Synthesis of 10,11-Dihydro-5,10-ethano-5*H*-dibenzo[*a*,*d*]cycloheptenes with Various Side Chains at Position 12

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Novel 5,10-ethano- and methano-bridged compounds **3**, **5**, and **10** were synthesized from known **1** and **7**. Difficulties inherent in further work with these and similar bridged ketols were circumvented by developing a new, independent, and unambiguous synthetic approach to 5,10-ethano-bridged 12-oxo compound **22** *via* Dieckmann closure of diester **18** to enolic keto ester **19**, hydrolysis, and decarboxylation. In order to reach **17**, the precursor of **18**, from either **12** or **15**, alkylation of malonic ester with 5-chloro-10-bromodibenzo[*a*,*d*]cycloheptene giving **13** and selective triethyl phosphonoacetate reaction of **15** and hydrolysis giving **16** were invoked, followed by further reactions through **14** and **16**, respectively, involving selective hydrolyses taking advantage of the relatively inert character of the 10-carboxamide group and the 10,11 double bond. Hydrogenation of the latter function in hot HOAc (Pd) is possible, given an inert group at position 10. A number of typical reactions of **19** and bridged ketone **22** are described, including hydride reduction of **19** to **20** and conversion of **22** to oximes **21**, to aldehyde **23** by $(CH_3)_2S(O)CH_2$, and to unsaturated nitrile **24a** and ester **24b** by Wadsworth–Emmons reactions. The latter, *via* intermediates **25** and methoxime **21b**, were converted by standard methods to a series of homologous, 12-ω-aminoalkyl compounds **26**.

A preceding paper[1] described a novel synthesis of 10-cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one and from it a number of 5,10-bridged heterocyclic compounds. An objective similar to that in the earlier work was to synthesize 5,10-*carbon* bridged 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes bearing functional groups suitable for further conversion to other moieties. As will be evident in this report, such a goal was reached by the use of classical synthetic methods.

Alkylations of the versatile intermediate **1**, *e.g.*, to **4** (Scheme I), were explored earlier,[1] and we now report on its Michael additions. With acrylonitrile and methyl acrylate in the presence of Triton B, **2a** and **2b**, respectively, were obtained from **1**. With a stronger base ($KOCMe_3$) the sterically favored closure to ethano-bridged ketols, **3a** and **3b**, respectively, occurred, **3a** predictably being formed more readily than **3b**. The change ketone → **3** was easily detected by disappearance of the intense uv 270-nm absorption. In the presence of NaH, ester **2b** similarly gave acid ketol **3c**. The related closure of **4** to a 5,10-methano-bridged ketol **5** was found to be less facile than **2** → **3**, as one might expect on steric grounds and from the greater efficiency of ethano as compared to methano bridging found by Nenitzescu, *et al.*, in exploring a different type of bridge closure ($\Delta^{10,11}$-π participation in solvolysis of 5-ω-hydroxyalkyl) in the same system.[2]

A related approach also explored was reaction of epoxy ketone **7** with nucleophiles. Earlier, **7** had been found to yield cyanoenone **15** with cyanide.[1] Reactions of **7**[3] with sodio ethylmalonate and ethyl cyanoacetate[4] now gave lactone ester **8a** and lactone nitrile **9**, respectively. With its highly reactive NCCHC=O system, compound **9** proved to be very sensitive to solvolysis, and with mere traces of base in methanol compound **10** was obtained. Ester **8a** was not so readily alcoholyzed, thus did not behave similarly and could be selectively hydrolyzed to **8b**. Reduction of **8a** with $NaBH_4$ and acidification of the resulting aqueous solution gave a crystalline substance, mp 224°, believed at first to be an acid, but lacking (ir, uv) a carbonyl group and on analysis proving to be a cyclic ether diol; thus reduction of the 1,3-dicarbonyl moiety to 1,3-diol had occurred. The compound contained both primary and secondary OH groups, and on acetylation formed a *mono-O*-acetyl derivative still containing a secondary OH attached to carbon 11 (nmr); this evidence eliminated other tentative structures and led to assignment of structures **11a** and **11b** to the ether diol and its monoacetyl derivative, respectively. Tosylation of **11a** led to formation of a reopened tetraol monotosylate.

Ketols **3**, **5**, and **10** were not useful for further work. Hydrolytic conditions tended to bring about the reverse of ketol closure, the same difficulty as has been encountered in similarly constituted, 9,10-ethano-bridged dihydroanthracenes.[5] Acid hydrolysis, for example, gave **6** from either **4** or **5**. The 10-carbonitrile group, attached to a quaternary C atom in **3** and **5**, is relatively resistant to useful attack, except by hydrogen. Hydrogenolysis of ketol OH might be applied, were it not for the presence of this equally reducible CN group. Our limited efforts with **3** and **5**, *e.g.*, preparation of **3d**, were terminated when there appeared reports on synthesis of less polyfunctional, methano-bridged compounds similar to **5** by somewhat different approaches.[6,7] Still another synthesis of a 12-carboalkoxy-5,10-methano-bridged compound lacking other, complicating functional groups had been described earlier.[8]

Bridged ketols having been found wanting as intermediates, we decided that, aside from photochemical rearrangements,[8,9] a stable ethano bridge with a useful functional group could be established by reaction between suitable substituents on positions 5 and 10 if

(1) G. N. Walker, D. Alkalay, A. R. Engle, and R. J. Kempton, *J. Org. Chem.*, **36**4, 66 (1971), with many references to prior art.

(2) E. Ciorănescu, M. Banciu, R. Jelescu, M. Rentzea, M. Elian, and C. D. Nenitzescu, *Rev. Roum. Chim.*, **14**, 911 (1969).

(3) F. Hoffmann La Roche, *Chem. Abstr.*, **65**, 15297 (1966); J. Rigaudy and L. Nedelec, *Bull. Soc. Chim. Fr.*, 400 (1960).

(4) See A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957).

(5) J. S. Meek, P. A. Monroe, and C. J. Bouboulis, *J. Org. Chem.*, **28**, 2572 (1963); see also T. W. Campbell, V. E. McCoy, J. C. Kauer, and V. S. Foldi, *ibid.*, **26**, 1422 (1961), and references cited therein.

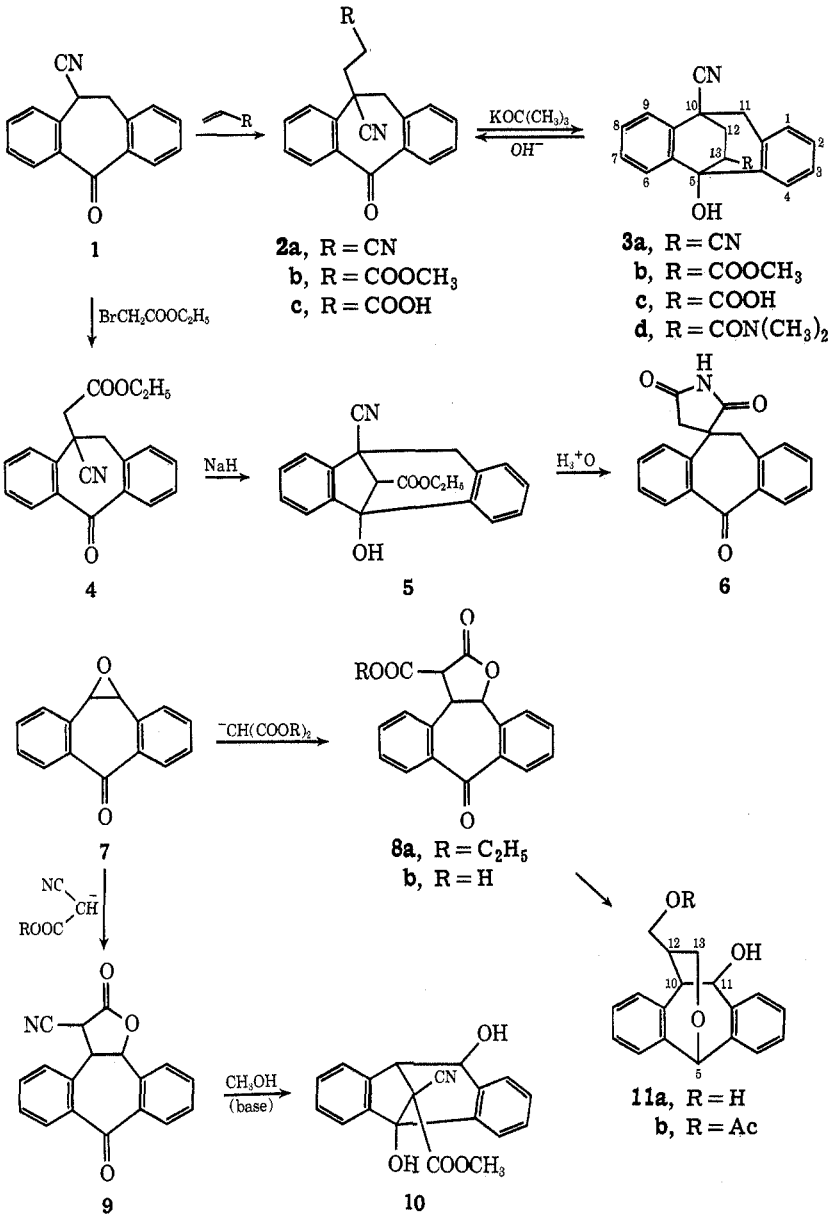
(6) W. Lettré, W. Winter, and K. Stach, German Patent 1,568,092 (1970); *Chem. Abstr.*, **74**, 141405 (1971). W. Winter, M. Thiel, K. Stach, K. Hardebeck, and E. Roesch, German Patent 1,953,334 (1971); *Chem. Abstr.*, **75**, 20048 (1971).

