Dibenzo[*a*,*d*]cycloheptene and related compounds. II.[1] The synthesis of some 11-substituted dibenzo[*b*,*e*]azepin-6-one, 5-substituted dibenzo[*a*,*d*]cycloheptene, and 12-substituted dibenzo[*a*,*d*]cyclooctene derivatives

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The synthesis of several 11-substituted-5,6-dihydro-11*H*-dibenzo[*b*,*e*]azepin-6-ones, and an improved method of preparing 5-cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene and 12-cyano-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene are described.

A description of the synthesis of epoxides from diaryl ketones and dimethylsulfonium methylide by a modified technique is given.

The nuclear magnetic resonance spectra of several of the 11-substituted dibenzo[*b*,*e*]azepin-6-ones are interpreted on the basis of a slow interconversion between diastereomeric boat conformers in which the C-11 substituent is quasi axial or quasi equatorial.

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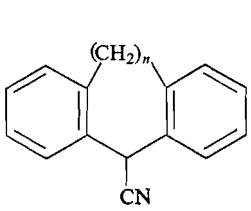
In connection with the synthesis of some compounds of potential pharmacological utility, we recently found it necessary to have available large amounts of the nitriles **1** (n = 2, 3) and **2**. The 7-membered nitrile **1** (n = 2) is well known, and has been prepared from the corresponding chloride and silver cyanide (2) or cuprous cyanide (3). The 8-membered nitrile (n = 3) has



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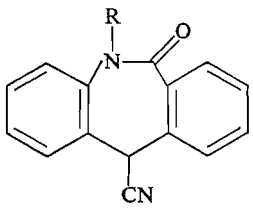

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apparently been prepared in the same way with silver cyanide, but it was not characterized (4). When these methods were applied to the synthesis of derivatives of **2**, mixtures which contained only moderate amounts of the desired materials were obtained. The solution to this problem was based on the observation that the epoxide **4** (n = 2) could be prepared in variable yield from dibenzosuberone (**3**, n = 2) and dimethylsulfonium methylide at 30–50°. This was doubly surprising in view of the known instability (5) of this ylid, and also because of a recently reported (6) failure to observe the formation of **4** (n = 2) from **3** (n = 2) and dimethylsulfonium methylide or dimethyloxosulfonium methylide. A careful study of the conditions for the reaction of dimethylsulfonium methylide with **3** (n = 2) in dimethyl sulfoxide (DMSO), showed that at 30–50°, the yields of **4** were not reproducible, and that at temperatures of ca. 15° no trace of product was ever observed. With these observations as a basis, it was found that **4** (n = 2) could be best produced by the addition of an excess (50%) of trimethylsulfonium iodide, in one or two portions at room temperature, to a slurry of sodium hydride in DMSO containing the dissolved ketone. There was no necessity to generate the dimethylsulfinyl carbanion as an ylid forming reagent; this observation was to be expected on the basis of work published several years ago by Franzen and Driesen (7). By this method, excellent yields of **4** (n = 2, 3) and the dibenzo[*b*,*e*]azepine derivatives **5** could be prepared in a matter of a few hours (see Table I). The epoxides were then converted to the nitriles by a classical sequence involving rearrangement of the epoxides to the aldehydes **6**, followed by dehydration (with hot acetic anhydride) of the oximes **7** obtained therefrom, to the nitriles **2** (see Table III). Dehydration of the oxime **7** (R = H) was exceptional in that the primary product was the imide **2** (R = CH_3CO; infrared (i.r.) absorptions at 1710 and 1687 cm^{-1}); hydrolysis to the nitrile **2** (R = H) was easily accomplished in refluxing aqueous acetonitrile.

[1]For Part I see ref. 1.

