Synthesis of 5-Oxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carboxylic Acids, Corresponding Nitriles, and Related Bridged Lactones, Hemiketals, Lactams, Amines, Amidoximes, and Amidines (5,10-Epoxymethano and 5,10-Iminomethano Compounds)

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Received June 12, 1970

Cyclization of cyano acid chlorides **2** gives novel dibenzsuberone nitriles **5**, hydrolyzed to corresponding keto acids **8** and converted by standard methods into amides **4**, **7**, and **11**, and acids **12**. Borohydride reduction of **5** and **8** gives *via* corresponding hydroxy nitriles and hydroxy acids, respectively, iminolactone **9**, previously alluded to as a borohydride conjugate reduction product of **6**, and bridged lactone **13**. Known compounds **6**, **14**, and **15** were prepared independently and points of identity correlating the new synthesis with known routes were established with compounds **6** and **12**. Bridged lactam **23** (giving derived compounds **24**) was prepared by hydrogenolysis of **22**, obtained by reaction of lactone **13a** with H_2NOH in refluxing glycol. Another route to bridged lactam, *via* internal displacement of chloroamide **20**, proved to be not general. Bridged keto amidoximes **27** were synthesized from keto nitriles, **5** and **26**, and Ni hydrogenolysis of **27** gave bridged keto amidines **28**. Hydroxy nitriles **31** and hydroxy amides **33**, from borohydride reduction of substituted keto nitriles **26** and corresponding bridged keto amides **30**, respectively, on treatment with concentrated HCl gave bridged lactams **32**, while lactones **36** were formed from **33** in the presence of more dilute acids or nitrous acid. Bridged amines (5,10-iminomethano compounds) **25** and **34** were prepared by borane or $LiAlH_4$ reduction of lactams. Bridged ethers (5,10-epoxymethano compounds) **18** and **35**, through appropriate hydride reductions, and a bridged hemiketal **40**, *via* keto ketal Grignard product **39**, were also prepared. Polyphosphoric acid cyclization of *o*-[2-cyano-2-(3,4-dimethoxyphenyl)]benzoic acid (**1e**) gives dibenzsuberone amide **4e**, an exception to the closures of other cyano acids **1** to 2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3-diones.

The study of linear tricyclic psychopharmacological compounds[1-4] has progressed in two decades from the phenothiazines[1] through iminodibenzyls[5] and dibenzo[*a*,*d*]cycloheptenes[6-8] to a number of related, tricyclic systems (thioxanthenes and dibenzo and pyrido oxepins, thiepins, azepines, diazepines, thiazepines, etc.) bearing basic side chains,[9-24] and with it have been developed the techniques for synthesis of a number of interesting intermediate dibenzo seven-membered cyclic compounds. One must forego here any attempt to review critically this large and interesting area (the citations given here are intended only to convey an idea of the importance of the field and indicate the volume and scope of chemistry done), and merely say that, while this field of work which began with imipramine[5] and amitriptyline[6-8] is still avidly pursued in many quarters, one of the most intriguing chemical aspects recently is perhaps the synthesis of *bridged* dibenzsuberans (dibenzo bicyclic compounds)[25-27] and hydroanthracenes.[28]

Thus, some time ago it was realized that in the

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(3) F. Häfliger and V. Burckhardt, *ibid.*, Vol. 1, 1964, Chapter 3.

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10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene ring system there is present a fairly ideal, steric template for one- and two-atom bridging reactions between positions 5 and 10. Some of the many 10,5-iminomethano compounds prepared by the Dobson–Davis group (from 10,11-epoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carboxylic acid and its derivatives)[25] are also available through newer applications[29] of the classical isopavine synthesis,[30] and 5,10-epoxy compounds closely related to amitriptyline, as well as other 5,10-epoxy-11-oxo and 5,10-ethano and methano compounds of the same class, have been reported.[31]

It occurred to us 2 years ago that the hitherto unknown and inaccessible 5,10-epoxymethano- and 5,10-iminomethano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes, and thus an entire, new area of compounds with possible value as drugs, might be made accessible if 5-oxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-10-carboxylic acids (or corresponding derivatives) could be prepared (Scheme I, **8**). Although corresponding dehydro keto acids **15** are known,[32-34] the hiatus between them and **8** would appear to be owing to difficulty in reduction of **15** and related compounds, as well as to the fact that keto nitrile **6** can neither be reduced selectively to **5** nor hydrolyzed (without rearrangement) to **15**.

In a formal sense, there have been two reports verging closely on what we are about to describe: one concerning the condensation of phthalaldehydic acids with *N*-methyloxindoles and PPA cyclization of the products thereof to 6*H*-benzo[5,6]cyclohept[1,2,3-*c*,*d*]indoline-1,6-diones (lactams of 1-amino-5-oxo-5*H*-dibenzo[*a*,*d*]-cycloheptene-11-carboxylic acids),[35] and the other describing closure with PPA of certain benzylhomophthalic acids and phthalides (having suitably placed aromatic methoxyl groups) to 2,3-dialkoxy-5-oxo-10,11-dihydrodibenzo[*a*,*d*]cyclohepene-10-carboxylic acids.[36] Neither route is general for preparation of keto acids **8** or **15**.

Another paper[37] from our laboratory reports synthesis of a number of cyano acids **1a–e** (Scheme I) *via* condensation of phthalaldehydic acid with various arylacetonitriles and reduction. These acid nitriles, with one exception reminiscent of the Indian work[36] as described below, did not give dibenzsuberone nitriles when cyclized with PPA but rather formed 2-benzazepine-1,3-diones.[37] However, after converting cyano acids **1** by PCl_5 to corresponding acid chlorides **2**, cyclization of **2a**, **b**, and **e** with Lewis acids did give respective keto nitriles **5**. In this closure, $AlCl_3$ in *sym*-tetrachloroethane[38] at 100° served well for the unsubstituted (**2a**) and *p*-methyl (**2b**) nitrile acid chlorides, and $SnCl_4$ was employed in the case of **2e** to avoid demethylation. Acid hydrolysis (HCl and HOAc) of keto nitriles **5** readily gave corresponding keto acids **8**. With these intermediates at hand in quantity, one could foresee many possible ways in which to elaborate bridged compounds.

Polyphosphoric acid cyclization of the dimethoxy cyano acid **1e**, in which there is an activating effect of *p*-methoxyl group on the benzene position capable of being electrophilically attacked internally, afforded specifically keto amide **4e** rather than 4-(3,4-dimethoxyphenyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine-1,3-dione.[37] This was evident from spectra and the fact that acid hydrolysis of **4e** gave keto acid **8e**, identical with that prepared by hydrolyzing keto nitrile **5e**. Keto acids **8** could also be converted to respective amides **4** *via* corresponding (crystalline) keto acid chlorides. Presumably because of the electrophilicity-enhancing effect of the R′ = OCH_3 group on the 5 ketone, compounds **4e** and **8e**, as well as the acid chloride corresponding to **8e**, tended to exist in the bridged (ψ) form to an extent somewhat greater than that displayed by other (**a**, **b**) corresponding members of the series, *e.g.* the acid chloride corresponding to **8a** existed only in the open form. In keto amides related to **4a**, it was observed, however, that the *N*-methyl amide specifically appeared to be partly ψ while other amides (N-substituted **4a**) were in the open form (for relevant ir and uv spectra, see Experimental Section).

Further evidence for structures **4**, **5**, and **8** was forthcoming in reductions of those ketones. Sodium borohydride reduction of keto amide **4e** gave hydroxy amide **7e**, and acid-catalyzed, palladium hydrogenolysis of **4e** or **7e** gave amide **11e**. Similar hydrogenolysis of keto acid **8a** gave acid **12**. Amide **11a** was also obtained from acid **12** as shown.

Sodium borohydride reduction of keto nitrile **5a** and keto acids **8** led, respectively, to bridged iminolactone **9** and bridged lactones **13**. In the **5a** reduction, the crude product contained a certain amount of noncrystalline material, evidently the *trans*-hydroxy nitrile **10**, but in the reduction of **8a** the product, after acidification, was essentially all lactone **13a**. Treatment of **9** with dilute acids at room temperature gave **13a**, thus (together with spectra) excluding a bridged lactam structure for **9**.

Iminolactone **9**, we suspected, was that very briefly mentioned "tetracyclic compound obtained instead" (of the expected hydroxy nitrile) by Gootjes, *et al.*,[34] in their work, *inter alia* on reduction of the dehydro keto nitrile **6**. It was of interest to settle this point, and at the same time provide additional proof of structure of the new keto nitriles and keto acids by relating them to known 5*H*-dibenzo[*a*,*d*]cyclohepten-5-ones. Therefore, we synthesized the 10-bromo ketone **16**[32-34] *via* 10,11-dibromo ketone from the dibenzsuberone and enone[39] and converted it by the reported methods,[32-34] as indicated in Scheme I, to **6**, **14**, and **15**. Sodium borohydride reduction of **6** did indeed give the same mixture of **9** and **10** as obtained from **5a**, the isolated

(29) J. H. Russel, British Patent 1,146,109 (1969); French Patent 6143M (1969); *Chem. Abstr.*, **71**, 30370 (1969).

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(32) W. Tochterman, U. Walter, and A. Mannschreck, *Tetrahedron Lett.*, 2981 (1964).

(33) F. Hoffmann-La Roche, Belgian Patents 659,599 and 659,786 (1965); *Chem. Abstr.*, **64**, 5023 (1966).

(34) J. Gootjes, A. B. H. Funcke, and W. Th. Nauta, *Arzneim. Forsch.*, **19**, 1936 (1969).

(35) J. Plostnieks, U. S. Patent 3,393,208 (1968).

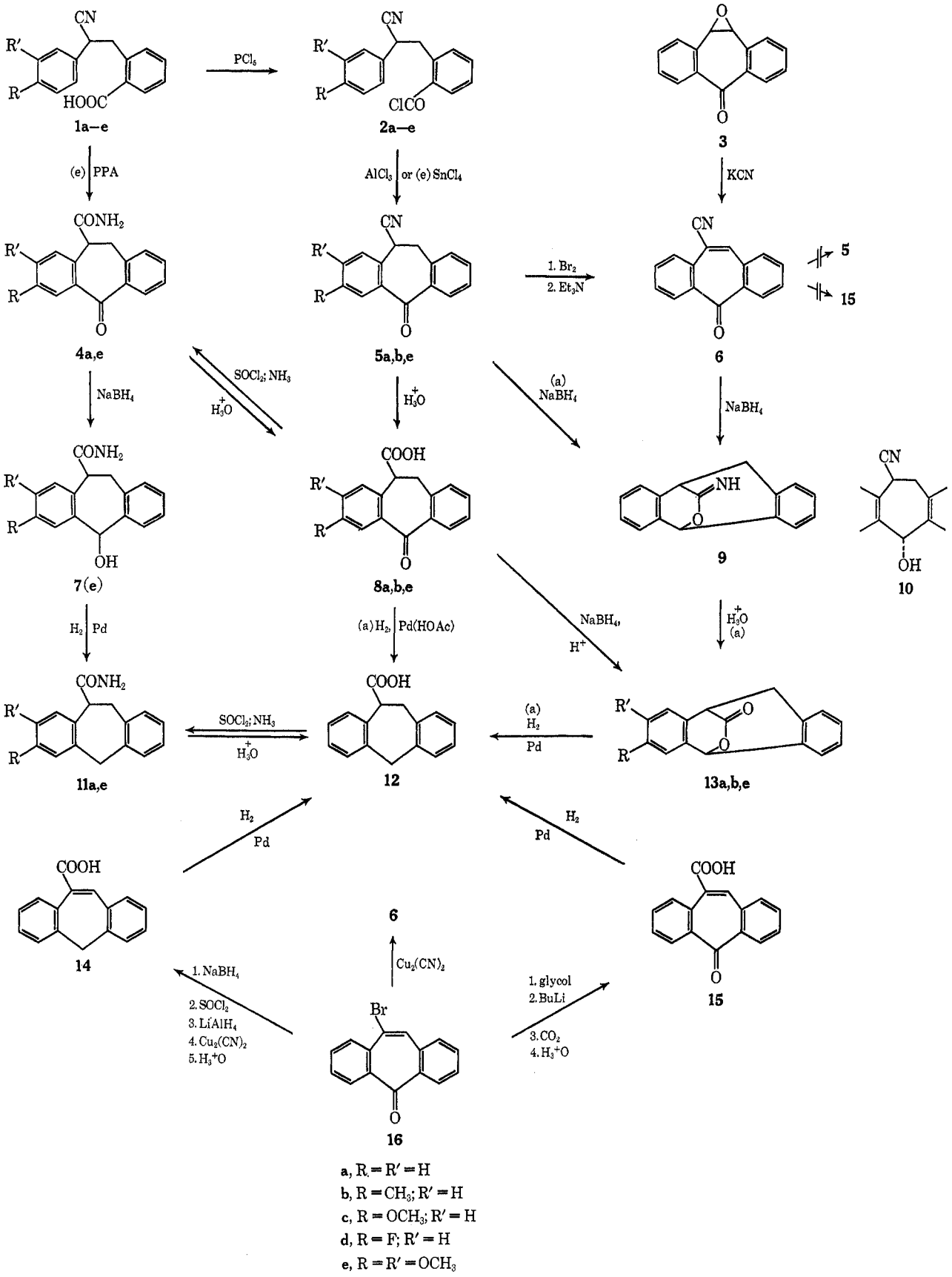
(36) J. N. Chatterjea and H. Mukherjee, *Experientia*, **16**, 2773 (1960); *J. Indian Chem. Soc.*, **37**, 379 (1960).

