New Psychotropic Agents. VI.[1] Basic Esters of 5-Hydroxydibenzo[a,d]cycloheptadiene-5-carboxylic Acid

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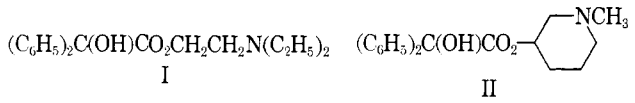
Treatment of dibenzo[a,d]cycloheptadiene-5-one with potassium followed by carbon dioxide gave 5-hydroxydibenzo[a,d]cycloheptadiene-5-carboxylic acid. The 2-diethylaminoethyl and 1-methyl-3-piperidyl esters were prepared as possible psychotropic agents. In addition the 2-diethylaminoethyl and 2-(diethylaminoethoxy)ethyl esters of dibenzo[a,d]cycloheptadiene-5-carboxylic acid were prepared. Pharmacological data concerning the central and autonomic nervous system activities of the compounds are presented together with the *in vitro* antispasmodic actions.

Certain basic esters of benzilic acid have, in addition to spasmolytic action, pronounced effects on the central nervous system. The 2-diethylaminoethyl ester (benactyzine, I) has been used as a tranquilizer[2] while 1-methyl-3-piperidyl benzilate (II) and related compounds[3] have marked psychotomimetic actions. Our recent results with some dibenzo[a,d]cycloheptadiene



I II

analogs of drugs containing the benzhydryl group[1] suggested the preparation of similar analogs of these two benzilates. In addition, the availability of dibenzo[a,d]cycloheptadiene-5-carboxylic acid[1] prompted the preparation of its 2-diethylaminoethyl and 2-(dimethylaminoethoxy)ethyl esters as potential spasmolytics.[4]

Treatment of dibenzo[a,d]cycloheptadiene-5-one (III) with lithium acetylide in liquid ammonia gave 5-ethynyldibenzo[a,d]cycloheptadiene-5-ol. Oxidation of this acetylenic alcohol with neutral, aqueous potassium permanganate[5] or with sodium dichromate in acetic acid failed to give 5-hydroxydibenzo[a,d]-cycloheptadiene-5-carboxylic acid (IV), the latter reagent giving chiefly the starting ketone (III). The failure to obtain 9-hydroxyfluorene-9-carboxylic acid by oxidation of 9-ethynyl-9-fluorenol has been reported.[6] The desired hydroxy acid was, however, obtained from III by treatment with potassium in liquid ammonia with subsequent carbonation. This method gives benzilic acid in 50% yield from benzophenone.[7] It could also be obtained in less pure form by treatment of the ketone with sodium in dimethoxyethane[6b] followed 18 hr. later by carbonation. Decreasing the reaction time to 1 hr. gave a lower yield of the hydroxy acid. The acid was somewhat unstable and could not be conveniently purified as such. Treatment with diazomethane gave the methyl ester, which could be readily purified. Interaction with phosphorus pentachloride[8] afforded 5-chlorodibenzo[a,d]cycloheptadiene-5-carbonyl chloride.

The basic esters were obtained by heating the appropriate acid and aminoalkyl chloride in 2-propanol.[9] The expected partial rearrangement of the basic side chain[10a,11] occurred when the hydroxy acid (IV) was treated with 1-methyl-3-chloropiperidine. A mixture of isomeric hydrochlorides (V and VI) resulted which could not be resolved conveniently as such but was converted directly to a mixture of the free bases. Heating this mixture at about 190° for 14 hr. gave the 1-methyl-3-piperidyl isomer which was purified by sublimation *in vacuo*. The 1-methyl-2-pyrrolidylmethyl isomer could be obtained in small amounts by chromatography of a hexane extract of the original mixture on silica gel. Examinations of the carbonyl regions in the infrared spectra were useful in determining the homogeneity of the isomers. The identity of the piperidyl ester was confirmed by acid hydrolysis and determination of the infrared spectrum of the resulting alcohol.[10a] Efforts to secure an authentic sample of this compound by interaction of 1-methyl-3-piperidinol with either methyl 5-hydroxydibenzo[a,d]cycloheptadiene-5-carboxylate in the presence of sodium methoxide[10a] or with the corresponding chloroacid chloride followed by treatment with water[12] were unsuccessful.

