or decreased rates of responding. An anorexogenic effect of **5A**, observed initially in cats, was confirmed in experiments with rats, where an appetite depressant action for **5A** was clearly demonstrated. The neurophysiological and biochemical mechanisms which underlie the effects observed with compound **5A** are as yet undetermined. That the mode of action includes a sympathomimetic mechanism, as in the case of *d*-amphetamine, is discounted tentatively on the evidence that the compound does not reverse to excitation the state of behavioral quiescence induced by prior administration of reserpine. That this material potentiates the action of hexobarbital, rather than antagonizing its effects, persuasively supports this interpretation. *In vivo* and *in vitro* tests have revealed no monoamine oxidase inhibiting properties for **5A**. Cardiovascular experiments seem to indicate that **5A** is devoid of the hypertensive and cardiac acceleratory effects associated with *d*-amphetamine. From these considerations we conclude that the behavioral effects observed with 3-methyl-4-(1-phenyl-2-propylamino)-2-phenylmorpholine hydrochloride depend for their manifestation upon other than sympathomimetic or monoamine oxidase inhibiting properties.

Anticonvulsants. II. Spiro Compounds. Dibenzo[*a*,*d*]cycloheptadiene-5,5′-hydantoins, -5,5′-oxazolidinediones, and -5,2′-succinimides

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Spiro{dibenzo[*a*,*d*]cycloheptadiene-5,5′-hydantoin} (IIa), an analog of diphenylhydantoin, was prepared by the rearrangement of dibenzo[*a*,*e*]cyclooctadiene-5,6-dione (III) with urea and alkali and by heating 5-hydroxydibenzo[*a*,*d*]cycloheptadiene-5-carboxylic acid (VII, R = H) with urea alone. Substitution of thiourea in the first method gave the corresponding spirothiohydantoin (V) which was then converted to the desthio compound (VI). The spirohydantoins IIb, IIc, and IV were prepared in the normal manner from dibenzo[*a*,*e*]cycloheptatriene-5-one (Ib), dibenzo[*a*,*d*]cyclooctadien-5-one (Ic), and dibenzo[*a*,*e*]cyclooctadiene-5-one *via* interaction with potassium cyanide and ammonium carbonate. This method, however, gave none of the spirohydantoin (IIa) from dibenzo[*a*,*d*]cycloheptadien-5-one (Ia). The interaction of methyl 5-hydroxydibenzo[*a*,*d*]cycloheptadiene-5-carboxylate (VII, R = CH_3) and urea in alkali gave a spirooxazolidinedione (VIII). The acid-catalyzed cyclization of 5-cyano-5-carboxyalkyldibenzo[*a*,*d*]cycloheptadienes (IXa–c) and an analogous cycloheptatriene (IXd) produced the corresponding spirosuccinimide and spiroglutarimide derivatives (Xa–d). A spiropyrrolidone (XIIIa) and a spiropiperidone (XIIIc) were formed by the hydrogenation of the methyl esters of the appropriate cyano acids (IXa,c). Heating the methyl ester of IXc with ammonia and hydrogen sulfide with subsequent cyclization of the thiocarboxamide (XV) by acid gave the spirothioglutarimide (XVI). The spiro{dibenzo[*a*,*d*]cycloheptadiene-5,2′-succinimide} (Xa) possessed a promising order of anticonvulsant action in mice while the spirohydantoins had, contrary to expectations, only minimal activities.

Our investigation of the dibenzo[*a*,*d*]cycloheptadiene analogs of anticonvulsants containing the benzhydryl group[1] has now been extended to the synthesis of certain spiro compounds. These include the analogs of diphenylhydantoin, -oxazolidinedione, -succinimide, and -glutarimide.[2] Similar spiro derivatives were also prepared from the dibenzo[*a*,*e*]cycloheptatriene, dibenzo[*a*,*d*]cyclooctadiene, and dibenzo[*a*,*e*]cyclooctadiene ring systems. The spirohydantoin derived from fluorenone has been reported to possess anticonvulsant action in humans.[3]

The interaction of dibenzo[*a*,*d*]cycloheptadiene-5-one (Ia) with ammonium carbonate and potassium cyanide in acetamide under a variety of conditions[4] failed to give the spirohydantoin IIa. In contrast, dibenzo[*a*,*e*]cycloheptatriene-5-one (Ib) gave IIb in 40% yield. Low yields of the spirohydantoin derived from xanthone have been reported,[5] although fluorenone forms the hydantoin in good yield.[4,6] It was possible to obtain the desired spirohydantoin IIa by hydrogenation of IIb over palladium or by rearrangement of dibenzo[*a*,*e*]cyclooctadiene-5,6-dione (III) with urea and alkali, following procedures used for the preparation of diphenylhydantoin from benzil.[7] In the absence of urea, alkali alone or with added copper sulfate[8] did not cause the rearrangement of diketone III to 5-hydroxydibenzo[*a*,*d*]cycloheptadiene-5-carboxylic acid (VII, R = H). The lower homolog of III, dibenzo[*a*,*d*]cycloheptadiene-10,11-dione, has been reported to undergo the benzilic acid rearrangement.[9] It was possible to convert the hydroxy acid (VII, R = H), prepared by a different method,[10] into the spirohydantoin IIa by heating it with urea at 135–140°, following a similar preparation for diphenyl-