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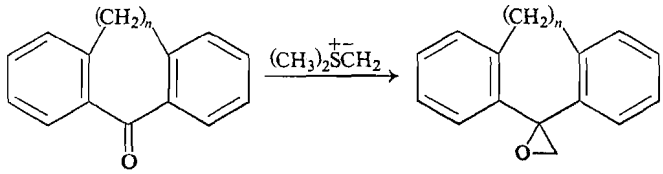
TABLE I

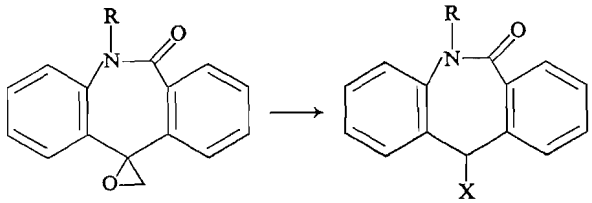
Yields and physical properties of the epoxides*

Compound	Yield (%)†	Reaction time (h)	Melting point (°C)	Crystallization solvent	% Calculated C	% Calculated H	% Calculated N	% Found C	% Found H	% Found N
4 (n = 2)	90	3.5‡	76–78	Alcohol	86.45	6.35	—	86.17	6.45	—
4 (n = 3)	98	3	Oil§	—	—	—	—	—	—	—
5 (R = H)	74–86‖	4	222–224	Acetonitrile	75.93	4.67	5.90	75.69	4.73	6.09
5 (R = CH_3)	74–80	4	116–117	Hexane	76.47	5.22	5.57	76.48	5.26	5.52

*The synthesis of other epoxides has been examined in a cursory way; e.g. benzophenone and benzaldehyde gave 85% 1,1-diphenyl oxirane and 55% phenyl oxirane respectively. Enolizable aldehydes and ketones have not been investigated.
†Unless specified otherwise, the yields refer to those of the purified products, here and in tables following.
‡This compound decomposed after a few days at room temperature or after ca. one month at 0°.
§We have not yet succeeded in obtaining this compound in crystalline form. Attempts to effect its purification by molecular distillation resulted in partial or complete rearrangement to the aldehyde. The epoxide was, therefore, not characterized.
‖An extra equivalent of sodium hydride was added to convert the lactam to its sodium salt.



3 **4**



5

6 X = CHO
7 X = CHNOH
8 X = COOH

An analogous series of transformations beginning with the epoxides **4** (n = 2 and 3) gave 5-cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**1**, n = 2; see Table II) and 12-cyano-5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene (**1**, n = 3) respectively. When the sequence **3** to **1** was effected without purification of the intermediates, the overall yields of the nitriles **1** (n = 2) and **1** (n = 3) were 55 and 70% respectively, based on the ketones **3** (n = 2 and 3). This represents the most efficient and convenient synthesis of these compounds which has been published to date.

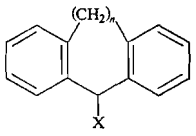
The oxidation of the aldehydes **6** to the carboxylic acids **8** was only moderately successful (see Table III). Nevertheless, this was found to be the most reliable method of preparing these compounds.

The i.r. and nuclear magnetic resonance (n.m.r.) spectra of the dibenzo[*b*,*e*]azepine derivatives[3] described above, are listed in Tables IV and V respectively. The i.r. spectral data were unexceptional and therefore require no comment. The n.m.r. spectra, on the other hand, were especially interesting since several of the *N*-substituted dibenzo[*b*,*e*]azepine derivatives showed two well separated resonances for the C-11 proton (in most, but not all cases, the *N*-substituent showed two closely spaced absorptions). The data presented in Table VI ("B" series) showed that the relative intensity of these absorptions was markedly dependent on

[3]The n.m.r. spectra of the dibenzo[*a*,*d*]cycloheptene and cyclooctene derivatives will be discussed in a forthcoming publication.