One ester, 2-(dimethylaminoethoxy)ethyl dibenzo-[a,d]cycloheptadiene-5-carboxylate, was prepared by interaction of dibenzo[a,d]cycloheptadiene-5-carbonyl chloride[1] with the requisite alcohol in pyridine.

Pharmacological Activity.—Four of the basic esters (1, 2, 5, and 6C) were tested in mice for potention of a sub-narcotic dose of ethanol and for mydriatic action; the results are found in Table II. In addition, 5 and 6C were compared to their respective benzhydryl compounds for their effects on motor activity in the motility cage method[13]; 10 animals were used at each dose studied. All administrations were given intraperitoneally. At a dose of 60 mg./kg., compound 5

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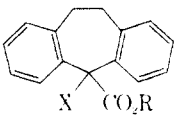
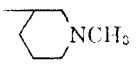
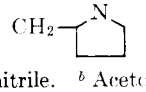
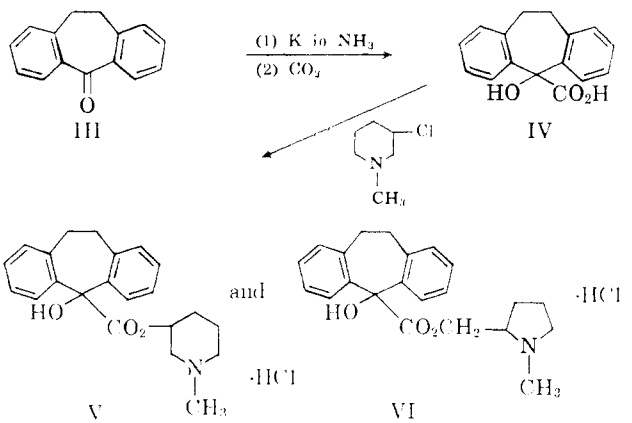
TABLE I

DIBENZO[a,d]CYCLOHEPTADIENE-5-CARBOXYLATES



X	R	No.	Salt	M.p., °C.	Yield, %	Recrystn. solv.	Formula	Analysis; calcd. over found C	H	Cl	N
H	$(CH_2)_2N(C_2H_5)_2$	1	HCl	201–202 dec.	77	[a]	$C_{22}H_{28}ClNO_2$			9.48	3.74
										9.46	3.99
H	$(CH_2)_2O(CH_2)_2N(CH_3)_2$	2	Citrate	100–104 dec.	46	[c]	$C_{28}H_{35}NO_{10}$	61.64	6.47		
								61.56	6.33		
H	C_2H_5	3		58–59	68	[e]	$C_{18}H_{18}O_2$	81.17	6.81		
								81.07	6.79		
HO	CH_3	4		139–140	65	[d,e]	$C_{17}H_{16}O_3$	76.10	6.01		
								76.06	6.31		
HO	$(CH_2)_2N(C_2H_5)_2$	5	HCl	227–228 dec.	57	[a]	$C_{22}H_{28}ClNO_3$	67.78	7.24	9.10	
								67.90	7.31	9.16	
		6A	Base	210–211 dec.			$C_{22}H_{25}NO_3$	75.18	7.17		3.99
								74.99	7.17		4.02
HO		6B	HCl + CH_3OH	218–219 dec.		[b]	$C_{23}H_{30}ClNO_4$	65.80	7.20	8.44	
								65.67	7.10	8.62	
		6C	HCl	211–213 dec.		[c]	$C_{22}H_{26}ClNO_3$	68.12	6.76	9.14	
								67.90	6.85	9.29	
HO		7	HCl	204–205		[g,h]	$C_{22}H_{26}ClNO_3$	68.12	6.76	9.14	
								67.90	6.94	9.28	

[a] Acetonitrile. [b] Acetone. [c] Hexane. [d] 2-Propanol. [e] Carbon tetrachloride. [f] Nitromethane. [g] Ether. [h] Methanol. [i] Dried *in vacuo* at 80° for 12 hr.



