Hydrolysis of Certain 5-Aminodibenzo[*a*,*d*]cycloheptanes

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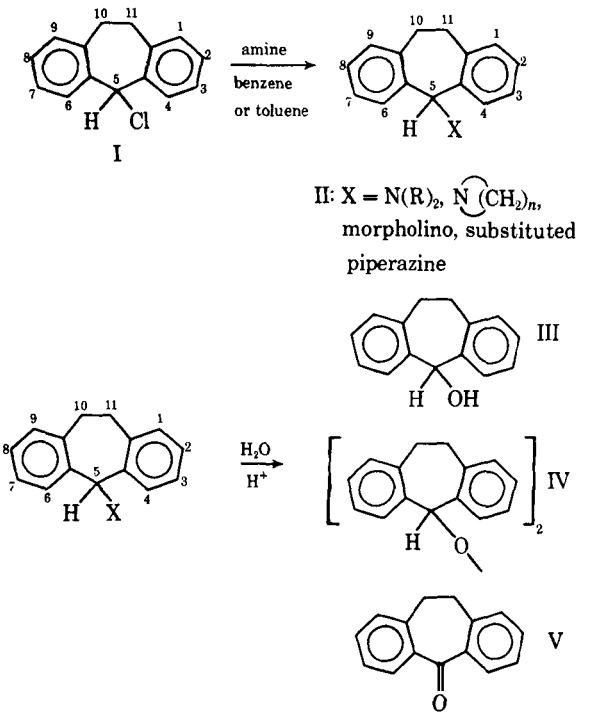
Abstract □ Factors involved in the relative reaction rates of hydrolysis of certain 5-aminodibenzo[*a*,*d*]cycloheptanes were investigated. Several compounds were prepared for examination of their breakdown in acidic media at various temperatures. Synthesis was carried out through condensation of 5-chlorodibenzo[*a*,*d*]cycloheptane with the appropriate amine in benzene. Kinetics were followed by the acid-dye method employing methyl orange as the anionic species of the ion-pair. Generally, the colored complexes were readily extractable into chloroform at pH 3.44. Considerable variation in the hydrolytic velocities of the several amines was noted, and the results are given along with Arrhenius parameters and other pertinent data for selected compounds. The degradation is characterized by cleavage of a carbon—nitrogen (amino) bond at the 5-position of the fused ring system leading to the secondary amine and 5-hydroxydibenzo[*a*,*d*]cycloheptane as well as other nonnitrogenous products. The transformation exemplifies breakage of a carbon—nitrogen linkage in dilute acidic solution under rather mild conditions dependent upon substituents on the amino group. The process possibly proceeds *via* a carbonium-ion intermediate or its equivalent.

Keyphrases □ 5-Amino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane derivatives—synthesis, hydrolysis rates, acid-dye monitoring □ Hydrolysis of 5-aminodibenzo[*a*,*d*]cycloheptanes—dilute aqueous acid □ Acid-dye technique—monitoring of hydrolysis rates of 5-aminodibenzo[*a*,*d*]cycloheptanes □ Methyl orange ion-pair formation—monitoring of hydrolysis rates of 5-aminodibenzo[*a*,*d*]cycloheptanes



Scheme I

It was previously observed in these laboratories that certain medicinally active agents possessed structural requisites for rupture of the amino carbon—nitrogen linkage present in dilute aqueous acid at ambient temperature. This work is concerned with several 5-amino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane derivatives, II, regarding their preparation (1) from the chloro intermediate, I, and their hydrolysis (Scheme I). Dialkyl and cycloalkyl amines and piperazines were studied, with pertinent results being reported in the text.

The transformation (II → products) illustrates an unusual cleavage of a C—N bond which occurs in dilute aqueous acid. The neutral molecules (III, IV, and V) represent the principal substances produced. The reaction may proceed through a resonance-stabilized carbonium ion or a kinetically equivalent mechanism.

EXPERIMENTAL

Preparation of Compounds—The compounds prepared are listed in Tables I and II. The general preparative procedures are illustrated with specific examples (7).

5-Diethylaminodibenzocycloheptane Hydrochloride (Table I, Compound 1)—A mixture of 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptane[1] (11.44 g., 0.05 mole) and diethylamine (3.66 g., 0.05 mole) was refluxed in 100 ml. benzene overnight. The reaction mixture was stripped of solvent *in vacuo*. The resultant solid was dissolved in 50 ml. methanol and treated with ether to the point of opalescence. The precipitate was collected and recrystallized twice from methanol–ether, yielding 3.1 g. (20%), m.p. 159–160°.

