[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Rearrangement of 2,3-Bis(*p*-aminophenyl)-2,3-butanediol. Structure of Amphenone B*

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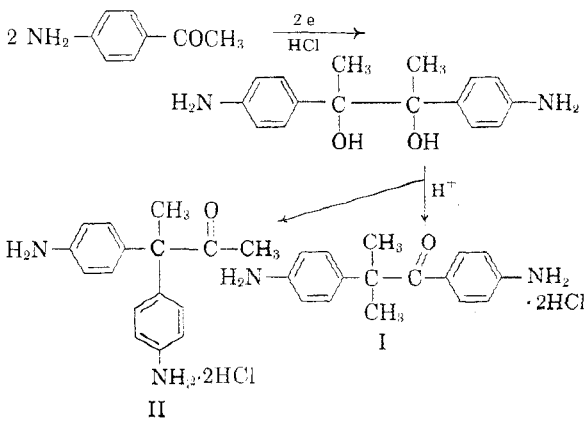
Received February 25, 1957

The pinacolone obtained by the acid rearrangement of 2,3-bis(*p*-aminophenyl)-2,3-butanediol is shown to be 3,3-bis(*p*-aminophenyl)-2-butanone (II), rather than 1,2-bis(*p*-aminophenyl)-2-methylpropanone-1 (I) as previously formulated.

The substance called Amphenone B, which causes suppression of cortical hormone secretion with concurrent adrenal hypertrophy,[1] is a valuable tool for the clinical control of the symptoms evidenced by Cushing's Syndrome associated with adrenal carcinoma.[2]

Amphenone B was originally prepared by Allen and Corwin[3] who obtained the pinacol, 2,3-bis-(*p*-aminophenyl)-2,3-butanediol, from *p*-aminoacetophenone by electrolytic reduction at constant potential.[4,5] Treatment with dilute hydrochloric acid gave the pinacolone dihydrochloride, Amphenone B, which was assigned the structure I.[6] This structure was based upon the following evidence. (a) The substance gave a negative iodoform test.[7] (b) Methylation of the amino groups, followed by treatment of the product with potassium hydroxide solution, afforded a substance whose melting point compared favorably with that of *p*-dimethylaminobenzoic acid.[8] (c) No evidence was observed for the formation of acetic acid which was expected from II upon treatment with alkali.



Since the original paper by Fittig[9] in 1860, the pinacol rearrangement has received intensive study by numerous investigators. Among these, Bailar[10] and Bachmann and coworkers[11] determined the effect of substituents on the "migratory aptitude" of groups in a large number of symmetrical benzopinacols, and provided a numerical system for predicting relative mobility. Additional data were supplied by Tiffeneau and Levy[12] for glycols containing both aliphatic and aromatic groups, which also showed some order in migrating ability. In none of these studies is information available for any compounds possessing a *p*-aminophenyl grouping. It is impossible, therefore, to assign to this group any numerical value to indicate its migratory aptitude relative to any other group. In the rearrangement which proceeds *via* a carbonium ion mechanism as proposed by Whitmore[13,14] the migratory aptitude is associated with the electron donating ability of the various groups. Accordingly

* Subsequent to the receipt of this manuscript there appeared a communication to the Editor was published showing the corrected structure for Amphenone B [W. L. Bencze and M. J. Allen, *J. Org. Chem*, **22**, 352 (1957)].

(1) R. Hertz, M. J. Allen and W. W. Tullner, *Proc. Soc. Expll. Biol. Med.*, **75**, 627 (1950); R. Hertz, W. W. Tullner and M. J. Allen, *Proc. Soc. Exptl. Biol. Med.*, **77**, 480 (1951); W. W. Tullner, M. M. Graff and R. Hertz, *Endocrinology*, **58**, 802 (1956).

(2) R. Hertz, J. A. Pittman and M. M. Graff, *J. Clin. Endocrinol. and Metabolism*, **16**, 705 (1956); G. W. Thorn, A. E. Renold, A. Goldfien, D. H. Nelson, W. J. Reddy and R. Hertz, *New Engl. J. Med.*, **254**, 547 (1956).

(3) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 117 (1950).

(4) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 114 (1950).

(5) N. J. Leonard, S. Swann, and G. Fuller, *J. Am. Chem. Soc.*, **75**, 5127 (1953).

(6) Subsequently M. J. Allen, *J. Chem. Soc.*, 1598 (1951), suggested a structure analogous to I for the pinacolone obtained from 2,3-bis(*p*-dimethylaminophenyl)-2,3-butanediol, which was prepared by the electrolytic reduction of *p*-dimethylaminoacetophenone. The assignment of structure was made entirely on the similarity of the infrared spectra.