(7) M. E. Christy, *Chem. Abstr.*, **72**, 121245 (1970).

(8) S. J. Cristol and B. J. Jarvis, *J. Amer. Chem. Soc.*, **88**, 3095 (1966).

(9) S. J. Cristol, *et al.*, *ibid.*, **87**, 4007 (1965); **90**, 5564 (1968); **91**, 214 (1969); *J. Org. Chem.*, **34**, 2363 (1969).

SCHEME I



those carbon atoms were saturated. The logical choice was Dieckmann closure (Scheme II), preferably in that diester with the carboalkoxy group attached at position 10 rather than 5, to avoid the foreseeable complications in a diphenylacetic acid analog. Available precursors were **12** and **15**.[1,10,11] Whereas **15** is now known to undergo conjugate addition of anions (and $NaBH_4$ reduction) at the unsaturated nitrile moiety, ketone **12** had been converted to the carbinol[10] and thence to the corresponding 10-bromo-5-chloro compound.[10] Using the latter, rather than attempting direct reaction of the 5-hydroxy compound with malonic acid,[12] we prepared **13** by alkylation of malonic ester, using NaH in DMF. From **13**, two alternate routes as shown were found, both rather tedious, converging on the easily purified acid amide **17**, and actually depending for their success on the relatively inert character of Br[13] or CN group in the dibenzotropone system. The more practical, albeit longer, of these two routes is that proceeding *via* **14**: the vinyl bromide withstands well the operations of hydrolysis, decarboxylation, and reesterification, whereas side reactions, perhaps bridging, conjugate addition of carbanion to $\Delta^{10,11}$ (to be explored further) may occur in **13** → **17**. A third, probably superior approach to **17** was *via* highly selective Wadsworth–Emmons–Arbuzov reaction of triethyl phosphonoacetate with the keto[14] group of **15**. Alkaline hydrolysis of the ester group in the resulting nitrile is accompanied (as in **14** → **17**) by conversion of nitrile to corresponding carboxamide, giving **16**. Completely selective, Pd-catalyzed hydrogenation of the exocyclic double bond in **16** (a mixture of isomers) can be carried out, giving **17**,

(10) J. Gootjes, A. B. H. Funcke, and W. T. Nauta, *Arzneim. Forsch.*, **19**, 1936 (1969); J. Gootjes, A. B. H. Funcke, and H. Timmerman, *ibid.*, **22**, 632 (1972).

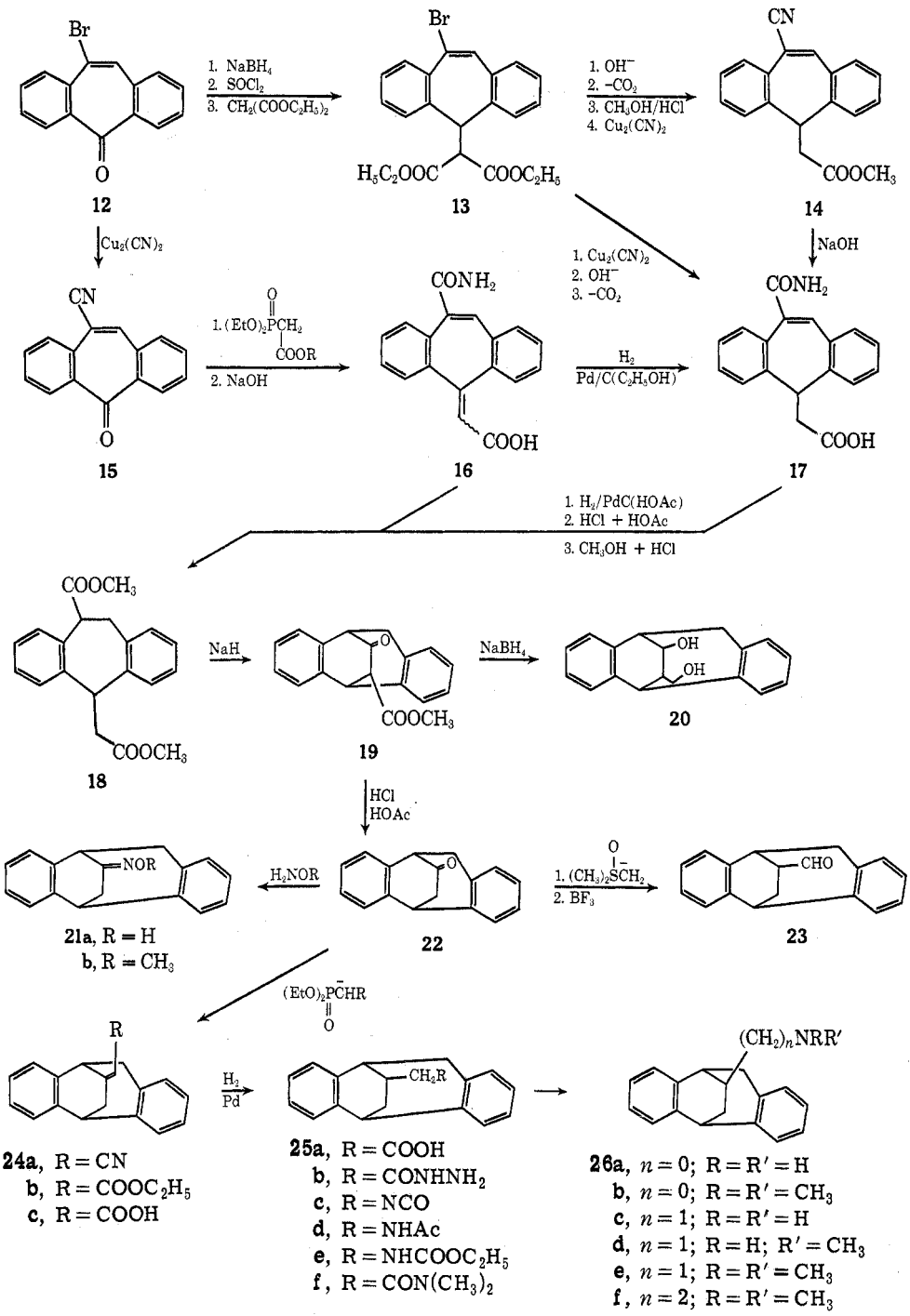
(11) T. A. Dobson and M. A. Davis, *Can. J. Chem.*, **49**, 1027 (1971).

(12) C. Vander Stelt, A. Haasjes, H. M. Tersteege, and W. T. Nauta, *Recl. Trav. Chim. Pays-Bas*, **84**, 1466 (1965).

(13) See F. Hoffmann La Roche, Netherlands Patent Application 6,600,-200 (1966); *Chem. Abstr.*, **64**, 5023, 5024 (1966).

(14) See L. H. Werner, S. Ricca, A. Rossi, and G. deStevens, *J. Med. Chem.*, **10**, 575 (1967); E. D. Bergmann and A. Solomonovici, *Synthesis*, 183 (1970).

SCHEME II



a single isomer, identical with that from the longer routes.

Further Pd-catalyzed hydrogenation of the relatively resistant 10,11 double bond in **17** was then done quantitatively in warm HOAc medium.[1] For this operation it is necessary to have the inert $CONH_2$ group (or, less readily achieved, a carboxyl group) in place of the reducible CN group at position 10. The straightforward, three-step sequence from **17** to **18** was carried out with no serious attempt to isolate crystalline intermediates, since each undoubtedly is a mixture of cis and trans isomer. We anticipated that equilibria (thermodynamic control) involving proton 10 in the presence of sufficiently strong base might serve to isomerize **18** favorably. Whether this actually occurred or **18** was predominantly the cis isomer cannot be stated precisely and soon became an academic question, for in fact Dieckmann closure of crude **18** in the presence of NaH in DMF gave crystalline, 30% enolic (nmr), bridged keto ester **19** in 70% yield.

Like other 1,3-dicarbonyl compounds, **19** was reduced by $NaBH_4$ to a diol, **20**. Hydrolysis and decarboxylation of **19** under alkaline conditions gave a *ca.* 50% yield of bridged ketone **22**, whereas refluxing HCl and HOAc gave **22** in 82% yield. Our multistep route to **22** is not the first synthesis of a compound of this type, but has the virtue of being unambiguous, whereas all previous work[2,9,12] has given 5,10-ethano-10,11-dihydrodibenzo[*a*,*d*]cycloheptenes as by-products or components of mixtures. In addition, the 12-oxo group

in **22** affords the handle required for equally unambiguous preparation of pharmacologically potentially interesting compounds, to which we proceeded forthwith.