depressed the activity of male rats by 35%, whereas its benzhydryl analog, benactyzine, is known to cause motor stimulation in animals.[14] In our hands this compound increased the activity by 167 and 210% when given at 5 mg./kg. and 25 mg./kg., respectively. The same relationship held for 6C and 1-methyl-3-piperidyl benzilate; which were compared in male mice. In doses up to the LD_{50}, 6C elicited no evidence of stimulation but caused a slight (11%) depression at 20 mg./kg. The benzilate ester increased the activity by 90 and 150% when administered at 2 mg./kg. and 10 mg./kg., respectively, a finding in substantial agreement with that of Biel, *et al.*[19] The distinct lack of stimulating property in the dibenzo[a,d]cycloheptadiene esters may be due, in part, to the nonplanarity of the ring system.[6]

The antispasmodic actions of the four esters and the nonbridged analogs were compared in the isolated guinea pig ileum by the method of Magnus (see Table III). The values obtained for the antiacetylcholine activity of the reference compounds was of the same order as those previously reported[14–16] with the exception of 1-methyl-3-piperidyl benzilate. In our hands this compound had an activity considerably less than the published values.[16b,17]

TABLE II

PHARMACOLOGICAL ACTIVITY *in Vivo*[a]

	Compound No. 1	2	5	6C
LD_{50} (approx.) mg./kg.	110–130	110–130	170–200	180–220
Narcosis potentiation, ED_{50} mg./kg.[b]	19 ± 4	40 ± 4	48 ± 5	17 ± 2
Mydriasis caused by 0.25 LD_{50}[c] (10 mice)	13.2	6.4	7.3	13

[a] All values are for i.p. injection in mice and are expressed in terms of the free base. [b] The compounds were injected into 10 animals at each dose 30 min. before the injection of a subnarcotic (4 g./kg.) ethanol, i.p. The strength of potentiation was determined by the number of animals which lost the righting reflex after pretreatment with each dose (all-or-none). The ED_{50} values were calculated from an average of 30 to 40 animals by Litchfield and Wilcoxon's method (*J. Pharmacol. Exptl. Ther.*, **96**, 99 (1949)). [c] The numbers represent unit increases over control pupil diameter; 40 is approximately the maximal dilation.

The introduction of an *o,o'*-ethylene bridge between the benzene rings of the basic esters did not, in general, markedly affect the antispasmodic activities. The exceptions were compound 5 which showed a significantly lower antiacetylcholine activity than did benactyzine and compound 1 which was more active against histamine than its parent compound, adiphenine. The introduction of a methylene bridge between the two benzene nuclei in adiphenine to give the related 9,10-dihydroanthracene-9-carboxylate has been reported to increase considerably the potency against histamine and to slightly reduce the antiacetylcholine activity.[15,18]

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Experimental[19]

5-Hydroxydibenzo[a,d]cycloheptadiene-5-carboxylic Acid A.—Potassium (9.8 g., 0.25 g.-atom) was dissolved in liquid ammonia (400 ml.) and a solution of dibenzo[a,d]cycloheptadiene-5-one (20.8 g., 0.1 mole) in dry ether (100 ml.) was added dropwise over 0.5 hr. The ammonia was allowed to evaporate by the application of gentle heat and the volume of the mixture was maintained by the occasional addition of fresh ether. A large excess of finely divided Dry Ice was carefully added and the mixture was stirred overnight. During this time the original blue color disappeared and a creamy white suspension was formed. This was poured into cold water and the ether layer was separated. Chilling and careful acidification of the aqueous layer gave a precipitate of the hydroxy acid which, on combination with the material obtained from the chloroform extracts of the acidic solution, amounted to 12.4 g. (49% yield) and which melted over a range of 140–220° dec. Recrystallization of a portion from chloroform–hexane gave a sample darkening at 160° and finally decomposing at 230°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 74.99; H, 5.46.

