

The Effect of Alkyl-Substitution in Drugs—V. Synthesis and Chemical Properties of some Dibenzo [*a,d*]1,4-cycloheptadienyl Ethers

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Introduction

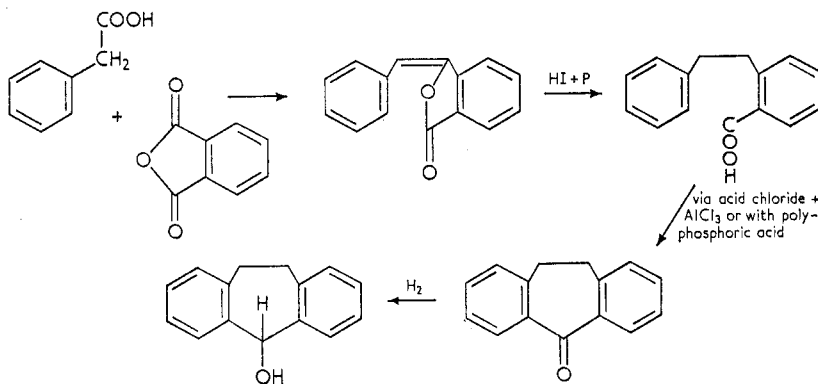
The relationship between structure and biological activity has been approached by us in recent years by studying, among other things, how the chemical, physicochemical and pharmacological properties of benzophenones, benzhydrols and benzhydryl amino ethers are altered by substitution, especially alkyl substitution. The results of the study of series of substituted dimethylaminoethyl benzhydryl ethers^{1,2} pointed to a strong influence of the spatial configuration of the molecule, especially with regard to the possible shapes of the side chain and the free rotation of one of the phenyl groups.

The influence of a type of substitution which would provide a bridge between the two phenyl groups and more or less immobilize them became of interest. Fluorenyl, xanthy and anthryl analogues with little biological activity have been recorded in the literature, but compounds with a bridge of two carbon atoms have not been described hitherto. Aminoethers of dibenzo[*a,d*]1,4-cycloheptadienol-5 and dibenzo[*a,e*]1,3,5-cycloheptatrienol-5 were therefore scheduled for synthesis. The first pharmacological results being not unfavourable, a number of substituted derivatives were also prepared.† Recently, a paper by Mychajlyszyn and Protiva³ came to our knowledge, in which they reported on work of a more limited scope along similar lines.

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† Patents applied for.

For the preparation of the aminoethers we used the 5-hydroxy-dibenzo[*a,d*]1,4-cycloheptadienes as starting products. These compounds were synthesized according to the following scheme used by Treibs and Klinkhammer^{4, 5, 7} who were the first to prepare the unsubstituted carbinol:



An analogous series of reactions was used to prepare halogen- and alkyl-substituted dibenzocycloheptadienes, starting from appropriately substituted phenylacetic acids. 2-Methyl, 4-methyl, 3,5-dimethyl, 4-*t*-butyl and 4-chlorophenylacetic acid yielded the corresponding benzaldehydes without much difficulty. The latter compounds could be smoothly converted into the substituted *ortho*-phenylethylbenzoic acids by reduction with a concentrated hydrogen iodide solution. The ring closure reaction may be carried out in various ways. We preferred the Friedel-Crafts reaction of the acid chloride with aluminium chloride in carbon disulphide to the ring closure with polyphosphoric acid. The former reaction yielded the ketones in good yields.

Dibenzo[*a,e*]1,3,5-cycloheptatrienones may be prepared from the dienones by bromination of the dienone and removal of one molecule of hydrogen bromide from the 10-bromo-compound, a method already described for the unsubstituted compound by Treibs and Klinkhammer⁵ and by Cope and Fenton.⁶ Bromination of dibenzocycloheptadienone with an excess of bromine leads to the formation of 10,11-dibromo-dibenzo[*a,d*]1,4-cycloheptadienone-5, a compound which Treibs⁵ prepared by addition of

bromine to dibenzocycloheptatrienone. When this substance is heated to the melting point, one molecule of hydrogen bromide is split off from the dibromide, yielding 10-bromodibenzo[*a,e*]1,3,5-cycloheptatrienone-5, likewise prepared by Treibs from the dibromide by means of potassium hydroxide. The reduction of the ketones to the carbinols is also possible by a variety of methods. We obtained good results with catalytic reduction and reduction with sodium amalgam, lithium aluminium hydride and aluminium isopropoxide.