TABLE II

Yields and properties of some dibenzo[a,d]cycloheptene and dibenzo[a,d]cyclooctene derivatives

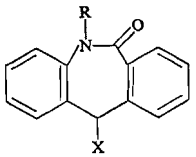


n	X	Yield (%)	Reaction time (h)	Melting point (°C)	Crystallization solvent	% Calculated C	% Calculated H	% Calculated N	% Found C	% Found H	% Found N
2	CHO	87–92	2	77–78*	Ether	86.45	6.35	—	86.50	6.44	—
3	CHO	90	2	87.5–89.5†	Hexane	86.40	6.83	—	86.45	6.86	—
2	CHNOH	90	3.5–5	165–166‡	Hexane: benzene (1:1)	80.98	6.37	5.90	80.85	6.40	5.85
3	CHNOH	90	5	166–169	Benzene: cyclohexane (1:1)	81.24	6.82	5.57	81.37	6.69	5.56
2	CN	55§	2‖	87–89	Cyclohexane: pet. ether (b.p. 35–60°); 1:1	—	—	—	—	—	—
3	CN	70§	2	190–192**	Cyclohexane	87.50	6.48	—	87.50	6.53	—

*Stable for several months at 0°.
†Sublimed at 75°/0.001 mm before analysis.
‡Only one isomer was characterized, here and for the oximes following.
§Yield based on starting ketone.
‖Mixed melting point undepressed; see ref. 2.
**Sublimed at 110°/0.001 mm before analysis.

TABLE III

Yields and properties of some 11-substituted 5,6-dihydro-11*H*-dibenzo[b,e]azepin-6-ones



X	R	Yield (%)	Reaction time (h)	Melting point (°C)	Crystallization solvent	% Calculated C	% Calculated H	% Calculated N	% Found C	% Found H	% Found N
CHO	H	68–84*	3.5	243–245	Acetonitrile	75.93	4.67	5.90	76.00	4.79	6.06
CHNOH	H	80	4	242–243	Methanol	71.41	4.80	11.11	71.40	4.92	10 98
CN	CH_3CO	80	5	172–174	Cyclohexane: benzene (1:2)	73.90	4.38	10.14	74.25	4.38	10.21
CN	H	76†	28	262–263	Ethanol	71.93	4.75	11.19‡	72.18	4.38	11.17
COOH	H	51	—	221–223	Acetonitrile	71.14	4.37	5.53	71.13	4.50	5.55
CHO	CH_3	87–92	3	159–160	Benzene: ether (3:1)	76.47	5.22	5.57	76.59	5.26	5.54
CHNOH	CH_3	85	3.5	181–182	Benzene	72.16	5.30	10 52	72.19	5.34	10 58
CN	CH_3	77	4.5	171–172	Benzene	77.40	4.87	11.28	77.53	4.89	11.18
COOH	CH_3	53–65	—	197–198	Acetonitrile	71.90	4.90	5.24	71.61	5.10	5.41
CO_2CH_3	CH_3	80–88	20§	186–188	Methanol	72.58	5.37	4.98	72.44	5.59	5.16

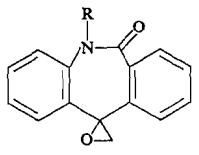
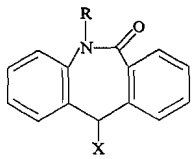
*Solvent, tetrahydrofuran.
†Yield based on oxime; the imide was usually not isolated, but deacetylated directly with 1:1 aqueous acetonitrile at reflux temperature.
‡Calculated for $C_{15}H_{10}ON_2 \cdot 0.9\ H_2O$. The n.m.r. spectrum indicated the presence of 0.85 moles of water; see Table V.
§A solution consisting of 6 ml of methanol and 0.09 ml of concentrated sulfuric acid for each gram of the carboxylic acid, was heated under reflux for the indicated period.