(37) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 461 (1971).

(38) P. Kranzlein, *Ber.*, **70**, 1952 (1937).

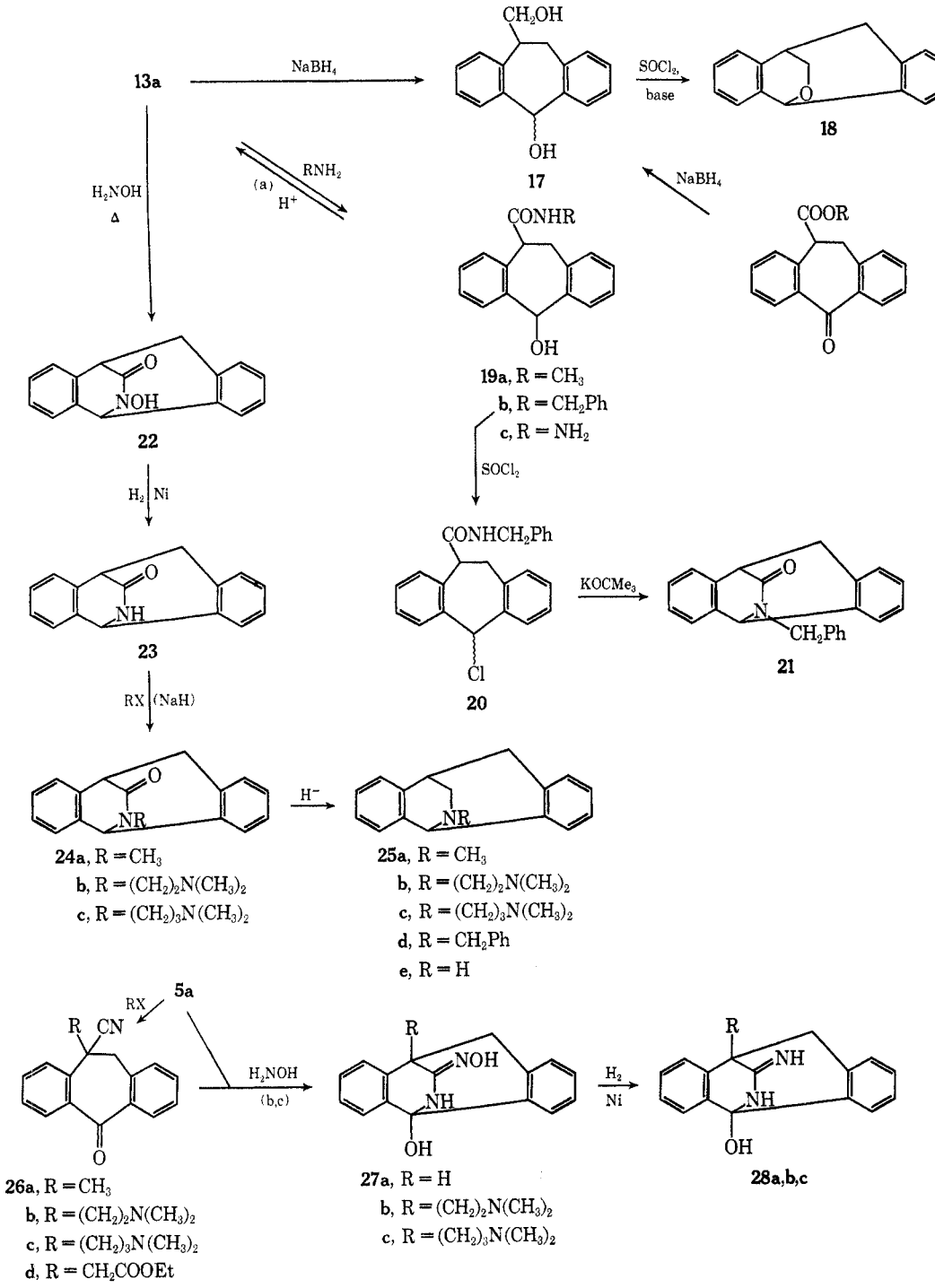
(39) S. Wawzonek, *J. Amer. Chem. Soc.*, **62**, 745 (1940); W. Treibs and H. J. Klinkhammer, *Ber.*, **84**, 671 (1951); A. C. Cope and S. W. Fenton, *J. Amer. Chem. Soc.*, **73**, 1668, 1673 (1951).

SCHEME I



iminolactone **9** being identical with that prepared from **5a**. Then, several additional and more direct correlations of **5a** and **8a** with known compounds were also made. Keto nitrile **6** was the product resulting from bromination of **5a** and dehydrobromination[39] of the resulting crude bromo nitrile with Et_3N, and was identical, not only with the sample of **6** from **16** with $Cu_2(CN)_2$ but also with that prepared in another novel way,

SCHEME II



the action of cyanide on known epoxy ketone **3**.[40] From hydrogenations[41] (Pd) of **14** (good yield) and of **15** (less efficacious, glacial acetic acid), there was obtained acid **12**, identical with that from **8a**. Thus there are now no less than three routes to **6** and four methods (including Pd hydrogenolysis of lactone **13a**, which was also done) for preparing **12**, but it is obvious that our new route is to date the only one leading to **5** and **8**. Synthesis of **12** from **8a** also is considerably more facile in practice, especially on moderate or large scale, than is preparing it from **14** or **15**.

(40) F. Hoffmann-La Roche, Netherlands Appln. 6,600,200 (1966); *Chem. Abstr.*, **65**, 15297 (1966).

(41) J. D. Loudon and L. A. Summers, *J. Chem. Soc.*, 3809 (1957).

Further work (Scheme II) with the promising **5**, **8**, and **13**, directed toward other, more elaborate, bridged compounds was undertaken. *A priori*, it seemed that it should be an easy matter to arrive at bridged lactams, but until several idiosyncratic aspects of the chemistry involved were fully understood, the goals eluded us. Esters (and the **4a** amide) from **8a** were expected to reduce with $NaBH_4$ to corresponding 5-hydroxy compounds, but when this was tried the product was instead diol **17** and gave bridged ether **18** on treatment with $SOCl_2$. Indeed, when lactone **13a** itself was reduced with $NaBH_4$ in excess, diol **17** and from it ($SOCl_2$) ether **18** again were formed. The lactone **13a** is quite unreactive to ammonia but could be made to react by heating

with primary amines (methylamine, benzylamine, H_2NNH_2) giving hydroxy amides **19a**, **b**, and **c**, respectively. Interestingly, **19a** reverted rather easily through loss of CH_3NH_2 (heat, or acids) to lactone **13a**, although **19b** and **c** were more stable.

From **19b** with $SOCl_2$ it was possible to prepare the 5-chloro amide **20**. On treatment with potassium *tert*-butoxide, **20** underwent internal displacement[42] of the very reactive benzhydryl chloride, forming *N*-benzyl bridged lactam **21**. Unfortunately, this route is not a general one to bridged lactams and amines of the type; after reduction of **21** to corresponding amine **25d**, attempted hydrogenolysis (or other cleavage) of the *N*-benzyl group resulted in ring opening (*i.e.*, rupture of the benzhydryl N bond) as well.

At this point a notable feature of dibenzsuberone nitriles **5** should be mentioned. With bases such as NaH, $NaNH_2$, potassium *tert*-butoxide, and even with various amines (pyrrolidine, piperidine), solutions of **5a** become lastingly very deep purple. Not only is the **5a** anion obviously an electron-delocalized chromophore like anions of other phenylacetonitriles, particularly those having *o*- or *p*-nitro or carbonyl substituents, but also it is quite reactive; *i.e.*, after generation it is held well and may react smoothly. Thus alkylations of **5a** with neutral and basic alkyl halides and with α-bromo esters, etc., in the presence of NaH in DMF and toluene, were found to proceed very well, giving a variety of substituted keto nitriles **26**. The keto acid corresponding to **26a**, like **8a**, gave corresponding bridged lactone **36** (R = CH_3) when reduced with $NaBH_4$ and acidified.

Thinking initially that reduction of oximes corresponding to keto acids, nitriles, esters, or amides might serve to place an amino substituent at position 5, we also explored reaction of various 5-keto compounds with hydroxylamine. Here again, evidence was found to indicate relatively high reactivity centering around the 10-cyano group and an expected, relative inertness of the 5-keto group. Keto acid **8a** and its corresponding esters and amide did not form oximes, or in fact react at all, with hydroxylamine under the usual conditions. The nitrile **5a**, however, reacted rather readily with H_2NOH; so also did several of the substituted keto nitriles **26b** and **c**. The products, **27**, all gave strong ferric chloride tests and thus logically were construed as being amidoximes. However, in none of these compounds was there the usual uv [270 mμ (ϵ ~14,000)] band characteristic of the conjugated 5 ketones; thus it was evident that the keto amidoximes existed virtually completely in the ring tautomeric form as shown in **27**. Further proof of the presence of an N–OH bond in the weakly basic **27a** as well as in the strongly basic **27b** and **c**, and a good synthesis for the equally ring-tautomeric (uv), corresponding ψ-keto amidines **28a–c**, was found in nickel-catalyzed hydrogenolysis of **27a–c**. However, further hydrogenolysis of **28** (Pd/C) again led to benzhydryl N-bond cleavage as in **25**.

Returning to the lactam problem *per se*, we capitalized on foregoing facts and found that lactone **13a** also reacted with hydroxylamine, provided the temperature was high enough (refluxing glycol). From this reaction was isolated the *N*-hydroxy lactam (bridged cyclic hydroxamic acid) **22** in high yield. Hydrogenolysis (nickel) of **22** then proceeded well, giving lactam **23**, after which straightforward alkylations (NaH) gave *N*-alkyl lactams **24**, in turn reduced with $LiAlH_4$ or borane to bridged amines **25**.