The observation of Mychajlyszyn and Protiva as to the smooth formation of the di-dibenzocycloheptadienyl ether from the carbinol is fully borne out by our experience. Even very careful handling of the reduction mixtures did not always prevent the formation of the diether. In fact the great difficulty encountered in the purification of some of the substituted carbinols was attributed to contamination with the corresponding diethers.

The next step in the synthesis of the desired ethers was the conversion of the carbinols into the 5-chlorodibenzocycloheptadiene derivatives. As both the carbinols and the diethers react with hydrogen chloride to form the chlorides, in some cases we gave up the attempt to purify the carbinols completely.

By heating the chlorides, which were not isolated, with two equivalents of the basic alcohol, with or without a solvent, the corresponding ethers were synthesized. An attempt to replace one equivalent of basic alcohol by tributylamine resulted in the formation of dibenzocycloheptadienyldene dibenzocycloheptadiene along with the ether. The ethers may also be prepared by other methods, e.g. by heating the carbinols with the amino alcohols and toluenesulphonic acid. The ethers are subject to hydrolysis in an acid medium. The sensitivity to acid varies considerably with the amino alcohol from which the ether was derived. Among the ethers those of dimethylaminoethoxyethanol showed the greatest readiness to split off the amino alcohol.

Salts of the amino ethers were prepared by addition of an ethereal solution of an organic acid to the amino ether likewise dissolved in ether. In this way salts with oxalic acid, maleic acid, fumaric acid and citric acid could be obtained without difficulty. In some instances the methiodide was also prepared.

A number of the compounds synthesized showed interesting

pharmacological properties, especially as anticholinergics and antihistaminics, about which we intend to report at a later date.

Experimental*

Substituted phenylacetic acids. The phenylacetic acid used in the condensation reaction with phthalic anhydride was a commercial product. The other acids were prepared by the following methods.

2-Methylphenylacetic acid. This acid was synthesized according to Julian *et al.*⁸ via the following steps: xylene \rightarrow α -bromoxylene \rightarrow 2-methylphenylacetone \rightarrow 2-methylphenylacetic acid.

4-Methylphenylacetic acid was prepared from 4-methylacetophenone by a Willgerodt reaction⁹ using morpholine and sulphur as described by Newman¹⁰ for the synthesis of 2-naphthylacetic acid. A mixture of 4-methylacetophenone (134 g, 1 mole) sulphur (48 g) and morpholine (130.5 g) was slowly warmed up and then refluxed for 15 h. The hot reaction mixture was poured into 600 ml of hot anhydrous ethanol. The morpholide which crystallized on cooling was filtered by suction and washed with ethanol. The unpurified compound, yield 153 g (75 per cent), m.p. 99–104°, was refluxed for 5 h with a mixture of glacial acetic acid (400 ml), concentrated sulphuric acid (60 ml) and water (90 ml). The reaction mixture was then decanted from some tarry products and poured into water (3000 ml). On cooling, the acid crystallized; it was filtered by suction and washed with water. The acid was purified by solution in aqueous sodium hydroxide and reprecipitation with hydrochloric acid. Yield 67 g (44 per cent), m.p. 91–93°.

4-t-Butylphenylacetic acid could be obtained by the following sequence of steps: *t*-butylbenzene \rightarrow 4-*t*-butylbenzyl chloride \rightarrow 4-*t*-butylphenylacetone \rightarrow 4-*t*-butylphenylacetonitrile as described by Skinner *et al.*¹¹

The nitrile was saponified in the following way. A mixture of the nitrile (105 g), ethanol (105 ml), potassium hydroxide (57 g) and water (27 ml) was refluxed for 5 h. The ethanol was distilled off and the remaining mixture diluted with water and acidified. The precipitate was filtered off, dried and crystallized from ligroin. Yield 93 g (80 per cent), m.p. 79.5–80.5°.

* All melting points are uncorrected.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.9; H, 8.3.

3,5-Dimethylphenylacetic acid. For the synthesis of this acid a method was adopted which was analogous to that used for the *t*-butyl derivative.^{12,13} The carboxylation of mesityl potassium¹⁴ was not very successful in our hands.