5-(4-Benzylpiperazinyl)dibenzocycloheptane (Table I, Compound 7)—A mixture of 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane[1] (11.44 g., 0.05 mole) and benzylpiperazine[1] (8.8 g., 0.05 mole) was refluxed in 100 ml. benzene overnight. The solvent was removed under reduced pressure; the resultant solid was treated with 50 ml. 0.1 *N* NaOH followed by three 50-ml. portions of distilled water and then collected on a Büchner funnel. This material was crystallized three times from acetone–methanol, yielding 6.1 g. (32%), m.p. 116–119°.

TLC of 5-Aminodibenzocycloheptanes (Table I)—The compounds in Table I were subjected to TLC using a system of chloroform–petroleum ether–ethylamine (60:40:2) on silica gel GF[2] plates. An ethanolic solution (10 μl., 10 mg./ml.) was spotted and the following R_f values were obtained (Table I: Compound Number and R_f): 1, 0.85; 2, 0.55; 3, 0.50; 4, 0.45; 5, 0.80; and 6, 0.05. They were visualized by means of Dragendorff's reagent or bromcresol purple (15 mg./100 ml. ethanol).

Solution Preparation and Solvents—*Citrate Buffer, pH 3.44*—Citrate buffer was prepared from 9.7 g. anhydrous citric acid in 900 ml. water. Thirty percent sodium hydroxide (10.5 ml.) was added, and the pH was adjusted to 3.44 with concentrated hydrochloric acid. The solution was made up to 1 l. with distilled water.

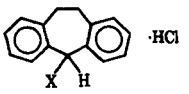
Methyl Orange Solution—Methyl orange[3], 250 mg., was placed in a 1-l. volumetric flask along with 3.3 ml. 0.1 *N* NaOH and 800 ml.

[1] Aldrich Chemical Co., Milwaukee, Wis.

[2] Analtech Inc., Newark, Del.

[3] Eastman No. 432.

Table I—Physical Constants of 5-Aminodibenzocycloheptanes



Compound	X	Melting Point[a]	Yield, %[b]	Molecular Formula	Analysis, %[a] Calc.	Found
1	$-N(CH_2CH_3)_2$	159–160° dec.	20	$C_{19}H_{23}N \cdot HCl$[c]	C 75.6	75.7
					H 8.0	8.0
					N 4.6	4.5
					Cl 11.7	11.7
2	$-NH(CH_2CH_2CH_2CH_3)_2$	165–170° dec.	17	$C_{28}H_{31}N \cdot HCl$[c]	C 77.2	77.7
					H 9.0	9.3
					N 3.9	4.1
					Cl 9.9	9.7
3		224–228°	15	$C_{19}H_{21}N \cdot HCl$[c]	C 76.1	76.3
					H 7.4	7.5
					N 4.7	4.3
					Cl 11.8	12.1
4		213–215°	22	$C_{20}H_{23}N \cdot HCl$[c]	C 76.5	76.5
					H 7.7	7.9
					N 4.5	4.6
					Cl 11.3	11.1
5		195–200°	18	$C_{19}H_{21}NO \cdot HCl$[c]	C 72.2	71.7
					H 7.0	7.0
					N 4.4	4.7
					Cl 11.2	11.5
6		110–112°[d]	—	$C_{20}H_{24}N_2$[e]	C —	—
					H —	—
					N —	—
					Cl —	—
7		116–119°[d]	32	$C_{26}H_{28}N_2$[f]	C 84.7	84.4
					H 7.7	7.9
					N 7.6	7.6
					Cl —	—

[a] Uncorrected melting points taken on a Thomas-Hoover capillary melting-point apparatus. [b] Yield calculated following total recrystallizations carried out for microanalytical sample. [c] Recrystallized from methanol–ethyl ether. [d] Free base. [e] Recrystallized from petroleum ether, obtained from Dr. W. Houlihan, Sandoz Pharmaceuticals (2). [f] Recrystallized from acetone–methanol. [g] Microanalytical results from Microanalytical Laboratory, Sandoz Pharmaceuticals, E. Hanover, NJ 07936

water. The contents were shaken to dissolve, and the pH of the solution was adjusted to 7.0 with 0.1 *N* HCl (dropwise) followed by dilution to volume with water.