the solvent polarity and the C-11 substituent. These phenomena are interpreted as another case of slow (on the n.m.r. time scale) interconversion of diastereomeric boat conformers in which the C-11 substituent is quasi axial or quasi equatorial, like that described recently by Lansbury *et al.* (8) and others (9, 10) for similar systems. A particularly informative spectrum was observed for the 5-methyl-11-methoxy dibenzazepinone (**9**). In DMSO-d_6 the methine

TABLE IV

Infrared spectra of some dibenzo[*b*,*e*]azepine derivatives

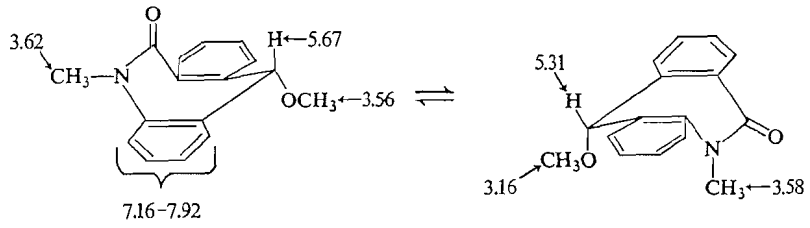
R	X	Medium	Frequency in cm^{-1} NH	CN	O ‖ —C—	O ‖ —C—N—	Other
*"A" Series**							
H	—	Nujol	3171	—	—	1661	—
CH_3	—	$CHCl_3$	—	—	—	1633	—
*"B" Series**							
H	CHO	Nujol	3177	—	1715	1651	2732†
CH_3	CHO	$CHCl_3$	—	—	1720	1637	2731†
CH_3CO	CN	$CHCl_3$	—	2250	1709	1685	—
H	CN	Nujol	3171	2246	—	1657	3485‡
CH_3	CN	$CHCl_3$	—	2247	—	1640	—
H	COOH	Nujol	3274, 3220 3170	—	1701	1635	2483§
CH_3	COOH	Nujol	—	—	1721	1614	2548§
CH_3	CO_2CH_3	$CHCl_3$	—	—	1738	1640	—

* *A* =  ; *B* = 

†Aldehyde C—H stretching absorption.
‡Water of crystallization.
§O—H Stretching absorption for carboxylic acid dimer.

protons showed two singlets at δ 5.31 and 5.67, while the methoxyl groups appeared as two singlets at δ 3.16 and 3.56. The integrated intensities of the two high field resonances, i.e. δ 5.31 and 3.16, for the methine and methoxyl protons respectively, indicated that these absorptions were due to the same and least abundant isomer. This isomer was assigned the quasi axial configuration **9***b*, on the expectation that an axially oriented methoxyl group would lie in the positive shielding region above the plane of the aromatic rings (11). Identical conclusions have been reached by Lansbury *et al.* (8) for 7-methoxy-7,12-dihydropleiadene and by Childs and Winstein (10) for the epimeric dibenzohomotropyl methyl ethers, and these results give much weight to our assignment. On the basis of the above information, for those compounds listed in Table VI ("B" series) which showed two signals for the C-11 proton, the axial configuration was assigned to that isomer having the C-11 proton resonance at higher field (i.e. H equatorial).

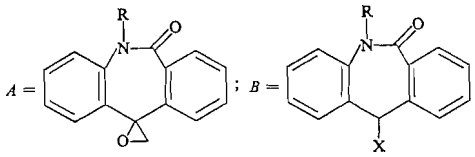
There were several interesting observations to be made from the data given in Tables V and VI ("B" series). Firstly, for those compounds which showed restricted inversion, the quasi axial isomer represented an appreciable fraction of the mixture. Indeed, when the 11-substituent was chlorine, the axial configuration was actually the