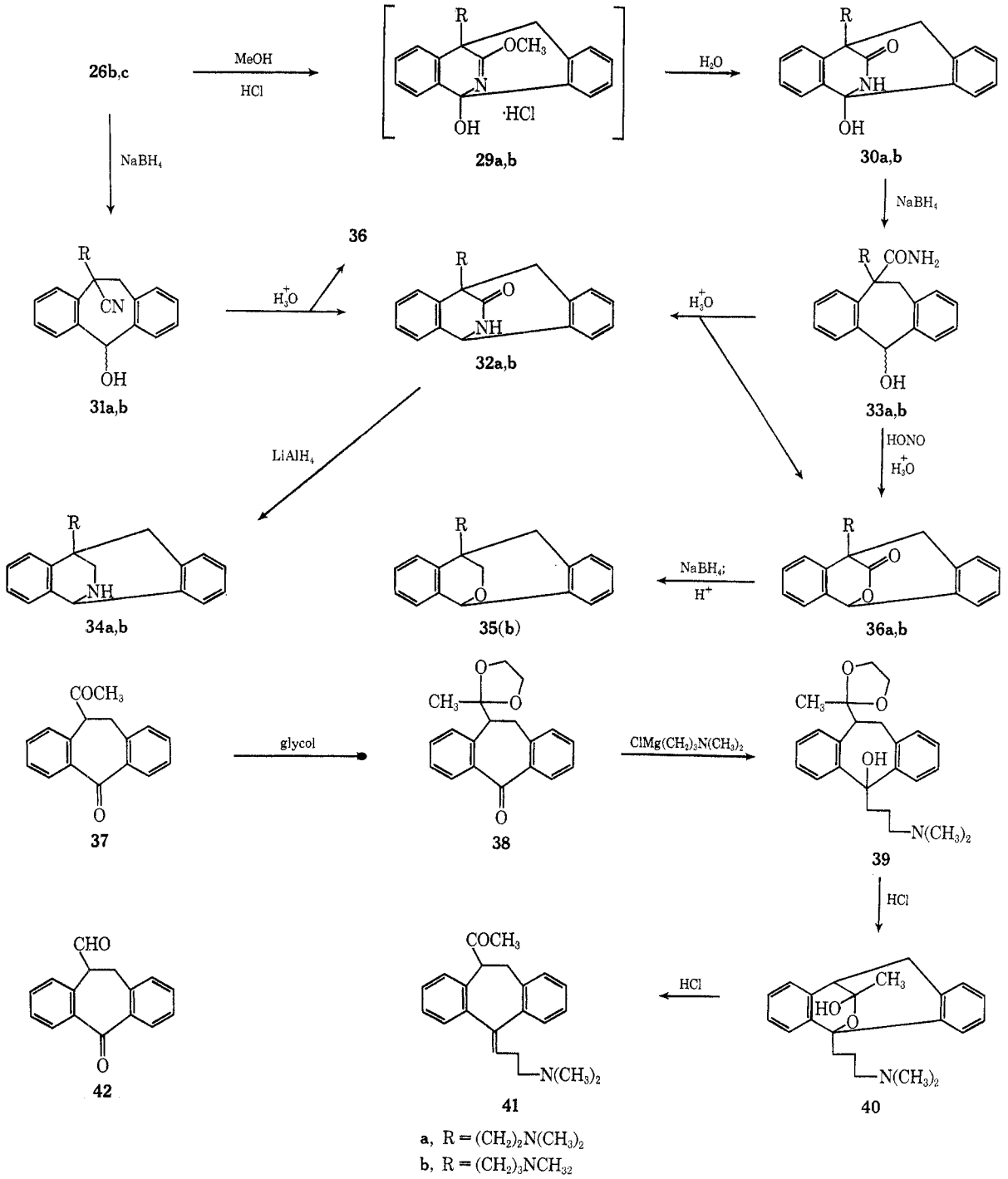
Synthesis of the projected, simpler, bridged heterocyclic compounds having been disposed of, there then remained the problem of synthesizing bridged lactones and lactams from 10-substituted keto nitriles **26**. It was evident in initial, exploratory work that a different approach to synthesis of, *e.g.*, **32** and **36** might be required, for on $NaBH_4$ reduction of **26b** and **c** little or no evidence of spontaneous iminolactone closure was found. Rather, from **26b** and **c** with borohydride (Scheme III) an isomeric mixture of hydroxy nitriles **31** in each case was formed. Also, caution in the amount of reagent used in these reactions was required, for (unlike **9**) there was both a tendency toward overreduction (benzhydrol hydrogenolysis) and, at least with **31b**, a tendency for ill-defined formation of anthracenes (*via* ring opening and reclosure, or other type of rearrangement) to occur in the presence of excess $NaBH_4$. One isomer of **31a** was eventually obtained crystalline; **31b** was not separated into its components but was characterized as a corresponding methiodide. Crude **31b**, and either crude **31a** mixture or its crystalline fraction, on boiling with concentrated hydrochloric acid gave principally the respective, basic, bridged lactams, **32b** and **a**. Structures **32** were particularly clear from nmr spectra, in which the benzhydryl proton doublet (δ 4.97, coupled to NH) collapsed to singlet on exchange of NH with deuterium. A marked contrast is to be seen between the **31** → **32** reactions and the formation of **9** *via cis*-hydroxy nitrile from **5a**; the nitrile group in **31** is much less reactive than in the latter case. For the most part, only when there is generated a carbonium ion from the carbinol at position 5 does CN interact, in the sense of a Ritter reaction.

The relatively unreactive nature of the nitrile group attached to the quaternary carbon atom was seen again in attempted methanolyses. Prolonged boiling of keto nitriles **26b** and **c** with methanolic HCl led to new products, thought at first to be imino ethers; however, initial analytical difficulties with these substances were resolved (nmr showed presence of extraneous methanol), and it emerged that respective bridged (uv) keto amides **30**, tending to crystallize as methanolates, were at hand. Thus the overall effect of the methanolytic reaction was partial hydrolysis, and, as in formation of **27**, nucleophilic attack on CN led to a bridged (ψ) derivative. Possibly ring tautomeric keto imino ethers **29** actually are intermediates in **26** → **30**, for it was observed that other strong acids (PPA, F_3CCOOH, concentrated HCl) did not convert **26** to **30** but gave mainly polymeric substances.

Keto amides **30** were reduced with $NaBH_4$ (again, as in **26**, with necessary circumspection) and with resulting, isomeric mixtures of hydroxy amides **33**, experiments involving treatment with acids under various conditions were tried Hot, strong, aqueous HCl again led **33** to form principally the respective lactams **32**, but refluxing **33a** with dilute HCl gave a separable mixture of lactam **32a** (mp 188°, ir 6.08 μ) and lactone **36a** (mp 163–165°, ir 5.75 μ). Similar observations were made with **33b**, reflux with 7% HCl leading almost exclusively to the lactone. Evidently, acid of low

(42) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **31**, 1905 (1966).

SCHEME III



a, R = $(CH_2)_2N(CH_3)_2$
b, R = $(CH_2)_3NCH_3$

strength less efficiently converts carbinol to carbonium ion and partial or complete hydrolysis of amide may intervene, leading to lactone. There is no conversion of lactam **32** to lactone **36** under any conditions tried, including use of nitrous acid. However, a better way to proceed from hydroxy amide **33** to lactone **36** was found in nitrous acid deamination of the amide.

Hydride reduction of basic, bridged lactams **32** gave bridged amines **34**. There was also applied that which had been learned from experiments leading to **18**; after acid solvolysis of **33a** and borohydride reduction of the crude product, basic bridged ether **35b** was isolated (in low yield) as corresponding hydrochloride.

Having placed appropriate (basic) side chains on the 10 carbon and the 13 atom of various, novel 5,10-bridged 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes, we wished to complete the work by preparing from **5a** at least one 5,10-bridged compound similarly substituted at position 5. Since organometallic reagents preferentially attacked the nitrile group of **5a** (with initial development of characteristic purple color of the anion), an inert group was needed at position 10, and, to secure it, acid chloride from **8a** was converted to diketone **37** using methylcadmium. Glycol reacted quite selectively with **37**, as expected, giving keto ketal **38**. Keto aldehyde **42** was also prepared, by Rosenmund reduction of keto acid chloride or better by Stephen reduction of the keto nitrile but was fairly unstable and could not be converted similarly to a monoacetal. Reaction of the Marxer Grignard reagent with **38** proceeded smoothly,

giving basic hydroxy ketal **39**. On treatment of **39**, under very mild conditions with HCl, glycol was removed and, not unexpectedly,[31] bridged hemiketal **40**, showing no evidence spectrally of a ketone group *per se*, emerged. Warm alcoholic HCl then led to dehydration and formation of basic, unsaturated ketone **41** (ir 5.87 μ), characterized as hydrochloride and apparently the anticipated mixture of two diastereoisomers.[6]

Experimental Section[43]

o-(**2-Cyano-2-phenylethyl**)**benzoyl Chloride** (**2a**).—To a stirred solution of 100 g of acid nitrile **1a**[37] in 2 l. of methylene chloride was added 100 g of PCl_5 in portions, during 0.5 hr. After the solution was allowed to stand for 2 hr at room tempersture, it was washed with water, and then (while chilling) with 2% NaOH solution, and finally with three additional portions of water. After drying ($MgSO_4$) and evaporating solvent, the residue, triturated with ether–ligroin (bp 38–56°), afforded 98 g of colorless crystals: mp 83–86°, raised on recrystallization (ligroin) to mp 87–89°; ir 4.46 and 5.75 μ; uv (hexane) 246 nm (ϵ 10,650) and 290 (2260); nmr ($CDCl_3$) δ 8.2 (m, 1, aromatic H ortho to –COCl), 7.3–7.7 (m, 8, remaining aromatic protons), 4.15 (quartet, 1, J^{AX} = 5 Hz, J^{BX} = 10 Hz, methine proton), and 3.4 (octet, 2, J^{AB} = 13 Hz, J^{AX} and J^{BX} = 5 and 10 Hz, respectively).

Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.49; N, 5.19. Found: C, 71.04; H, 4.64; N, 5.28.

The dried acid chloride was stored in desiccator or closed container at 0° until used.

Treatment of a sample of the cyano acid chloride with NH_4OH gave the corresponding amide nitrile: mp 154–155.5° on recrystallization from ethanol; ir 2.90, 3.18, 4.47, and 6.02 μ.

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.06; H, 5.32; N, 11.01.

With methanol, the cyano acid chloride gave corresponding nitrile methyl ester: mp 119–121° (from ether); ir 4.47 and 5.85 μ.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.98; H, 5.4; N, 5.34.

Other substituted cyano acid chlorides **2** were prepared by the same procedure from previously reported cyano acids.[37]

Compound 2b gave colorless crystals from ether–EtOAc: mp 69–72°; ir 4.45 and 5.67–5.70 μ; uv 247 nm (ϵ 11,000) and 291 (2300).

Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.95; H, 4.97; N, 4.93. Found: C, 71.81; H, 5.3; N, 4.65.

Compound 2c similarly prepared had mp 119–120°; ir 4.45 and 5.69–5.75 μ; uv 227 nm (ϵ 14,690), 246 (9340), 275 (2470), 282 (2770), and inflections 250 (8990) and 294 (1990).

Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.11; H, 4.70; N, 4.67. Found: C, 68.4; H, 4.85; N, 4.60.

Compound 2d gave colorless crystals from ligroin (bp 39–53°): mp 84–85.5°; ir 4.45 (weak) and 5.71 μ (broad); uv 247 nm (ϵ 11,850), 269 (1980), and 290 (2440); nmr ($CDCl_3$) δ 8.3 (m, 1, aromatic H ortho to ClCO group), 6.9–7.6 (m, 7, remaining aromatic H), 4.15 (dd, 1, methine proton α to CN, J^{AX} = 5.4 Hz, J^{BX} = 10.4 Hz), and 2.93–3.66 (octet, centered δ 3.35, 2, J^{AB} = 13 Hz, J^{BX} = 10.5 Hz, J^{AX} = 5.4 Hz).

Anal. Calcd for $C_{16}H_{11}ClFNO$: C, 66.79; H, 3.85; N, 4.86. Found: C, 67.04; H, 3.83; N, 4.55.

Compound 2e was recrystallized from EtOAc: mp 99–101°; ir 4.45 and 5.68–5.72 μ; uv 230 nm (ϵ 17,250) and 280 (4690).

Anal. Calcd for $C_{18}H_{16}ClNO_3$: C, 65.55; H, 4.89; N, 4.24. Found: C, 65.63; H, 5.03; N, 4.25.

10-Cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**5a**).—A solution of 69.5 g of cyano acid chloride **2a** in 700 ml of *sym*-tetrachloroethane was treated with 120 g of anhydrous $AlCl_3$ and the mixture heated on a steam cone (air condenser) 2.5 hr with swirling or (magnetic) stirring. Evolution of HCl was copious during the first 0.5–0.7 hr, and most of the $AlCl_3$ dissolved. After pouring the chilled solution into ice and excess hydrochloric acid, adding *ca.* 2 l. of ether, and shaking, the organic layer was separated and washed with the following in sequence: two portions of water, an excess of 2% NaOH solution, and three portions of water. Evaporation of the dried ($MgSO_4$), brown solution gave an oil which was induced to crystallize (initially by scratching a sample on watch glass with ether, in later runs by seeding), and the material was triturated with ether–ligroin, to give 40 g of light tan crystals, mp 105–108°, sufficiently pure for further work, Recrystallization from methanol (or ether) gave a pure sample: mp 112–113°; ir 4.46 and 6.07 μ; uv 268 nm (ϵ 14,460) and 341 (490); nmr ($CDCl_3$) δ 8.0 (m, 2, aromatic protons peri to C=O), 7.6–7.1 (m, 6, remaining aromatic H), 4.4 (q, 1, J^{AX} = 3.8 Hz, J^{BX} = 6.5 Hz, methine H), and 3.54–3.49 (doublets, 1 each, J^{AX} and J^{BX} as for δ 4.4, but J^{AB} indiscernible).

Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.01. Found: C, 82.40; H, 4.78; N, 6.06.

The corresponding 2,4-dinitrophenylhydrazone required 1 week to precipitate when prepared in aqueous ethanolic (H_2SO_4) solution: orange crystals from ethyl acetate, mp 260–262°.

Anal. Calcd for $C_{22}H_{15}N_5O_4$: C, 63.92; H, 3.66; N, 16.94. Found: C, 64.27; H, 3.51; N, 16.69.

Keto Nitrile 5b.—Cyclization of **2b** (48 g) with $AlCl_3$ (58 g) in *sym*-tetrachloroethane (720 ml) by the same procedure gave **5b**, recrystallized from ethyl acetate–ether: mp 119–120°; ir 4.45 and 6.03 μ; uv 270 nm (ϵ 14,650); nmr (CDCl) very similar to that of **5a**.

Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.57; H, 5.12; N, 5.63.

Keto Nitrile 5e.—To stirred solution of 10.4 g of anhydrous stannic chloride in 40 ml of benzene was added (0.3 hr) a solution of 10 g of cyano acid chloride **2e** in 50 ml of benzene. After standing at room temperature, protected from moisture, overnight, hydrolysis with ice and HCl and further work-up as in the preceding experiments gave 6.2 g of keto nitrile, crystallizing from methanol–EtOAc: mp 136–138°; ir 4.46 and 6.15 μ (sharp, moderate–intense peaks); 224, 290, and 326 nm (ϵ 17,100, 9890, and 8020, respectively); nmr ($CDCl_3$) δ 7.77 (s, 1, peri Ar proton between MeO and C=O), 8.0 (m, 1, other Ar proton peri to C=O), 7.2–7.6 (m, 3, Ar protons), 6.95 (s, 1, peri Ar proton between MeO and CN), 4.41 (q, 1, J^{AX} = 3.5 Hz, J^{BX} = 6.5 Hz, methine H), 3.97 (s, 6, methyl of MeO groups), and 3.51 (d, 1, J = 3.5 Hz) and 3.46 (d, 1, J = 6.5 Hz) in which J^{AB} was nearly indiscernible (signals of the CH_2 group).

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.82; H, 5.19; N, 4.81.

Hydrolysis of Keto Nitriles 5 to Keto Acids 8.—A solution of 25 g of **5a** in 200 ml of glacial HOAc and 300 ml of concentrated hydrochloric acid was refluxed 3 hr, the volume of the solution was then reduced to ~ 100 ml *in vacuo*, and the material was treated with ice water. The crude acid was collected and taken into 5% sodium bicarbonate solution, and the aqueous solution washed with ether and acidified with HCl. A washed (H_2O) and dried ($MgSO_4$) ether extract of the reprecipitated acid on evaporation gave 25 g of crystals of **8a**: mp 140–142°, raised on further recrystallization (ether) to mp 144–145°; ir 5.91 and 6.09 μ; uv 207 and 268 nm (ϵ 23,950 and 14,940, respectively).

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.44; H, 4.73.

Derivatives of 8a.—The corresponding acid chloride was prepared using thionyl chloride: colorless crystals from ether; mp 108–110°; ir 5.59 and 6.07 μ; uv 264 nm (ϵ 14,930).

Anal. Calcd for $C_{16}H_{11}ClO_2$: C, 70.98; H, 4.10. Found: C, 71.0; H, 4.06.

The corresponding amide **4a**, from the acid chloride and NH_4OH, after recrystallization from ethanol–ether had mp 161–162°; ir 2.91, 3.02, 3.12, 6.01, 6.10, and 6.19 μ; uv 268 nm (ϵ 10,110).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.45; H, 4.98; N, 5.40.

The corresponding methyl ester, prepared from either acid or acid chloride and recrystallized from methanol–ether (Norit) had mp 50–52°; ir 5.74 and 6.08 μ; uv 268 nm (ϵ 14,760).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.39; H, 5.24.

The corresponding *N*,*N*-diethyl amide, from acid chloride and diethylamine, was recrystallized from ether: mp 85–86°; ir 6.02 and 6.11 μ; uv 268 nm (ϵ 13,490).

(43) Melting points were obtained using Thomas–Hoover stirred silicone oil bath. Infrared spectra (Nujol mulls, unless otherwise noted) were taken on a Perkin-Elmer double beam instrument, ultraviolet spectra (methanol solutions, unless otherwise noted) with a Cary 14 recording spectrophotometer, and nmr spectra using a Varian A-60 apparatus with TMS internal standard.

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.29; H, 6.84; N, 4.68.

The corresponding *N*-methyl amide, from acid chloride and methylamine, was recrystallized from methanol: ir 3.06, 3.25, 5.99, and 6.11 μ; uv 269 nm (ϵ 7210), indicating partially ring-tautomeric form.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.16; H, 5.49; N, 5.27.

Keto acid 8b was obtained by similar hydrolysis of **5b**, in quantitative yield and recrystallized from ether: mp 166–168°; ir 5.92 and 6.09 μ; uv 270 nm (ϵ 14,160).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.97; H, 5.49.

Keto acid 8e was obtained (2.5 g) by similar hydrolysis of **5e** (4 g) and recrystallized from ether–ethyl acetate: mp 195–196°; ir (Nujol) 3.14 and 5.75 μ; ir ($CHCl_3$) little or no unbonded OH peak, 5.86 with weaker shoulder at 5.75 μ; uv 244, 291, and 330 nm (ϵ 14,640, 9750, and 7610, respectively); nmr (DMSO) δ 7.6 (s, 1, peri proton between MeO and C=O), 7.9 (m, 1, other Ar proton peri to C=O), 7.2–7.5 (m, 3, aromatic protons), 6.95 (s, 1, peri H between MeO and COOH), 4.3 (t, 1, J = 4.5 Hz, methine), 3.83 (s, 6, methoxyl CH_3), and 3.45 (d, 2, J = 4.5 Hz, methylene).

Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.30; H, 5.18.

The corresponding acid chloride was prepared using $SOCl_2$ and recrystallized from ether: mp 130–131°; ir 5.60 and 6.10 μ; uv 242, 290, and 324 nm (ϵ 20,300, 10,190, and 7560, respectively); nmr ($CDCl_3$) δ 7.93 (m, 1, peri aromatic H adjacent to ketone on unsubstituted aryl ring), 7.78 (s, 1, peri aromatic H between MeO and ketone), 7.1–7.5 (m, 3, aromatic H), 6.6 (s, 1, peri aromatic H between MeO and COCl), 4.52 (t, 1, J = 4.5 Hz, methine), 3.9 (two singlets, 6, methoxyl CH_3) and 3.63 (d, 2, J = 4.5 Hz, methylene).

Anal. Calcd for $C_{18}H_{15}ClO_4$: C, 65.36; H, 4.57. Found: C, 65.74; H, 4.64.

Keto Amide 4e.—A mixture of 5.5 g of acid nitrile **1e** and 168 g of polyphosphoric acid was heated at 100° and stirred 1 hr. The bright red solution was cooled and stirred with ice and water; the resulting light yellow, crude crystals were collected, washed with water, and dried. After trituration with methanol, there was obtained 3.5 g of product, mp from *ca.* 220°, insoluble in dilute alkali. A pure sample was obtained by recrystallization from a relatively large volume of ethanol: colorless crystals; mp 226–229° (melt greenish); ir 2.93, 3.19, 5.96, 6.16, and 6.30 μ; uv 245, 290, and 328 nm (ϵ 15,580, 9710, and 7330, respectively); nmr (DMSO) δ 7.58 (s, 1, peri proton between MeO and C=O), 7.87 (m, 1, other proton peri to C=O), 7.1–7.5 (m, 3, aromatic H), 6.87 (s, 1, peri proton between MeO and $CONH_2$), 4.1 (t, 1, J = 5 Hz, methine), 3.82 (s, 6, methoxyl CH_3), and 3.42 (d, 2, J = 5 Hz, methylene).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.18; H, 5.61; N, 4.33.

Hydrolysis of this compound (1.7 g) with refluxing (4 hr) hydrochloric and acetic acids (25 ml each) gave keto acid **8e** (1.2 g), mp 196–198°, identical (mmp 194–196°, undepressed; spectra identical) with the sample of **8e** from the preceding experiment.

Hydroxy Amide 7e.—Sodium borohydride (3 g) reduction of **4e** (0.3 g, suspended in MeOH), evaporation of most of the methanol from the resulting solution, treatment with water, and ether trituration of the collected, washed, and dried solid, followed by recrystallization from ethanol and methanol, gave colorless crystals: mp 247–249° dec; ir 2.81, 2.95, 3.05, 3.13, 6.02, and 6.18–6.22 μ; uv 282 nm (ϵ 3360) with infl 240 and 288 nm.

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.30; H, 6.02; N, 4.24.

Amide 11e.—In the presence of 10% Pd/C (1.5 g), keto amide **4e** (1.5 g) (or **7e**) in glacial HOAc (150 ml) was hydrogenated at 3 atm and 70° for 1 hr. Filtration, evaporation, and recrystallization of the residue (methanol) gave (quantitatively) bluish white crystals: mp 238–240°; ir 2.95, 3.05, 3.13, 6.02, and 6.18–6.22 μ; uv 285 nm (ϵ 3580).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.51; H, 6.38; N, 4.60.

10,11-Dihydro-5,10-epoxymethano-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (Lactone 13a).—A solution of 20.7 g of keto acid **8a** in 300 ml of methanol was treated with excess $NaBH_4$ (31 g) in portions, cautiously at first because of vigorous effervescence. After heating 0.5 hr on a steam cone and evaporating most of the methanol, the cooled residue was taken into water (300 ml) and the solution acidified with HCl. The collected, water-washed, and dried, voluminous crystals were dissolved in ether and the filtered solution was concentrated, to yield 14 g of lactone, mp *ca.* 148°. A sample, recrystallized from ether, had mp 153–154°; ir 5.75 μ; uv 264 nm (ϵ 500); nmr ($CDCl_3$) δ 6.9–7.4 (m, 8, aromatic H), 5.94 (s, 1, benzhydryl proton), 4.08 (t, 1, J^{AX} = J^{BX} = 4 Hz, methine H at position 10), and 3.33 (octet, 2, J^{AX} = 18 Hz; methylene).

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.11; H, 4.82.

By the same $NaBH_4$ reduction, followed by acidification, were prepared the following compounds.

Lactone 13b, recrystallized from ether, had mp 149–151°; ir 5.78 μ; uv benzenoid; nmr similar to that of **13a**.

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.84; H, 5.45.

Lactone 13e, recrystallized from ether–ethyl acetate, had mp 196–197°; ir 5.77 μ; uv 210, 248, and 286 nm (ϵ 42,000, 5320, and 4810, respectively); nmr ($CDCl_3$) δ 7.4–7.0 (m, 4, aromatic protons of the unsubstituted phenyl), 6.82 (s, 2, peri protons adjacent to methoxyls), 5.88 (s, 1, benzhydryl H), 4.02 (t, 1, J^{AX} = J^{BX} = 3.5 Hz, methine H of position 10), 3.87 (s, 6, methoxyl CH_3), and 3.37 (octet, 2, J^{AB} = 18 Hz, methylene protons).

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.26; H, 5.49.