Ketone **22**, having been well characterized as oxime (**21a**) and 2,4-dinitrophenylhydrazone, and by reduction with $NaBH_4$ to corresponding 12-ol, was found to behave typically, if somewhat sluggishly, in reactions with a number of other reagents. Mannich reactions were very poor, and **22** was acylated at position 13 with HCOOEt and ethyl oxalate to give somewhat low yields of typical enols. Our primary objective was to introduce an array of homologous, basic side chains (**26**, n = 0–3) to permit at least preliminary assay of the drug potential of the ring system.

Reduction of methoxime **21b** with $LiAlH_4$, superior to that of **21a**, gave **26a**, which was in turn Eschweiler–Clarke methylated to give **26b**. Reaction of ketone **22** with $(EtO)_2(P{=}O)CH_2COOEt$ (NaH in glyme)[15] gave a high yield of **24b**, as nearly all one isomer, evidently the one depicted, which is least eclipsed in models and presumably is analogous to the predominant isomer of nitrile **24a** from reaction of **22** with $(EtO)_2P(O)CH_2CN$ which showed (nmr) a downfield shift of the proton 10 signal owing to deshielding by the CN group. Reaction of **22** with dimethylsulfoxonium methylide[16] to give an epoxide, converted by BF_3 to aldehyde **23**, was less practical, and Wittig ($Ph_3P{=}CHR$) reactions of **22** did not work at all. It was decided to proceed from **24b,c**, particularly since hydrolysis and hydrogenation (10% Pd/C) led to **25a** in high yield. By $LiAlH_4$ reduction of amides (**25f**), easily prepared *via* acid chloride from **25a**, good yields (n = 2) of amines, *e.g.*, **26f**, were secured. Nitrous acid converted the acid hydrazide **25b** smoothly to the corresponding azide, which in turn Curtius rearranged easily (reflux in benzene) to isocyanate **25c**, not characterized other than by its typical ir 4.40-μ absorption but converted with Ac_2O to **25d** (in turn hydrolyzed to **26c**) and with EtOH to urethane **25e**.[17] The latter on $LiAlH_4$ reduction gave a very good yield of **26d**, in turn methylated with CH_3I to provide **26e**. Finally, **22** on reaction with $ClMg(CH_2)_3N(CH_3)_2$ in THF gave a mixture of two isomeric, basic, tertiary carbinols (n = 3; R, R^1 = CH_3), which did not dehydrate smoothly, completing the present array of substances.

Experimental Section

Melting points were obtained using a Thomas-Hoover (silicone oil bath) apparatus; infrared spectra (Nujol mulls unless otherwise noted) were taken with a Perkin-Elmer double-beam instrument; ultraviolet spectra (methanol solutions unless otherwise noted) were measured with a Beckman recording spectrophotometer; and nmr spectra were recorded using a Varian A-60 apparatus with TMS internal standard.

10-(β-Cyanoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one-10-carbonitrile (2a).—A solution of 3.4 g of keto nitrile 1[1] in 20 ml of THF containing 0.7 ml of 40% methanolic benzyltrimethylammonium methoxide was treated with 1.2 ml of acrylonitrile at 25°. The temperature rose spontaneously to 40° and the purple color originally present faded and disappeared. After standing for 0.5 hr the solution was treated with a few milliliters of glacial HOAc and poured over ice water. An ether extract of the material was washed (H_2O), dried ($MgSO_4$), and evaporated. A small amount of **3a** was present, and crystallized first; it was removed with the aid of ether. The residual oil (3 g) then crystallized, and on trituration with methanol afforded colorless crystals: mp 95–105°, raised on recrystallization from methanol and drying *in vacuo* to 105–107°; ir 4.43–4.46 and 6.06 μ; uv 269 nm (ϵ 11,760).

Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.70; H, 4.66; N, 9.74.

5-Hydroxy-5,10-ethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,13-dicarbonitrile (3a).—A solution of 1 g of **2a** and 0.5 g of $KOC(CH_3)_3$ in 15 ml of *tert*-butyl alcohol was heated on a steam cone for 25 min. An insoluble salt separated from the orange-brown solution. Treatment of the cooled suspension with 2 ml of glacial HOAc, then water, converted the precipitate to a crystalline product, which was collected, washed with water, dried, and recrystallized from methanol to give a quantitative yield of colorless crystals: mp 293–295°; ir 2.92 and 4.43–4.46 μ; uv 260 nm (ϵ 440).

Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.90; H, 4.69; N, 9.69.

Compound **3a** was also prepared directly from **1**, again in virtually quantitative yield, as follows. Keto nitrile **1** (4 g) in 25 ml each of THF and *t*-BuOH was treated with 0.68 ml of 40% Triton B methoxide and cyanoethylated by adding 2 ml of acrylonitrile. Then 2.1 g of K *tert*-butoxide was added, the solution was boiled for 40 min, and the product was isolated as in the preceding experiment, giving 4 g of crude solid, mp *ca.* 265–280°, recrystallization of which from methanol afforded 3.5 g of **3a**, mp 287–290°. Further purification gave material identical with the preceding sample.

Compound **3a** resisted 4-hr reflux with concentrated HCl and glacial HOAc solution, overnight treatment with excess PCl_5 in CH_2Cl_2 solution, and 9-hr reflux with saturated methanolic HCl. Treatment with aqueous bases gave poorly characterized material, uv λ_{max} ~270 nm (ϵ *ca.* 10,000).

Compounds 2b and **3b** were both obtained in appreciable amount in the following experiment. **1** (5 g) in 30 ml of THF with 0.7 ml of 40% Triton B methoxide (methanol solution) was treated with 3.2 ml of methyl acrylate, which caused a temperature rise from 23° to 43° and disappearance of the intense purple color. After 0.8 hr the reddish solution was rewarmed to 40° briefly, then chilled, neutralized with HOAc, and treated with cold water, and the oily products were extracted with ether. The washed ($NaHCO_3$ solution) and dried ($MgSO_4$) ether solution on evaporation gave 4.9 g of yellow oil; in the presence of ether this gave 0.6 g of **3b**, mp 215–222°. A pure sample, recrystallized from EtOAc, had mp 230–232°; ir 2.94, 4.46, and 5.85 μ; uv 262 nm (ϵ 410); nmr ($CDCl_3$) δ 7.0–8.1 (m, 8, aromatic H), 4.83 (s, 1, D_2O exchanges, OH), 3.6 (s, 3, ester CH_3), 3.36–3.60 (m, 3, bridge methine and 11-methylene protons) and 2.78 (d, 2, J = 7.6 Hz, bridge CH_2).

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.35; H, 5.43; N, 4.45.

The material remaining from isolation of **3b** consisted of crude **2b** (4.3 g) as an oil, ir 4.45, 5.77, and 6.07 μ, uv 268 nm (ϵ 18,490). On further treatment with K *tert*-butoxide in *tert*-butyl alcohol this material afforded additional **3b** admixed with corresponding acid **3c**.

Compound **2b** was reduced with $NaBH_4$ to a corresponding cyanoester carbinol [not crystalline, ir 2.94, 4.47, and 5.80 μ; uv 262 nm (ϵ 550)] which reacted readily with $SOCl_2$. Attempts to bring about internal displacement of Cl in the resulting 5-chloro cyano ester with agents such as NaH and K *tert*-butoxide were not successful.

10-Cyano-5-hydroxy-5,10-ethano-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cycloheptene-13-carboxylic Acid (3c).—A stirred solution of 3.5 g of **2b** in 45 ml of DMF was treated with 0.55 g of 56% NaH (oil) without cooling, and following a moderately exothermic reaction the solution was warmed on a steam cone gently (*ca.* 70°) for periods of 10 min each at 2-hr intervals over the course of 6 hr. The cooled solution was treated with ice and water. Acidification (HCl) of the ether-washed, alkaline solution gave several crops of crystals totalling 2.3 g, mp 195–205°. Recrystallization from ether gave a pure sample of the acid mp 208–210°; ir 2.89 4.44, and 5.88 μ; uv lacking conjugated C=O band; the sample tenaciously held solvents.

Anal. Calcd for $C_{19}H_{13}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 73.94; H, 4.75; N, 4.03.

Esterification of a sample of the acid with saturated methanolic HCl (3 hr reflux) gave **3b**: mp 229–230° (from EtOAc); mixture

(15) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(16) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1353 (1965).

(17) See P. A. S. Smith, *Org. React.*, **3**, 337 (1946).

melting point with **3b** from preceding experiment, 229–230° (undepressed); ir identical.

The corresponding *N,N*-dimethylamide (**3d**) was obtained by treating 1 g of **3c** with 50 ml of $SOCl_2$ (reflux 5 min) and the acid chloride, after removal of excess reagent, with excess dimethylamine. After evaporation, treatment with water, isolation of neutral product, and recrystallization from ether there were obtained crystals: mp 224–226°; ir 3.12, 4.50, and 6.15 μ.