(7) This cannot be used to support structure I. Pinacolone itself was shown by R. Poggi, *Atti soc. ital. progresso sci., XXI Reunione*, **2**, 376 (1933), to give a negative iodoform test. Similarly C. C. Price and G. R. Mueller, *J. Am. Chem. Soc.*, **66**, 634 (1944), observed the same result with 3,3-dianisyl-2-butanone.

(8) No mixed melting point or other evidence was provided.

(9) R. Fittig, *Ann.*, **114**, 54 (1860).

(10) J. C. Bailar, *J. Am. Chem. Soc.*, **52**, 3596 (1930).

(11) W. E. Bachmann and F. H. Moser, *J. Am. Chem. Soc.*, **54**, 1124 (1932); W. E. Bachmann and H. R. Steinberger, *J. Am. Chem. Soc.*, **55**, 3819 (1933); **56**, 170 (1934).

(12) M. Tiffeneau and J. Levy, *Bull. soc. chim. France*, [4] **49**, 1647, 1767, 1698 (1931).

(13) F. C. Whitmore, *J. Am. Chem. Soc.*, **54**, 3274 (1932).

(14) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1954, pp. 247–257. See also E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 45-49.

one might conclude that the amino group should supply tremendous impetus in effecting phenyl migration. In acid solution, however, $-NH_3^+$, which imparts electron attracting properties, would be expected to produce an opposite effect. The methyl group, which might now be considered as a competing electron donating group, could possibly displace phenyl as the migrating group. The conclusions arrived at by Allen and Corwin could be interpreted in conformance with this idea. This explanation is not, however, in accord with results obtained in these laboratories.

Physical data gathered on samples of Amphenone B, which were prepared according to the method described, are not in agreement with the structure I. The infrared spectrum in mineral oil mull shows only nonconjugated carbonyl absorption in the vicinity of 1705 cm.$^{-1}$ rather than a doublet at 1682 and 1665 cm.$^{-1}$ as determined for the conjugated carbonyl in *p*-aminoacetophenone hydrochloride. The carbonyl absorption for Amphenone free base is found at 1704 cm.$^{-1}$; for *p*-aminoacetophenone the carbonyl absorption occurs at 1636 cm.$^{-1}$ These differences in ketone absorption establish that Amphenone B cannot be structurally related to *p*-aminoacetophenone as was previously postulated. Furthermore, the substance in hexachlorobutadiene mull shows no absorption in the region which can be associated with the *gem*-dimethyl grouping which is required by structure I.

Differences in the ultraviolet spectra of Amphenone B and *p*-aminoacetophenone hydrochloride afford additional evidence for the nonconjugated carbonyl group in the former. *p*-Aminoacetophenone in 0.01 *N* ethanolic sulfuric acid shows absorption maxima at 233 and 318 mμ with molar absorbtivities (a_M) of 7075 and 19,325, respectively. Amphenone B in the same solvent has absorption maxima at 248 and 292 mμ with molar absorptivities of 3275 and 1075, respectively. It has been shown[15] that phenyl substitution on a saturated carbon atom α to a carbonyl group imparts enhanced absorption to that carbonyl in the region of 290 mμ. In no case, however, was the intensity of the absorption greater than that which could be attributed to the phenyl group(s). On the other hand, when a ketone is conjugated with a phenyl group there is an even greater increase in the intensity of the absorption as well as a shift to longer wave lengths. Thus, the larger molar absorptivity of *p*-aminoacetophenone at 318 mμ indicates the presence of a conjugated carbonyl group, whereas the weak absorption of Amphenone B which lies at 292 mμ strongly suggests a nonconjugated ketone.

The polarographic behavior was studied in 75% ethyl alcohol–25% water containing 0.1*M* tetramethylammonium hydroxide as a supporting electrolyte. Half-wave potentials of -2.05 and -2.12 volts *vs.* a mercury pool anode were found for Amphenone and acetone, respectively. The half-wave potential observed for *p*-aminoacetophenone under identical conditions was -1.67 volts. This is additional support for the conclusions drawn from spectral data, since structure I would be expected to reduce in the same potential range as does *p*-aminoacetophenone, rather than at potentials normally found for nonconjugated ketones.[16]

From our material, prepared *via* electrolytic reduction, we obtained the analytically pure free base of Amphenone B and found it to have the same melting point as that reported by the previous authors. Moreover, all of the data described above agreed completely with that obtained from samples prepared at the National Cancer Institute.[17] Because of this overwhelming evidence and the equivalence in physiological activity, we feel that not only can there be no doubt as to the identity of our material with that of Allen and Corwin, but also that the previously assigned structure is incorrect.