All other solvents and solutions were of chemical reagent quality and were used without further treatment.

Kinetic Procedures—A solution containing 25 mg. of each compound (Table I) was placed in 100 ml. 0.1 *N* HCl in volumetric flasks previously equilibrated at the specified temperatures, giving about 10^{-3} *M* solutions. Four-milliliter aliquots of the acidic solution were periodically withdrawn and neutralized with 0.1 *N* NaOH (4 ml.) followed by 4 ml. pH 3.44 citrate buffer and 25 ml. methyl orange solution. The aqueous layer was extracted three times with 30-ml. portions of chloroform in a separatory funnel, and the chloroform solutions were collected and made up to 100 ml. in a volumetric flask. The absorption spectra of the yellow-colored complexes were recorded on a spectrophotomer[4] over the range of 350–500 nm.

Other kinetic procedures were carried out by the same analytical method after adjusting the pH of the aliquot drawn from the reaction flask to 3.44 prior to addition of methyl orange indicator.

The reaction products, except dibutylamine, gave no color attributable to ion-pair formation with methyl orange when extracted using 10^{-3} *M* concentrations. Additionally, the intensity of the colorimetric analysis was not altered when the by-products were mixed at 10^{-3} *M* with intact molecules.

Synthesis and Properties of Reaction Products—*5-Hydroxydibenzo*[a,d]*cycloheptane* (*III*)—One gram of *N*-(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-*N'*-methylpiperazine (Table I, Compound 6) was dissolved in 20 ml. ethanol with addition of 0.1 *N* HCl to 150 ml. After 3 hr. of stirring at room temperature, the white solid was collected on a filter and dried. A solution of 250 mg. of the powder in 0.5 ml. chloroform was streaked on a preparatory silica gel GF plate (thickness 1000 μ) and run in petroleum ether–chloroform (40:60). The spot corresponding to the alcohol was scraped and eluted with chloroform followed by filtration and evaporation, yielding 22 mg. of a white powder, m.p. 90–92°, corresponding to the authentic alcohol[5], m.p. 91–92°.

Bis(10,11-dihydro-5H-dibenzo[a,d]*cyclohepten-5-yl Ether* (*IV*)—One hundred milligrams of 5-diethylaminodibenzo[*a,d*]cycloheptane (Table I, Compound 1) was heated in 50 ml. 0.1 *N* HCl for 6.5 hr. at 80°. The flask was allowed to remain overnight; it was then filtered and the white solid was collected and dried. The white material was carefully washed with cold petroleum ether to remove contaminating ketone and alcohol, yielding 36 mg. (55%) of the bis-ether, m.p. 122–126° [lit. (2) m.p. 128°]. Mass spectroscopy showed a molecular ion at 402, giving two fragments at $M^+ = 209$ and193.

Anal.—Calc. for $C_{30}H_{26}O$: C, 89.5; H, 6.5. Found: C, 89.4; H, 6.8.

Dibenzosuberone (*V*)—One hundred milligrams of 5-(1-piperidino)dibenzo[*a,d*]cycloheptane (Table I, Compound 4) was heated 36 hr. in 50 ml. 0.1 *N* HCl at 80°. The resultant white solid was left overnight, filtered, and dried, yielding 12 mg. solid. The solid, when dissolved in methanol followed by TLC on silica gel GF plates in chloroform–diethylamine (100:1), exhibited four spots with one at R_f 0.7, the same as that for authentic dibenzosuberone[5]. Other development solutions [(*a*) chloroform and (*b*) chloroform–petroleum ether (60:40)] produced similar R_f values for both the ketone and the unknown.

The white solid (0.5 mg.) in 0.5 ml. methyl alcohol was spotted followed by development in chloroform–diethylamine (100:1). The spot corresponding to the ketone was eluted in methyl alcohol (50 ml.) and gave a UV spectrum between 350 and 220 nm. superimposable with one for 0.002 mg./ml. dibenzosuberone with $\lambda_{max.}$ 270 nm.

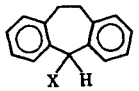
TLC of Degradation Products—Compounds III, IV, and V (alcohol, ether, and ketone) were chromatographed on silica gel GF plates, spotting 20 μl. of solution containing 5 mg./ml. The R_f values found on development in chloroform–diethylamine (100:1) were: III, 0.25; IV, 0.75; and V, 0.98.