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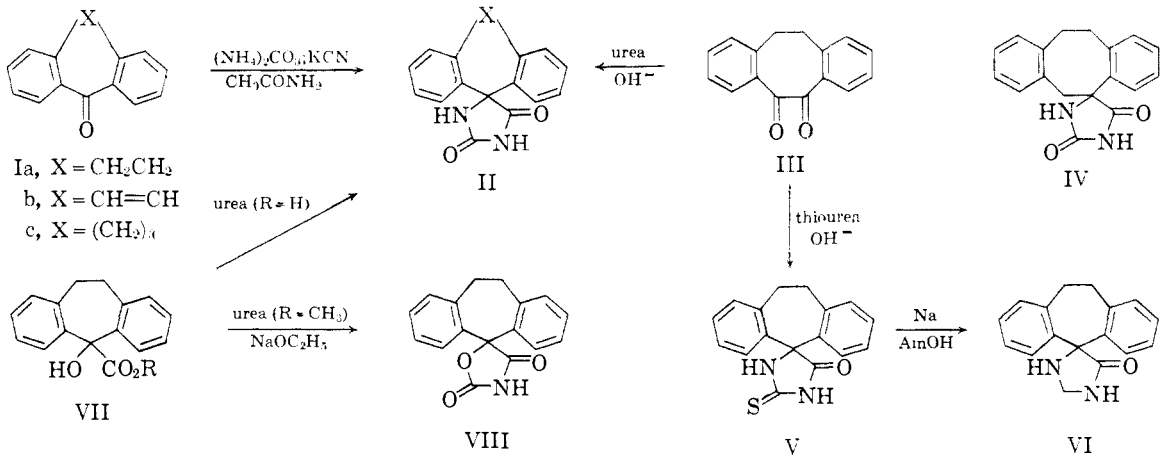
hydantoin.[7b] If the mixture was gradually heated to 220°[11] an intractable mixture resulted from which none of the desired hydantoin could be isolated. In a manner similar to that used for the preparation of 5,5-diphenyl-2-thiohydantoin,[12] the interaction of diketone III with thiourea and alkali gave the spirothiohydantoin (VI) in 31% yield. Removal of the sulfur to give spiro{dibenzo[*a,d*]cycloheptadiene-5,4′-imidazolidin}-5′-one (VI) was best accomplished by the action of sodium in amyl alcohol.[13] As was the case with 5,5-diphenyl-2-thiohydantoin,[14] the action of Raney nickel on the spirothiohydantoin was not straightforward and gave little or none of the desired compound. The action of ammonium carbonate and potassium cyanide on dibenzo[*a,d*]cyclooctadien-5-one (Ic) and dibenzo[*a,e*]cyclooctadien-5-one gave the corresponding spirohydantoins (IIc and IV) in yields of 5 and 82%, respectively. Compound IV may be considered as an analog of 5-benzyl-5-phenylhydantoin which was reported to have anticonvulsant activity.[2]

Methyl 5-hydroxydibenzo[*a,d*]cycloheptadiene-5-carboxylate (VII, R = CH_3) could be obtained from the acid and diazomethane[10] or directly from the ketone (Ia) by treatment with sodium and dimethyl carbonate, a method used to prepare methyl benzilate from benzophenone.[15] The condensation of the ester with urea in the presence of sodium ethoxide[16] gave the spirooxazolidinedione (VIII) in good yield. Treatment of this with ethereal diazomethane readily furnished the N-methyl derivative (XVII).



The cyano acids IXa–d were prepared by alkylation of 5-cyanodibenzo[*a,d*]cycloheptadiene and -[*a,e*]cycloheptatriene with the appropriate bromo ester, with subsequent saponification under mild, alkaline conditions. The alkylation was best carried out in ethanol with sodium ethoxide as described for the condensation of diphenylacetonitrile with halo esters[17]; the use of sodium hydride[18] in toluene gave, in each case, lower yields. Potassium *t*-butoxide[19] in *t*-butyl alcohol gave none of the cyano acid IXb.

The cyclization to the spirosuccinimide Xa was accomplished by heating IXa with boiling, concentrated hydrochloric acid, conditions which are reported to give not the imide but α,α-diphenylsuccinic acid from 3-cyano-3,3-diphenylpropionic acid.[17a,b,20] Reaction times from 1.5 to 12 hr. were employed without markedly affecting the yield of Xa; some of the corresponding diacid (XIa) was obtained from the longer periods. A similar method gave the spirosuccinimides Xb and Xd. Preparation of the former compound gave, in addition to a small quantity of unchanged cyano acid, a by-product having the characteristics of an anhydride (absorption at 1850, 1775, 1000, and 940 $cm.^{-1}$) while the synthesis of the latter gave an acidic material, presumably XId, which could not be purified satisfactorily. The formation of the anhydride by-product was not unexpected in view of the report that the analogous 3-cyano-3,3-diphenyl-2-methylpropionic acid on heating with hydrochloric acid gave only α,α-diphenyl-β-methylsuccinic anhydride.[21] Miller and Long[17a] have prepared α,α-diphenylsuccinimides by treating the diacid with an amine and subsequent heating at elevated temperatures. Treatment of XIa with methylamine in this manner failed, however, to give the spirosuccinimide; decarboxylation occurred and the amide (XII) was isolated. The spirosuccinimide derived from fluorene also could not be prepared by this method owing to extensive decarboxylation.[17a]

α,α-Diphenylglutarimide has been prepared from 4-cyano-4,4-diphenylbutyric acid by treatment with 80–85% sulfuric acid[22] or preferably by boiling with acetic acid containing a small amount of sulfuric acid.[23] Application of the first method to IXc gave none of the spiroglutarimide (Xc) while the second procedure gave the cyclic product in 51% yield. As has been reported for 4-cyano-4,4-diphenylbutyric acid,[17c,22a] IXc was unaffected by boiling with concentrated hydrochloric acid. It may be noted that 4-cyano-4,4-

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diphenyl-2-methylbutyric acid readily formed the corresponding glutarimide under these conditions.[23]