From the data which have accumulated, the alternate structure II appeared more likely to be correct. Accordingly, 3,3-bis(*p*-aminophenyl)-2-butanone dihydrochloride was synthesized from acetophenone. The pinacol, 2,3-diphenyl-2,3-butanediol, was prepared according to Sisido and Nozaki[18] who employed the excellent method of Newman.[19] Treatment with acid[18] gave the pinacolone, 3,3-diphenyl-2-butanone, whose structure has been satisfactorily established.[20] Its infrared spectrum was in complete agreement with this structure and showed carbonyl absorption at 1707 cm.$^{-1}$ which was previously identified in the spectrum of Amphenone B. Nitration of the pinacolone with a mixture of nitric and sulfuric acids gave a gum from which was isolated a dinitrated product whose infrared spectrum carried a characteristic doublet at 850 and 855 cm.$^{-1}$, a fact indicating the presence of *p*-phenyl substituents. The 3,3-bis(*p*-nitrophenyl)-2-butanone was reduced catalytically at atmospheric pressure in the presence of 5% palladium charcoal, and the diamine which resulted was converted into the dihydrochloride salt. This material was identical in every respect with all previous samples of Amphenone B which we have examined. The fact that all of the infrared

(15) W. D. Kumler, L. A. Strait and E. L. Alpen, *J. Am. Chem. Soc.*, **72**, 1463 (1950).

(16) I. M. Kolthoff and J. J. Lingane, *Polarography*, Interscience Publishers, New York, N. Y., 1952, 2nd ed., Vol. II, ch. XXXIX.

(17) Generously supplied by Dr. Roy Hertz and Dr. Bernard R. Landau, National Cancer Institute, Bethesda, Md.

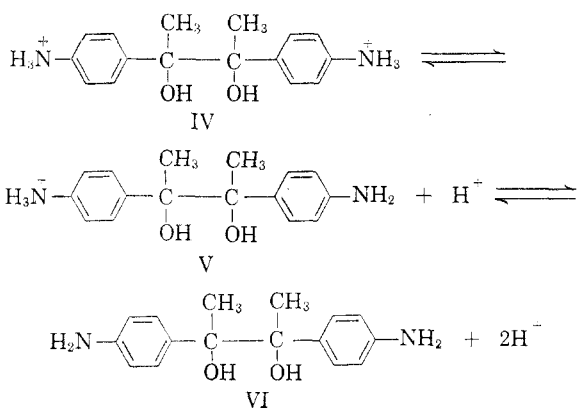
(18) K. Sisido and H. Nozaki, *J. Am. Chem. Soc.*, **70**, 776 (1948).

(19) M. S. Newman, *J. Am. Chem. Soc.*, **62**, 1683 (1940).

(20) W. Thörne and T. Zinke, *Ber.*, **11**, 1988 (1878).

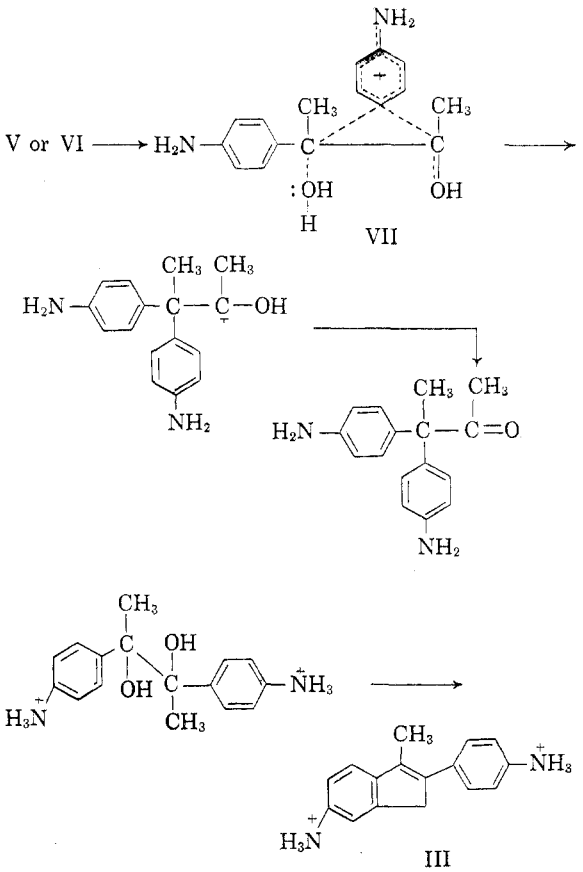
curves are superimposable is conclusive evidence for *para*-nitration of the starting pinacolone.[21]