9a *9b*

TABLE V

Nuclear magnetic resonance spectra of some dibenzo[b,e]azepine derivatives



			Chemical shifts in p.p.m. (δ) from tetramethylsilane*				
R	X	Solvent	—N—CH_3	C-11	Aromatic hydrogens	NH	Other
	"A" Series						
H	—	DMSO-d_6: $CDCl_3$ (9:1)	—	—	7.13–8.10	10.75	3.07, 3.63†‡
CH_3	—	$CDCl_3$	3.63	—	7.02–8.05	—	3.08, 3.64†§
	"B" Series						
H	CHO	CF_3COOH: $CDCl_3$ (9:1)	—	5.08‖	7.32–8.28	10.38	9.95**
CH_3	CHO	$CDCl_3$	3.47	4.50	7.17–8.10	—	9.85**
$COCH_3$	CN	$CDCl_3$	—	4.85, 5.75	7.28–8.22	—	3.05, 3.10††
H	CN	DMSO-d_6	—	6.00	7.28–8.05	10.92	3.37‡‡
CH_3	CN	$CDCl_3$	3.67, 3.72	4.90, 5.50	7.22–8.05	—	—
H	COOH	CF_3COOH: $CDCl_3$ (9:1)	—	5.15	7.32–8.05	10.35	—
CH_3	CO_2CH_3	$CDCl_3$	3.50 or 3.65§§	4.70	7.13–8.02	—	3.50 or 3.65§§

*All absorptions, except those due to the aromatic hydrogens and the epoxide —CH_2—, were singlets.
†Epoxide —CH_2—.
‡These absorptions were broad.
§In pyridine, the high field absorption was a clearly visible AB quartet (J_{AB} = 6.1 c.p.s.), and the low field absorption was an AB quartet (J_{AB} = 5.4 c.p.s.) partially obscured by the *N*-methyl peak. In $CDCl_3$ the epoxide methylenes were singlets for this compound.
‖This proton resonates at δ 5.24 in DMSO-d_6.
**Aldehyde —CH—.
††Acetyl methyl absorptions.
‡‡Water of crystallization; 0.85 H_2O.
§§One singlet due to the *N*-methyl and the other due to the *O*-methyl hydrogens.

preferred one. This was not especially surprising, since Lansbury *et al.* have shown (8) that the axial configuration is favored over the equatorial in the dihydropleiadene series. Secondly, all the *N*-unsubstituted compounds in the "B" series (Tables V and VI) had only one sharp resonance for the C-11 proton. In those cases where a comparison was made, the position of this absorption was about halfway between the corresponding peaks in the *N*-methyl compounds. This would seem to indicate that these *N*-unsubstituted compounds are undergoing rapid inversion at the temperature of the measurement (37°). However, such a conclusion is unjustified in the absence of variable temperature studies. Whatever the explanation, it is indeed curious that the nitrogen substituent should have such a profound effect on the n.m.r. spectra of these compounds. Lastly, two of the *N*-methyl dibenzazepinones (Table V, "B" series), e.g. X = CHO and CO_2CH_3, also showed only a sharp singlet for the C-11 proton. Once again, without variable temperature spectra, a choice between fast inversion and configurational homogeneity cannot be made, but the high field position of the methine resonance may well be an implication of the latter.

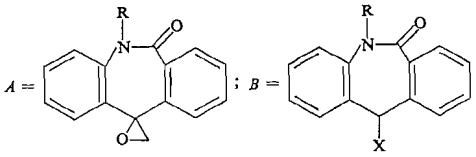
The n.m.r. spectra of both epoxides (Tables V and VI, "A" series) showed evidence of restricted inversion. In as much as spiro fusion, such as is present in these epoxides, might, like a double bond, slow down the rate of inversion (e.g. compare refs. 9 and 12), this would also tend to implicate rapid inversion of the *N*-unsubstituted compounds discussed above.