B.—A 50% dispersion of sodium in paraffin wax (Gray Chemical Inc., 1.4 g., 0.03 g.-atom) was suspended in dry 1,2-dimethoxyethane (25 ml.) and to the mixture was added dibenzo[a,d]cycloheptadiene-5-one (5.2 g., 0.025 mole). A deep blue color developed almost at once. The mixture was stirred for 18 hr., carbonated, and the excess of sodium was destroyed with a little 2-propanol. Water was added, the neutral materials were extracted into ether, and the alkaline layer was acidified to give 5.5 g. of crude hydroxy acid as a yellow oil. Treatment with diazomethane (see below) gave the methyl ester m.p. 133–137° (from 2-propanol–hexane), yield, 2.0 g. (30%, based on the ketone).

Methyl 5-Hydroxydibenzo[a,d]cycloheptadiene-5-carboxylate (4).—An ethereal solution of diazomethane derived from N-nitrosomethylurea (20.6 g., 0.2 mole) was added to a chilled solution of the hydroxy acid obtained in (A) (16.0 g., 0.06 mole) in ether (100 ml.) until a yellow color persisted. The excess of diazomethane was destroyed by the cautious addition of acetic acid and the solution was washed with dilute bicarbonate and dried. Evaporation and one recrystallization of the residue from carbon tetrachloride–hexane (charcoal) gave 10.2 g. (65%) of the ester, m.p. 137–139°. An analytical sample (from 2-propanol) had m.p. 139–140° (see Table I).

5-Chlorodibenzo[a,d]cycloheptadiene-5-carbonyl Chloride.—Phosphorus pentachloride (12.1 g., 0.058 mole) was mixed with the hydroxy acid (7.0 g., 0.028 mole) and after about 2 min. an exothermic reaction ensued causing the temperature to rise to 75°. When this had subsided, the mixture was heated on the steam bath for 15 min. and the volatile materials were then removed by heating *in vacuo*. Recrystallization of the product from petroleum ether (b.p. 100–120°) (charcoal) and from carbon tetrachloride gave 4.6 g. (57%), m.p. 152–153° dec.

Anal. Calcd. for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.16; Cl, 24.35. Found: C, 66.15; H, 4.55; Cl, 24.16.

5-Ethynyldibenzo[a,d]cycloheptadiene-5-ol.—A stream of purified acetylene was passedin to lithium amide prepared from lithium (2.1 g., 0.3 g. atom) and liquid ammonia (400 ml.) containing a crystal of ferric nitrate. After 1.5 hr., dibenzo[a,d]cycloheptadiene-5-one (20.8 g., 0.1 mole) was added dropwise followed by dry ether (300 ml.). The mixture was stirred overnight at ambient temperature and was then treated with ammonium chloride (21 g.) followed by water. The ethereal layer was separated, dried, and evaporated. There was obtained 21.0 g. (90% yield) of product, m.p. 78–79°, unchanged on recrystallization from hexane.

Anal. Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.06; H, 5.86.

2-(Dimethylaminoethoxy)ethyl Dibenzo[a,d]cycloheptadiene-5-carboxylate (2).—A solution of 2-(dimethylaminoethoxy)-ethanol (2.31 g., 0.017 mole) in dry pyridine (5 ml.) was added dropwise to a slurry of dibenzo[a,d]cycloheptadiene-5-carbonyl chloride (4.45 g., 0.017 mole) in pyridine (10 ml.). The mixture was stirred at room temperature for 1 hr. and then heated on the steam bath for 45 min. It was cooled, diluted with water, and made alkaline with sodium carbonate. The product was taken up in benzene and the organic layer was washed well with water to remove most of the pyridine. This was followed by extraction with cold, dilute hydrochloric acid; the acidic layer was extracted with ether and then made alkaline. The liberated oil was collected in ether and the solution was dried and evaporated to furnish 3.9 g. of product. The citrate salt, rosettes from acetone, had m.p. 100–104° dec. (4.4 g., 46% yield) (see Table I).

(19) Melting points were read on a Thomas-Hoover Uni-melt apparatus.