The amines (Table I) were dissolved in 0.1 *N* HCl (100 mg./20 ml.). The heterogeneous solution was spotted directly (20 μl.) or

[4] Cary 14.

[5] Aldrich Chemical Co.

Table II—Substituent Effect on Rate of Degradation of 5-Aminodibenzo[*a*,*d*]cycloheptanes (~8 × 10^{-4} *M*) in 0.1 *N* HCl at 80°



Compound	X	Molecular Weight	*k*, hr.$^{-1}$	Molar Absorptivity, ϵ[a]
1	—$N(CH_2CH_3)_2$·HCl	301.9	0.57	8.33 × 10^3
2	—$N(CH_2CH_2CH_2CH_3)_2$·HCl	358.0	—[b]	6.44 × 10^3
3	—N⟨⟩·HCl	299.9	0.0031	10.6 × 10^3
4	—N⟨⟩·HCl	313.9	0.0083	6.39 × 10^3
5	—N⟨O⟩·HCl	315.9	—[c]	Nil[d]
6	—N⟨N—CH_3⟩	292.4	Fast[e]	15.2 × 10^3
7	—N⟨N—$CH_2C_6H_5$⟩	368.5	Fast[e]	—[d]

[a] Absorptivity measured employing 4 ml. sample (0.25 mg./ml.), 4 ml. 0.1 *N* NaOH, 4 ml. pH 3.44 buffer, and 25 ml. methyl orange solution (see *Experimental*) followed by extraction of the resultant complex into 100 ml. chloroform. [b] No applicable assay method. [c] Degradation rapid but difficult to measure. [d] No satisfactory formation of colored complex observed. [e] Reacts rapidly at 23°, 0.1 *N* HCl.

dissolved in a little methanol prior to spotting. This was done between 6 and 96 hr. periodically. The silica gel GF plates were developed using chloroform–diethylamine (100:1).

pKa Evaluation—The pKa of monobasic compounds (Table I, Compounds 1–5) were approximated using partial titration of 0.005 mole with 0.5-ml. increments of 0.1 *N* KOH. The amines were dissolved in 50% ethanol–water to solubilize the free base. Estimates of the pKa values were in the range 7.2–7.6 under these conditions following the method of Albert and Sergeant (3).

RESULTS AND DISCUSSION

Determination of Rate Constants—The kinetic parameters delineating decomposition of several 5-aminodibenzo[*a*,*d*]cycloheptanes, II, were examined by following the loss of absorbance by the acid-dye method (4). UV methods could not be employed because of the lack of usable spectra. The acid-dye or ion-pair technique proved invaluable due to its specificity for the reaction under investigation. Splitting of the C—N linkage at the 5-position of the tricyclic nucleus, II, leads to products which give no appreciable color formation with methyl orange.

Table III—Observed First-Order Rate Constants (*k*, hr.$^{-1}$) for Disappearance of 5-Diethylaminodibenzo[*a*,*d*]cycloheptane in Aqueous Solution[a,b]

Buffer	pH[c]	50°	60°	70°	80°
Hydrochloric acid					
1.0 *N*	0.1	0.022	0.071	0.20	0.58
0.1 *N*	1.1	0.020	0.068	0.21	0.54
0.025 *N*	1.7	—	—	—	0.57
Phosphate[d]	2.0	—	—	0.22	0.55
Phosphate[d]	3.0	0.021	0.070	—	0.57
Acetate[e]	4.0	—	—	—	0.59
Acetate[e]	5.0	0.018	0.060	0.19	0.54

[a] Followed by acid-dye method, initial concentration 8.33 × 10^{-4} *M*. [b] Each kinetic run reported was repeated in triplicate with results found reproducible (±10%). [c] pH values measured on Metrohm pH meter. pH of hydrochloric acid solutions determined from activity coefficients employing *Reference 8*. The slight variation with temperature for the solutions is not considered. [d] Solutions made from 0.05 *M* $NaH_2PO_4 \cdot H_2O$ with H_3PO_4 added to give proper pH. [e] Acetate made to ionic strength 0.1.