Experimental

The melting points were determined in a Gallenkamp melting point apparatus and are not corrected. The i.r. spectra were measured in chloroform (unless specified otherwise) on a Perkin–Elmer 237-B grating spectrophotometer. The n.m.r. spectra were recorded at 60 Mc.p.s. on a Varian A-60A spectrometer at ca. 37°

TABLE VI

Conformational composition of some dibenzo[*b*,*e*]azepine derivatives at 37°



R	X	Solvent	Chemical shifts: C_{11}—H δe	C_{11}—H δa*	Other δe	Other δa	Conformational composition (%)† e	a
	"A" Series							
H	—	DMSO-d_6	—	—	3.60‡	3.08‡	24§	76§
		Pyridine: DMSO-d_6(1:1)	—	—	3.51	2.77	22	78
CH_3	—	$CDCl_3$	—	—	3.64	3.07	6	94
		DMSO-d_6	—	—	3.68	3.18	21	79
		Pyridine	—	—	2.96	2.43	9	91
	"B" Series							
CH_3	OCH_3‖·¶	$CDCl_3$	5.07	5.45	3.65[a]	3.25[a]	77	23[b]
		DMSO-d_6	5.31	5.67	3.56	3.16	60	40[b]
H	OCH_3‖·¶	DMSO-d_6	5.37		3.29		?	
H	OH‖·[c]	DMSO-d_6	5.82		—	—	?	
CH_3	OH‖·[c]	DMSO-d_6	5.62	5.93	—	—	90	10
CH_3	Cl‖·[d]	$CDCl_3$	5.83	6.33	—	—	19	81
		DMSO-d_6	6.55	6.76	—	—	8	92
H	CN	DMSO-d_6	6.00		—	—	?	
CH_3	CN	DMSO-d_6	5.83	6.18	—	—	53.5	46.5
		$CDCl_3$	4.90	5.50	—	—	83	17
$COCH_3$	CN	$CDCl_3$	4.85	5.75	—	—	68	32
		DMSO-d_6	5.88	6.72	—	—	54	46

*a = axial; e = equatorial.
†Determined from the integrated areas of the methine resonance in the "B" series and the methylene resonance in the "A" series.
‡Refers to the epoxide —CH_2— throughout the "A" series.
§Orientation of epoxide —CH_2—.
‖These compounds were prepared in connection with other work (13) and were fully characterized.
¶Prepared from the chloro compounds and methanolic sodium methoxide.
[a]Methoxyl absorptions. In $CDCl_3$, the *N*-methyl peak is unresolved and absorbs at δ 3.65. In DMSO-d_6 the *N*-methyl group appears as two peaks at δ 3.58 (a) and 3.62 (e).
[b]The isomeric composition determined from the methoxyl absorptions was within 1% of the value obtained from the methine absorptions.
[c]Prepared from the corresponding ketones by reduction with sodium borohydride in methanol.
[d]Prepared from the alcohol and thionyl chloride.

(probe temperature). The chemical shifts are recorded as p.p.m. (δ) from internal tetramethylsilane, with tetramethylsilane taken as zero.

Dibenzosuberone was purchased from the Aldrich Chemical Company. 5,6,7,12-Tetrahydrodibenzo[*a*,*d*]cycloocten-12-one was prepared according to the method of Winthrop *et al.* (14). 5,6-Dihydro-11*H*-dibenzo[*b*,*e*]azepine-6,11-dione was prepared by the method of Caronna and Palazzo (15) in 85–90% yield.

5-Methyl-5,6-dihydro-11H-dibenzo[b,e]azepine-6,11-dione

This compound has previously been prepared by the alkylation of the sodium salt of the dioxo compound with methyl iodide. The anion was generated with sodamide in refluxing toluene (16). We have found that the sodium salt is more conveniently generated with sodium hydride in dimethyl formamide at room temperature. The addition of an excess of methyl iodide to this salt produced the *N*-methyl compound in yields of 85–90%.