TABLE III

ANTISPASMODIC ACTIVITY IN ISOLATED GUINEA PIG ILEUM

Compound	Antiacetylcholine EC_{50}, μg./ml.[a]	Antiacetylcholine % atropine	Antihistamine EC_{50}, μg./ml.[a]	Antihistamine % promethazine
1	0.12	3.3	0.10	4.0
Adiphenin	.10	4.0	.90	0.44
2	1.2	0.33	1.8	.23
Dimethoxanate[b]	1.1	.37	1.4	.27
5	0.2	2.0	0.7	.6
Benactyzine	.009	44	1.6	.25
6C	.2	2.0	0.4	1.0
1-Methyl-3-piperidyl benzilate	.08	5.0	.2	2.0
Atropine	.004	100		
Promethazine			.004	100

[a] The mean value was obtained from a minimum of 3 ileal strips from 2 or more guinea pigs at each of 3 or more concentrations. The mean values were plotted and the median effective concentration (EC_{50}) was calculated. All values are expressed in terms of the free base. [b] 2-(Dimethylaminoethoxy)ethyl phenothiazine-10-carboxylate was used as the reference compound in this case.

1-Methyl-3-piperidyl 5-Hydroxydibenzo[a,d]cycloheptadiene-5-carboxylate (6).—A mixture of the hydroxy acid (7.45 g., 0.029 mole) and 1-methyl-3-chloropiperidine (3.87 g., 0.029 mole) in dry 2-propanol (60 ml.) was heated under reflux for 19 hr. The solution was evaporated *in vacuo* and the residue was dissolved in water (900 ml.) containing a little hydrochloric acid. The solution was extracted with ether and then made alkaline with sodium bicarbonate. Extraction with benzene and evaporation of the solvent gave a mixture of the isomeric 3-piperidyl and 2-pyrrolidylmethyl esters as a gummy semisolid (6.6 g.). These were present in about equal amounts as shown by thin-layer chromatography of a sample on silica gel using 10% methanol in benzene as solvent (R_f values 0.55 ± 0.05 and 0.42 ± 0.05, respectively) and by examination of the infrared spectrum in the carbonyl group region. The crude mixture was stirred with a little hexane, filtered, and the filtrate set aside. The solid (6.1 g., m.p. 135–200°) was then heated in a Wood's metal bath at 180–190° (decomposition occurred if the temperature rose above 210°) for about 14 hr. or until the product contained none of the 2-pyrrolidylmethyl isomer. Sublimation at 180° (0.05 mm.) gave the 3-piperidyl ester, m.p. 209–212°; ν_{max} 1722 cm.$^{-1}$ (ester carbonyl). The hydrochloride crystallized from nitromethane as fine needles, m.p. 226–227° dec., and from methanol as a solvated form (cubes), m.p. 218–219° dec. Drying of the latter *in vacuo* at 70° for 12 hr. gave the pure salt. An analytically pure sample of the base, m.p. 210–211° dec., was obtained by treating the salt with dilute bicarbonate solution (see Table I).

The structure of the product was confirmed by acid hydrolysis of a sample following the procedure of Biel, *et al.*[10a] The acidic mixture was heated under reflux for 1.5 hr. and after it had been made strongly alkaline it was heated for a further 15 min. on the steam bath in an effort to complete the hydrolysis. The infrared spectrum of the product indicated the presence of some carbonylic material but the presence of the band at 987 cm.$^{-1}$ and absence of one at 1198 cm.$^{-1}$ was in agreement with the finding of Biel, *et al.*, for the spectrum of 1-methyl-3-hydroxypiperidine.

1-Methyl-2-pyrrolidylmethyl Dibenzo[a,d]cycloheptadiene-5-carboxylate (7).—The hexane filtrate from the crude mixture of isomeric esters described above was evaporated to give 0.5 g. of an oil which contained mainly the 2-pyrrolidylmethyl ester. Thick-layer chromatography of a portion on silica gel gave the pure compound which exhibited a split carbonyl band [1743 (intense) and 1720 cm.$^{-1}$ (weak)]. The hydrochloride was recrystallized from methanol–ether and was chromographically homogeneous; m.p. 204–205°, depressed on admixture with the other isomer.

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Some Reactions and Derivatives of 2,2-Diphenylcyclopentanone[1a]

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The preparation of several potential analgetics derived from 2,2-diphenylcyclopentanone and the reaction of some intermediate compounds is reported. An improved synthesis of the ketone is demonstrated.