The spirosuccinimide Xa gave the N-methyl- (XVIII) and N-3-dimethylaminopropyl (XIX) derivatives when a methanolic solution was treated with sodium followed by the appropriate alkylating agent.[18] Reduction with lithium aluminum hydride in tetrahydrofuran failed to give the 4′-deoxy derivative. The isomeric 1′-deoxy compound, a spiropyrrolidone (XIIIa), was obtained by catalytic hydrogenation of the methyl ester of IXa, following the conditions used for the preparation of 4,4-diphenylpyrrolidin-2-one.[19,24] Similar treatment of the methyl ester of IXc furnished the spiropiperidone (XIIIc) which in turn was reduced with lithium aluminum hydride to the corresponding spiropiperidine (XIV). The latter is a cyclic analog of the antidepressant agent 5-(3-methylaminopropylidene)dibenzo[*a,d*]cycloheptadiene (desmethylamitriptyline).[25] Following the conditions used for the corresponding benzhydryl compound,[26] a methanolic solution of the methyl ester of IXa was heated with ammonia and hydrogen sulfide to give the thiocarboxamide derivative (XV). This was then cyclized to the spirothioglutarimide (XVI) by treatment with acid.

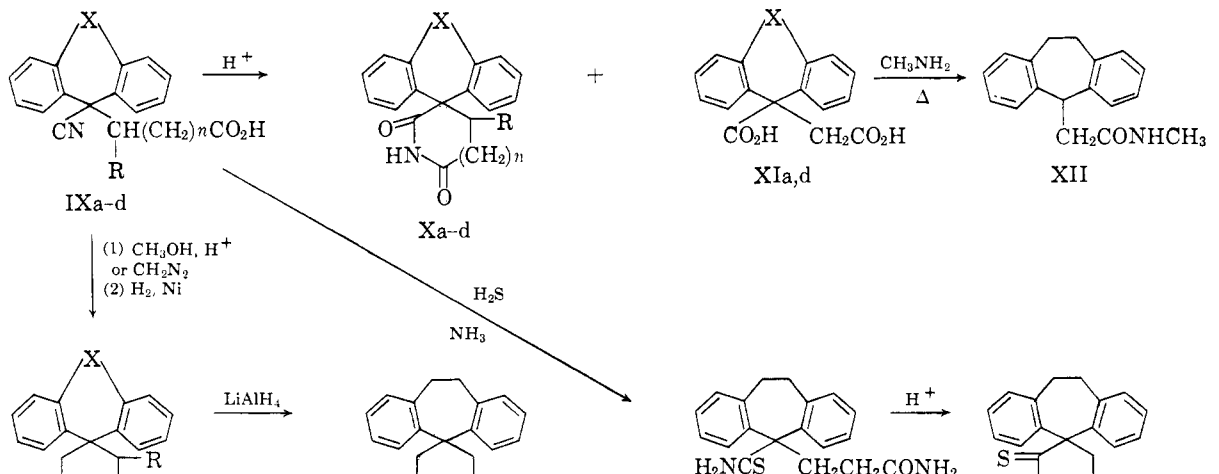
5,5-Diphenylbarbituric acid has been prepared from diphenylmalonyl chloride[27] which may be derived from diphenylketene and oxalyl chloride.[28] A convenient route to the ketene is the dehalohydrogenation of diphenylacetyl chloride with tripropylamine in ether.[29] The treatment of dibenzo[*a,d*]cycloheptadiene-5-carbonyl chloride[30] or dibenzo[*a,d*]cycloheptatriene-5-carbonyl chloride[1] with this base gave, however, only small amounts of the corresponding ketenes (absorption at 2110 cm.$^{-1}$; ν_{max} 2110 cm.$^{-1}$ (diphenylketene)) which could not be conveniently separated from the unchanged starting materials. Carrying out the reaction under more vigorous conditions led to extensive decomposition. Diphenylacetic acid on treatment with sodium–naphthalene complex in tetrahydrofuran followed by carbonation gives diphenylmalonic acid in 60% yield.[31] Application of this method to dibenzo[*a,d*]cycloheptadiene-5-carboxylic acid failed to give practical amounts of the corresponding diacid. Attempted carbethoxylation of ethyl dibenzo[*a,d*]cycloheptadiene-5-carboxylate[10] with diethyl carbonate[32] in the presence of sodium hydride similarly failed to give the 5,5-diester.

Biological Activity.—The biological activities of the spirohydantoin derivatives were investigated in mice. Our tests included acute toxicity, anticonvulsant activity, and neurotoxic effect. The details of the methods were described previously.[1] The compounds were injected in the form of suspensions which were made up with 4 to 5 drops of Tween-80 in 10 ml. of water. In most cases the approximate LD_{50} values were determined using at least 20 mice per compound; in other cases the LD_{50} values were determined by the method of Litchfield and Wilcoxon,[33] injecting 4 to 5 doses to groups of 10 mice each.

The protective effects of the compounds against the tonic phase of maximal electroshock seizures (MES) and against the tonic phase of pentylenetetrazole convulsions were tested in a similar way to that described by Swinyard, *et al.*[34]

The ataxia produced by the compounds was measured in mice by means of the rotating bar test[35]; using groups of 10 mice, the ED_{50} values were calculated.

The biological activities of the spiro analogs of diphenylhydantoin (IIa–c) depended markedly on the



a, X = CH_2CH_2, R = H, n = 0; b, X = CH_2CH_2, R = CH_3, n = 0; c, X = CH_2CH_2, R = H, n = 1; d, X = CH=CH, R = H, n = 0

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nature of the bridge joining the two aromatic rings. As mentioned above, the fluorene spirohydantoin had good anticonvulsant action.[3] Our compounds with different bridges were practically devoid of anticonvulsant activity. Moreover, the spirodibenzo[*a,d*]cyclooctadiene derivative (IIc) proved to be a potent convulsant. Mice receiving 30–40 mg./kg. intraperitoneally exhibited characteristic behavior which consisted of over-all tremors interrupted by spastic convulsions. The tremors resembled in part those caused by Tremorine® but there were no signs of parasympathetic stimulation (salivation, drop in body temperature, etc.). This compound was also one of the most toxic of the series but mice receiving convulsant doses recovered fully after the convulsions had stopped (3–4 hr.).