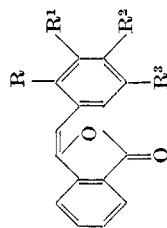
4-Chlorophenylacetic acid. This acid was also prepared from the nitrile. The 4-chlorobenzyl chloride which served as a starting product for the nitrile was obtained following the directions of Koishi and Nakazawa.¹⁵ The chloride was converted into the nitrile in the same way as described for benzylocyanide,¹⁶ yield 80 per cent, boiling range 139–144°/18 mm. The saponification was carried out as described for the *t*-butyl compound. The acid was crystallized from ligroin (boiling range 80–100°) and melted at 103–105°. Yield 68 per cent.

Benzalphthalides. All benzalphthalides were prepared by analogy with the preparation of the unsubstituted benzalphthalide as described by Weiss.¹⁷ The solvents used for crystallization were acetic acid or benzene. For melting points, analyses and yields see Table I. 4-Methylbenzalphthalide had previously been prepared by Ruhemann.¹⁸

2-Phenethylbenzoic acids. These compounds were prepared from the benzalphthalides by reduction with hydriodic acid. The synthesis of 2-(2-methylphenethyl)-benzoic acid will serve as an example. One mole of 2-methylbenzalphthalide was refluxed for 15 h with 550 ml of hydriodic acid (57 per cent) and 3 moles of red phosphorus. After the reaction the liquid was decanted and the remaining solid first washed with water and then extracted with a sodium hydroxide solution. The alkaline solution was acidified and the oil which precipitated extracted with ether. The ethereal solution was dried with sodium sulphate and concentrated. The residue was crystallized several times from ligroin (boiling range 80–100°), yield 68 per cent. The pure compound melted at 118–119.5°. For data on melting points, yields and analyses see Table II.

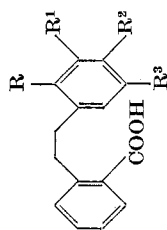
Ketones. The preparation of the ketones was carried out in a way similar to that described here for 1-methyl-dibenzo[*a,d*]1,4-cycloheptadienone-5. 2-(2-Methylphenethyl)benzoic acid (24 g, 0.1 mole) was refluxed with thionyl chloride (35.7 g, 0.3 mole).

Table I



R	R ¹	R ²	R ³	Analysis, %						m.p., °C	Yield, %
				Calcd.			Found				
				C	H	Cl	C	H	Cl		
H	H	H	H	81.87	5.16		81.3	5.1		100-101	see ref. ¹⁷
CH ₃	H	H	H							134-135	70
H	H	CH ₃	H	82.14	6.47		82.3	6.5		149-150	see ref. ¹⁸
H	H	<i>t</i> -C ₄ H ₉	H	81.57	5.63		81.4	5.5		107-108	60
H	CH ₃	H	CH ₃	70.18	3.51	13.82	70.3	3.6	13.6	143-145	65
H	H	Cl	H							144-145	67

Table II



R	R ¹	R ²	R ³	Analysis, %				Mol. wt.		m.p., °C	Yield, %
				Calcd.		Found		Calcd.	Found		
				C	H	C	H				
H	H	H	H	79.97	6.71	80.0	6.8	240.3	240	130-131	68
CH ₃	H	H	H	79.97	6.71	80.2	6.7	240.3	239	119-120	65
H	H	CH ₃	H	80.85	7.80	80.7	7.7	282.4	283	81-83	65
H	H	<i>tert</i> -C ₄ H ₉	H	80.29	7.13	80.4	7.4	254.3	258	130-132	65
H	CH ₃	H	CH ₃	69.10	5.02	69.1	5.0	260.7	258	115-116	74
H	H	Cl	H							121-123	62

see refs. 6, 19

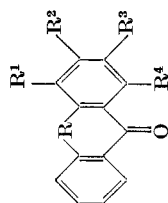
After the reaction, the excess of thionyl chloride was distilled off. The crystalline residue was dissolved in carbon disulphide (150 ml) and the solution added dropwise to aluminium chloride (20 g, 0.15 mole). Evolution of hydrogen chloride started immediately. The reaction mixture was refluxed for 6 h and then poured onto ice. The carbon disulphide layer was separated, and the aqueous solution was extracted with ether. The combined organic layers were dried and concentrated and the residue crystallized from ligroin (boiling range 80–100°). Yield 18.5 g (83 per cent), m.p. 67.5–68.5°.