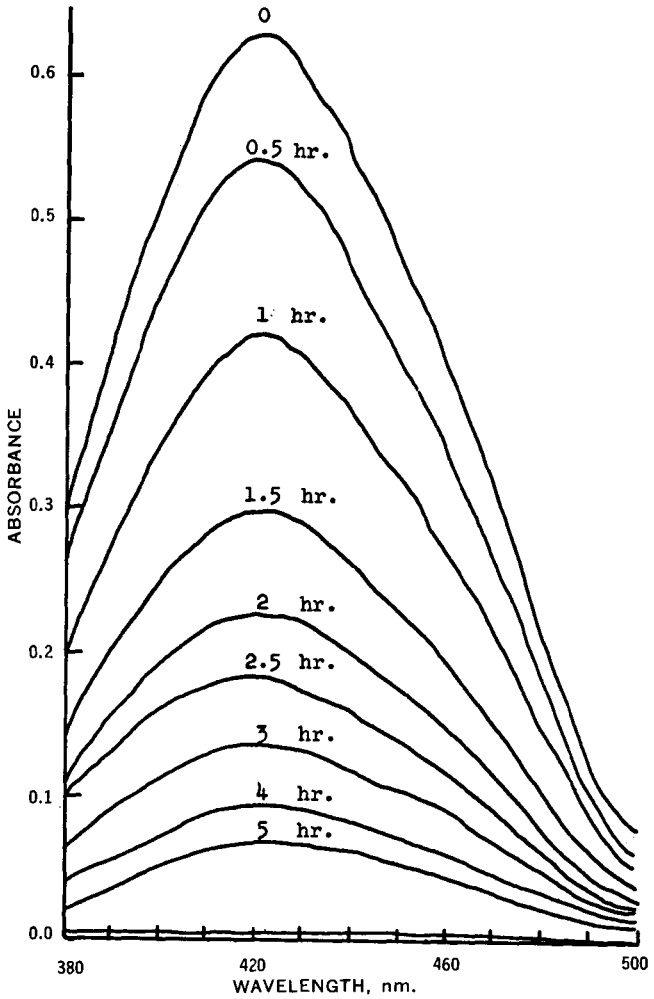


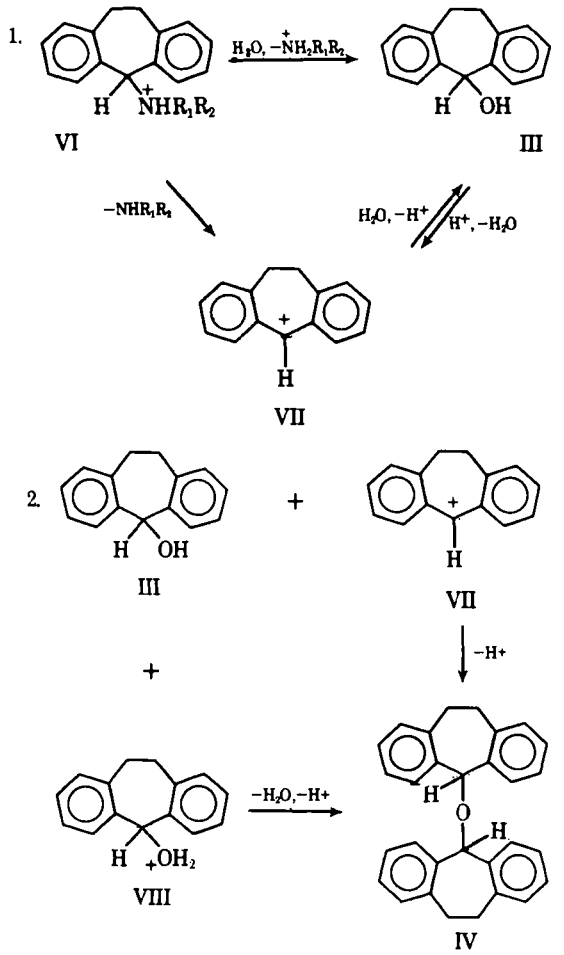
Figure 1—*Curve for absorbance diminution of 5-diethylaminodibenzo*[a,d]*cycloheptane (Table I, Compound 1) in initial concentration of 8.33 × 10^{-4} mole/l. at 80° using 0.1* N *HCl. Times are given on the figure, with the absorbance peak of 420 nm. Four-milliliter aliquots were withdrawn, neutralized with 4 ml. 0.1* N *NaOH, and buffered with 4 ml. pH 3.44 buffer followed by addition of 25 ml. methyl orange solution (see* Experimental*). The colored complex was extracted into 100 ml. $CHCl_3$ and monitored on a recording spectrophotometer (Cary 14).*

Hydrolysis was monitored utilizing methyl orange ion-pair formation with amines at pH 3.44 (5). The yellow complex was extracted into chloroform with $\lambda_{max.}$ in the region of 420 nm. for the compounds in Tables I and II. The morpholino and benzylpiperazino substituents (Table II, Compounds 5 and 7) did not give proper Lambert–Beer relationships and were not determined utilizing ion-pair extraction. The reasons for this sort of behavior have been suggested as unfavorable partition ratios of the complexes, extraction of complexes having molar ratios other than 1:1, or extraction of the amines as free bases (6).