Preparation of the Epoxides

A 250 ml three-necked flask containing a magnetic stirring bar, and fitted with a thermometer, a gas inlet, and a calcium chloride drying tube, was flame dried. A flow of purified dry nitrogen was initiated through the apparatus and 1.28 g of a 56% dispersion of sodium hydride in mineral oil (29.9 mmoles)[4] were placed in the flask. The sodium hydride was twice washed with petroleum ether (b.p. 35–60°) to remove the mineral oil, and then 75 ml of dry dimethyl sulfoxide and 19.3 mmoles of the ketone were added. The mixture was stirred to effect solution of the ketone, and then 6.0 g of trimethylsulfonium iodide were added all at once (for larger scale reactions the salt was sometimes added in two equal

[4]When the ketone was 5,6-dihydro-11*H*-dibenzo[*b*,*e*]azepine-6,11-dione, an extra equivalent of sodium hydride was added to convert the lactam to its sodium salt.

portions because of excess frothing). After stirring for the specified time (see Table I) at room temperature, the solution was poured into a large excess of cold water containing a little sodium chloride. The mixture was extracted with benzene (or the product was collected by filtration if it crystallized), the extract was washed well with water, dried over sodium sulfate, and then evaporated *in vacuo*. The residue was then crystallized from the solvent indicated in Table I.

Rearrangement of the Epoxides

To a solution of the epoxide (27 mmoles) in 150 ml of anhydrous dichloromethane or tetrahydrofuran, were added 1.6 ml of boron trifluoride etherate. The solution was stirred at room temperature for the specified time (see Tables II and III), then washed with sodium carbonate solution (10%), with water, and then it was dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was crystallized from the solvent indicated in the Tables.

Preparation of the Nitriles

The aldehyde (42.2 mmoles), hydroxylamine hydrochloride (3.57 g, 51.5 mmoles), dry pyridine (40 ml), and dry ethanol (160 ml) were heated under reflux for the times indicated in Tables II and III and then the solvent was removed *in vacuo*. The residue was taken up in dichloromethane, washed with 10% hydrochloric acid, then with water, and finally dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was crystallized from a suitable solvent.

For the preparation of the nitriles, the oximes were not purified, but used directly in the manner indicated below.

Oxime (30.3 mmoles) and 150 ml of acetic anhydride were heated at reflux temperature for the times indicated in Tables II and III. The acetic anhydride was then removed *in vacuo*, and the residue was taken up in dichloromethane, extracted with 5% sodium carbonate solution, and then with water. The dichloromethane was dried over sodium sulfate, evaporated *in vacuo*, and the residue was crystallized from a suitable solvent.

In the preparation of 11-cyano-5,6-dihydro-11*H*-dibenzo[*b*,*e*]azepin-6-one the primary product was the 5-acetyl derivative (see text). Deacetylation was effected by heating a solution of the imide in 1:1 aqueous acetonitrile (20 ml/g) at reflux for 28 h. The major portion of the product crystallized when the solution had cooled to room temperature; the remainder was recovered by evaporation of the mother liquor and crystallization of the residue.

In the case of 5-cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene, the crude cyanide was taken up in the minimum amount of benzene and placed on a dry packed column of Fluka neutral alumina (act. II, 30–50 g of alumina/g of crude nitrile). The product was eluted with benzene and appeared in the first few fractions of the eluant. This chromatography was necessary to remove an orange-colored impurity.

Oxidation of the Aldehydes to the Carboxylic Acids

The aldehyde was dissolved in glacial acetic acid (10 ml/g for **6** (R = CH_3), or 120 ml/g for **6** (R = H) and titrated with 0.649 *M* sodium dichromate in 2.5 *M* sulfuric acid at a rate such that the reaction temperature did not exceed 30°. A 10% excess of the oxidant was used for **6** (R = CH_3) and a 2% excess for **6** (R = H). When the addition was completed, the mixture was stirred at room temperature for ½ h, and then poured into a large volume of cold water. The product was extracted into dichloromethane, the extract was washed well with water, dried over sodium sulfate, and then evaporated *in vacuo*. The residue was crystallized from a suitable solvent (see Table III).

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