The anticonvulsant effects of 5,5-diphenyltetrahydroimidazolin-4-one and 5,5-diphenyloxazolidine-2,4-dione have been demonstrated in humans.[2b] Their bridged analogs, VI and VIII, respectively, had only very weak activity in our tests.

As has been reported,[3a] α,α-diphenylsuccinimide was found to have good anticonvulsant activity. The most active anticonvulsant in the present investigation was the corresponding spirodibenzo[*a,d*]cycloheptadiene analog (Xa). It afforded protection in mice in doses as low as 5% of its LD_{50} and had very good oral absorption together with a low order of neurotoxic effect (ataxia). The related 1′-deoxy compound (XIIIa) also had a good order of anti-MES activity when given intraperitoneally but had neurotoxic effect in relatively low doses. The remaining compounds had only minimal activities.

Experimental

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

Dibenzo[*a,e*]cyclooctadiene-5-one. A.—Phosphorus tribromide (201 g., 0.07 mole) dissolved in dry benzene (15 ml.) was added gradually to a solution of 2-(2-phenethyl)benzyl alcohol[37] (159 g., 0.07 mole) in dry benzene (1000 ml.) maintained between 0 and 5°. The mixture was stirred for 1.5 hr., poured carefully onto a large excess of crushed ice, and the benzene layer was washed with cold water, then dilute bicarbonate solution, and dried. Evaporation of the solvent left 208 g. of 2-phenethylbenzyl bromide[37] as an oil. If the reaction mixture was not kept cold throughout, considerable amounts of dibenzo[*a,d*]cycloheptadiene,[30] m.p. 76°, were also formed. The action of boiling 48% hydrobromic acid on the alcohol gave in our hands only this hydrocarbon.

B.—The bromide was converted, *via* the nitrile, to 2-phenethylphenylacetic acid,[35,38] m.p. 92–93°, in 79% yield. A small amount of 2-phenethylphenylacetamide, m.p. 119–121° (from benzene–hexane) was also produced during the acid hydrolysis of the nitrile (0.6%).

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.54; H, 7.16; N, 5.67.

C.—Cyclization of the acid with polyphosphoric acid[35,38] gave dibenzo[*a,e*]cyclooctadien-5-one, which in larger preparations was best purified by distillation; b.p. 150–160° (0.1–0.2 mm.), m.p. 94–95° (lit.[37] m.p. 93–94°).

Dibenzo[*a,e*]cyclooctadiene-5,6-dione (III).—A solution of dibenzo[*a,e*]cyclooctadien-5-one (11.0 g., 0.05 mole) and selenium dioxide (8.0 g., 0.074 mole) in acetic anhydride (15 ml.) was kept in an oil bath maintained between 140–150° for 3.5 hr. The mixture was cooled and the precipitated solids were filtered. The product was isolated by stirring the filter cake with chloroform, removal of the selenium, and evaporation of the solvent, thus giving 8.9 g. of the diketone, m.p. 131–133°. The original acetic anhydride filtrate was added to warm water, the mixture was extracted with chloroform, the organic phase washed with water, then dried and evaporated. One recrystallization of the residue from 2-propanol gave a further 1.4 g. of product (total yield 82%), m.p. 130–132° (lit.[37] m.p. 131–132°).

The treatment of dibenzo[*a,e*]cyclooctadien-5-one with butyl nitrite and sodium ethoxide with subsequent decomposition of the isonitroso ketone by formaldehyde and hydrochloric acid according to the published method[37] gave a lower yield of product which was also difficult to obtain in a pure state.

Methyl 5-Hydroxydibenzo[*a,d*]cycloheptadiene-5-carboxylate (VII, R = CH_3).—A solution of dibenzo[*a,d*]cycloheptadien-5-one (Ia; 10.4 g., 0.05 mole) in dry ether (50 ml.) was added to sodium (2.3 g., 0.1 g.-atom) dissolved in liquid ammonia (200 ml.) and thereupon a solution of dimethyl carbonate (4.5 g., 0.05 mole) in ether (50 ml.) was added. The mixture was stirred at ambient temperature for 3 hr., and ammonium chloride (5.4 g., 0.1 mole) was carefully added. The ammonia was evaporated, ether was added, and the mixture was filtered. Evaporation of the ether and recrystallization of the residue first from carbon tetrachloride and then from 2-propanol gave 2.4 g. (18%) of the ester, m.p. 137–139°.

5-Cyanodibenzo[*a,d*]cycloheptadiene-5-acetic Acid (IXa).—A solution of 5-cyanodibenzo[*a,d*]cycloheptadiene[30] (55.0 g., 0.25 mole) and sodium ethoxide (from 8.1 g., 0.35 g.-atom, of sodium) in absolute ethanol (400 ml.) was heated under reflux for 1 hr.; a green color developed. The solution was cooled to room temperature and treated dropwise with ethyl bromoacetate (58.5 g., 0.35 mole). The mixture was then heated under reflux for 3 hr., filtered, and evaporated. The resulting ester was hydrolyzed by heating under reflux for 15 min. with potassium hydroxide (20 g.) in 1:1 ethanol–water (300 ml.). The bulk of the ethanol was removed *in vacuo*, the solution diluted with water, and extracted with ether. Acidification of the alkaline layer gave 62.7 g. (91%) of the cyano acid, m.p. 171–174°. An analytical sample melted at 173–175° (from aqueous ethanol or ethyl acetate).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.18; H, 5.53; N, 5.03.

