.0 g, 0.04 mole) and PBr_3 (34 g, 0.12 mole) in benzene (100 ml) was carried out as above except that the heating time was decreased to 10 min. There was obtained 11.5 g (98%) of product, mp 110–111°, unchanged on recrystallization from hexane; λ_{max}^{EtOH} 246 mμ (ε 15,800). For material prepared by a different method, the reported[46] melting point was 108–110°. An attempted preparation from the diol and boiling 48% HBr was unsuccessful.

5-(2-Bromoethyl)-10,11-dihydro-5H-dibenz[*b,f*]azepine.—A solution of 10,11-dihydro-5H-dibenz[*b,f*]azepin-5-ethanol[47] (7.5 g, 0.03 mole) in dry benzene (70 ml) was cooled to 5° and treated with PBr_3 (8.4 g, 0.03 mole) in benzene (30 ml). The mixture was processed as described above to give 4.0 g (42%) of material: mp 90–91° (from hexane); λ_{max}^{EtOH} 211, 254 mμ (ε 26,100, 9450). The compound could not be obtained completely pure and was used as such for the preparation of **18**.

5-(3-Chloropropyl)-10,11-dihydro-5H-dibenz[*b,f*]azepine was prepared in 35% yield as described,[48] bp 160–166° (0.3 mm), lit.[48] bp 150–160° (0.2–0.3 mm).

Anal. Calcd for $C_{17}H_{18}ClN$: Cl, 13.06; N, 5.16. Found: Cl, 12.82; N, 4.81.

1,1-Diphenyl-1,3-propanediol.—A solution of 3,3-diphenyl-3-hydroxypropionic acid *t*-butyl ester[43] (44.9 g, 0.15 mole) in THF (600 ml) was reduced with $LiAlH_4$ (8.6 g, 0.22 mole) giving 32.0 g (94%) of the diol, mp 87–90°. A pure sample was obtained from 2-propanol–hexane; mp 91–93°; lit.[49] for a mixture of isomers, mp 87–91°.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.03; H, 7.14.

A 3-*p*-toluenesulfonate ester was prepared following a procedure used for the corresponding dibenzocycloheptene analog.[2a] It rapidly decomposed on attempted isolation and was used in the crude form for the preparation of **22** by method B.

3-Bromo-1,1-diphenyl-1-propene. A.—A solution of the preceding diol (15.0 g, 0.07 mole) in dry benzene (100 ml) was kept at 5° while PBr_3 (18.4 g, 0.07 mole) dissolved in the same solvent (100 ml) was added dropwise. The mixture was heated under reflux for 2 hr, cooled, and poured into water. Distillation of the organic layer afforded 15.5 g (86%) of product, bp 132° (0.1 mm), mp 41–42°, raised to 42–43° on recrystallization from pentane; lit.[50] mp 37–39°; λ_{max}^{EtOH} 254 mμ (ε 17,900).

B.—A solution of 1,1-diphenyl-1-propene[51] (24.2 g, 0.125 mole), N-bromosuccinimide (22.2 g, 0.125 mole), and benzoyl peroxide (0.1 g) in CCl_4 (100 ml) was heated under reflux for 16 hr. The precipitate was filtered, the solvent was evaporated, and the residue was recrystallized from pentane to give 22.9 g (67%) of the bromo olefin, mp 44–46°. Using this procedure, Ziegler[52] obtained an oil, bp 96–98° (0.05 mm), which could not be solidified due to the presence of an impurity.

Anal. Calcd for $C_{15}H_{13}Br$: Br, 29.31. Found: Br, 29.31.

(42) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1673 (1951).

(43) K. Sisido, H. Nozaki, and O. Kurihara, *ibid.*, **74**, 6254 (1952).

(44) Preparation carried out by Mr. R. Otson.

(45) L. G. Humber, M. A. Davis, R. A. Thomas, R. Otson, and J. R. Watson, *J. Heterocyclic Chem.*, **3**, 247 (1966).

(46) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Med. Chem.*, **7**, 392 (1964).