A small amount of residual absorbance, A_∞, was noted, usually less than one-tenth of the initial absorbance. The relationship is:

$$\log(A - A_\infty) = \log(A_0 - A_\infty) - kt/2.303 \qquad \text{(Eq. 1)}$$

where A_0, A, and A_∞ are absorbances of the ion-pair complex in chloroform at times = zero, t, and infinity, respectively, and k is the apparent or observed first-order rate constant. Figure 1 illustrates a typical curve for absorbance loss as a function of time for 5-diethylaminodibenzo[*a*,*d*]cycloheptane (Table II, Compound 1). The diethylamino analog reacts far faster than any of the other monobasic amines studied. An anomally in this series is the dibutylamino derivative (Table II, Compound 2), which appeared



Scheme II

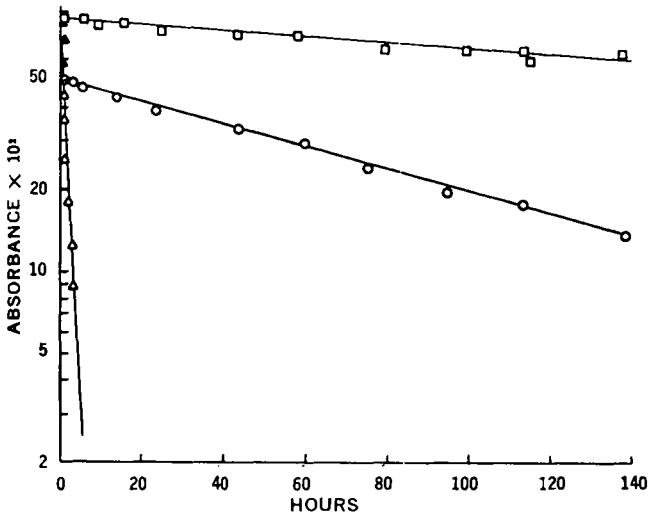


Figure 2—*Observed or apparent first-order plots for hydrolysis of 5-aminodibenzo*[a,d]*cycloheptanes (Tables I and II) in 0.1* N *HCl at 80°. Initial concentrations (25 mg./100 ml.) were analyzed by adjusting 4-ml. samples to pH 3.44 and treatment with methyl orange solution followed by extraction with 100 ml. $CHCl_3$. Absorbances were read at about 420 nm. Key: △, diethylamino; ○, piperidino; and □, pyrrolidino.*

stable colorimetrically after 300 hr. at 80° using 0.1 *N* HCl. This is a consequence of ion-pair formation between dibutylamine and methyl orange invalidating the assay. The substituted piperazines (Tables I and II, Compounds 6 and 7) possess the greatest instability in acidic solution, with velocities too great to measure easily in 0.1 *N* HCl at 23°. The second nitrogen appears to facilitate rupture of the C—N bond. The morpholino substituent at the 5-position seems to bring about good reactivity, although it could only be estimated by TLC separation of products due to the unavailability of analytical methodology.

Products of Solvolysis of 5-Aminodibenzocycloheptanes (Tables I and II)—The carbon—nitrogen linkage between C-5 of the dibenzocycloheptane moiety and the amine nitrogen, II, is split in aqueous solution (pH 0.1–5.0). The principal compounds produced from the diethylamino, dibutylamino, piperidino, pyrrolidino, and morpholino analogs (Table I, Compounds 1–5) are the ether, alcohol, and ketone (Scheme I, Compounds III, IV, and V).

These substances (III, IV, and V) were isolated from the various aminodibenzocycloheptanes in 0.1 *N* HCl at 80°. As a consequence of their relative insolubility in the reaction medium, they precipitated and could be separated by filtration or preparative TLC (see *Experimental*). The morpholino and benzylpiperazino derivatives showed a fourth unknown spot between the ketone and ether, R_f 0.8.