2-{5-Cyanodibenzo[*a,d*]cycloheptadiene-5}-propionic Acid (IXb).—In a manner similar to the one described above, the nitrile (11.0 g., 0.05 mole), sodium (1.7 g., 0.07 g.-atom), and ethyl 2-bromopropionate (12.7 g., 0.07 mole) in ethanol (150 ml.) gave the crude ester together with 4.0 g. of unchanged nitrile, m.p. 89–90°. Hydrolysis by potassium hydroxide (5.0 g.) in aqueous ethanol as above gave a neutral fraction (2.7 g.) containing a little unchanged ester, together with the desired acid. Recrystallization from ethyl acetate–hexane gave prisms, m.p. 164–166° (3.1 g., 21%).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.34; H, 6.12; N, 4.80.

3-{5-Cyanodibenzo[*a,d*]cycloheptadiene-5}-propionic Acid (IXc).—The nitrile (22.0 g., 0.10 mole), sodium (3.44 g., 0.14 g.-atom) and ethyl 3-bromopropionate (27.1 g., 0.14 mole) in ethanol (250 ml.) interacted and the resulting ester was hydrolyzed with potassium hydroxide (15 g.). The acid was recrystallized from ethyl acetate, m.p. 146–147° (15.9 g., 55%).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 77.82; H, 6.19; N, 4.61.

5-Cyanodibenzo[*a,e*]cycloheptatriene-5-acetic Acid (IXd).—The interaction of 5-cyanodibenzo[*a,e*]cycloheptatriene[1] (13.0 g., 0.06 mole), sodium (1.73 g., 0.075 g.-atom), and ethyl bromoacetate (12.5 g., 0.075 mole) in ethanol (200 ml.) gave the desired ester together with unchanged nitrile, (7.8 g.), m.p. 100–101°. Hydrolysis with potassium hydroxide (5.0 g.) in aqueous methanol gave a further 1.3 g. of the nitrile together with the desired acid. Recrystallization from ethyl acetate–hexane gave 1.7 g. (10%) of product, m.p. 195–196°.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.16; H, 5.29; N, 5.18.

3-{5-Cyanodibenzo[*a,d*]cycloheptadiene-5}-propionic Acid Methyl Ester A.—A suspension of the cyano acid (IXc) (21.8 g., 0.08 mole) in ether (250 ml.) was treated with a slight excess of ethereal diazomethane. Evaporation of the solvent and recrystallization of the residue from methanol gave 16.3 g. (71%) of the methyl ester, m.p. 85–86°.

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Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.52; H, 6.22; N, 4.47.

B.—Following a procedure for the analogous benzhydryl compound,[23] a solution of 5-cyanodibenzo[*a,d*]cycloheptadiene (10.9 g., 0.05 mole) in methanol (30 ml.) containing sodium (0.1 g.) was heated under reflux while methyl acrylate (4.7 g., 0.055 mole) was added dropwise through the condenser. Heating was continued for 1 hr., the solvent removed *in vacuo*, and the residue was taken up in benzene. The solution was washed with water, then dried and evaporated, and the residue was triturated with a little methanol. Recrystallization from this solvent furnished 3.2 g. (21%) of product, m.p. 85–87°.

3-{5-Thiocarbamoyldibenzo[*a,d*]cycloheptadiene-5}-propionamide (XV).—An ice-cold mixture of the preceding methyl ester (5.5 g., 0.02 mole) and methanol (70 ml.) was saturated with ammonia and then hydrogen sulfide. It was then heated in an autoclave at 125° for 4 hr., cooled, and evaporated. The residue was slurried with water, then a little chloroform, and the insoluble material was recrystallized from methanol to give 2.0 g. (34%) of product, m.p. 219–221° dec. An analytical sample melted at 222–224° dec.

Anal. Calcd. for $C_{19}H_{20}N_2OS$: N, 8.64; S, 9.87. Found: N, 8.58; S, 9.88.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,4′-imidazolidine}-2′,5′-dione (IIa). (A).—An intimate mixture of 5-hydroxydibenzo[*a,d*]cycloheptadiene-5-carboxylic acid[10] (2.54 g., 0.01 mole) and urea (1.25 g., 0.02 mole) was heated in an oil bath at 135–140° for 6 hr.; water and ammonia were evolved. The cooled mixture was pulverized and triturated well with dilute sodium hydroxide solution. The alkaline filtrate was acidified and the precipitate thus formed was slurried in dilute sodium bicarbonate solution, filtered, and dried. There was obtained 0.2 g. (7%) of the crude spirohydantoin, m.p. 279–280°, raised to 309–311° dec. on recrystallization from 1-propanol–hexane mixture.

B.—A mixture of spiro{dibenzo[*a,e*]cycloheptatriene-5,4′-imidazolidine}-2′,5′-dione (3.3 g.) and 10% palladium on charcoal (1.0 g.) in absolute ethanol (200 ml.) was shaken at ambient temperature for 10 hr., under an atmosphere of hydrogen with an initial pressure of 3.5 kg./cm.^{2}. The mixture was filtered, the filtrate was combined with the ethanol washings of the catalyst, and the solvents were removed *in vacuo*. The residue which contained a little unchanged starting material was recrystallized to give 0.6 g. (18%) of product, m.p. 309–311° dec., identical with the sample prepared above; λ_{max}^{EtOH} 242 (i), 267(i), 277(i), and 297(i) mμ (ε 2120, 970, 690, and 37).