(47) (a) Rhône-Poulenc, French Patent 1,215,599 (1960); *Chem. Abstr.*, **55**, 14488 (1961); (b) J. R. Geigy, A.-G., British Patent 907,785 (1962); *Chem. Abstr.*, **58**, 5646 (1963).

(48) J. W. Cusic, U. S. Patent 3,123,610 (1964).

(49) H. M. Walborsky and C. Columbini, *J. Org. Chem.*, **27**, 2387 (1962).

(50) K. Ziegler and P. Tiemann, *Ber.*, **55**, 3406 (1922).

(51) S. C. Hussey, C. S. Marvel, and F. D. Hagar, *J. Am. Chem. Soc.*, **52**, 1122 (1930).

(52) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann. Chem.*, **551**, 80 (1952).

4-Bromo-1,1-diphenyl-1-butene. A.—A procedure for the preparation of α-(3-chloropropyl)benzhydrol[53] was adapted as follows. An ethereal solution of phenylmagnesium bromide (3 *M*; 100 ml, 0.3 mole) was added to a solution of ethyl 4-bromobutyrate (19.5 g, 0.1 mole) in ether (150 ml) at 0°. The solution was heated under reflux for 2 hr and decomposed with ice-cold NH_4Cl solution, and the product was extracted with benzene. The solvent was removed, and a portion of the residue was triturated with hexane to give α-(3-bromopropyl)benzhydrol, mp 93–95°, λ_{max}^{EtOH} 258 mμ (ε 913). The main portion gradually underwent dehydration at room temperature or on warming to 45° *in vacuo*. The process was completed by heating it in benzene under reflux for 3 hr with a crystal of iodine. Distillation afforded the bromo olefin (10.9 g, 38%), bp 140–150° 10.4 mm), $n^{25}D$ 1.6089, λ_{max}^{EtOH} 252 mμ (ε 14,450), lit.[54] bp 140–148° (0.35 mm).

B.—A mixture of 1,1-diphenyl-1,4-butanediol[55] (12.1 g) and 48% HBr (60 ml) was heated under reflux for 2.5 hr. Water (200 ml) was added, and the product was taken into benzene. Distillation gave 10.4 g (73%) of the bromo olefin, bp 131° (0.08 mm).

4-Carbethoxy-4-phenyl-1-propargylpiperidine (VI).—A stirred mixture of 4-carbethoxy-4-phenylpiperidine (from 20.8 g, 0.08 mole of the hydrochloride) and Na_2CO_3 (14 g) in benzene (200 ml) was treated dropwise with a solution of redistilled propargyl bromide (7.4 g, 0.07 mole) in benzene (10 ml). The solution was kept at room temperature for 1.5 hr, diluted with ether (300 ml), and filtered. Carbon dioxide was added, the precipitate was filtered, and the solvent was evaporated giving 13.6 g (72%) of product, mp 48–49°, unchanged on recrystallization from pentane; $\nu_{max}^{CCl_4}$ 3315 (C≡C), 1718 cm^{-1} (ester C=O). The use of 1 equiv of triethylamine as condensing agent was equally satisfactory.

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.48; H, 7.73; N, 5.37.

The **hydrobromide** had mp 187–188° (from 2-propanol).

Anal. Calcd for $C_{17}H_{22}BrNO_2$: C, 57.95; H, 6.30; Br, 22.68. Found: C, 57.35; H, 5.98; Br, 23.06.

2,2-Diphenyl-2-ethylthioacetic Acid.—A modification of the published[56] procedure was used. Concentrated H_2SO_4 (135 ml) was added dropwise (1.5 hr) to a stirred mixture of benzilic acid (100 g, 0.44 mole) and ethanethiol (33 g, 0.53 mole) in glacial acetic acid (500 ml); the internal temperature was maintained at 40°. After half of the acid had been added, the mixture was homogeneous, and a red color developed; a precipitate then separated. The mixture was stirred at room temperature for an additional 1.5 hr and poured into ice–water (600 ml). The precipitate was washed well with water and dissolved in $CHCl_3$, and this solution was repeatedly extracted with water until all traces of mineral acid were removed. Removal of the solvent left 110 g (92%) of product, mp 128–132°. One recrystallization from CCl_4 gave 90.5 g, mp 131–132°, in agreement with the reported value.