3-Methyl-dibenzo[a,e]1,3,5-cycloheptatrienone-5. To a solution of 22 g (0.1 mole) of 3-methyl-dibenzo[a,d]1,4-cycloheptadienone-5 in 100 ml of carbon tetrachloride, 13.5 g (0.1 mole) of bromosuccinimide was added. After the mixture had been refluxed for 8 h, the succinimide was filtered off and the filtrate concentrated. The oily residue was dissolved in pyridine (15 ml) and the solution was refluxed for 2 h. The reaction mixture was then poured out into aqueous sulphuric acid and the oily reaction product extracted with ether. The ethereal solution was dried over sodium sulphate after which the ether was evaporated. The residue was crystallized from ligroin and melted after some purifications at 81–84°. Yield 78 per cent.

10,11-Dibromo-dibenzo[a,d]1,4-cycloheptadienone-5. To a solution of 5 g (0.024 mole) of dibenzocycloheptadienone in carbon tetrachloride, 7.7 g (0.048 mole) of bromine was added. The reaction mixture was stirred for 2 h. The dissolved hydrogen bromide was eliminated by passing a stream of dry air through the solution, from which a crystalline solid separated during this operation. The crystals were filtered off and purified by crystallization from acetic acid and benzene. The compound which was only slightly soluble in ethanol and in ligroin melted at 204–206°. Yield 65 per cent. The dibromoketone proved to be identical with the 10,11-dibromo compound prepared from dibenzocycloheptatrienone and bromine. At the melting point, hydrogen bromide escaped, yielding 9-bromodibenzocycloheptatrienone, m.p. 113–114°. For data on melting points, yields and analyses of the ketones see Table III.

The carbinols. The carbinols could be obtained from the ketones in various ways. They were often difficult to purify,

Table III



R	R ¹	R ²	R ³	R ⁴	Analysis, %				m.p. or boiling range, °C	Yield, %
					Calcd.		Found			
					C	H	C	H		
-CH ₂ -CH ₂ -	H	H	H	H	86.44	6.35	86.4	6.3	32	see refs. 4, 5, 6, 19
-CH=CH-	H	H	H	H	86.44	6.35	86.7	6.3	89	see refs. 4, 18
-CH ₂ -CH ₂ -	CH ₃	H	H	H	87.23	5.49	87.1	5.6	67-68	83
-CH ₂ -CH ₂ -	H	H	CH ₃	H	86.44	6.35	86.7	6.3	34-35	81
-CH=CH-	H	H	CH ₃	H	87.23	5.49	87.1	5.6	80-81	78
-CH ₂ -CH ₂ -	H	H	<i>t</i> -C ₄ H ₉	H	86.33	7.63	86.5	6.9	160-162/1 mm	83
-CH ₂ -CH ₂ -	CH ₃	H	CH ₃	H	86.41	6.40	86.5	6.9	110-112	50
-CH ₂ -CH ₂ -	H	H	Cl	H	74.23	4.57	74.0	4.4	63-64	40

presumably owing to the presence of amounts of diethers, which easily form from the carbinols in the presence of acid and at elevated temperatures. Decomposition of the reaction mixtures after reduction with sodium amalgam, aluminium isopropoxide, lithium aluminium hydride or potassium boron hydride was therefore invariably carried out with cooling and with as small an excess of acid as possible. Even with these precautions formation of the diether could not always be avoided. An example of the method used for reductions with lithium aluminium hydride is given below.

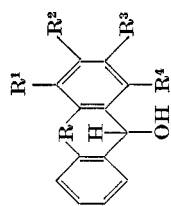
3-Methyl-dibenzo[a,e]1,3,5-cycloheptatrienol-5. An ethereal solution of ketone, (11.5 g, 0.052 mole) was added to a solution of LiAlH_4 (1.0 g, 0.026 mole) in ether (200 ml). The mixture was then refluxed for 4 h, after which it was decomposed by addition of moist ether and aqueous acetic acid. The ethereal layer was washed with water, dilute sodium hydroxide solution and again with water, and subsequently dried on sodium sulphate. Evaporation of the solvent yielded 8.5 g of a crystalline compound melting at $118\text{--}119.5^\circ$ after crystallizations from ligroin (boiling range $60\text{--}80^\circ$).

For data on melting points, yields and analyses of the carbinols see Table IV.

Ethers. Though ethers may be prepared from the carbinols and the amine alcohols by a variety of methods, most of the ethers were synthesized as follows.