10,11-Dihydro-12-imino-5,10-epoxymethano-5*H*-dibenzo[*a*,*d*]cycloheptene (Iminolactone, 9).—Solution of 5.2 g of keto nitrile **5a** in 200 ml of methanol was treated with excess $NaBH_4$ (*ca.* 8 g) in portions during 5–10 min; when the exothermic, effervescent reaction subsided, the solution was evaporated (steam cone, 15 min) to remove most of the methanol. Addition of water to the cooled material gave partly crystalline solid, which was collected, washed with water, and dried. The crude material (4.9 g) on fractional crystallization from ether afforded a total of 3.7 g of crystals, mp *ca.* 177–182°, of fairly pure iminolactone, and the remaining material (mostly **10**) was a glass. Further recrystallization from ether gave a pure sample: mp 181.5–183.5°; ir 3.12 (moderate, sharp) and 5.98 μ (intense, sharp); uv benzoid; nmr ($CDCl_3$) δ 7.0–7.4 (m, 9, aromatic H and 1 D_2O exchanged, NH), 5.73 (s, 1, benzhydryl H), 4.12 (t, 1, J^{AX} = J^{BX} = 3.5 Hz, methine), and 3.38 (octet, 2, J^{AX} = J^{BX} = 3.5 Hz, J^{AB} = 18 Hz, methylene).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.70; H, 5.67; N, 5.89.

On treatment with 18% hydrochloric acid at room temperature (overnight) the iminolactone gave lactone **13a**: mp 153.5–155° after recrystallization from ether; mmp (with preceding sample of **13a**) 153.5–155.5° (undepressed); ir and nmr spectra identical.

Mother liquors remaining from the purification of **9**, on standing a year (capped vial), afforded an odor of NH_3 and, on recrystallization of residue from methanol, a sample of lactone **13a**, mp 151–153°, identical with preceding specimens.

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-10-carboxylic Acid (12). A.—A solution of 15 g of keto acid **8a** in 200 ml of glacial HOAc with 5 g of 10% Pd/C was hydrogenated at 3 atm and 70° for 2 hr. Evaporation of the filtered solution and crystallization in presence of ether–ligroin (bp 38–56°) gave 10.5 g of product: mp 111–114°, raised on recrystallization from the same solvents to mp 120–121°; ir 5.91 μ; nmr ($CDCl_3$) δ 11.8 (s, 1, D_2O exchanged, carboxyl H), 7.1 (s, 8, aromatic protons), and 4.5–3.0 (m, 5, not first-order resolvable, methylene and methine protons).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.90; H, 5.93.

B.—Hydrogenation of lactone **13a** (1.5 g) in glacial HOAc (100 ml) in the presence of 10% Pd/C (2.5 g) at 3 atm and 70° for 5 hr, filtration, evaporation, isolation of acidic material through sodium bicarbonate extraction of the crude residue and acidification, and recrystallization from ether–ligroin gave colorless crystals, mp 117–119°, mmp (with A product) 117–120° (undepressed), and ir spectra identical.

C.—A solution of 0.7 g of 5*H*-dibenzo[*a*,*d*]cycloheptene-10-carboxylic acid (**14**)[34] in 50 ml of 2% aqueous potassium carbonate[41] was stirred with 10% Pd/C under hydrogen at room temperature for 71 hr. Filtration, acidification with 2% HCl, extraction with ether, and evaporation of the washed (H_2O) and dried ($MgSO_4$) ether solution gave a colorless, glassy sample,

crystallizing immediately and completely when seeded with A or B sample: mp 118–120°; mmp (with sample A) 119–121° (undepressed); infrared and nmr spectra were identical.

D.—Hydrogenation of 0.35 g of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-10-carboxylic acid (**15**)[33] in the presence of 1 g of 10% Pd/C in glacial HOAc at 3 atm and 70° for 3.5 hr, filtration, evaporation, and fractional crystallization of the residue (ether–ligroin) gave a sample of **12**, spectrally identical with preceding ones.

The acid chloride corresponding to **12**, prepared using $SOCl_2$, was not crystalline but was converted readily to a number of derivatives, *e.g.*, corresponding amide **11a**: mp 188–189° after recrystallization from methanol; ir 6.05 μ.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.94; H, 6.16; N, 5.74.

Acid 12b was prepared by hydrogenolysis of **8b** and recrystallized from methanol: mp 153–155°; ir 5.88 μ.

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.20; H, 6.42.

10-Cyano-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (6). A. Bromination.—A solution of 12.7 g of keto nitrile **5a** and 12 g of bromine in 300 ml of benzene was let stand 2 days (room temperature). The ether-diluted, washed ($NaHCO_3$ solution, water) and dried solution on evaporation gave 18 g of crude bromo keto nitrile, a slightly fuming, viscous, yellow oil which did not crystallize.

B. Dehydrobromination.—On addition of excess triethylamine to crude A product, there was an exothermic reaction and rapid formation of crystals. After stirring 3 hr and adding water, the crystals were collected, washed with water, dried (yield 12.4 g), triturated with ether, and recrystallized from methanol: mp 175–176°, undepressed on admixture with an authentic sample (lit.[34] mp 171–172°) prepared by reaction of 10-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one with $Cu_2(CN)_2$ in DMF[34]; ir and other spectra were the same as the latter.

The cyanoenone **6** was also obtained as follows. A. Epoxidation of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (11.8 g) in CH_2Cl_2 (350 ml) with 87% *m*-chloroperbenzoic acid (25 g) at room temperature overnight and isolation of epoxide **3** by evaporation of the washed (5% NaOH solution, water) and dried ($MgSO_4$) solution gave, after trituration with ether, 7.5 g of epoxy ketone **3**: mp 113–119°, raised on recrystallization (ether) to mp 127–130° (lit.[40] mp 127–130°); ir 6.01 μ; uv 211, 256, and 295 nm (ϵ 25,600, 9990, and 2250, respectively).

Anal. Calcd for $C_{15}H_{10}O_2$: C, 81.06; H, 4.54. Found: C, 81.38; H, 4.38.

B.—Potassium cyanide (1.2 g) and epoxy ketone (1.8 g) in water (10 ml) and ethanol (25 ml) was refluxed 1.5 hr, after which the solution was evaporated to smaller volume and treated with water, and the gummy, reddish solid was collected, washed (water), dried, and purified by recrystallization from ether: colorless crystals; mp 175–176°; mixture melting point with preceding samples undepressed; and spectra identical with latter; ir 4.47 and 6.08 μ; uv 212, 254, and 316 nm (ϵ 14,990, 32,240, and 15,490, respectively) with infl 244 nm.

Anal. Calcd for $C_{16}H_9NO$: C, 83.10; H, 3.92; N, 6.06. Found: C, 82.94; H, 4.04; N, 5.94.

Reduction of a sample of this cyanoenone in methanol with $NaBH_4$ by the procedure already described for preparation of **9**, gave **9**, mp 171–174°, after recrystallization from methanol. The infrared spectra of the two samples were identical.

Attempts to hydrolyze (HCl or H_2SO_4 with HOAc), methanolyze (CH_3OH + HCl), or convert the cyanoenone to corresponding amide (H_2SO_4) were unsuccessful.

Diol 17.—Lactone **13a** (1 g) in 100 ml of methanol was reduced with excess $NaBH_4$ (3 g, added in portions) while heating on a steam cone (20 min) and, after addition of water to cooled residue, neutral material was extracted with ether. The washed (water) and dried ($MgSO_4$) ether solution on evaporation gave nearly quantitative yield of crystals, mp 85–95°, apparently a mixture of diastereoisomers; recrystallization from ether gave a sample, mp 95–105°, ir 3.01 μ (broad, intense).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.26; H, 6.75.

The same material, and from it in turn the cyclic ether as described in the next experiment, was also obtained when methyl ester, amide, or *N*-methyl amide corresponding to **8a** were reduced similarly with $NaBH_4$.

Bridged Ether 18.—On treatment of 3.1 g of crude diol from preceding experiments with 20 ml of $SOCl_2$ there was rapid reaction. After 5 min, removal of excess reagent *in vacuo* (steam cone) gave a crystalline, but unstable, residue (1.6 g). The latter was treated with an excess of either concentrated NH_4OH or methanolic sodium methoxide to give, on subsequent addition of water, colorless crystals which in each case were collected, washed with water, dried, and recrystallized from methanol: mp 98–99°; ir devoid of C=O and OH bands; uv (benzenoid); nmr δ 5.42 (s, 1, benzhydryl H); and mass spectrum (*m*/*e* 222) confirming the structure.

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.48; H, 6.34.

Hydroxy Amide 19b.—Lactone **13a** (12.5 g) and benzylamine (25 ml) were heated together on a steam cone for 20 hr. The residue remaining after removal of excess amine *in vacuo* was taken into warm EtOAc and the solution diluted with ether. The crystalline product (12.5 g, mp 150–153°) was collected. Recrystallization from methanol gave pure material: mp 160–161°; ir 2.96, 6.03, and 6.29 μ.

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.51; H, 6.14; N, 4.12.

Similar reaction of lactone **13a** (1.5 g) with boiling, 40% aqueous methylamine solution (80 ml) for 15 hr, evaporation of excess reagent, and one recrystallization of residual crystals from ethanol gave a sample of hydroxy amide **19a**, mp 178–181°, ir 3.07 and 6.13 μ. This compound gradually reverted to **13a**, however, on attempted further recrystallization from various solvents and drying at 80°, and a completely pure sample could not be obtained. In $SOCl_2$, the reversion to lactone **13a** was immediate.

Anal. Calcd for $C_{17}H_{17}NO_2 \cdot H_2O$: C, 71.56; H, 6.71; N, 4.91. Found: C, 72.13; H, 6.49; N, 4.5.

Hydroxy acid hydrazide 19c, obtained by heating **13a** with hydrazine at 100° overnight and recrystallized from methanol, had mp 219–221°; ir 2.81, 3.02, and 6.14–6.20 μ.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.85; H, 6.08; N, 10.37.

13-Benzyl-10,11-dihydro-5,10-iminomethano-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (21). A.—Chloro amide **20** was obtained by treating **19b** (5.3 g) with $SOCl_2$ (60 ml) and after standing 3 min removing excess reagent *in vacuo* while warming gently on a steam cone. Attempts to purify the glassy, somewhat unstable, residue (4.8 g) using ether or EtOAc were not successful; the crude material gave a strong Beilstein (Cu) test for chlorine.

B.—Treatment of crude A in 200 ml of *tert*-butyl alcohol with 2 g of potassium *tert*-butoxide under reflux (1 hr), followed by removal of solvent *in vacuo* and addition of water, gave crude, oily crystals. The washed (water) and dried ($MgSO_4$) ether extract afforded on evaporation 3.0 g of colorless crystals: mp 151–153°, raised on further recrystallization (ether) to mp 156–157°; ir 6.02 μ and devoid of NH or OH bands.

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 85.09; H, 5.63; N, 4.40.

Hydrogenolysis of this lactam in glacial HOAc at 70° afforded amide **11a**, mp 189–190°, identical with authentic specimen.

Bridged Amine 25d.—Lithium aluminum hydride (8 g) reduction of **21** (6.2 g) in THF (200 ml) under reflux (5 hr), subsequent addition of water (40 ml) and ether (600 ml), filtration, and evaporation of dried (K_2CO_3) solution gave crude base which was converted by ethereal ethanolic HCl to the corresponding hydrochloride: colorless crystals from methanol–ethanol; mp 198–200°, resolidifying and melting 246–248° dec; ir devoid of OH, NH, or C=O bands; nmr (DMSO) δ 6.06 (s, 1, benzhydryl proton).

Anal. Calcd for $C_{23}H_{21}N \cdot HCl \cdot {}^1/_2H_2O$: C, 77.40; H, 6.50; N, 3.93. Found: C, 77.56; H, 6.52; N, 3.90.

Hydrogenolysis of the amine·HCl (1.25 g) in ethanol (150 ml) and methanol (50 ml) in the presence of 10% Pd/C (1.5 g) at 60° for 2 hr and recrystallization of the product (0.8 g) from ethanol gave **10,11-dihydro-10-aminomethyl-5*H*-dibenzo[*a*,*d*]cycloheptene hydrochloride**, mp 229–231°; the identically same compound (ir, nmr) was obtained by borane or $LiAlH_4$ reduction of amide **11a** and conversion of basic product to corresponding hydrochloride.

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.97; H, 6.98; N, 5.39. Found: C, 74.30; H, 6.92; N, 5.39.