Method A. 5-[3-(4-Carbethoxy-4-phenylpiperidino)propylidene]-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene (12A).—A solution of 5-(3-bromopropylidene)-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene[2a] (10.0 g, 0.03 mole), 4-carbethoxy-4-phenylpiperidine (6.5 g, 0.03 mole), and triethylamine (3.2 g, 0.03 mole) in dry benzene (50 ml) was heated under reflux for 18 hr. The mixture was cooled and diluted with dry ether (75 ml), and the precipitate was filtered. The residual secondary amine was removed by the addition of Dry Ice, and the filtered solution was evaporated *in vacuo*. The residual oil was treated with charcoal in hot hexane to give 12.8 g of product, mp 86–87°. An analytical sample was obtained on recrystallization from ethanol (see Table I); λ_{max}^{EtOH} 237 mμ (ε 15,500). The use of a second equivalent of the secondary amine as the acid acceptor gave similar results.

Small samples of the base were treated with 1 equiv of the following acids: citric, monopotassium phthalate, acetic, fumaric, malonic, cyclohexylsulfamic, *p*-toluenesulfonic, sulfuric, H_3PO_4, hypophosphorous, and HCl. The acetate salt was the most water soluble, but none dissolved between 0.5 and 1%. A 4% suspension of the micronized hydrochloride in saline was used for the biological studies.

5-[2-(4-Hydroxy-4-phenylpiperidino)ethylidene]-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene (8A).—A well-stirred mixture of 5-(2-bromoethylidene)-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene (15.3 g, 0.04 mole), 4-phenyl-4-piperidinol (7.8 g, 0.04 mole), and powdered Na_2CO_3 (11.0 g) in 1-butanol (170 ml) was heated under reflux for 20 hr. Acetone (500 ml) was added, and the filtered solution was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ and ether and treated with a little Dry Ice; the insoluble materials were filtered. Removal of the solvents left 13.4 g, mp 156–158°. Recrystallization gave 9.5 g of product, λ_{max}^{EtOH} 240 mμ (ε 15,700).

Method B.—5-[2-(4-Carbethoxy-4-phenylpiperidino)ethylene]-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ol Hydrochloride (6).—A solution of 10,11-dihydro-5-hydroxy-5H-dibenzo[*a*,*d*]-cycloheptene-5-ethanol *p*-toluenesulfonate[2a] (17.8 g, 0.044 mole) and 4-carbethoxy-4-phenylpiperidine (from 26.2 g, 0.087 mole of the hydrochloride) in methanol (100 ml) was kept at room temperature for 2 hr. The temperature was gradually raised to boiling and held there for 18 hr. The solvent was evaporated and replaced by ether, and the precipitate was filtered. The solution was extracted with aqueous $NaHCO_3$ and dried. Treatment with CO_2 removed the unchanged normeperidine, and the residual oil, obtained on removal of the solvent, was converted to the hydrochloride: λ_{max}^{EtOH} 251, 257, 262 mμ (ε 480, 613, 629); yield 7.1 g.

Method C. 5-[2-(4-Carbethoxy-4-phenylpiperidino)ethylidene]-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene Hydrochloride (7).—A solution of **6** (1.8 g) in ethanol was saturated with HCl and heated under reflux for 2.5 hr. Removal of the solvent followed by one recrystallization of the residue from ethanol–ether gave 0.8 g of product, mp 174–175°, λ_{max}^{EtOH} 242 mμ (ε 16,000).

The salts with hydrochloric and glycerophosphoric acids were water soluble to the extent of about 0.1%. Those with acetic, maleic, oxalic, and hydrobromic acid were less soluble.