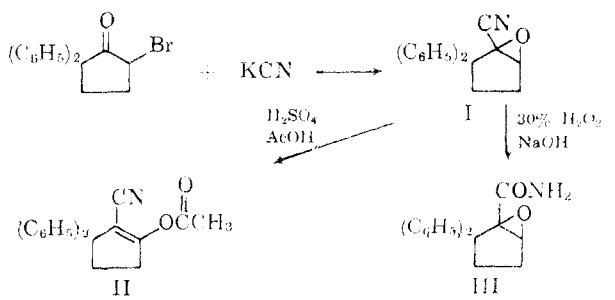
Previous publications[2-4] have disclosed the preparation of several substituted 2,2-diphenylcyclopentanones and have pointed out the structural relationships to the methadone class of analgetics. It was of interest to us to enlarge the scope of this synthesis and study various derivatives of these ketones.

The preparation of 2,2-diphenylcyclopentanone[3] consisted of the alkylation of diphenylacetonitrile with γ-chlorobutyronitrile followed by cyclization of the dinitrile and vigorous hydrolysis of the 2,2-diphenyl-5-cyanocyclopentanoneimine. Since the alkylation gave a mixture of products which was difficult to separate, this method gave a poor yield of the 2,2-diphenyladiponitrile. It was felt that if a trimethylene halide were used in the alkylation, the resulting halonitrile could be transformed to the dinitrile readily. Trimethylene iodide and trimethylene bromide gave largely 2,2,6,6-tetraphenylpimelonitrile, but the use of trimethylene chlorobromide, with dioxane as the solvent, gave virtually a quantitative yield of 5-chloro-2,2-diphenylpentanenitrile. The replacement of the halide with a nitrile group, using dimethylformamide as the solvent, was accomplished in an 87% yield. The 2,2-diphenyladiponitrile[5,6] melted at 66–67°, which confirms previous[3] results from these Laboratories.

Cyclization of the dinitrile gave 2,2-diphenyl-5-cyanocyclopentanoneimine[3] and a small quantity of a high melting compound which analyzed for the cyclic dimer,[7] 2,2,7,7-tetraphenyl-5,10-dicyano-1,6-diiminocyclodecane. Although the 5-membered imino nitrile has been hydrolyzed to give several products,[3] at no time has 2,2-diphenyl-5-cyanocyclopentanone been isolated. This keto nitrile and the corresponding keto acid were of interest to us. The inability to obtain this keto nitrile by preferential hydrolysis of the imino group is in contrast to the reactivity of other 2,2-disubstituted-5-cyanocyclopentanoneimines.[8] The bulky phenyl groups undoubtedly decrease the reactivity of the imino function as has been observed for other hindered imines.[9] The imino nitrile did not form a hydrochloride when an ether solution of the free base was saturated with hydrogen chloride. Diazotization of the imine-enamine nitrile with butyl nitrite–hydrogen chloride[10] gave a minute quantity of a solid which was not the desired material.

It appeared feasible to prepare 2,2-diphenyl-5-cyanocyclopentanone in the way 2-cyanocyclohexanone has been prepared from 2-bromocyclohexanone.[11] Treatment of 5-bromo-2,2-diphenylcyclopentanone[3] with potassium cyanide in water, ethanol, or dimethylformamide gave a product (I) isomeric with the desired keto nitrile. The infrared spectrum of I did not have any carbonyl absorption but did show the presence of nitrile and a strong absorption at 11.3 μ due to the 1,2-epoxide linkage.[12] The formation of I under these conditions had been predicted by Tchoubar.[13] Since it has been shown[14] in a hindered α-bromo ketone that the displacement of the bromine by methoxide was facilitated in liquid ammonia, the use of sodium cyanide in liquid ammonia was attempted, but this was also unsuccessful. Treatment of I with sulfuric acid followed by acetic acid gave an enol ester (II). Treatment of I with 30% hydrogen peroxide in the presence of sodium hydroxide gave the epoxy amide III.

CHART I



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