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.58; H, 5.92; N, 8.37.

Ethyl 10-Cyano-5-hydroxy-10,11-dihydro-5,10-methano-5*H*-dibenzo[*a*,*d*]cycloheptene-12-carboxylate (5).—Preparation of keto cyano ester **4** (mp 101–103°) was described previously.[1] When the alkylation of **1** (15 g) with ethyl bromoacetate was carried out in the presence of excess NaH (DMF) and the solution was allowed to stand for 5 hr before work-up, or when **4** was treated with NaH as described in the preceding experiment, there was obtained a mixture of **4** and **5** from which **5** (5.2 g, mp 163–165°) separated readily on fractional crystallization with methanol. Recrystallization from the same solvent gave colorless crystals: mp 166–168°; ir 2.86, 4.45, and 5.83 μ; uv benzenoid; nmr ($CDCl_3$) δ 6.8–7.8 (m, 8, aromatic H), 4.14 (q, 2, J = 7 Hz, methylene of ester), 3.87 (s, 1, D_2O exchange, OH), 3.78 (s, 1, bridge methine), 3.44 (q, 2, J = 17.5 Hz, 11-methylene), and 1.06 (t, 3, ester CH_3).

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.5; H, 5.43; N, 4.42.

Attempted selective hydrolyses (and other reactions) of **5** were not successful. However, hydrolysis (concentrated HCl, glacial HOAc, 3 hr reflux) of **4** or **5** gave keto imide **6**, crystallizing directly from the hydrolysis solution on addition of water as colorless crystals (from EtOAc): mp 246–248°; ir 5.64, 5.90, and 6.07 μ; uv 208 and 269 nm (ε 24,060 and 12,640, respectively); nmr (DMSO) δ 11.4 (s, 1, D_2O exchange, NH), 7.2–8.1 (m, 8, aromatic H), 3.48 (q, 2, J = 15 Hz, 11-methylene), and 2.80 (q, 2, $J \cong 15$ Hz, methylene of imide).

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.37; H, 4.18; N, 4.74.

Keto Lactone Ester 8a.—To a solution of 2.5 g of sodium in 250 ml of absolute ethanol was added 20 ml of ethyl malonate, then 10.9 g of epoxy ketone **7**.[1,8] The solution on reflux (2.5 hr) first turned deep red and within 1 hr became a thick suspension of sodio salt. The cooled mixture was filtered; the salt was washed with two small portions of ethanol, dissolved in 250 ml of water at 70°, and acidified strongly with hydrochloric acid. After standing for 1–2 hr, the resulting suspension of crystals was filtered, and the crude product was washed with water, dried, and triturated with methanol: yield 11.2 g of colorless crystals; mp 163–165°, raised on recrystallization from methanol to mp 168–170°; ir 5.63, 5.79, and 6.12 μ; uv 269 nm (ε 14,510); nmr ($CDCl_3$) δ 7.1–8.3 (m, 8, aromatic H), 5.63 (d, 1, J = 10 Hz, 11-methine adjacent to oxy), 4.1–4.75 (m, 3, methylene of ester and methine), and 1.34 (t, 3, methyl of ester). After D_2O exchange of the enolic proton, δ 4.45 (d, 1, J = 10 Hz, 10-methine) was seen.

Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.60; H, 4.89.

Hydrolysis of **8a** with either concentrated HCl and glacial HOAc (2 hr reflux) or 10% KOH (3 hr reflux, followed by acidification) gave samples (ir identical) of the corresponding keto lactone acid **8b**, as solvated crystals: melting point varying from 171–173° dec (from ether) to 199–201° (from methanol); soluble in $NaHCO_3$ solution and recovered subsequently by acidification; ir 3.10 (broad, OH), 5.60, 5.76, and 6.13 μ; uv 269 nm (ε 15,920); nmr (DMSO) 7.2–8.2 (m, 8, ArH), 5.88 (d, 1, J = 10 Hz, 11-methine), and 4.43–4.48 (m, 2, remaining CH) resolved by D_2O exchange to δ 4.45 (d, 1, J = 10 Hz, 10-methine proton). The carboxyl H was buried in the base line.

Anal. Calcd for $C_{18}H_{12}O_5 \cdot {}^1/_2H_2O$: C, 68.14; H, 4.13. Found: C, 68.42; H, 3.93.

Keto Nitrile Lactone 9.—Ethyl cyanoacetate (3 ml) was added to a solution of 0.5 g of sodium in 50 ml of absolute ethanol, followed by 1.5 g of epoxy ketone **7**, and the solution was refluxed for 2 hr. The very deep red solution, on chilling or evaporation, deposited a thick precipitate of sodium salt, which was collected, washed with ether–ethanol, and treated with 10% HCl. The crystals were collected, washed (H_2O), dried (1.1 g yield), and triturated and recrystallized with methanol to give material: mp 247–250° dec; ir 4.42, 5.61, and 6.08 μ; uv 269 nm (ε 12,680).

Anal. Calcd for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.52; H, 3.61; N, 4.85.

On warming, solutions of **9** (especially in alcohols) gradually lost the uv 269-nm absorbance. A satisfactory nmr spectrum was not obtained.

Compound 10.—Methanol solutions of **9** on reflux gradually became mixtures of **9** and **10**, as was evident from uv spectra, and the change was hastened by presence of a very small amount of $NaOCH_3$. The product, easily separated from any remaining **9** by use of methanol, was recystallized from ether: mp 186–188° dec; ir 2.84, 2.89, 4.47 (weak), and 5.79 μ; uv lacking conjugated C=O band. The compound did not give a satisfactory nmr spectrum.

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.25; H, 4.47; N, 4.35.

Bridged Dihydroxy Ether 11a.—Treatment of a suspension of 6 g of **8a** in methanol (100 ml) with sodium borohydride (*ca.* 10 g) in portions gave a solution, which was heated for 0.5 hr on a steam cone, and the residue was cooled and treated with water. The resulting colorless solution was acidified with HCl. Colorless crystals which emerged were collected, washed with water, and dried, mp 217–221° (yield 3.5 g). The compound was insoluble in aqueous alkali. Recrystallization from methanol afforded a pure sample: mp 223–225°; ir 3.00 and 3.08 μ; uv showing no conjugated C=O peak; nmr (DMSO) δ 7.0–7.7 (m, 8, ArH), 5.48 (s, 1, proton 5), 5.22 (d, 1, J = 5 Hz, D_2O exchange, 11-OH), 4.93 (m, 1, proton 11; D_2O exchange giving d, 1, J = 3 Hz), 4.5 (t, 1, J = 5 Hz, D_2O exchange, primary OH), 3.65–3.20 (m, 5, both CH_2 and proton 10), and 1.9 (m, 1, not D_2O exchange, proton 12).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.80; H, 6.47.

Monoacetate 11b was obtained when 0.7 g of **9** was heated with 40 ml of acetic anhydride at 100° for 3.5 hr. Evaporation of the excess reagent and recrystallization of the residue from ethyl acetate–ether gave crystals: mp 180–181.5°; ir 3.00 and 5.75 μ; nmr ($CDCl_3$) δ 7.1–7.7 (m, 8, ArH), 5.46 (s, 1, proton 5), 4.86 (m, 1, proton 11; shifting to δ 6.39, d, 1, J = 4 Hz, on reaction of OH with $Cl_3CCONCO$), 3.6–4.1 (m, 4, methines 10 and 12, and methylene adjacent to OR), 3.41 (m, 1, D_2O exchange, OH), 2.12 (m, 2, methylene 13), and 2.02 (s, 3, CH_3 of acetyl).

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.87; H, 6.29.

Tosylation of **11a** by the standard procedure gave crystals, from ethyl acetate, mp 172–173° dec, ir 3.05 μ. The nmr spectrum and analysis indicate that the compound was a monotosylate of a tetracarbinol.

Anal. Calcd for $C_{25}H_{26}O_6S$: C, 66.05; H, 5.77. Found: C, 65.83; H, 5.64.

***trans*-10,11-Dibromo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-one.**—This intermediate (for dehydrobromination to **12**) was prepared in two ways. (A) A solution of 103 g of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one in 1 l. of CCl_4 was treated with 84 g of bromine and allowed to stand for 3 days. The product was collected, 174 g (95%) of crystals, mp 212–214° dec (lit.[18] mp 211°). (B) A solution of 104 g of 10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cyclohepten-5-one in 700 ml of CCl_4 was treated with 93 g of *N*-bromosuccinimide and 0.5 g of dibenzoyl peroxide, and refluxed gently for *ca.* 1 hr or until all NBS was converted to floating succinimide. After filtration the solution was charged with 93 g of additional NBS and 0.5 g of benzoyl peroxide, and warmed again until reflux occurred spontaneously. When the reaction subsided, the crystalline mixture was collected (188 g), washed with 500 ml of 5% NaOH solution to remove succinimide and with water, and dried, to give a total of 146 g (80%) of crystals, mp 208–210°.

10-Bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (12).—Dehydrobromination of 50 g of 10,11-dibromo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one by refluxing with a solution of 17 g of 85% KOH in 900 ml of methanol for 2 hr gave a quantitative yield of crystals, mp 116–118° (lit.[13,18] mp 116°).