C.—A mixture of dibenzo[*a,e*]cyclooctadiene-5,6-dione (III; 0.6 g., 0.0025 mole), ethanol (1 ml.), and 50% sodium hydroxide solution (1.5 ml.) was stirred for 10 min. at room temperature. Urea (0.3 g., 0.005 mole) was added and the mixture was heated under reflux for 2 hr.; a dark red color developed. It was cooled, diluted with water (10 ml.), and the precipitate was collected. Recrystallization from aqueous acetic acid afforded 0.1 g. of material, m.p. 219–220°, whose properties did not support the expected 3α,6α-disubstituted tetrahydroimidaz[*d*]imidazole-2,5-(1H,4H)dione (glycoluril) structure.[7,39]

The alkaline filtrate was acidified and the resulting precipitate was recrystallized once from 1-propanol–hexane to give 0.1 g. (14%) of the spirohydantoin, m.p. 312°.

Spiro{dibenzo[*a,e*]cycloheptatriene-5,4′-imidazolidine}-2′,5′-dione (IIb).—A mixture of dibenzo[*a,e*]cycloheptatrien-5-one (Ib, 13.4 g., 0.062 mole), potassium cyanide (5.6 g., 0.086 mole), and ammonium carbonate (25.0 g.) in fused acetamide (90 g.) was placed in an autoclave and kept at 135–145° for 84 hr. The mixture was cooled, stirred with water (300 ml.), and filtered; acidification of the filtrate gave an insignificant amount of product. The water-insoluble material was stirred with dilute hydrochloric acid, filtered and dried, and then triturated with several portions of ether in order to remove unchanged ketone. The product was recrystallized from dimethylformamide–2-propanol mixture to give 6.8 g. of the spirohydantoin (40% yield based on the initial quantity of ketone); m.p. >360°; λ_{max}^{EtOH} 297 mμ (ε 13,350). An analytical sample was obtained by sublimation at 250° (0.05 mm.).

Spiro{dibenzo[*a,d*]cyclooctadiene-5,4′-imidazolidine}-2′,5′-dione (IIc).—A mixture of dibenzo[*a,d*]cyclooctadien-5-one[40] (13.8 g., 0.062 mole), potassium cyanide (5.6 g., 0.086 mole), ammonium carbonate (30 g.), and acetamide (100 g.) was heated at 155° for 84 hr. The cooled mixture was stirred into cold water (1 l.) containing a little sodium hydroxide. The insoluble material was filtered to give 11.3 g. of unchanged ketone, m.p. 145–148°. The filtrate was acidified and the precipitate thus formed was sublimed at 250° (0.05 mm.) to give 1.0 g. of the hydantoin, m.p. 255–257°. Purification by recrystallization from ethanol or chloroform could not be effected due to the tendency of the material to deposit in solvated forms.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,4′-imidazolidin}-5′-one-2′-thione (V).—A mixture of the diketone (III, 7.7 g., 0.033 mole) and 50% sodium hydroxide (2.6 ml.) in ethanol (150 ml.) was stirred for 10 min., treated with thiourea (2.5 g., 0.033 mole), and heated under reflux for 15 min. Part of the solvent was removed *in vacuo* and the mixture was added to water and filtered. Acidification of the filtrate and recrystallization of the product from ethanol–hexane gave 3.0 g. (31%), m.p. 232–233°.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,4′-imidazolidin}-5′-one (VI).—Sodium (2.3 g., 0.1 g.-atom) was added in small portions to spiro{dibenzo[*a,d*]cycloheptadiene-5,4′-imidazolidin}-5′-one-2′-thione (2.7 g., 0.009 mole) in dry amyl alcohol (30 ml.). The mixture was heated at 100° for 0.5 hr. (foaming). Methanol (25 ml.) was added and the heating was continued for an additional 0.2 hr. The cooled mixture was added to water, the organic layer was separated, combined with the ethylene dichloride extracts of the aqueous layer, washed with water, and evaporated. Recrystallization of the residue from ethanol afforded 1.0 g. (42%) of product, m.p. 201–202°.

Spiro{dibenzo[*a,d*][1,4]cycloheptadiene-5,5′-oxazolidine}-2′,4′-dione (VIII).—To a solution of sodium (0.65 g., 0.028 g.-atom) in anhydrous ethanol (25 ml.) was added methyl 5-hydroxydibenzo[*a,d*]cycloheptadiene-5-carboxylate (7.5 g., 0.028 mole) and dry urea (1.7 g., 0.028 mole). The mixture was stirred and heated under reflux for 16 hr., ammonia being evolved. The solution was concentrated *in vacuo*, cooled, and diluted with cold water (100 ml.). A little sodium hydroxide was added and the mixture was extracted with ether. The aqueous layer was acidified with cooling and the liberated product was taken up in ether. Washing the ether with water followed by drying and evaporation gave tan crystals, m.p. 185–189° dec. (5.9 g., 80%). The product was obtained as prisms from 2-propanol–hexane, m.p. 194–196° dec., deposition of the crystals from the solution being complete only after 2 to 3 days.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,5′-oxazolidine}-3′-methyl-2′,4′-dione (XVII).—A solution of the preceding compound (2.7 g., 0.01 mole) in ether (75 ml.) was treated at 5° with an ethereal solution of diazomethane derived from N-nitrosomethylurea (3.0 g., 0.03 mole) until a permanent yellow color remained. The solution was kept for an additional 0.5 hr. and was then evaporated *in vacuo*. Recrystallization of the residue from carbon tetrachloride–hexane afforded 2.5 g. (89%) of product, m.p. 152–153°.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,3′-pyrrolidine}-2′,5′-dione (Xa).—A well stirred mixture of 5-cyanodibenzo[*a,d*]-cycloheptadiene-5-acetic acid (20.0 g.) and concentrated hydrochloric acid (150 ml.) was heated under reflux for 8 hr. It was diluted with water and the precipitate was filtered and stirred with sodium bicarbonate solution. The alkali-insoluble material was collected and recrystallized from aqueous ethanol to give 14.8 g. (74%) of the spirosuccinimide, m.p. 218–220°.