In view of the mechanism discussed earlier one must conclude that in spite of salt formation in the acidic medium, the *p*-aminophenyl group still has a greater "migratory aptitude" than a methyl group. That the carbonium ion mechanism is applicable to this situation cannot be disputed, since the preponderance of evidence supports this concept.[14] We wish to suggest that the *para*-amino substituent on phenyl does indeed exert a powerful driving force by virtue of its electron donating character and that this substituted phenyl must be the group that migrates, but only when conditions are favorable. A proton might not approach the hydroxyl group of the pinacol unless either one or both of the amino groups are not protonated.[22] One can visualize an equilibrium between IV, V, and VI. When a proton approaches the hydroxyl



group of either V or VI, the phenyl group simultaneously migrates *via* the phenonium ion (VII)[23] under the influence of the *p*-amino substituent. In strong acid, on the other hand, the equilibrium represented by IV $\rightleftharpoons$ V $\rightleftharpoons$ VI is shifted to the left, and rearrangement occurs at a much slower rate.

Thus, the rate of rearrangement must be *p*H dependent, and available evidence suggests that this may be the case. It was shown[3] that treatment of the pinacol with concentrated hydrochloric acid gave only a 30% yield of pinacolone, the major product (61%) being 2-(*p*-aminophenyl)-3-methyl-6-aminoindene (III) which arises by cyclodehydration.[24] In dilute acid solution the only product isolated (67%) was the pinacolone. We feel that the acid concentration does not determine which group migrates but rather influences only the rate of reaction. If the amino groups remain protonated, two alternatives are presented. First, no reaction will take place and starting material will be recovered. Second, side reactions and the formation of by-products should occur. In this case the latter course is followed and the substituted indene (III) is obtained.[25,26] Just where the *p*-amino group lies with relation to other *para* phenyl substituents in migratory aptitude remains to be determined.



EXPERIMENTAL[27]

3,3-Bis(p-nitrophenyl)-2-butanone. A solution of 22.4 g. (0.1 mole) of 3,3-diphenyl-2-butanone[18] in 65 g. of concentrated sulfuric acid was cooled to −10° and treated dropwise with a mixture of 29 g. of concentrated nitric acid (*d* 1.42) and 90 g. of concentrated sulfuric acid which was

(21) Dr. Bernard R. Landau has informed us that he has prepared the pinacolone from *p*-dimethylaminoacetophenone and has found the infrared spectrum to be similar to that of Amphenone B (*cf.* ref. 6). It follows therefore that this substance is the 3,3-bis(*p*-dimethylaminophenyl)-2-butanone.

(22) One can only speculate as to which condition is required. It can be argued on theoretical grounds that both amino groups must be free.

(23) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3863 (1949).

(24) W. Hausmann and A. E. W. Smith, *Nature*, **161**, 892 (1948). A diene may be the intermediate in the case of the amino compound, but is not required.

(25) A somewhat analogous situation exists in the case of 1,2-dimethyl-1,2-cyclopentanediol. The *cis* form rearranges normally to give 2,2-dimethylcyclopentanone, but the *trans* form, because of unfavorable stereochemistry, cannot participate in this type of reaction and gives only tar (*cf.* ref. 14).

(26) Although —$N(CH_3)_2$ of 2,3-*bis*(*p*-dimethylaminophenyl)-2,3-butanediol would be expected to have a stronger salt-forming tendency than —NH_2, the same mechanism applies. Here, however, *p*H is more critical and very dilute acid must be used if indene formation is to be avoided (*cf.* ref. 6, 21).

(27) Melting points are uncorrected.

cooled to 0°. The mixture was shaken during the addition, and the temperature was held at −5° by immersion in a freezing mixture when necessary. After standing at −5° for 20 min. longer it was poured onto crushed ice. The tan gummy solid which formed was filtered, washed with cold water, and dried. There was obtained 22.7 g. of material which failed to solidify completely, and which could not be crystallized. A portion (6.9 g.) was chromatographed over Florisil using various mixtures of Skellysolve B (b.p. 60–71°) and acetone as eluant. A fraction eluted with Skellysolve B containing 7.5% acetone gave a colorless solid which was recrystallized from 95% ethyl alcohol. There was obtained 2.1 g. of material which melted at 140–165°. An analytical sample melted at 165.5–167.5°.