10-Bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol.—After 48 g of **12** in 300 ml of methanol was treated with 4.5 g of $NaBH_4$, 80 ml of water was added, the methanol was evaporated, and the solidified oil was collected, washed with dilute HCl and water, and dried, yield 40.5 g, mp 123–126° (lit.[10] mp 121–123°); recrystallization from cyclohexane gave colorless crystals, mp 122–124°, uv 210 nm (ε 39,010) and 283 (13,670).

(18) W. Treibs and H. J. Klinkhammer, *Ber.*, **84**, 671 (1951); W. Tochtermann, K. Oppenländer, and U. Walter, *ibid.*, **97**, 1318 (1964).

10-Bromo-5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptene.—By the action of 25 ml of $SOCl_2$ on a chloroform solution of 42 g of carbinol from the preceding experiment, after 1 hr at room temperature and evaporation and recrystallization from benzene and ether, the chloro compound, reported as not crystalline,[10] was obtained as crystals, mp 127–129°, uv 213 nm (ε 31,630) and 284 (13,540).

Anal. Calcd for $C_{15}H_{10}BrCl$: C, 58.95; H, 3.30. Found: C, 58.92; H, 3.72.

Diethyl 5-(10-Bromo-5*H*-dibenzo[*a*,*d*]cycloheptenyl)malonate (13).—Sodium hydride (15 g of 56%, in oil, washed with ligroin) was suspended in DMF (20 ml), diethyl malonate (25.6 g) was added gradually with cooling (40° or less), and an ether–DMF solution of the chlorobromo compound from the preceding experiment was added in one portion. The exothermic reaction was allowed to proceed and boil off the ether. After 0.5 hr, cold water was added and an ether extract of the product was washed twice with water, dried ($MgSO_4$), and evaporated, giving 65 g of crude **13**. On long standing the oil crystallized. A sample, recrystallized from ethanol, had mp 84–86°; ir 5.74 and 5.80 μ (sharp doublet); uv 211 nm (ε 32,340) and 291 (13,640); nmr ($CDCl_3$) δ 7.71 (s, 1, proton 11), 8.1–7.2 (m, 8, ArH), 4.88 (d, 1, J = 11.5 Hz, proton 5), 4.27 (d, 1, J = 11.5 Hz, malonic CH), 3.90 (2 overlapping q, 4, J = 7 Hz, ester CH_2 groups), and 0.96 (2 overlapping t, 6, J = 7 Hz, ester CH_3 groups).

Anal. Calcd for $C_{22}H_{21}BrO_4$: C, 61.55; H, 4.93. Found: C, 61.71; H, 5.14.

Hydrolysis (150 ml of 10% NaOH and 300 ml of ethanol, 3 hr reflux) of 58 g of crude bromo diester **13** gave the corresponding **diacid**, 35 g of crystals from ether–ligroin: mp 207–208° dec; ir 5.80–5.85 μ; uv 210 nm (ε 32,050) and 290 (12,840); Beilstein test positive; nmr (DMSO) δ 7.78 (s, 1, proton 11), 8.0–7.2 (m, 8, ArH), 4.83 (d, 1, J = 12 Hz, proton 5), and 3.98 (d, 1, J = 12 Hz, malonic CH); COOH δ *ca.* 12 (very broad, 2, D_2O exchange).

Anal. Calcd for $C_{18}H_{13}BrO_4$: C, 57.93; H, 3.51. Found: C, 58.17; H, 3.79.

A neutral by-product isolated in this hydrolysis (9.4 g) proved to be 10-bromodibenzo[*a*,*d*]cyclohepten-5-ol, mp 123–125°, identical with the authentic sample.

5-(10-Bromodibenzo[*a*,*d*]cycloheptenyl)acetic Acid.—The 10-bromo diacid (19.5 g) was heated at 230° (oil bath) for 10 min until evolution of CO_2 ceased. Trituration of the cooled, dark melt with ether gave 16 g (94%) of gray crystals, mp 228–231°. A colorless sample after recrystallization from ethanol had mp 230–232°; ir 5.89 μ; uv 210 nm (ε 35,160) and 286 (14,220) with inflection at 236 nm; nmr (DMSO) δ 7.82 (s, 1, proton 11), 8.0–7.1 (m, 8, ArH), 4.64 (t, 1, J = 8 Hz, proton 5), and 2.68 (d, 2, J = 8 Hz, CH_2); COOH δ *ca.* 12 (very broad, 1, D_2O exchange)

Anal. Calcd for $C_{17}H_{13}BrO_2$: C, 62.02; H, 3.98. Found: C, 62.31; H, 4.19.

The corresponding methyl ester was prepared by refluxing the bromo acid with 30 parts of saturated, methanolic HCl for 3 hr and isolated as usual: 91% yield of neutral oil, ir 5.80 μ, uv 210 nm (ε 32,530) and 288 (13,200), strong Beilstein test.

Ester Nitrile 14.—To a solution of 41 g (0.12 mol) of crude bromo ester from the preceding experiment in 200 ml of DMF (reagent grade) was added 22.4 g (0.125 mole) of cuprous cyanide, and the mixture was stirred and refluxed for 2.5 hr. Water and an excess of NH_4OH were added to the cooled solution, and the product was extracted with chloroform. The organic solution was diluted with ether, washed with dilute HCl and water, dried ($MgSO_4$), and evaporated to give 38.5 g of crude, red oil. The material did not crystallize; a rewashed (ether solution), dried sample of the oil still contained some DMF; ir 4.52 and 5.78 μ; uv 231 nm (ε 19,960) and 304 (15,700).

Acid Amide 17.—Crude **14** (90 g) was refluxed with 400 ml of 10% NaOH and 500 ml of ethanol for 4 hr; the solution was evaporated to remove most of the ethanol and refluxed for 4 hr longer. The diluted, hot solution was treated with Norit, washed with chloroform, cooled, and acidified with HCl, and the tan precipitate was collected, washed with water, and dried. The crude acid when triturated with ethanol gave 31 g of slightly discolored crystals, mp 226–236°, suitable for further work. Recrystallization from ethanol or aqueous HOAc gave a sample as colorless crystals: mp 241–244°; ir 2.92, 3.02, 3.10, 5.90, and 6.05 μ; uv 210 nm (ε 30,580) and 290 (13,220); nmr (DMSO) δ 7.77 (s, 1, proton 11), 7.9–7.1 (m, 10, 2 slowly D_2O exchange, ArH and $CONH_2$), 4.61 (t, 1, J = 7.5 Hz, proton 5), and 2.66 (d, 2, J = 7.5 Hz, CH_2); COOH δ far downfield (1, D_2O exchange).

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 74.01; H, 4.94; N, 4.72.

Diethyl 5-(10-Cyano-5*H*-dibenzo[*a*,*d*]cycloheptenyl)malonate.—Reaction of 63 g of **13** with $Cu_2(CN)_2$ in DMF (3 hr reflux) as described for **14** afforded, after a similar work-up, 51 g of viscous oil. A filtered, ether solution of the crude material on slow evaporation gave a sample of the diester nitrile as colorless crystals: mp 143–145° (from ether); ir 4.51 and 5.74–5.79 μ; uv 210 nm (ε 32,100), 231 (19,500), and 306 (16,160); nmr ($CDCl_3$) δ 7.80 (s, 1, proton 11), 8.0–7.2 (m, 8, ArH), 4.93 (d, 1, J = 11.5 Hz, proton 5), 3.99 (d, 1, J = 11.5 Hz, malonic CH), 3.89 (2 overlapping q, 4, J = 7 Hz, ester CH_2), and 0.97 (2 overlapping t, 6, J = 7 Hz, ester CH_3).

Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.94; H, 5.84; N, 3.94.

Hydrolysis of 50 g of the crude diester nitrile by 2.5-hr reflux with 200 ml of 10% NaOH solution and 200 ml of ethanol gave, on acidification of the diluted, ether-washed, and Norit-treated solution, 22 g of crude solids, from which, on trituration with ether–ethyl acetate, there was obtained 6 g of the corresponding amide malonic acid: mp 164–167° dec after recrystallization from ether–acetone or water; ir broad, bonded OH, 5.86 and 6.08 μ; uv 294 nm (ε 13,420) and inflection at 212 (35,000); nmr (DMSO) δ 7.56 (s, 1, proton 11), 7.7–7.1 (m, 10, 2 D_2O exchange, ArH and $CONH_2$), 4.80 (d, 2, J = 11.5 Hz, proton 5), and 3.93 (d, 1, J = 11.5 Hz, malonic CH); COOH δ *ca.* 12 (very broad, 1, D_2O exchange).

Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.52; H, 4.53; N, 3.73.

Decarboxylation of 5.6 g of the diacid amide at 230°, trituration of the cooled melt with ether–acetone, and recrystallization from ethanol gave 3 g of **17**, mp 242–245°, spectra identical with those of the first sample, mixture melting point undepressed.