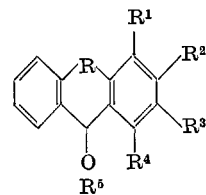
Dibenzocycloheptadienol-5 (63.1 g, 0.3 mole) was dissolved in benzene and hydrogen chloride was then passed through the solution for half an hour. The solution was dried with calcium chloride and, after filtration, evaporated to dryness to remove all hydrogen chloride. The residue was dissolved in xylene (350 ml) and added to a boiling solution of tropine (84.6 g, 0.6 mole) in xylene (180 ml). The reaction mixture was refluxed for 3 h, cooled, and the separated tropine hydrochloride filtered off. The filtrate was washed with water, dried and the solvent evaporated to yield an oily residue which was distilled under high vacuum; boiling range $172\text{--}178^\circ/0.1$ mm, yield 61.5 g (65 per cent). Though in this reaction the chloride was not isolated, it may be purified by crystallization from ligroin (boiling range $80\text{--}100^\circ\text{C}$), m.p. $103\text{--}104^\circ$.

Table IV



R	R ¹	R ²	R ³	R ⁴	Analysis, %						m.p., °C	Yield, %
					Calcd.			Found				
					C	H	Cl	C	H	Cl		
—CH ₂ —CH ₂ —	H	H	H	H							91-92	see refs. 5, 7
—CH=CH—	H	H	H	H							119-120	see ref. 20
—CH ₂ —CH ₂ —	CH ₃	H	H	H	85.66	7.19		85.3	7.0		97-100	90
—CH ₂ —CH ₂ —	H	H	CH ₃	H	85.66	7.19		85.3	7.0		124-126	87
—CH=CH—	H	H	CH ₃	H	86.44	6.35		86.1	6.2		118-120	75
—CH ₂ —CH ₂ —	H	H	<i>t</i> -C ₄ H ₉	H	85.66	8.33		86.3	7.5		102-104	80
—CH ₂ —CH ₂ —	H	CH ₃	H	CH ₃	85.69	7.62		86.3	7.5		117-118	75
—CH ₂ —CH ₂ —	H	H	Cl	H	73.62	5.36	14.49	72.8	5.2	14.6		

Table V



R	R ¹	R ²	R ³	R ⁴	R ⁵	Salt with
—CH ₂ —CH ₂ —	H	H	H	H	dimethylaminoethyl-	maleic acid
—CH ₂ —CH ₂ —	H	H	H	H	dimethylaminopropyl-	oxalic acid
—CH ₂ —CH ₂ —	H	H	H	H	5-diethylamino-2-pentyl-	oxalic acid
—CH ₂ —CH ₂ —	H	H	H	H	dimethylaminoethoxyethyl-	oxalic acid
—CH ₂ —CH ₂ —	H	H	H	H	N-pyrrolidylethyl-	oxalic acid
—CH ₂ —CH ₂ —	H	H	H	H	N-morpholinoethyl-	oxalic acid
—CH ₂ —CH ₂ —	H	H	H	H	1-methyl-4-piperidyl-	maleic acid
—CH ₂ —CH ₂ —	H	H	H	H	2,2,6-trimethyl-4-piperidyl-	maleic acid
—CH ₂ —CH ₂ —	H	H	H	H	tropinyl-	maleic acid
—CH ₂ —CH ₂ —	H	H	H	H	tropinyl-	methiodide
—CH ₂ —CH ₂ —	H	H	H	H	pseudotropinyl-	fumaric acid
—CH=CH—	H	H	H	H	dimethylaminoethyl-	maleic acid
—CH=CH—	H	H	H	H	tropinyl-	maleic acid
—CH ₂ —CH ₂ —	CH ₃	H	H	H	tropinyl-	oxalic acid
—CH ₂ —CH ₂ —	H	H	CH ₃	H	dimethylaminoethyl-	maleic acid
—CH ₂ —CH ₂ —	H	H	CH ₃	H	tropinyl-	maleic acid
—CH=CH—	H	H	CH ₃	H	tropinyl-	maleic acid
—CH ₂ —CH ₂ —	H	H	<i>t</i> -C ₄ H ₉	H	tropinyl-	maleic acid
—CH ₂ —CH ₂ —	H	CH ₃	H	CH ₃	tropinyl-	fumaric acid
—CH ₂ —CH ₂ —	H	H	Cl	H	dimethylaminoethyl-	maleic acid
—CH ₂ —CH ₂ —	H	H	Cl	H	dimethylaminoethoxyethyl-	oxalic acid