Method D. 5-[2-(4-Carbethoxy-4-phenylpiperidino)ethylene]-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene Hydrochloride (3).—Compound 7 (5.0 g) dissolved in ethanol (100 ml) was hydrogenated under 3 kg/cm^2 and 25° using Pt catalyst. About 75% of the theoretical amount of hydrogen was consumed after 27 hr. Recrystallization of the crude product gave 1.1 g, λ_{max}^{EtOH} 263 mμ (ε 808).

Method E. 5-[2-(4-Phenyl-4-propionoxypiperidino)ethylidene]-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene Hydrobromide (9).—A solution of the piperidinol **8A** (6.5 g) in propionic anhydride (65 ml) containing concentrated H_2SO_4 (0.1 ml) was heated at 70° for 4 hr and at 90° for 17 hr. The solvent was removed *in vacuo* and a benzene solution of the residue was extracted with several portions of dilute $NaHCO_3$ solution. The oil obtained on evaporation contained a strong ester-carbonyl band ($\nu_{max}^{CHCl_3}$ 1740 cm^{-1}) and only a trace of the starting alcohol. The hydrobromide was recrystallized to give 3.9 g, λ_{max}^{EtOH} 243 mμ (ε 16,500).

Method F. 5-(4-Carbethoxy-4-phenylpiperidinomethyl)-5H-dibenzo[*a*,*d*]cyclohepten-5-ol (2).—A solution of the spiroepoxide V (7.8 g, 0.04 mole) and 4-carbethoxy-4-phenylpiperidine (from 26.9 g, 0.10 mole of the hydrochloride) in absolute ethanol (40 ml) was heated under reflux for 4 hr. The solvent was evaporated and replaced by ether (150 ml), and the solution was treated with CO_2. The precipitate was filtered, and the solution was evaporated to give the crude product as an oil. This was converted to the oxalate salt, mp 197–198° dec (from ethanol), which could not be obtained pure. Regeneration of the base gave 5.2 g of material, λ_{max}^{EtOH} 295 mμ (ε 13,100).

Method G. 5-[3-(4-Carbethoxy-4-phenylpiperidino)-1-propynyl]-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-ol Hydrochloride (11).—A solution of 4-carbethoxy-4-phenyl-1-propargylpiperidine (VI, 1.35 g, 0.005 mole) in dry ether (20 ml) was added to sodamide (from 0.12 g, 0.005 g-atom of sodium) in liquid NH_3 (50 ml). After 5 min, a solution of 10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one (1.03 g, 0.005 mole) in ether (10 ml) was added dropwise, and the mixture was stirred for 1 hr. An excess of NH_4Cl was added, the NH_3 was allowed to evaporate, and the precipitate was filtered. Removal of the solvent gave an oil (2.5 g) which on trituration with hot hexane and crystallization from ethyl acetate furnished a sample of the base (1.1 g), mp 155–157°, which could not be obtained pure. The hydrochloride had mp 180–181° dec: λ_{max}^{EtOH} 251, 257, 263 mμ (ε 752, 842, 870).

(53) P. A. Barrett and S. Wilkinson, British Patent 683,950 (1952).

(54) S. H. Graham and A. J. S. Williams, *J. Chem. Soc.*, 4066 (1959).

(55) F. Hamaguchi, *Yakugaku Zasshi*, **82**, 1088 (1962); *Chem. Abstr.*, **58**, 4492 (1963).

(56) E. G. Brain, F. F. Doyle, K. Hardy, A. A. W. Long, M. D. Mehta, D. Miller, J. H. C. Nayler, M. J. Soulal, E. R. Stove, and G. R. Thomas, *J. Chem. Soc.*, 1445 (1962).

Method H. 5-[3-(4-Carbethoxy-4-phenylpiperidino)propionyl]-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (15A).—Paraformaldehyde (1.8 g, 0.06 mole) was added to a mixture of VIIa[18,57] (7.1 g, 0.03 mole) and 4-carbethoxy-4-phenylpiperidine hydrochloride (8.6 g, 0.03 mole) in 1,2-dimethoxyethane (40 ml). The reaction mixture was heated under reflux for 1 hr, treated with an additional 1.0 g of paraformaldehyde, and heated for another 2 hr. After cooling, a little insoluble material was removed by filtration, and the solvent was evaporated. The residue, on shaking with $CHCl_3$ and $NaHCO_3$ solution afforded the crude base as an oil. Conversion to the hydrobromide salt gave 7.8 g, mp 186–188°. An analytical sample had mp 192–193°, λ_{max}^{EtOH} 264 mμ (ε 890). The spectrum of an aqueous solution remained the same after keeping for 1 week at room temperature.