Acid Amide 16. A. Arbuzov Reaction.—A suspension of 0.8 g of 56% NaH in 30 ml of dimethoxyethane (dried over CaH_2) was stirred and cooled while 4.5 g of triethyl phosphonoacetate (5 min) was added, and stirring was continued at room temperature until a clear solution was obtained (10 min). A solution of 3.4 g of cyano enone **15**[10] in 20 ml of dimethoxyethane was added. The solution was warmed gently (50°) for 4.5 hr and allowed to stand at room temperature for 3 days. After addition of ice water (300 ml) the material was extracted with ether, and the ether solution was washed thrice with water, dried ($MgSO_4$), and evaporated to give *ca.* 5 g of cyano ester as an oil: ir 4.49, 5.82, and 6.13 μ; uv 233 nm (ε 27,000) and 298 (12,500) with inflection at 268 nm.

B. Hydrolysis.—Crude A in 30 ml of ethanol and 10 ml of water with 4 g of NaOH was refluxed for 3.5 hr; slight NH_3 evolution occurred, and the red solution became light orange. Acidification of the diluted solution gave crude **16**, which was collected, washed with water, and triturated with methanol; 2.5 g of crystals, mp *ca.* 250–262°, a mixture of isomers. Recrystallization gave a pure sample of the higher melting compound: mp 286–290°; ir 3.05, 3.16, and 5.95–6.03 μ (doublet); uv 229 nm (ε 30,650) and inflection at 273 (14,300); nmr (DMSO) δ 8.0–7.2 (m, 11, 2 slowly D_2O exchange, ArH, $CONH_2$, and proton 11), and 5.92 (s, 1, =CH–); COOH δ far downfield (very broad, 1, D_2O exchange).

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.16; H, 4.42; N, 4.80.

Hydrogenation of 2 g of **16** in warm (60°) ethanol (60 ml) and ethyl acetate (200 ml) in the presence of 1.5 g of 10% Pd/C for 2 hr, filtration, and evaporation of the solvents gave acid amide **17** as crystals from ethanol: mp 243–246°; ir 2.94, 3.05, 3.13, 5.91 and 6.07 μ; uv 210 nm (ε 33,010) and 289 (12,570); identical by spectra and mixture melting point with the first sample of **17**.

Methyl 5-(10-Carbomethoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenyl)acetate (18). A. Hydrogenation of 30 g of **17** in 500 ml of glacial acetic acid in the presence of *ca.* 12 g of 10% Pd/C at 50-lb pressure and 80° for 20 hr resulted in uptake of 95% of the calculated amount of H_2. Filtration and evaporation afforded 31 g of pale yellow glass. A sample, reprecipitated from alkaline solution, extracted with ether, and dried *in vacuo*, was colorless and did not crystallize: ir NH_2 bands, 5.86, and 6.01 μ; uv benzenoid.

B. Hydrolysis of 30 g of crude acid amide from A by 5-hr reflux with 300 ml of glacial HOAc and 200 ml of concentrated HCl, evaporation of excess reagents, and treatment with water gave a tan precipitate of mixed isomers of diacid which was col-

lected, washed with water and dried: yield 26 g, mp 200–205°. The isomers could not be separated efficiently by fractional crystallization from various solvents. A sample, reprecipitated from NaOH solution by dilute HCl, ether extracted, ether triturated, and dried *in vacuo* had mp 237–241° and may have been one of the isomers in reasonably pure form: ir broad, bonded OH and 5.89 μ (intense, sharp); uv 262 nm (ε 1070), 270 (1010), and 280–290 (640).

C. Esterification of 26 g of crude diacid isomer mixture from B by 6-hr reflux with 500 ml of methanolic HCl, removal of excess reagent *in vacuo*, and addition of water gave oil which was extracted with ether. The ether solution was washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated to give 28 g of **18** as an oil, sufficiently pure for further use, ir 5.77 μ, uv 262 nm (ε 720) and 265 (790).

Methyl 10,11-Dihydro-12-oxo-5*H*-5,10-ethanodibenzo[*a*,*d*]cycloheptene-13-carboxylate (19).—Dieckmann closure of 10 g of crude **18** in 15 ml of DMF was carried out by adding 2.4 g of 56% NaH in 10 ml of DMF during 2 hr, keeping the temperature at 20–30° by means of external cooling. The dark brown solution was poured into 400 ml of water and the oily solution was treated with 9 ml of 18% HCl. The colorless, crude product usually could be filtered; if too sticky it was extracted with ether. An ether solution of the water-washed, dried ($MgSO_4$) material was filtered and evaporated, giving 8.4 g of viscous, pale yellow oil. Crystallization occurred in methanol, giving 6.4 g (71%) of colorless crystals: mp 116–118°, raised to 119–121° on recrystallization from methanol; ir 5.75, 5.86, 6.06, and 6.19 μ; $FeCl_3$ test deep purple; uv 260–264 nm (ε 3390) and 267 (3470) with inflection at 275 (3110); nmr ($CDCl_3$) δ 11.6 (0.3 H, readily D_2O exchange).

Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.72; H, 5.76.

Compound **19** was *partly* soluble in 5% NaOH solution. Use of K *tert*-butoxide in the Dieckmann closure also gave **19** but in lower yield.

The closure of **18** with NaH was carried out with amounts *ca.* four times those described above by the same procedure, with essentially the same results. Although total, crude **19** (90% yield could be carried through hydrolysis, decarboxylation, with fairly good results (*e.g.*, 65 g of crude **19** gave 34 g of **22** as described under **22**), it was found best to isolate **19** in crystalline form by means of methanol before proceeding further.

The corresponding 2,4-dinitrophenylhydrazone could be recrystallized from aqueous methanol as orange, ill-defined crystals, mp 131–135°, ir 5.78, 6.19, and 6.28 μ.

Anal. Calcd for $C_{25}H_{20}N_4O_6$: C, 63.55; H, 4.27; N, 11.86. Found: C, 63.85; H. 4.26; N, 11.67.

Diol 20.—From $NaBH_4$ reduction of a sample of **19** (in methanol) there were obtained colorless crystals, from ether, mp 174–175°, ir 3.04 μ (very strong).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.29; H, 6.84.

5,10-Ethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (22).—A solution of 19 g of **19**, in 150 ml each of concentrated HCl and glacial HOAc was refluxed for 2 hr. Most of the reagent was removed *in vacuo*, the residue was treated with water, the product was extracted with ether, and the washed (2% NaOH, H_2O) and dried ($MgSO_4$) ether solution was evaporated. The ketone crystallized nicely in ether or ethanol: 12.5 g (82%) of colorless crystals: mp 144–147°, raised to 148–149° on recrystallization from ether; ir 5.84 μ; uv benzenoid, with moderate end absorption; nmr ($CDCl_3$) δ 7.5–6.9 (m, 8, ArH), 4.06 (q, 1, J = 3.0, J' = 4.4 Hz, proton 5 coupled to nonequivalent protons 13), 3.78 (t, 1, J = 4 Hz, J' = 4 Hz, proton 10 coupled to 11), 3.30 (q, 2, J_{ax} = 4 Hz, J_{gem} = 7.0 Hz, protons 11), apd 2.88 (m, 2, $J \simeq 3$ Hz, $J' \simeq 4.4$ Hz, protons 13).

Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.27; H, 6.14.

The corresponding 2,4-dinitrophenylhydrazone was prepared as usual (aqueous ethanolic H_2SO_4) and recrystallized from ethanol as yellow crystals, mp 193–195°, ir 6.18, 6.25 μ.

Anal. Calcd for $C_{23}H_{18}N_4O_4$: C, 66.66; H, 4.38; N, 13.52. Found: C, 66.67; H, 4.59; N, 13.29.

Formylation of 1 g of **22** with HCOOEt (5 ml) in the presence of dry $NaOCH_3$ (from 0.13 g of Na) in dry ether (250 ml) gave a *ca.* 50% yield of the enolic, corresponding 13-hydroxymethylene compound as slightly pink crystals from ether: mp 141–143°; ir 6.01 and 6.28 μ; 268 nm (ε 7820) and 275 (7800); $FeCl_3$ positive; nmr not first-order resolvable.

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.37; H, 5.20.

Similar $NaOCH_3$-mediated reaction with ethyl oxalate gave the enolic 13-$COCOOCH_3$ derivative as crystals from ethanol: mp 169.5–171°; ir 5.79, 6.12, and 6.26 μ; uv 304 nm (ε 7270) and inflection at 276 (5980).

Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.16; H, 5.34.

5,10-Ethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-12-ol.—From treatment of 0.5 g of **22** with 0.8 g of $NaBH_4$ in methanol, evaporation, and addition of water, there was obtained a colorless solid, mp 146–151°, recrystallizing from cyclohexane to give colorless crystals: mp 151–155°; ir 3.07 μ; uv 266 nm (ε 1080), 270 (980), and 274 (1130); nmr ($CDCl_3$) too complex to discern J values.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.33; H, 6.87.