13-Hydroxy-10,11-dihydro-5,10-iminomethano-5*H*-dibenzo[*a*,*d*]cyclohepten-12-one (22).—Hydroxylamine HCl (35 g) in water (20 ml) was neutralized at 0° by slowly adding NaOH (14 g) in water (10 ml), ethylene glycol (120 ml) was added, the solution was filtered, lactone **13a** (5.25 g) was added; the solution

was refluxed 13 hr and kept at 100° for 4 days. The product, crystallized on addition of water, was collected, washed with water and ether, and dried: yield 3.75 g; mp 233–236°, raised on recrystallization from ether to mp 237–239°; ir 6.05 μ and bonded OH; nmr (DMSO) δ 5.41 (s, 1, benzhydryl proton).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.65; H, 4.94; N, 5.55.

The *N*-hydroxyl lactam gave a deep purple $FeCl_3$ test.

Bridged Lactam 23.—To a solution of 19.5 g of **22** in 1800 ml of ethanol was added 6 teaspoons of Raney nickel (washed with water and ethanol), and the suspension was shaken under H_2 (3 atm) at 70° for 1.5 hr. The warm suspension was filtered, the catalyst was leached with several portions of hot ethanol, and the combined filtrates were evaporated. The yield of ethanol–ether triturated, colorless crystals was 15 g: mp 226–228°, not raised on recrystallization from ethanol; ir 3.04 (moderate, broad) and 6.10 μ with subsidiary bands 5.96 and 6.2–6.25 μ; nmr (DMSO) δ 8.8 (d, 1, J = 5.5 Hz, exchange with D_2O, NH), 6.9–7.5 (m, 8, aromatic protons), 5.18 (d, 1, J = 5.5 Hz, benzhydryl proton, collapsing to s on deuteration of NH), 3.72 (t, 1, $J \simeq 4$ Hz, methine), and 3.17 (octet, 2, J^{AB} = 19 Hz, $J^{AX} = J^{BX}$ = 4 Hz, methylene).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.99; H, 5.45; N, 6.06.

N-Alkylation of 23.—Compound **24a**, for example, was prepared by treating 5.5 g of **23** in 400 ml of toluene with 1.15 g of NaH (56%, oil) and after 3 min with 50 ml of iodomethane. The suspension was refluxed and stirred 3.3 hr, then cooled, diluted with ether, washed with water, dried ($MgSO_4$), and evaporated to small volume; the crystals (5.6 g) were collected with the aid of ether. A sample recrystallized from ether had mp 245–246°; ir 6.07 μ; nmr ($CDCl_3$) δ 6.9–7.4 (m, 8, aromatic protons), 4.82 (s, 1, benzhydryl H), 3.9 (t, 1, J = 3.5 Hz, methine), 3.26 (octet, 2, J^{AB} = 18 Hz, $J^{AX} = J^{BX}$ = 3.5 Hz, methylene), and 3.02 (s, 3, *N*-methyl).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.20; H, 6.15; N, 5.62.

By similar procedure using 2–3 equiv of appropriate *N*,*N*-dimethyl-β- and -γ-chloroalkylamines, there were prepared the following *N*-alkyl lactams.

Compound 24b, after evaporation of dried (K_2CO_3) organic solution and recrystallization from ether–ligroin, had mp 86.5–88°, ir 6.08–6.10 μ.

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.24; H, 7.17; N, 8.88.

Compound 24c, from ether, had mp 125.5–127°, ir 6.03 μ.

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.67; H, 7.77; N, 8.72.

Bridged Amines 25.—Lithium aluminum hydride reduction of lactams **24** in THF as described for amine **25d** and, when appropriate, conversion of crude products to suitable derivatives by standard procedures, gave the following compounds.

Compound 25e was obtained from reduction of **24** (R = H); the hydrochloride was obtained from ethanol–ether, mp 272–274° dec.

Anal. Calcd for $C_{16}H_{15}N \cdot HCl$: C, 74.55; H, 6.26; N, 5.44. Found: C, 74.73; H, 6.05; N, 5.44.

Compound 25a was obtained as the hydrochloride, from ethanol–ether, mp 251–253°.

Anal. Calcd for $C_{17}H_{17}N \cdot HCl$: C, 75.12; H, 6.67; N, 5.15. Found: C, 75.04; H, 6.57; N, 5.26.

Compound 25b was an oil; the corresponding dipicrate was recrystallized from methanol, mp 233–234° dec.

Anal. Calcd for $C_{32}H_{30}N_8O_{14}$: C, 51.20; H, 4.03; N, 14.93. Found: C, 51.36; H, 3.84; N, 15.2.

Compound 25c, also an oil, was characterized as the dipicrate, mp 229–230° dec (from methanol).

Anal. Calcd for $C_{33}H_{32}N_8O_{14}$: C, 51.83; H, 4.22; N, 14.66. Found: C, 51.77; H, 4.60; N, 14.38.

10-Cyano-10-(β-dimethylaminoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (26b).—A swirled solution of 35.1 g of keto nitrile **5a** in 125 ml of DMF was treated with 7.2 g of NaH (56%, oil) with occasional brief cooling, 250 ml of 1.39 *M* dried toluene solution of β-dimethylaminoethyl chloride was added to the very deep purple solution, and the mixture was heated on a steam cone with stirring 2.5 hr; additional chloro amine solution (100 ml) was added after 0.8 hr. At the end of the reaction period, the deep purple color had been discharged. The deep reddish, cooled suspension was stirred into ice and water (1 l.), ether was added, the organic layer was washed (three portions of water) and dried (K_2CO_3), and the solvents were evaporated. The crude, red-brown oil was taken into 1 l. of ether, and the dried (K_2CO_3) solution filtered and treated with a slight excess of 5% ethanolic HCl to precipitate the corresponding hydrochloride: 28 g, crystallizing in ethanol–ether as a solvated form; mp 217–220° dec; after recrystallization from ethanol–ether and drying at 80° *in vacuo*, mp 204–206° dec; ir 4.45 and 6.02 μ as well as bands indicative of aminium chloride; uv 269 nm (ε 13,910).

Anal. Calcd for $C_{20}H_{20}N_2O \cdot HCl$: C, 70.47; H, 6.21; N, 8.22. Found: C, 70.32; H, 6.41; N, 8.05.

The corresponding free base, prepared from purified hydrochloride with NaOH solution, extracted with ether, dried (K_2CO_3), and isolated by evaporation, was a colorless oil, ir 6.02 μ.

Compound 26c was prepared by essentially the same procedure, from **5a** (30 g) and γ-dimethylaminopropyl chloride (50 ml) in 65 ml of DMF and 100 ml of toluene in the presence of 5.6 g of NaH (56%, oil), and also isolated as the hydrochloride (22.5 g): mp 199–201°; ir 4.47 and 6.03 μ; uv 269 nm (ε 13,870).

Anal. Calcd for $C_{21}H_{22}N_2O \cdot HCl$: C, 71.07; H, 6.53; N, 7.90. Found: C, 71.18; H, 6.91; N, 7.73.

The corresponding base was not crystalline.

Compound 26a, prepared by alkylation of **5a** in DMF with iodomethane in the presence of NaH, was an oil and was characterized by hydrolysis (HCl and HOAc, 3-hr reflux) to the corresponding **keto acid**: mp 142–144° (from ether); ir 5.90 and 6.06 μ; uv 268 nm (ε 12,440).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.60; H, 5.08.

Sodium borohydride (12 g) reduction of this keto acid (5 g) in methanol (100 ml) under reflux (0.5 hr) and after evaporation acidification of the aqueous solution of hydroxy acid, gave the 10-methyl-substituted bridged **lactone** (**36**, R = CH_3): yield 5 g; colorless crystals (from ether); mp 174–175°; ir 5.78 μ.

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.6; H, 5.64. Found: C, 81.8; H, 5.71.

Compound 26d, prepared by similar alkylation of **5a** with ethyl bromoacetate and recrystallized from methanol, had mp 101.5–103.5°; ir 4.48, 5.80, and 6.05 μ; uv 269 nm (ε 12,930).

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.27; H, 5.24; N, 4.33.

Bridged (ψ) Keto Amidoximes 27.—Solutions of hydroxylamine, prepared from 40 g of $H_2NOH \cdot HCl$ and 16 g of NaOH in 150 ml of water at 0°, and keto nitrile **5a** (16 g) in 250 ml of ethanol were combined and refluxed 4 hr. On addition of 1.5 l. of ice and water, **27a** crystallized and was collected, washed with water, dried (yield 8 g), and recrystallized from methanol: colorless crystals; mp 182–183°; ir 2.91 and 6.01 μ; uv 266 and 274 nm (ε 2400 and 2100, respectively).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.29; H, 5.31; N, 10.49.

The amidoxime gave a deep red test with $FeCl_3$.

The **hydrochloride of 27a**, recrystallized from ethanol–acetone, had mp 184–188° dec, and was solvated (nmr), ir 5.96 μ and NH, OH bands.

Anal. Calcd for $C_{16}H_{14}N_2O_2 \cdot HCl$: C, 63.47; H, 4.99. Found: C, 63.44; H, 5.32.

Compound 27b, prepared by 3-hr reflux of **26b** (3.75 g) with H_2NOH (from 9 g of $H_2NOH \cdot HCl$ and 4 g of NaOH) in 35 ml of water and 55 ml of ethanol and precipitated from the chilled, diluted solution by dilute NaOH, was collected, washed, dried (yield 2.8 g), and recrystallized from methanol: mp 236–238°; ir 6.04–6.10 μ and a very broad OH band; uv showing no conjugated ketone; $FeCl_3$ test wine-red.

Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.13; H, 6.97; N, 12.09.

Compound 27c, from 8 g of **26c**, 19 g of $H_2NOH \cdot HCl$ and 8 g of NaOH in 80 ml of water, and 100 ml of ethanol by the same procedure as in the preceding experiment, was obtained (6 g) and recrystallized from ether: mp 216–217°; ir 3.04 and 6.10 μ: uv devoid of conjugated C=O; $FeCl_3$ test deep green.

Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 72.16; H, 7.33; N, 11.74.

Bridged (ψ) Keto Amidines 28.—A solution of 3.5 g of amidoxime **27a** in 280 ml of ethanol was shaken under H_2 (3 atm) in the presence of 1 teaspoon Raney nickel at 60° for 2 hr. The catalyst was filtered and leached with five portions of ethanol, and the combined filtrates were evaporated to give 3 g of amidine **28a**: mp 261–262° dec (from ethanol); ir 2.94, 3.12, and 6.03 μ; $FeCl_3$ test negative.

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.89; H, 5.42; N, 11.14.

The corresponding hydrochloride crystallized from ethanol as a hemihydrate: mp 284–286°; ir 3.13 (intense, broad) and 5.97 μ (sharp); uv 265 nm (ϵ 1060).

Anal. Calcd for $C_{16}H_{14}N_2O \cdot HCl \cdot {}^1/_2H_2O$: C, 64.97; H, 5.45; N, 9.47. Found: C, 64.34; H, 5.07; N, 9.21.

Hydrogenation of **28a** in glacial acetic acid in the presence of Pd/C at 70° for 4 hr resulted in hydrogenolysis and solvolysis as well, giving amide **11a** on work-up, mp 189–191°, mixture melting point with preceding sample undepressed.

Compound 28b was obtained by hydrogenation of **27b** in ethanol with Raney nickel as for **28a** and recrystallized from ethanol: colorless crystals; mp 262–264°; ir 5.98, 6.19 μ and multiple NH and OH band; $FeCl_3$ test negative.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.65; H, 7.49; N, 13.27.

The corresponding dihydrochloride had mp 294–296° after recrystallization from ethanol, ir 5.96 μ and very broad NH band.

Anal. Calcd for $C_{20}H_{23}N_3O \cdot 2HCl$: C, 60.91; H, 6.39. Found: C, 60.56; H, 6.70.

Compound 28c, in quantitative yield from hydrogenation (Raney nickel) of **27c**, was recrystallized from ethanol: mp 192–194°; ir 2.96, 3.12, 3.20, and 6.25 μ; uv benzenoid and end absorption.

Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.11; H, 7.25; N, 12.30.

The corresponding dihydrochloride was recrystallized from methanol–ethanol, mp 329–330° dec.

Anal. Calcd for $C_{21}H_{25}N_3O \cdot 2HCl$: C, 61.76; H, 6.67; N, 10.29. Found: C, 61.91; H, 6.65; N, 10.28.