Acidification of the bicarbonate solution gave 3.3 g. of white crystals, m.p. 197–198°, unchanged on recrystallization from ethyl acetate–2-propanol mixture. This material was the corresponding succinic acid, 5-carboxydibenzo[*a,d*]cycloheptadiene-5-acetic acid (XIa).

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.63; H, 5.68; N, nil.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,3′-pyrrolidine}-1′-methyl-2′,5′-dione (XVIII) A.—The preceding succinimide (6.9 g., 0.025 mole) was added to sodium methoxide (2.7 g., 0.05 mole) dissolved in methanol (70 ml.) and the clear solution was treated dropwise with dimethyl sulfate (6.3 g., 0.05 mole). The mixture was gradually heated to boiling and kept there for 15 min. Chilling afforded 6.1 g. (84%) of the product as white needles, m.p. 136–137°, unchanged on recrystallization from ethyl acetate–hexane mixture.

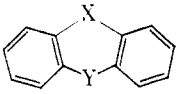
B.—5-Carboxydibenzo[*a,d*]cycloheptadiene-5-acetic acid (4.5 g., 0.015 mole) was added in portions to methylamine (25% in water, 20 ml.) to form a clear solution which soon thickened to a heavy paste. This was heated gradually to 210° and held there

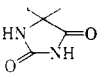
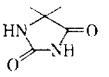
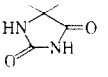
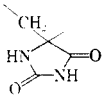
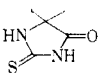
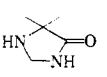
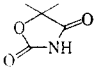
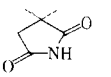
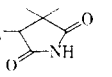
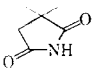
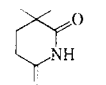
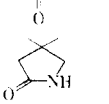
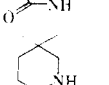
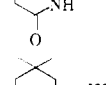
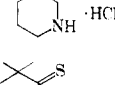
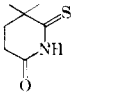
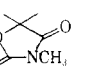
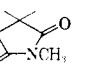
(39) R. G. Neville, *J. Org. Chem.*, **23**, 1588 (1958).

(40) S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart, and R. Gaudry, *J. Med. Chem.*, **6**, 130 (1963).

TABLE I

SPIRODIBENZOCYCLOALKADIENES AND -TRIENES



No.	X	Y	M.p., °C.	Recrystn. solvent	Yield, %	Formula	Calcd., % / Found, % C	H	N
IIa	CH_2CH_2		309–311 dec.	*a*, *b*	18	$C_{17}H_{14}N_2O_2$	73.36 73.02	5.07 5.11	10.07 10.04
IIb	CH=CH		>360	*c*, *d*, *e*	40	$C_{17}H_{12}N_2O_2$	73.90 73.94	4.38 4.54	10.14 10.12
IIc	$(CH_2)_3$		255–257	*e*, *f*	5	$C_{18}H_{16}N_2O_2$	73.95 73.72	5.52 5.69	9.58 9.60
IV	CH_2CH_2		298–300	*b*, *d*, *g*	82	$C_{18}H_{16}N_2O_2$	73.95 73.96	5.52 5.77	9.58 9.66
V	CH CH$_2$		232–233	*b*, *h*	31	$C_{17}H_{14}N_2OS$	69.37 69.53	4.80 5.11	9.52[q] 9.40
VI	CH_2CH_2		201–202	*h*	42	$C_{17}H_{16}N_2O$	77.25 77.05	6.10 6.28	10.60 10.50
VIII	CH_2CH_2		194–196 dec.	*b*, *d*	80	$C_{17}H_{15}NO_3$	73.11 72.85	4.69 4.87	5.02 5.01
Xa	CH_2CH_2		218–220	*h*, *i*	74	$C_{18}H_{15}NO_2$	77.96 77.57	5.45 5.56	5.05 5.04
Xb	CH_2CH_2		238–240	*h*, *j*	43	$C_{19}H_{17}NO_2$	78.33 78.18	5.88 5.86	4.81 4.73
Xd	CH=CH		218	*b*, *h*	15[n]	$C_{18}H_{13}NO_2$	78.51 77.98	4.76 4.59	5.10 5.00
Xe	CH_2CH_2		213–214	*k*	51	$C_{19}H_{17}NO_2$	78.33 78.18	5.88 6.04	4.81 4.63
XIIIa	CH_2CH_2		201–202	*b*, *h*	43	$C_{18}H_{15}NO$	82.10 81.77	6.51 6.45	5.32 5.55
XIIIc	CH_2CH_2		211–212	*h*	70	$C_{19}H_{19}NO$	82.28 82.21	6.91 6.85	5.05 5.04
XIV	CH_2CH_2		263–265 dec.	*h*, *l*		$C_{19}H_{22}ClN$	11.82[p] 11.74		4.67 4.48
XVI	CH_2CH_2		174–175	*b*, *m*	36	$C_{19}H_{17}NOS$	74.25 73.94	5.58 5.59	4.56[r] 4.83
XVII	CH_2CH_2		152–153	*b*, *n*	89	$C_{18}H_{15}NO_2$	73.70 73.96	5.15 5.30	4.78 4.68
XVIII	CH_2CH_2		136–137	*b*, *m*	84	$C_{19}H_{17}NO_2$	78.33 78.43	5.88 5.71	4.81 4.84
XIX	CH_2CH_2		224–225	*d*		$C_{23}H_{27}ClN_2O_2$	69.25 69.05	6.82 6.51	8.89[p] 8.99

[a] 1-Propanol. [b] Hexane. [c] Dimethylformamide. [d] 2-Propanol. [e] Sublimed at 250° (0.05 mm.). [f] Deposited as a solvated form on recrystallization from chloroform. [g] Sublimed at 220–250° (0.1 mm.). [h] Ethanol. [i] Water. [j] Sublimed at 200° (0.1 mm.). [k] Acetonitrile. [l] Ether. [m] Ethyl acetate. [n] Carbon tetrachloride. [o] Prepared by heating IXd under reflux for 2 hr. with concentrated HCl. [p] Chlorine. [q] *Anal.* Calcd.: S, 10.87. Found: S, 10.76. [r] *Anal.* Calcd.: S, 10.41. Found: S, 10.12.