Regeneration of the base gave material, mp 109–110°, λ_{max}^{EtOH} 264 mμ (ε 910). It was converted to the **hydrochloride salt**, mp 181–182°. Heating this salt (0.1 g) with 37% aqueous formaldehyde (5 drops) and a little HCl in acetone (3 ml) on the steam bath for 10 min gave only unchanged material; mp and mmp 181–182°. This stability may be compared to that of the nonbridged analog (**30**, see below).

Method I. 5-[3-(4-Hydroxy-4-phenylpiperidino)propionyl]-10,11-dihydro-5H-dibenzo[a,d]cycloheptene Hydrochloride (16).—5-(3-Dimethylaminopropionyl)-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (VIIb) hydrochloride was prepared as described[18] from VIIa except that the heating time was increased to 48 hr. The product, mp 177–178° (lit.[18] mp 175–176°), was converted to the methiodide which could not be readily purified.

Powdered Na_2CO_3 (2.0 g) was added to a solution of 4-phenyl-4-piperidinol (0.53 g, 0.003 mole) in dry DMF (15 ml) followed by the above methiodide salt (1.65 g, 0.004 mole); a strong odor of trimethylamine was evolved. The mixture was stirred overnight, filtered, and added to water (100 ml). The precipitate thus formed was collected in ether, and the solution was dried and evaporated to give 1.2 g of an amorphous solid. This was converted to the hydrochloride (0.6 g), λ_{max}^{EtOH} 263 mμ (ε 826).

Method J. 1,1-Diphenyl-3-(4-hydroxy-4-phenylpiperidino)-1-propanol Hydrochloride (23).—A solution of 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-piperidinol[10] (7.8 g, 0.025 mole) in dry THF (25 ml) was added dropwise to phenyllithium from Li (2.2 g, 0.032 g-atom) and bromobenzene (24.7 g, 0.16 mole) in THF (100 ml). The reaction mixture was heated under reflux for 1 hr, cooled, and poured into ice-cold NH_4Cl solution. Extraction of the product into benzene followed by removal of the solvent gave 15.0 g of a gummy solid which contained none of the starting ketone. Recrystallization from ethyl acetate or nitromethane–ether gave 0.8 g of material, mp 176–177°, which was not the desired product. It was eventually obtained, as the hydrochloride (1.6 g), from the mother liquors; λ_{max}^{EtOH} 258 mμ (ε 652).

1-(3,3-Diphenyl-2-oxopropyl)-4-phenyl-4-piperidinol Hydrochloride (27).—A mixture of 3-bromo-1,1-diphenyl-2-propanone[58] (1.1 g, 0.004 mole) and 4-phenyl-4-piperidinol (1.3 g, 0.008 mole) in dioxane (15 ml) was stirred for 16 hr at room temperature. Ether (25 ml) was added, the precipitate was filtered, and the solvent was evaporated leaving 1.3 g, mp 167–169°. This product was dissolved in acetone–ether and the hydrochloride (0.2 g) was prepared; mp 195–196°, ν_{max}^{Nujol} 1733 cm^{-1} (C=O), λ_{max}^{EtOH} 257 mμ (ε 815).

1-(3,3-Diphenyl-1-oxopropyl)-4-phenyl-4-piperidinol (28).—The filtrate from the preparation of the preceding hydrochloride was evaporated and the residue was recrystallized from ethyl acetate to give 0.2 g of material, mp 191–192°, $\nu_{max}^{CHCl_3}$ 1625 cm^{-1} (amide C=O), λ_{max}^{EtOH} 258 mμ (ε 725).