The ketone is likely a product of air oxidation of the alcohol, since no attempt was made to exclude oxygen from the reaction solutions.

The dibutylamino and diethylamino compounds resulted in almost exclusive formation of the ether, IV, with traces of alcohol and ketone. This compound could be isolated from heated acidic solutions of these amines by filtration of the precipitate followed by washing with petroleum ether.

The alcohol, III, was prepared from the *N*-methylpiperazino analog. It was obtained by preparative TLC on silica gel GF plates. The purified material was identical with an authentic sample of the alcohol.

The ketone was eluted from preparative TLC plates. It exhibited spectral and chromatographic properties similar to those of an authentic sample of the ketone.

Methyl orange extraction failed with the morpholino compound, which prevented quantitative treatment regarding the reaction velocity of its solvolysis.

Dibutylamine formed an ion-pair complex with the anionic dye, giving an extinction coefficient approximately equal to that of the starting material. However, the partition ratio (chloroform:pH 3.44 aqueous buffer) was considerably different from that of the dibutylaminodibenzocycloheptane. This left no method of analysis for the dibutylamino analog which was not treated quantitatively.

The other amine portions failed to produce colored complexes that interfered with the assay method.

The alcohol, 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptane-5-ol (III), appears to be an intermediate in formation of the bis-ether, IV. When subjected to heating in solutions of water with addition of hydrochloric acid or ethanol–0.1 *N* HCl at 60°, large quantities of the ether were noted, indicative of its production through the alcohol. A second spot, R_f 0.85 in chloroform–diethylamine (100:1), was observed; it may be the ethyl ether but it was not characterized.

Reaction Pathways—The transformation of the parent compound to the alcohol may be postulated as occurring through either water reaction with a carbonium ion, VII, or water attack on the protonated amine. Both cases are kinetically equivalent, leading to the alcoholic intermediate. Carbonium ions of the type generated from the alcohol and amine would be resonance stabilized from the two phenyl rings, giving a total of seven resonance-stabilized structures with the positive charge distributed over the tricyclic nucleus. Seven-membered rings are well known for relative ease of carbonium-ion formation (9).

From the alcoholic intermediate, III, common to the substances investigated, a plausible reaction course may be postulated (Scheme II). Conversion of the alcohol into the bis-ether in aqueous acid further strengthens the prospect of reaction routes similar to those in Scheme II.

The bis-ether, IV, may be formed by reaction of the alcohol, III, with the carbonium ion, VII, or the protonated VIII (Scheme II, part 2). It is difficult to distinguish between the two routes.

Dibenzosuberone may have been the result of air oxidation of the alcohol, since no attempt was made to exclude oxygen from the reaction media.

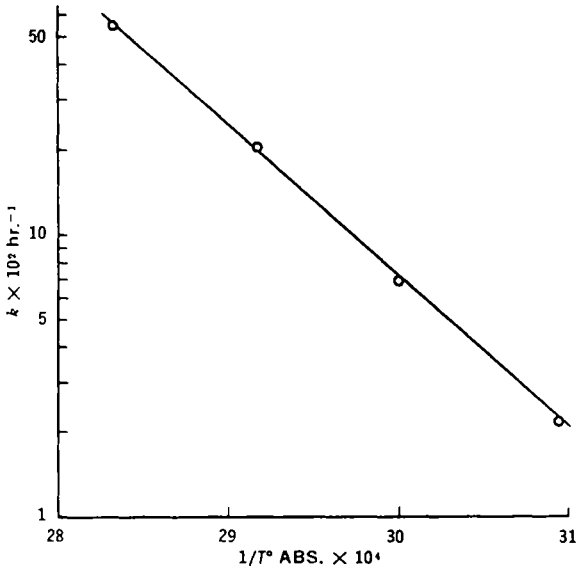


Figure 3—*Typical Arrhenius plot for observed first-order velocity constants related to decomposition of 5-diethylaminodibenzo*[a,d]*-cycloheptane (Table I, Compound 1) in 0.1* N *HCl at various temperatures.*

Figure 2 presents log absorbance plots as a function of time in 0.1 *N* HCl. It is evident that the rate constants vary considerably. The diethylamino compound was chosen for most of the work because of its relatively short half-life compared to other compounds.