Aldehyde 23.—A suspension of 0.45 g of NaH (56%) and 3.3 g of trimethyl sulfoxonium iodide[16] in 50 ml of DMSO was warmed very gently and stirred until nearly all the material dissolved (15 min), ketone **22** (1.0 g) in 10 ml of DMSO was added, and the solution was stirred at 35° for 1.3 hr and allowed to stand overnight. After addition of 500 ml of cold water and extraction of the material with ether, the washed and dried ($MgSO_4$) ether solution was evaporated, and the residual yellow oil (1.1 g) was placed in 25 ml dry ether, the solution was chilled, and 0.7 ml of 47% BF_3 etherate was added. After standing for 0.8 hr at room temperature, the decanted ether solution was washed with dilute $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated to give *ca.* 1.0 g of crude **23** as a colorless, viscous oil, ir 5.80 μ.

The 2,4-dinitrophenylhydrazone recrystallized from ethanol–ethyl acetate as yellow, fluffy needles, mp 238–240° dec.

Anal. Calcd for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.32; H, 4.89; N, 13.15.

Oxime 21a.—Ketone **22** was refluxed for 2 hr with aqueous, ethanolic, NaOH-neutralized $H_2NOH \cdot HCl$ solution, and the crystals appearing on dilution were collected, washed and recrystallized from benzene, mp 146–149°, ir 3.09 and 6.00 μ.

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.93; H, 6.12; N, 5.32.

Methoxime 21b.—Ketone **22** (5 g) and 8.4 g of *O*-methylhydroxylamine HCl in 200 ml of methanol were treated with 5.4 g of $NaOCH_3$ in 50 ml of methanol, and the solution was refluxed for 4 hr. Evaporation and addition of water gave crystals which, after being collected, washed (H_2O), and dried, weighed 5.6 g, mp 151–156°, evidently a mixture of syn and anti forms; ethanol recrystallization gave colorless crystals, mp 156–161°, ir 6.09 μ.

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.36; H, 6.36; N, 5.50.

Amine 26a.—Crude methoxime (5.6 g) together with 4.1 g of $LiAlH_4$ in 200 ml of dry THF (the reaction did not proceed in Et_2O) was refluxed and stirred for 6 hr, the cooled suspension was treated with 25 ml water (stirring) and after 1 hr filtered, the THF was removed *in vacuo*, and an ether solution of the crude base was dried (K_2CO_3) and evaporated, giving 5 g of acid-soluble, pale yellow oil. The amine was converted to the corresponding hydrochloride with ethereal HCl, *ca.* 5 g of crystals, mp 132–136°. Trituration with ethyl acetate gave the predominant and least soluble isomer, 3.3 g of colorless crystals, mp 149–151°, nmr very complex.

Anal. Calcd for $C_{17}H_{17}N \cdot HCl$: C, 75.12; H, 6.67; N, 5.15. Found: C, 75.03; H, 6.43; N, 4.97.

From the EtOAc filtrate, on evaporation there remained 1.7 g of glassy material, crystallizing in ether, and which, on recrystallization from acetone–ether or ethanol–ether, gave what appeared to be a pure sample of the lesser isomer, mp 262–264°.

Amine 26b.—Primary amine **26a**, regenerated from 3.2 g of the principal isomer hydrochloride of the preceding experiment, was heated on a steam cone with 25 ml of anhydrous HCOOH and 5 ml of 36% formalin for 6 hr; effervescence ceased after 2 hr. A water solution of the residue remaining after evaporation of the reagents *in vacuo* was washed with ether and made basic by addition of 10% NaOH. The base was extracted with ether, the water-washed, dried (K_2CO_3) solution was evaporated, and the crude base (2.3 g, oil) was converted to the corresponding hydrochloride. A water solution of the ether-titurated salt was treated with NaOH to regenerate a better sample of the base, which was isolated by extraction with ether as before and for

characterization converted to the picrate; yellow crystals from ethanol, mp 247–249°.

Anal. Calcd for $C_{25}H_{24}N_4O_7$: C, 60.97; H, 4.91; N, 11.38. Found: C, 60.73; H, 4.97; N, 11.70.

Nitrile 24a.—Diethyl phosphonoacetonitrile (1.1 g) was added in portions to a stirred suspension of 0.3 g of 56% NaH in 20 ml of THF, followed 10 min later by 1.2 g of **22** in 25 ml of THF. Gentle reflux for 1 hr deposited a viscous, orange syrup (water-soluble, in work-up). The cooled, supernatant THF solution was treated with water, the oil was extracted with ether, and the water-washed, dried ($MgSO_4$) ether solution was evaporated, yielding 1.3 g of turbid, colorless oil, soon crystallizing on standing, apparently a mixture of isomers (mp *ca.* 160–175°). Recrystallization from ether afforded colorless crystals: mp 189–191°; ir 4.51 and 6.17 μ; nmr ($CDCl_3$) δ 7.4–7.0 (m, 8, ArH), 5.20 (t, 1, $J \cong 2$ Hz, vinyl H long-range coupled to protons 13), 4.43 (t, 1, $J \cong J' \cong 4$ Hz, proton 10 coupled to 11), 3.93 (q, 1, $J = 2.5$, 4.5 Hz, proton 5 coupled to 13), 3.30 (q appearing to be t, 2, $J_{ax} = 4$, $J_{gem} \simeq 4.5$ Hz, protons 11), and 3.0 (m, 2, somewhat simplified by irradiating vinyl proton, protons 13).

Anal. Calcd for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.79; H, 5.96; N, 5.26.

Ester 24b.—Sodium hydride (3.5 g of 56% in oil) was washed with ligroin and suspended in 70 ml of dimethoxyethane, and the suspension was stirred while 22 g of triethyl phosphonoacetate was added gradually with cooling to prevent the temperature from exceeding 25–30°; stirring was continued until a clear solution was obtained,[15] ketone **22** (13.0 g) was added, and the solution was warmed to 70° (air condenser) for 5 hr; after standing overnight it was warmed again to 70° for 1.5 hr. Work-up as in the preceding experiment after adding 1 l. of water gave *ca.* 20 g of oil which crystallized on standing (or seeding with samples from preliminary runs). Trituration with ether–ligroin gave several crops of colorless crystals totalling 9 g, mp 83–87°. Recrystallization from ether gave a pure sample: mp 86.5–88.5°; ir 5.88 and 6.10 μ (intense); uv 266 nm (ϵ 1660) with inflection at 219 (32,850); nmr ($CDCl_3$) of this and all succeeding compounds, in agreement with structure but not first-order interpretable.

Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.68; H, 6.62. Found: C, 83.10; H, 6.57.

Acid 24c.—The entire, crude product from the preceding experiment was hydrolyzed with 100 ml of concentrated HCl and 190 ml of glacial HOAc (3.5-hr reflux). The solution was distilled *in vacuo* to smaller volume, water was added, and the crystals were collected, washed with water, and air dried: 14.8 g of crude solid, mp *ca.* 180–245°. Trituration with ether removed oily material effectively, giving 10.1 g of colorless crystals, mp 240–254°; a second ether trituration raised the melting point to 267–272°, and recrystallization from ethyl acetate gave a pure sample of the single isomer, mp 273–274°, ir 5.95 (very intense) and 6.11 μ (intense).

Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.65; H, 5.86.

Acid 25a.—A solution of 6.5 g of Et_2O-triturated **24c** in 150 ml of ethanol and 100 ml of ethyl acetate containing 2 g of 10% Pd/C was shaken under 45 lb of H_2 at 50° for 5 hr. The filtered solution was evaporated to give 6.5 g of crystals, mp 172–180°. Recrystallization from ether gave a sample, mp 184–186°, ir 5.88 μ.

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.28; H, 6.31.

Similar reduction of ester **24b** gave an oil, ir 5.80 μ, and no C=C absorption.

The corresponding *N*,*N*-dimethylamide **25f** was prepared by sequential treatment of the acid with $SOCl_2$ (20 min reflux) and reaction with Me_2NH in benzene. Evaporation of washed (H_2O) and dried ($MgSO_4$) ether–benzene solution gave crystals, mp 134–136° (from ether), ir 6.12 μ.

Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.54; H, 7.77; N, 4.58.

Amine 26f.—Lithium aluminum hydride (1.4 g) reduction of 2.3 g of amide **25f** in 25 ml of THF and 125 ml of ether (6 hr reflux), hydrolysis (7 ml of water), filtration, and evaporation of the dried (K_2CO_3) solution gave 2.2 g of the amine as an oil. It was converted to the hydrochloride (2.5 g): mp 286–287° dec after recrystallization from methanol–ether; ir 3.88 and 4.04 μ.

Anal. Calcd for $C_{21}H_{25}N \cdot HCl$: C, 76.92; H, 7.99; N, 4.27. Found: C, 76.71; H, 7.63; N, 4.42.

Acid hydrazide 25b was prepared either by refluxing crude ester from hydrogenation of **24b** with hydrazine or by adding a benzene solution of acid chloride (from **25b**) to excess hydrazine, with stirring: colorless crystals (from ether–benzene); mp 180–182°; ir 3.00 and 6.06–6.14 μ (doublet).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.81; H, 6.97; N, 9.60.