1-(4,4-Diphenyl-3-oxobutyl)-4-carbethoxy-4-phenylpiperidine Hydrobromide (30A).—The Mannich reaction between 1,1-diphenyl-2-propanone (8.4 g, 0.04 mole), 4-carbethoxy-4-phenylpiperidine hydrochloride (11.3 g, 0.04 mole), and paraformaldehyde (2.4 g, 0.08 mole) in 1,2-dimethoxyethane (45 ml) containing 5 drops of concentrated HCl was carried out as described for method H. The mixture was heated for 3.5 hr, cooled, and diluted with ether. The precipitated hydrochloride was combined with a further amount obtained by evaporation of the solvents and trituration of the residue with ether, giving a total of 16.1 g. It was converted *via* the free base to the hydrobromide: mp 193–195° dec; $\lambda_{max}^{50\%\ EtOH}$ 258, 290 mμ (ε 515, 202). On keeping this solution for 1 week at room temperature or for 2 hr at 70° the two peaks were obscured by end absorption and the shape of the resulting curve was very similar to the one described by Wilson and Kyi[26] for the decomposition of a related Mannich base. A portion of the purified salt was converted to the **hydrochloride 30B**, mp 169–171° (see Table III).

1-(3-Oxobutyl)-4-carbethoxy-4-phenylpiperidine Hydrochloride (XI). A.—A portion of the crude base described in the preceding experiment (which contained some unchanged paraformaldehyde) was dissolved in acetone and treated dropwise with ethereal HCl. During the addition an exothermic reaction set in and the initially formed precipitate redissolved. The mixture was chilled and the deposited product was recrystallized from acetonitrile–ether; mp 160–161° dec, undepressed by the sample prepared below; λ_{max}^{EtOH} 258 mμ (ε 322).

Anal. Calcd for $C_{18}H_{26}ClNO_3$: C, 63.54; H, 7.71; Cl, 10.43; N, 4.12. Found: C, 63.90; H, 7.97; Cl, 10.48; N, 4.01.

When a sample of *purified* base in acetone was treated with ethereal HCl, only the expected hydrochloride of 1-(4,4-diphenyl-3-oxobutyl)-4-carbethoxy-4-phenylpiperidine (**30B**) was obtained; mp and mmp 165–167°.

B.—A mixture of 4-carbethoxy-4-phenylpiperidine hydrochloride (10.8 g, 0.04 mole) and paraformaldehyde (2.4 g, 0.08 mole) in acetone (40 ml) and ethanol (15 ml) containing 5 drops of concentrated HCl was heated under reflux for 10 hr. Filtration and evaporation of the solvent gave 13.4 g (99%) of product, mp 162–163° dec. Recrystallization from acetone gave a sample, mp 162–164° dec. For material prepared by a different route, Protiva, *et al.*,[59] report mp 147–150°.

Method K. 2-(4-Carbethoxy-4-phenylpiperidino)ethyl 2,2-Diphenyl-2-ethoxyacetate (32).—A solution of 2,2-diphenyl-2-ethoxyacetic acid[60] (5.12 g, 0.02 mole) and 1-(2-chloroethyl)-4-carbethoxy-4-phenylpiperidine (from 6.7 g, 0.02 mole, of the hydrochloride)[61] in 2-propanol (40 ml) was heated under reflux for 16 hr. The solvent was evaporated, and the residue was shaken with $NaHCO_3$ solution and ether. Evaporation of the ether gave an oil which crystallized from pentane; mp 81–86° (5.0 g). An analytical sample had mp 87–88°.

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(58) C. L. Stevens and C. T. Lenk, *J. Org. Chem.*, **19**, 538 (1954).

(59) M. Protiva, J. O. Jilek, J. Pomykáček, J. Jirkovský, and Z. J. Vejdeläk, *Collection Czech. Chem. Commun.*, **28**, 2627 (1963).

(60) B. Wladislav and A. M. J. Ayers, *J. Org. Chem.*, **27**, 281 (1962).

(61) B. Elpern, P. Carabateas, A. E. Soria, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **81**, 3784 (1959).