Table III illustrates the kinetics of the diethylamino compound. An apparently invariant reaction rate constant at each specified temperature between 1 *N* HCl and pH 5 is evident. The studies were not carried to higher pH values due to precipitation of the free base (pKa approximately 7.4) from aqueous solution. These data imply that the process is a function of the rate of decomposition of protonated species, BH^+. The fraction of BH^+ probably approaches 1 for pH 5 and below. The following expression may be written regarding the reaction velocity constant:

$$k_{obs.} = k_o f_{BH^+}; \quad k_{obs.} = k_o \frac{[H^+]}{[H^+] + K_a}; \quad \text{or } k_{obs.} = k_o \quad \text{(Eq. 2)}$$

where $f_{BH^+} = 1$ (pH 5 and below). Water attack on protonated substrate and ionization of protonated amine to a carbonium ion with eventual production of alcohol in both cases are kinetically indistinguishable by ordinary methods (10).

The morpholino and dibutylamino derivatives degraded at measurable rates but were not studied due to the absence of suitable analytical techniques. The two substituted piperazines (Table I, Compounds 6 and 7) are extremely short lived in aqueous acidic solutions. The second piperazine nitrogen in some manner facilitates cleavage of the C—N bond. The two latter substances produce a fourth product of the reaction, which has not yet been identified.

Figure 3 shows the Arrhenius plot (11) using the relationship:

$$\ln k = -E_a/RT + \text{constant} \quad \text{(Eq. 3)}$$

for determination of the apparent energy of activation for 5-diethylaminodibenzo[*a,d*]cycloheptane. The value, as determined graphically, is 24.0 kcal./mole in 0.1 *N* HCl.

SUMMARY

Several 5-aminodibenzo[*a,d*]cycloheptanes were synthesized and examined regarding their reactivity in aqueous acidic solution. The differences in the compounds studied were in the amine portion of the molecule with various dialkyl, cycloalkyl, and piperazino analogs utilized. All prepared compounds exhibited degradative tendencies under the reaction conditions employed.

The acid-dye method was employed for analytical purposes. The technique is specific for the process when the amines generated do not form ion pairs with methyl orange. This procedure has its usual limitations as certain longer chain amines, *e.g.*, dibutylamine, form complexes with the anionic dye, while the morpholino substituent did not produce sufficient extractable color for analytical applicability.

The principal products of the solvolysis of monobasic amines were characterized and are: 1, 10,11-dihydro-5*H*-dibenzo[*a,d*]-cycloheptane-5-ol; 2, dibenzosuberone; and 3, bis(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl) ether. The ketone is likely a side-product of air oxidation of the alcohol.

The reaction sequence studied was initiated by a somewhat novel cleavage of a labile C—N bond between the 5-position of the tricyclic nucleus and the amino nitrogen. This linkage in some cases is broken at ambient temperatures in dilute acid. The reaction sequence considered may proceed through a resonance-stabilized carbonium ion or kinetically equivalent solvent attack on protonated substrate.

The general order of reactivity for the amino analogs is: piperazino > dialkylamino > cycloalkylamino.

REFERENCES

(1) N. V. Koninklijke Pharmaceutische Fabrieken voorheen Brocades-Stheeman and Pharmacia, British pat. 969,023; through *Chem. Abstr.*, **62**, 2782h(1965).

(2) V. Mychajlyszyn and M. Protiva, *Coll. Czech. Chem. Commun.*, **24**, 3955(1959); through *Chem. Abstr.*, **54**, 8766e(1960).

(3) A. Albert and E. P. Sergeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, pp. 16–42.

(4) T. Higuchi and E. Brochmann-Hanssen, "Pharmaceutical Analysis," Interscience, New York, N. Y., 1961, pp. 413–418.

(5) W. A. Dill and A. J. Glazko, *J. Biol. Chem.*, **179**, 395(1959).

(6) G. Schill, *Acta Pharm. Suecica*, **2**, 13(1965).

(7) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," Wiley, New York, N. Y., 1953, p. 668.

(8) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed., Reinhold, New York, N. Y., 1958.

(9) W. E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **76**, 3103(1954).

(10) E. R. Garrett, *J. Pharm. Sci.*, **51**, 811(1962).

(11) "Advances in Pharmaceutical Sciences," A. H. Beckett, H. S. Bean, J. E. Carless, and E. R. Garrett, Eds., Academic Press, London, England, 1967, p. 1.

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