Isocyanate 25c. A. Azide.—A solution of 4.5 g of hydrazide **25b** in 45 ml of glacial HOAc and 25 ml of 18% aqueous HCl was chilled in ice, stirred, and treated slowly with an excess (starch–I^- test) of concentrated aqueous $NaNO_2$ solution. The oily azide separated immediately. After 10 min, ice water was added, the oil was extracted with ether (500 ml), and the ether solution was washed with two portions of ice water, iced $NaHCO_3$ solution, and two more portions of water, and dried ($MgSO_4$), and filtered.

B. Curtius Rearrangement.—The ether solution from A was diluted with 200 mg of dry benzene, evaporated to a volume of *ca.* 150 ml, heated gradually, and when N_2 evolution appeared to be practically complete the solution was refluxed for 0.5 hr. Evaporation then gave 4.5 g of pale yellow glass, ir 4.37–4.42 μ (intense). The material was used in subsequent operations without undue delay.

Urethane 25e.—Ethanol (150 ml) was added to crude **25c** or its benzene solution (50–100 ml) and the solution was refluxed for 1 hr. Evaporation then gave 4.5 g of pale yellow, viscous oil, ir 3.05 and 5.90–6.05 μ, also used soon in subsequent reactions.

Acetamide 25d.—In a separate experiment, crude, dry azide solution (from 1 g of **25b**) was treated with 2 ml of glacial HOAc and 15 ml of acetic anhydride, the ether was distilled, and the remaining solution was heated on the steam cone for 1 hr (N_2 evolution for 10 min) and then evaporated. The yellow residue crystallized rapidly in ether, giving 0.75 g of colorless crystals, mp 160–162° (from ether), ir 2.99 and 6.08 μ.

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.76; H, 7.47; N, 4.86.

Amine 26c.—Prolonged (8 hr) reflux of 0.5 g of **25d** in 45 ml of concentrated HCl and 20 ml of glacial HOAc, evaporation *in vacuo*, and alkalinization of an ether-washed, aqueous solution of the residue gave colorless crystals, purified with some difficulty by recrystallization from ether–ligroin, mp 115–117°, ir 3.15 μ (weak, intermolecular bonding).

Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62; mol wt, 249.34. Found: C, 86.59; H, 7.33; N, 5.67; M^+, 249.

Acetylation (Ac_2O) gave again **25d**.

Amine 26d.—A solution of 4.6 g of crude **25e** in 10 ml of THF was added to 1.9 g of $LiAlH_4$ in 200 ml of ether, and the suspension was stirred and refluxed for 4.5 hr. After treatment of the cooled suspension with water (5 ml), filtration of the dried (K_2CO_3) solution and evaporation gave *ca.* 3.8 g of crude amine, pale orange oil (ir NH band) which was converted to 3.1 g of hydrochloride, mp 237–247°, purified by recrystallization from ethanol–ether, mp 252–256°, ir 3.65 and 4.11 μ.

Anal. Calcd for $C_{19}H_{21}N \cdot HCl$: C, 76.10; H, 7.40; N, 4.67. Found: C, 76.48; H, 7.21; N, 4.49.

Amine 26e.—Amine **26d** (1.5 g, regenerated from hydrochloride), in 50 ml of dry ether was treated with 4 ml of iodomethane. On standing, a precipitate of hydroiodide gradually accumulated, and after 5 hr was collected and recrystallized from ethanol–ether, colorless crystals, mp 272–276° dec.

Anal. Calcd for $C_{20}H_{23}N \cdot HI$: C, 59.26; H, 5.97; N, 3.46. Found: C, 59.47; H, 6.04; N, 3.63.

The amine, generated by treatment of the hydriodide with 5% NaOH solution and the aid of methanol, extracted with ether, and isolated by evaporation of the water-washed, dried (K_2CO_3) ether solution was an oil, lacking NH ir absorption. It was converted in turn to the hydrochloride, recrystallized from ethanol–ether, mp 249–252°, ir 3.70 and 4.10 μ.

Anal. Calcd for $C_{20}H_{23}N \cdot HCl$: C, 76.53; H, 7.71; N, 4.46. Found: C, 76.61; H, 7.82; N, 4.43.

Registry No.—**2a**, 36736-52-4; **3a**, 36736-53-5; **3b**, 36826-34-3; **3c**, 36736-54-6; **3d**, 36736-55-7; **5**, 36736-56-8; **6**, 36826-36-4; **8a**, 36736-57-9; **8b**, 36736-58-0; **9**, 36736-59-1; **10**, 36736-60-4; **11a**, 36736-61-5; **11a** tosylate, 37767-81-0; **11b**, 36736-63-7; **13**, 36736-64-8; **13** diacid, 36736-65-9; **16**, 36736-66-0; **17**,

36736-67-1; **18**, 36736-68-2; **19**, 36736-69-3; **19** DNP, 36736-70-6; **20**, 36736-71-7; **21a**, 36736-72-8; *syn*-**21b**, 36744-46-4; *anti*-**21b**, 36744-47-5; **22**, 36736-73-9; **22** DNP, 36736-74-0; **22** (13-hydroxymethylene derivative), 36736-75-1; **22** (13-$COCOOCH_3$ derivative), 36736-76-2; **23** DNP, 36736-77-3; **24a**, 36736-78-4; **24b**, 36736-79-5; **24c**, 36736-80-6; **25a**, 36736-81-9; **25b**, 36736-82-0; **25d**, 36736-83-1; **25f**, 36736-84-2; **26a** HCl, 36736-85-3; **26b** picrate, 36736-86-4; **26c**, 36736-87-5; **26d** HCl, 36736-88-6; **26e** HI, 36736-89-7; **26e** HCl, 36736-90-0; **26f** HCl, 36736-91-1; 10-bromo-5-chloro-5*H*-dibenzo[*a*,*d*]cycloheptene, 36736-92-2; 5-(10-bromodibenzo[*a*,*d*]cycloheptenyl)acetic acid, 36736-93-3; diethyl 5-(10-cyano-5*H*-dibenzo[*a*,*d*]cycloheptenyl)malonate, 36736-94-4; 5-(10-carboxamide-5*H*-dibenzo[*a*,*d*]cycloheptenyl)malonic acid, 36736-95-5; 5,10-ethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-12-ol, 36736-96-6.

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Hybridization in Fused Strained Rings by the Maximum Overlap Method. II. Benzocyclobutene and Benzocyclopropene[1a]

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The hybridization in benzocyclobutene and benzocyclopropene is considered using the method of maximum overlap. The results show considerable variations of s–p content of hybrids describing the molecular skeleton. In benzocyclopropene the hybrids of the carbon atom at the fusion site are $sp^{1.99}$, $sp^{3.20}$, and $sp^{1.34}$, the first two describing the propene ring, the latter being directed outward. In benzocyclobutene the corresponding hybrids show lesser deviations from sp^2 forms. For the C_3 ring the directions of the calculated hybrids deviate from bond directions by the expected values 20–25°, giving the so-called bent bonds. For C_5 rings the deviation angles are close to zero, which gives rise to asymmetrically half-bent bonds where benzene joins the small rings. The calculated hybrids are used for a prediction of spin–spin coupling constants $J_{C^{13}-H}$ which are discussed and compared with the experimentally available data.

The hybridization model has been found very useful for discussion of such molecular properties as bond angles, bond lengths, bond energies, spin–spin coupling constants, proton acidities, etc.[2] Approximate hybridization parameters may be found by transforming available semiempirical molecular orbitals to localized orbitals. An alternative procedure arises from use of localized models, one or which is the method of maximum overlap.[3] This method utilizes the assumption that a large bond overlap results in a stronger bond. Although this approach is based on intuitive concepts and cannot be derived rigorously from the first principles, it is expected to yield useful results in systems with covalent bonding.[4] Moreover an application to a large number of structurally related molecules, like for example hydrocarbons, may be expected to give a good description of many molecular properties.

In this paper we consider an application of the maximum overlap method to two highly strained fused-ring hydrocarbons, benzocyclobutene and benzocyclopropene. This work is a continuation of the study of fused-ring systems initiated by the work on biphenylene and benzo[1,2:4,5]dicyclobutene.[5] These molecules are characterized by unusual constraints and are of considerable interest as their aromatic ring will produce changes in bond lengths, and as a consequence unusual spectral and chemical properties are expected.[6] The simple description in terms of sp^2 and sp^3 hybrids is clearly not adequate for such molecules. More general hybrids of the form sp^n, where n is not restricted to integers 2 and 3, lead to a problem of establishing the hybrid exponent n. The situation is complicated by the presence of opposing tendencies of individual hybrids to increase or decreasd their s content and to reorient as to balance the total bond overlap. The molecular structure of benzocyclobutene and benzocyclopropene introduces bond angles of 150 and 180° which indicate that the hybrids must have unusual s–p content.

The maximum overlap method has been described in the literature.[2-4] Briefly, we search for optimal exponents n of all individual sp^n hybrids of a given molecule which would make a sum of suitably weighted bond overlaps maximum. The weighting factors are introduced to account for the fact that the bond overlap–bond energy ratio is different for CH and CC bonds. These factors take care of a "scaling" of the problem

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