Bridged (ψ) Keto Amides. 10-(β-Dimethylaminoethyl)-10,11-dihydro-5-hydroxy-5,10-iminomethano-5*H*-dibenzo[*a*,*d*]cycloheptene-12-one (30a).—A hydrogen chloride saturated solution of 15 g of **26b** in 1 l. of methanol was refluxed 7 hr, the solution being cooled and re-treated every 2 hr with HCl. Removal of solvent on a steam cone and (next day) trituration of the semisolid residue with methanol–ether afforded 14.3 g of **30a** hydrochloride: mp 283–286° dec, raised on recrystallization (methanol) to mp 287–289° dec; ir 3.16 and 5.97 μ; uv lacking conjugated C=O band; nmr indicated slight MeOH solvation.

Anal. Calcd for $C_{20}H_{22}N_2O_2 \cdot HCl$: C, 66.93; H, 6.46; N, 7.81. Found: C, 67.30; H, 6.38; N, 7.65.

The free base, liberated with NaOH solution, isolated by ether extraction, and recrystallized from methanol, had mp 208–209° and was also a methanolate, ir 3.13 and 5.98 μ.

Anal. Calcd for $C_{20}H_{22}N_2O_2 \cdot CH_3OH$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.60; H, 7.27; N, 7.99.

Compound 30b.—Treatment of 5 g of **26c** with methanolic HCl (8 hr) and isolation as in the preceding experiment gave 2 g of slightly discolored hydrochloride, mp *ca.* 228° dec. Recrystallization from methanol–ether gave colorless crystals: mp 245–247° dec, after drying *in vacuo;* ir 5.95–6.03 μ together with OH band; uv 266 and 274 nm (ϵ 1000 and 950, respectively).

Anal. Calcd for $C_{21}H_{24}N_2O_2 \cdot HCl$: C, 67.64; H, 6.76; N, 7.51. Found: C, 67.88; H, 6.73; N, 7.39.

The base was obtained either from pure hydrochloride or from mother liquors remaining after isolation of the sample of hydrochloride, by action of NaOH solution. The crude base, initially not crystalline after extraction with ether and evaporation of the dried (K_2CO_3) solution, was reconverted to the hydrochloride and the hydrochloride was converted again to base using K_2CO_3 solution. The crystalline residue, remaining after evaporation of the washed (H_2O) and dried (K_2CO_3) ether extract, on recrystallization from ether gave colorless crystals: mp 210–212°; ir 3.14 and 6.01μ; uv 260–268 and 274 mn (ϵ 850).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.11; H, 7.44; N, 8.29.

Hydroxy Nitriles 31.—A solution of 8 g of **26c** in methanol (100 ml) was treated with *ca.* 17 g of NaBH in portions during 5–10 min. The solution was warmed gently on a steam cone 10 min, and then cooled and diluted with ice water. The collected, washed (water), and dried product (7 g) was taken up in ether, and the dried (K_2CO_3) and filtered solution was allowed to evaporate slowly. From the residue with the aid of ether and a small amount of ethanol were obtained several crops (3.2 g) of a crystalline isomer of **31b**: mp 175–176° after recrystallization from ethanol; ir 4.47 μ and bonded OH band; uv devoid of conjugated C=O; nmr ($CDCl_3$) δ 7.0–7.6 (m, 8, aromatic protons), 5.60 (s, 1, benzhydryl H), 4.53 and 3.03 (doublets, 1 each, J^{AB} = 14 Hz, magnetically nonequivalent methylene protons), and 1.8–2.2 (m, 12, methylenes and *N*-methyl of side chain).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.73; H, 7.63; N, 8.80.

The material (*ca.* 4 g) remaining in the filtrates after collection of the crystalline portion was a pale yellow glass having similar spectral characteristics and may have been mainly the other isomer of **31b**.

The corresponding hydrochloride, prepared from crystalline **31b** and recrystallized from ethanol–ether, had mp 211–212° dec, ir 2.94 (broad) and 4.48 μ.

Anal. Calcd for $C_{21}H_{24}N_2O \cdot HCl$: C, 70.67; H, 7.06; N, 7.85. Found: C, 70.69; H, 7.50; N, 8.04.

Compound 31a was prepared by similar $NaBH_4$ reduction of **26b** and isolated by extraction with ether as a viscous, colorless glass or amorphous solid, apparently a mixture of isomers: ir broad, bonded OH, and 4.47 μ.

A corresponding methiodide methanolate was prepared from crude **31a** with iodomethane in ether and recrystallized from methanol–ether, mp 235–237° dec, ir 3.00 and 4.46 μ.

Anal. Calcd for $C_{21}H_{25}IN_2O \cdot CH_3OH$: C, 55.00; H, 6.09; N, 5.83. Found: C, 55.35; H, 6.18; N, 5.78.

Recrystallization from ethanol rather than methanol gave the hydrated salt, mp 241–242°.

Anal. Calcd for $C_{21}H_{25}IN_2O \cdot H_2O$: C, 54.08; H, 5.84; N, N, 6.01. Found: C, 54.18; H, 5.92; N, 5.96.

Were the borohydride reductions leading to **31** prolonged beyond 15–20 min with an excessively large amount of $NaBH_4$ present, further reduction and, in the case of **31b**, formation of anthracene (uv) by-products of undetermined structure, were encountered. In one attempted preparation of **31a** involving a large excess of $NaBH_4$ and 3 hr of heating (steam cone), there was isolated **10-cyano-10-(β-dimethylaminoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene as** the corresponding hydrochloride: mp 288–290° (from ethanol); ir 4.47 μ.

Anal. Calcd for $C_{20}H_{22}N_2 \cdot HCl$: C, 73.49; H, 7.09; N, 8.57. Found: C, 73.74; H, 7.06; N, 8.59.

Hydroxy Amides 33.—Reductions of ψ-keto amides **30** with $NaBH_4$ in methanol were carried out by the same procedure as for **31**, and the respective products were isolated by dilution with water, extraction with ether, and evaporation of the well-washed (water) and dried (K_2CO_3) solutions.

Compound 33a, a colorless glassy mixture of isomers which did not crystallize, was characterized by converting a sample to corresponding methiodide: mp 235–238° dec after recrystallization from ethanol; ir 2.96–3.14 (broad, intense) and 5.98–6.05 μ; uv devoid of conjugated C=O.

Anal. Calcd for $C_{21}H_{27}IN_2O_2$: C, 54.08; H, 5.84; N, 6.01. Found: C, 54.36; H, 5.81; N, 6.00.

Compound 33b crystallized partly, and the crystalline isomer (from ether) had mp 164.5–166°; ir 2.87, 2.98–3.18, and 5.96–5.99 μ; uv lacking conjugated C=O.

Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.73; H, 7.76; N, 8.20.

Bridged Lactams 32.—A solution of crude **31a** (3.5 g) in 100 ml of concentrated HCl was refluxed 3.5 hr. After removal of most of the aqueous HCl *in vacuo*, a cooled, filtered water solution of the residue was made basic with K_2CO_3 and the material extracted with ether. Evaporation of the washed (H_2O) and dried (K_2CO_3) ether solution and crystallization of the residue (ether) gave 1.3 g of **32a**: colorless crystals; mp 187.5–188°; ir 6.08 μ (shoulder, 6.01 μ); nmr ($CDCl_3$) δ 7.0–7.6 (m, 9, aromatic protons and NH), 5.0 (d, 1, J = 5.2 Hz, collapsing to s when NH deuterated, benzhydryl proton), 3.05 (q, 2, J = 17 Hz, methylene), and 2.35–2.60 (m, 10, side chain CH_2 and NMe_2).

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.52; H, 7.33; N, 9.15.

The corresponding hydrochloride was recrystallized from ethanol–ether: mp 252–254°; ir 2.89–296, 3.06, and 6.00 μ.

Anal. Calcd for $C_{20}H_{22}N_2O \cdot HCl \cdot {}^1/_2H_2O$: C, 68.26; H, 6.88; N, 7.96. Found: C, 67.98; H, 6.61; N, 7.74.

The same **32a** was obtained by similar treatment of hydroxy amide **33a** with concentrated HCl.

Compound 32b, similarly prepared by the action (3.5 hr of reflux) of concentrated HCl (400 ml) on 7.6 g of crystalline hydroxy nitrile **31b** in 5.4 g yield, had mp 168–170°; ir 6.01 μ and a highly bonded NH band; nmr ($CDCl_3$) δ 8.0 (d, 1, exchanged with D_2O, NH), 6.8–7.5 (m, 8, aromatic protons), 4.97 (d, 1, J = 5.4 Hz, collapsed to s on deuteration of NH, benz-

hydryl proton), 2.98 (q, 2, J^{AB} = 17.7 Hz, methylene), and 1.5–2.5 (m, 12, methylenes and NCH_3 of side chain).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.95; H, 7.68; N, 8.79.

The corresponding hydrochloride had mp 251–252° (from ethanol–ether); ir 2.91, 3.16, and 6.02 μ.

Anal. Calcd for $C_{21}H_{24}N_2O \cdot HCl$: C, 70.67; H, 7.06; N, 7.85. Found: C, 71.04; H, 7.18; N, 7.92.

Bridged Amines 34.—Borane (50 ml, 1 *M* THF solution) reduction of **32a** (1.7 g) in 50 ml of THF under reflux (4.5 hr), treatment of the cooled solution with 25 ml of water, hydrolysis (15 ml of concentrated HCl and 30 ml of glacial HOAc, reflux 0.8 hr), and isolation of crude base (after basifying the evaporated solution with NaOH solution) by ether extraction and evaporation of the washed (water) and dried (K_2CO_3) solution gave 0.8 g of oily **34a**, characterized as the dipicrate, yellow crystals (from methanol), mp 233° dec (sintering at 147–148°).

Anal. Calcd for $C_{32}H_{30}N_8O_{14} \cdot H_2O$: C, 50.00; H, 4.20; N, 14.58. Found: C, 49.97; H, 4.40; N, 14.28.

Compound 34b.—Similar reduction of **32b** with borane, or reduction of 5.2 g of **32b** with 12 g of $LiAlH_4$ in 300 ml of THF according to usual procedure, gave 4 g of oily amine, also characterized as the dipicrate, mp 266–267° dec (from methanol).

Anal. Calcd for $C_{33}H_{32}N_8O_{14}$: C, 51.85; H, 4.22; N, 14.66. Found: C, 51.97; H, 4.09; N, 14.60.

Bridged Lactone 36a.—A solution of 5 g of hydroxy amide **33a** in 100 ml of 12% hydrochloric acid and 50 ml of methanol chilled to −10° was treated slowly with 25 g of $NaNO_2$ in 60 ml of water (0.5 hr); additional methanol (*ca.* 50 ml) was added to ensure complete solution. After standing 5 hr at −10 to 0° and overnight at room temperature, the solution was warmed 20 min on a steam cone, chilled, and made basic with K_2CO_3 solution, and the material extracted with ether. The ether solution was washed with six portions of water, dried (K_2CO_3), and evaporated. Crystals formed and were collected with the aid of ether: 2.0 g; mp 159–160°, raised on recrystallization (ether) to mp 163.5–164.5°; ir 5.75 μ; nmr ($CDCl_3$) δ 7.0–7.6 (m, 8, aromatic H), 5.95 (s, 1, benzhydryl H), 3.18 (q, 2, J^{AB} = 18 Hz, methylene), and 2.2–2.6 (m, 10, methylenes and *N*-methyl of side chain).

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.17; H, 6.77; N, 4.40.

The corresponding hydrochloride was recrystallized from ethanol, mp 260–262° dec, ir 5.79 μ.

Anal. Calcd for $C_{20}H_{21}NO_2 \cdot HCl$: C, 69.86; H, 6.45; N, 4.07. Found: C, 69.62; H, 6.53; N, 4.25.

The same lactone was obtained as a by-product on repetition of a preparation of lactam **32a**. After 3.5 hr of reflux of a filtered solution of 7.5 g of crude hydroxy amide **33a** in 400 ml of 8% aqueous alcoholic (*ca.* 1:1) HCl and isolation of crude base (K_2CO_3) *via* ether extraction, there was obtained first 1.7 g of lactam **32a**, mp 187–189°, and, on further concentration of ether filtrates, 0.75 g of **36a**, mp 163–165°; mixture melting point with the sample from nitrous acid reaction was undepressed; ir spectra were identical. The residue (3 g) remaining from isolation of these two compounds, a yellow oil, did not afford additional crystalline material.