Anal. Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.92. Found: C, 61.29; H, 4.14; N, 9.24.

3,3-Bis(p-aminophenyl)-2-butanone dihydrochloride. To a solution of 1.0 g. of 3,3-bis(*p*-nitrophenyl)-2-butanone in 50 ml. of purified dioxane was added 0.15 g. of 5% palladium charcoal and the mixture was shaken with hydrogen at atmospheric pressure until slightly more than the theoretical amount had been absorbed. The mixture was filtered and the solvent removed at 25° under reduced pressure. The residue was dissolved in 35 ml. of absolute ethyl alcohol and the solution was saturated with dry hydrogen chloride gas. It was evaporated to dryness under vacuum at room temperature to remove excess hydrogen chloride. The solid was suspended in 20 ml. of absolute ethyl alcohol, an equal volume of ethyl acetate added, and the mixture cooled overnight. The solid was filtered, washed with 20 ml. of a 1:1 mixture of absolute ethyl alcohol and ethyl acetate, and dried. There was obtained 0.86 g. of material melting at 252° (dec.).

The reported melting point is 272–275°.[3] We have found that this varies depending upon the rate of heating and the apparatus used. Our samples have melted between 250 and 282°; our most consistent results were obtained with a bath rather than a block.

Anal. Calcd. for $C_{16}H_{20}Cl_2N_2O$: C, 58.72; H, 6.16; N, 8.56; Cl, 21.67. Found: C, 58.44; H, 6.38; N, 8.49; Cl, 21.10.

The free base prepared by treatment of an aqueous solution of the salt with dilute ammonium hydroxide was purified by recrystallization from hot water. It melted at 137–138.5° (reported 137.5–138°[3]).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.44; H, 7.22; N, 10.94.

The infrared curves were obtained using a Perkin-Elmer model 21 Infrared Spectrophotometer equipped with sodium chloride optics and cells.

Acknowledgments. We wish to thank Prof. Melvin S. Newman and Dr. George Slomp for helpful suggestions. Our thanks also go to Dr. James L. Johnson, Mr. Marvin Grostic, and Mrs. Gunther Fonken for assistance in the preparation and interpretation of the infrared spectra, and Mr. James E. Stafford for the preparation of the ultraviolet spectra. Microanalyses were performed by Mr. William A. Struck and associates of the Analytical Chemistry Section of The Upjohn Co.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF STANFORD UNIVERSITY]

Attempted Syntheses of Compounds Containing the 1,6-Diazacyclodecapentaene Ring

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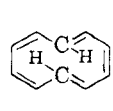
Received February 27, 1957

Attempts to prepare 2,3:4,5:8,9-tribenzo-1,6-diazacyclodecapentaene by the reaction of 2,2′-diaminobiphenyl with *o*-phthaldehyde gave only red polymeric compounds. Attempts to prepare the 7-methyl tribenzo derivative by the cyclization of *N*-benzylidene-*N*′-acetyl-2,2′-diaminobiphenyl with phosphorus oxychloride gave instead the cyclic amidine, *N*,*N*′-(2,2′-biphenylene)cinnamidine.

According to the calculations of Hückel,[2] completely conjugated, planar, monocyclic compounds having $(4n + 2)$ unsaturation (π) electrons, where n is any integer, should have aromatic properties. The only known examples of this rule are compounds for which $n = 1$. The simplest example where $n = 2$ would be cyclodecapentaene (I).

The steric interference of the internal hydrogen atoms in structure I is such, however, that the molecule cannot be planar. Although models indicate that the molecule probably is possible, at least in the *trans* conformation, it would not be expected to have aromatic properties. 9,10-Dihydronaphthalene (II), in either the *cis* or *trans* configuration, likewise appears to be only moderately strained but again would not be expected to be aromatic. 1,6-Diazacyclodecapentaene, on the other hand, appears to be reasonably strainless in the Fisher-Hirschfelder model, and even in the Briegleb model the unshared pairs of electrons on the nitro-



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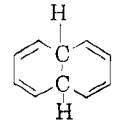

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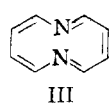

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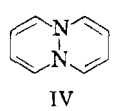

IV

(1) American Cyanamid Company Fellow, 1953–54, Eli Lilly Company Fellow, 1954–55, Eastman Kodak Fellow, 1955–56.

(2) E. Hückel, *Z. Physik*, 70, 204 (1931).