Analysis, %						Mol. wt.		m.p., °C	Yield, %
Calcd.			Found			Calcd.	Found		
C	H	N	C	H	N				
69.50	6.85		69.9	7.1				118-120	65
68.55	7.06	3.64	67.8	7.3	3.4	385.4	387	135-136.5	50
70.73	7.99	3.18	70.2	8.0	3.3	465.5	459	148-149	43
66.48	7.04	3.38	66.5	7.0	3.6	415.5	418	123-124	69
69.49	6.85	3.53	69.4	7.1	3.5	397.5	402	137-139	45
66.80	6.58	3.39	66.7	6.3	3.3	421.5	419	142-143	55
70.90	6.90	3.31	71.4	6.9	3.5	422.5	425	151-152	60
71.65	7.57	3.09	71.9	7.3	3.2	451.6	451	195-196	40
72.14	6.95	3.12	72.2	7.1	3.4	449.5	448	133-136	50
60.63	6.36	2.95	60.4	6.1	2.7	475.4	470	190-191	80
72.14	6.95	3.12	72.2	7.2	3.3	449.5	443	155-159	30
69.85	6.37	3.55	69.6	6.5	3.5	395.4	403	125-128	57
72.46	6.54	3.13	72.2	6.5	3.3	447.5	440	173-175	25
71.38	7.14	3.20	70.7	7.3	3.1	437.4	433	177-178	58
70.05	7.11	3.41	70.5	7.1	3.6	411.5	412	124-125	38
72.54	7.17	3.02	72.0	7.3	2.8	463.5	454	161-162	25
72.87	6.77	3.03	72.4	6.7	3.1	461.5	452	188-189	40
73.64	7.77	2.77	73.7	7.8	2.7	453.6	449	222-223	40
72.92	7.39	2.93	72.4	7.0	2.9	477.3	469	163-166	40
64.02	6.07	3.24	64.2	6.1	3.4	431.9	433	131-132	42
61.39	6.27		60.9	6.0	^a	449.9	453	124-126	20

^a Chlorine: calcd. 7.89; found 7.5.

Anal. Calcd. for $C_{15}H_{13}Cl$: C, 78.77; H, 5.73; Cl, 15.50. Found: C, 78.5; H, 5.6; Cl, 15.2.

Salts of the bases were prepared by solution of the base in ether and addition of an organic acid in ether until no further precipitate was formed. In some cases only the oxalate could be obtained in a crystalline state. Crystallization of the salts is possible from ethanol, acetone, ethyl acetate, chloroform or from mixtures of these solvents with ether.

Some salts of the base described above have the following melting points: maleate: 133–135.5°, fumarate: 181–182.5°, citrate: 164.5–166°, succinate: 157–159°. Aqueous solutions of these salts which have a pH < 5 decompose after some hours of standing, yielding a crystalline precipitate which consists of the corresponding carbinol. Neutral solutions, however, are stable.

For data on melting points, yields, analyses, etc. see Table V. In most cases the yields mentioned were obtained in reactions carried out only a few times; they by no means represent the maxima attainable under the conditions used. Low yields are due to losses accompanying the purification of the salts.

Summary. In order to obtain information about the relationship between structure and activity in the dibenzocycloheptadienyl aminoether series, aminoethers were prepared of dibenzo[*a,d*]1,4-cycloheptadienol-5, dibenzo[*a,e*]1,3,5-cycloheptatrienol-5 and some of their alkyl- and chlorine-substituted derivatives. These carbinols with substituents in one of the benzo-groups were synthesized in the following way. Substituted benzal-phthalides were prepared by condensation of various substituted phenylacetic acids with phthalic anhydride. Reduction converted the benzal-phthalides into the 2-phenethylbenzoic acids which were ring-closed yielding the dibenzo[*a,d*]cycloheptadienones. Trienones could be prepared from them by reaction with bromine and elimination of one molecule of hydrogen bromide. The ketones were reduced to the carbinols, which were converted into the corresponding aminoethers. Methyl and *t*-butyl groups and chlorine atoms were used as substituents. For the synthesis of the ethers described the following amino alcohols were used: dimethylaminoethanol, dimethylaminopropanol, dimethylaminoethoxyethanol, 5-diethylaminopentanol-2, *N*-pyrrolidinoethanol, *N*-morpholinoethanol, 1-methyl-4-piperidinol, 2,2,6-trimethyl-4-piperidinol, tropine and pseudotropine.

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