Lactone 36b.—Experiments similar to the foregoing ones, involving treatment of **33b** with nitrous acid and its hydrolysis with 7% hydrochloric acid, were carried out. In each case, colorless to pale yellow, oily base was isolated; ir (5.76 μ) spectra of these samples were very similar to that of **36a**. However, even after removal of any lactam **32b**, attempts (including tlc) to obtain crystalline lactone using various solvents and procedures were not successful. The hydrochloride, picrate, and corresponding methiodide (solvated, mp *ca.* 200–208°, ir 2.9 and 5.76 μ) also did not crystallize.

Bridged Ether 35b.—After hydrochloric acid–methanol (300 ml) treatment of 2.5 g of crude **33b** (reflux 8 hr), the crude, basic, oily product (2.3 g) was reduced with excess $NaBH_4$ (added in portions to a MeOH solution). Addition of water, extraction with ether, and evaporation of the dried (K_2CO_3) ether solution gave 1.2 g of oil: ir 2.8–3.0 μ (broad OH bands), and a peak 5.81 μ, indicating that the material was a mixture of the diol and hydroxy ester. An ether solution of the material, on treatment with ethanolic HCl, gave 0.55 g of **35b** hydrochloride: colorless crystals; mp 235–238°, raised on recrystallization (ethanol) to 244–245°; ir and uv devoid of carbonyl bands.

Anal. Calcd for $C_{21}H_{25}NO \cdot HCl$: C, 73.34; H, 7.62; N, 4.07. Found: C, 73.10; H, 7.49; N, 3.88.

Diketone 37.—To dimethylcadmium (from 3.3 g of Mg, iodomethane, and 26.2 g of anhydrous $CdCl_2$) in 250 ml of ether was added 18 g of **8a** acid chloride in 300 ml of dry benzene. The suspension was boiled (stirring) to remove ether and refluxed (78°) and stirred 1.5 hr. After hydrolysis (ice, water, and excess HCl) and isolation of neutral product as usual, there was obtained 6.1 g of crystals, mp 90–97°. Recrystallization from methanol (or ether) gave pure material: mp 117–118°; ir 5.86 and 6.07 μ; uv 206 and 269 nm (ε 24,860 and 14,450, respectively); nmr ($CDCl_3$) δ 8.0 (m, 2, aromatic H peri to 5-keto group), 7.0–7.6 (m, 6, remaining aromatic H), 4.17 (t, 1, *J* = 5.0 Hz, methine), 3.52 (d, 2, *J* = 5.0 Hz, equivalent methylene protons), and 1.95 (s, 3, methyl of ketone).

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.83; H, 5.64.

The corresponding mono-2,4-dinitrophenylhydrazone formed rapidly, crystallized in ethanol, and was recrystallized from ethanol–ethyl acetate: yellow crystals; mp 161–163°; ir 6.07, 6.17, and 6.27 μ.

Anal. Calcd for $C_{23}H_{18}N_4O_5$: C, 64.18; H, 4.22; N, 13.02. Found: C, 64.49; H, 4.00; N, 12.72.

Keto Ketal 38.—A solution of 14.6 g of **37**, 19 ml of ethylene glycol, 3 ml of $MeSO_3H$, and 500 ml of benzene was refluxed 6 hr under a Dean-Stark trap, collecting 2.5 ml of water. The cooled, washed (3% NaOH solution, water), dried ($MgSO_4$), and evaporated solution afforded 11.6 g of crystals from ether: mp 140–141°; ir 6.09 μ; uv 208 and 266 nm (ε 27,430 and 14,200, respectively).

Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.43; H, 6.22.

Basic Hydroxy Ketal 39. A.—Grignard reagent was prepared as follows. Magnesium (1.5 g) under a small amount of dry ether was first treated with 5 ml of iodomethane. After 5–10 min, when reaction had begun, the supernatant solution was decanted and replaced with 20 ml of fresh ether. Dropwise addition of a dried (CaH_2) solution of 20 ml of *N*,*N*-dimethyl-γ-chloropropylamine in 25 ml of THF was then begun immediately and carried out over the course of 1 hr, leading to smooth, mildly exothermic consumption of the magnesium.

B.—A solution of 7.3 g of keto ketal **38** in 80 ml of THF was added, and the solution (protected from moisture) was refluxed 5 hr. The cooled solution was poured into water (500 ml) containing NH_4Cl (15 g). The ether extract of the material, after washing (water) and drying (K_2CO_3), was evaporated. The resulting yellow oil crystallized in the presence of ether, giving 5.3 g of colorless crystals, mp 118–120°, soluble in dilute HCl. Recrystallization from ether gave a pure sample, mp 122–123°, ir and uv devoid of ketone absorption. First-order analysis of nmr was not possible but spectrum was in agreement with the structure.

Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.28; H, 8.18; N, 3.59.

Basic Bridged Hemiketal 40.—The usual preparation of the hydrochloride from **39**, by adding 5% ethanolic HCl to an ethereal solution of **39**, afforded a quantitative yield of colorless crystals: mp 185–188° (from ethanol–ether); ir 3.11 μ and no carbonyl peak; uv devoid of carbonyl bands.

Anal. Calcd for $C_{22}H_{27}NO_2 \cdot HCl$: C, 70.66; H, 7.55; N, 3.75. Found: C, 71.0; H, 8.0; N, 3.90.

The corresponding base, **40**, prepared by treating the hydrochloride with Na_2CO_3 solution, extracting with ether, and recrystallizing from ether, had mp 135–137°, ir (bonded OH 3.13–3.23 μ), and uv devoid of carbonyl bands.

Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.38; H, 7.68; N, 4.15.

10-Amitryptylline Methyl Ketone 41.—Either **39** or **40** (2 g) in 100 ml of 5% ethanolic HCl was refluxed 4 hr. Evaporation *in vacuo*, treatment of a water solution of the residue with K_2CO_3, extraction of base with ether, and evaporation of washed (H_2O) and dried (K_2CO_3) ether solution gave an oil (ir 5.85 μ). Reconversion to the hydrochloride and (fractional) recrystallization of the salt from acetone and ethanol–ether afforded colorless samples: mp 156–159°, mp 161–166°, and mp 164–167°; ir spectra of these (5.87 μ, C=O) were virtually identical; uv 206 and 236 nm (ε 42,420 and 12,700, respectively).

Anal. Calcd for $C_{22}H_{25}NO \cdot HCl$: C, 74.27; H, 7.36; N, 3.94. Found: C, 74.17; H, 7.39; N, 3.96.

Keto Aldehyde 42.—An ethereal (1 l.) solution of 3.2 g of keto nitrile **5a**, saturated with dry HCl and treated with 11 g of anhydrous $SnCl_2$, was allowed to stand overnight. After de-

canting the supernatant solution, the oily deposit was treated with water; the resulting, bright red material was shaken with warm, dilute hydrochloric acid and ether. The ether solution was washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated. Ether trituration of the yellow, oily residue gave colorless crystals, careful recrystallization of which (ether) afforded a pure sample: mp 84–85.5°; ir 5.81 (shoulder 5.73) and 6.04 μ; uv 204 and 270 nm (ϵ 30,270 and 14,420, respectively); nmr ($CDCl_3$) δ 9.45 (s, 1, aldehyde), 8.13 and 7.87 (multiplets, 1 each, aromatic H peri to ketone), 7.1–7.6 (m, 6, remaining aromatic H), 4.03 (t, 1, J = 4.5 Hz, methine), and 3.55 (unsymmetrical doublet of doublets, J = 4.5 Hz, methylene).

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.53; H, 5.05.

The keto aldehyde was also obtained less pure and in lower yield by Rosenmund reduction of **8a** acid chloride. The compound was unstable to heat and to bases.

The corresponding mono-2,4-dinitrophenylhydrazone was prepared as usual and recrystallized from ethanol–ethyl acetate: yellow crystals; mp 210–211°; ir 6.11, 6.17, and 6.29 μ.

Anal. Calcd for $C_{22}H_{16}N_4O_5$: C, 63.46; H, 3.87; N, 13.46. Found: C, 63.19; H, 3.59; N, 12.95.

Registry No.—**2a,** 26899-68-3; **2a** (amide nitrile)' 26899-69-4; **2a** (nitrile methyl ester), 26899-70-7; **2b,** 26963-65-5; **2c,** 26963-66-6; **2d,** 26899-71-8; **2e,** 26899-72-9; **3,** 4444-44-4; **4a,** 26963-68-8; **4e,** 26899-73-0; **5a,** 26899-74-1; **5a** (2,4-dinitrophenylhydrazone), 26899-75-2; **5b,** 26899-76-3; **5e,** 26899-77-4; **6,** 26899-78-5; **7e,** 26899-79-6; **8a,** 26899-80-9; **8a** (acid chloride), 26899-81-0; **8a** (methyl ester), 26899-82-1; **8a** (diethyl amide), 26899-83-2; **8a** (*N*-methyl amide), 26899-84-3; **8b,** 26899-85-4; **8c,** 26899-86-5; **8e** (acid chloride), 26899-87-6; **9,** 26899-88-7; **11a,** 26899-89-8; **11e,** 26899-90-1; **12a,** 26899-91-2; **12b,** 26899-92-3; **13a,** 26899-93-4; **13b,** 26899-94-5; **13e,** 26899-95-6; **17,** 26899-96-7; **18,** 26899-97-8; **19a,** 26899-98-9; **19b,** 26899-99-0; **19c,** 26900-00-5; **21,** 26900-01-6; **22,** 26900-02-7; **23,** 26963-69-9; **24a,** 26900-03-8; **24b,** 26963-70-2; **24c,** 26900-04-9; **25a** (HCl), 26900-05-0; **25b** (dipicrate), 26900-06-1; **25c** (dipicrate), 26900-07-2; **25d** (HCl), 26900-08-3; **25e** (HCl), 26900-09-4; **26a** (keto acid), 26963-71-3; **26b** (HCl), 26900-10-7; **26c** (HCl), 26909-71-7; **26d,** 26963-72-4; **27a,** 26909-72-8; **27a** (HCl), 26909-73-9; **27b,** 26909-74-0; **27c,** 26909-75-1; **28a,** 26963-73-5; **28a** (HCl), 26909-76-2; **28b,** 26909-77-3; **28b** (2HCl) 26963-74-6; **28c,** 26909-78-4; **28c** (2HCl), 26909-79-5; **30a,** 26909-80-8; **30a** (HCl), 26909-81-9; **30b,** 26909-82-0; **30b** (HCl), 26909-83-1; **31a** (methiodide), 26909-84-2; **31b,** 26909-85-3; **31b** (HCl), 26909-86-4; **32a,** 26909-87-5; **32a** (HCl), 26909-88-6; **32b,** 26909-89-7; **32b** (HCl), 26909-90-0; **33a** (methiodide), 26963-75-7; **33b,** 26909-91-1; **34a** (dipicrate), 26909-92-2; **34b** (dipicrate), 26963-76-8; **35b** (HCl), 26909-93-3; **36** (R = CH_3), 26909-94-4; **36a,** 26909-95-5; **36a** (HCl), 26909-96-6; **36b,** 26963-77-9; **37,** 26909-97-7; **37** (2,4-dinitrophenylhydrazone), 12441-27-9; **38,** 26909-98-8; **39,** 26909-99-9; **40,** 26910-00-9; **40** (HCl), 26910-01-0; **41** (HCl), 26910-02-1; **42,** 26910-03-2; **42** (2,4-dinitrophenylhydrazone), 12441-26-8; 10,11-dihydro-10-aminomethyl-5*H*-dibenzo[*a*,*d*]-cycloheptene (HCl), 1586-15-8; *N*-cyano-10-(β-dimethylaminoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, 26910-05-4.

Acknowledgment.—We are indebted to Mrs. Angela Aretakis for literature search work, to Mr. Louis Dorfman, Miss Ruth Behnke, and Miss Natalie Cahoon for spectra and aid in interpretation thereof, to Mr. George Robertson and Mr. Rudolf Oeckinghaus for microanalytical data, to Mr. Shyam Sunder for some technical assistance, and to Mr. Robert Dziemian and Miss Ann Smith for large-scale preparation of certain intermediates.