TABLE II

RESULTS OF THE PHARMACOLOGICAL INVESTIGATIONS[a]

Compound	LD_{50}, i.p.	MES ED_{50}, i.p. (oral)	Antipentylenetetrazole ED_{50}, oral	Ataxia ED_{50}, oral
IIa	160	>50	>50	28 ± 4
IIb	>1000	210 ± 37 (>400)	67 ± 17	>400
IIc	85	>20		27 ± 4
IV	>1000	>400	>400	>400
VI	330	216 ± 14 (>200)	>200	>200
VIII	650	153 ± 3 (>400)	>400	>400
Xa	750	35 ± 6 (38 ± 5)	33 ± 3	430 ± 38
Xb	>1000	175 (>400)		>400
Xc	900	>400	>400	>400
XIIIa	440	40 ± 2 (105 ± 7)	82 ± 5	112 ± 22
XIIIc	>1000	200 ± 18 (255 ± 28)	410 ± 40	440 ± 68
XIV	35	5 ± 0 6		15
XVI	650	>150		
XVII	>1000	>400		>400
XVIII	1100	172 ± 12 (510 ± 37)	145 ± 17	>600
Diphenylhydantoin sodium	170 ± 13	9.6 ± 1.6 (8.9 ± 1)	7 ± 0.5	84 ± 9

[a] Doses in mg./kg.

for 5 min. On cooling, a light brown gum was obtained which was triturated with cold aqueous ethanol and the resulting precipitate was collected and stirred with sodium bicarbonate solution. The insoluble material (3.5 g.) was collected, dried, and recrystallized from carbon tetrachloride–hexane to give N-methyl dibenzo[*a,d*]cycloheptadiene-5-acetamide (1.1 g.), as short, white needles, m.p. 149–150°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.19; H, 6.99; N, 5.67.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,3′-pyrrolidine}-1′-(3-dimethylaminopropyl)-2′,5′-dione (XIX).—The spirosuccinimide (Xa; 5.5 g., 0.02 mole) and sodium methoxide (1.12 g., 0.022 mole) in methanol (60 ml.) was treated with 3-dimethylaminopropyl chloride (from 6.3 g., 0.04 mole of the hydrochloride). The solution was heated under reflux for 1.5 hr., evaporated, and the residue was stirred with a little dilute sodium hydroxide solution. The insoluble oil was taken into chloroform and the solution was washed with water, dried, and evaporated to furnish 6.0 g. of a sticky solid, m.p. 103–104°. Recrystallization from ethyl acetate–hexane gave 5.3 g. (73%) of the free base, m.p. 105–106°.

Anal. Calcd. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.42; H, 7.25; N, 7.67.

The hydrochloride was prepared in the usual manner (see Table I.).

Spiro{dibenzo[*a,d*]cycloheptadiene-5,3′-piperidine}-2′,6′-dione (Xc).—A mixture of 3-{5-cyanodibenzo[*a,d*]cycloheptadiene-5}-propionic acid (7.0 g.), glacial acetic acid (30 ml.), and concentrated sulfuric acid (15 drops) was heated under reflux for 3 hr. The mixture was evaporated *in vacuo* and the residue was triturated with warm, dilute sodium bicarbonate solution until effervescence was complete. The insoluble material was collected and recrystallized from acetonitrile giving prisms m.p. 213–214° (3.6 g., 51%).

Acidification of the aqueous filtrate gave 2.0 g. of unchanged cyano acid.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,4′-pyrrolidin}-2′-one (XIIIa).—5-Cyanodibenzo[*a,d*]cycloheptadien-5-acetic acid was converted to the methyl ester by heating it under reflux for 8 hr. with methanol containing a little *p*-toluenesulfonic acid. A solution of the ester (9.8 g.) in methanol (100 ml.) was hydrogenated over Raney nickel with an initial pressure of 80 kg./cm.^{2} for 18.5 hr. at 100°. The catalyst was filtered, the solution was evaporated, and the residue was recrystallized from ethanol–hexane to give 3.8 g. (43%), m.p. 201–202°.

Spiro{dibenzo[*a,d*]cycloheptadiene-5,3′-piperidine}(XIV).—A solution of the spiropiperidone (XIIIc; 4.2 g., 0.015 mole) in dry tetrahydrofuran (100 ml.) was added gradually to lithium aluminum hydride (1.14 g., 0.030 mole) in the same solvent (10 ml.). The mixture was heated under reflux for 12 hr., cooled, then hydrolyzed and filtered. The solvent was removed and the residue was recrystallized from ether to give 2.0 g. (50%) of the base, m.p. 130–131°.

Anal. Calcd. for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.56; H, 7.90; N, 5.23.

The hydrochloride was prepared (see Table I.).

Spiro{dibenzo[*a,d*]cycloheptadiene-5,3′-piperidin}-6′-one-2′-thione (XVI).—A solution of 3-{5-thiocarbamoyldibenzo-[*a,d*]cycloheptadiene-5}-propionamide (1.5 g.) in acetic acid (15 ml.) was warmed to 70° and concentrated sulfuric acid (0.2 ml.) was added. It was then kept at 100° for 1 hr., cooled, and poured into ice–water. The precipitated solid was filtered, washed with water, and dried. Recrystallization from ethyl acetate–hexane gave 0.5 g. (36%) of product as leaflets, m.p. 174–175°.

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