The values of $k_t$ in this system are several orders of magnitude lower than those found in radical polymerizations, which are usually about $10^7$ l. mole$^{-1}$ sec.$^{-1}$, yet polymers of relatively low molecular weights are produced. The reason for this is apparent when the concentrations of growing chains are compared. At maximum rate of polymerization, there are about $10^{-3}$ $M$ of growing chains in this system in contrast to $10^{-8}$ $M$ for radical polymerizations. Therefore, the actual rate of termination in this system is a hundred- to a thousand-fold faster than the free radical systems, leading to polymers of considerably lower molecular weights.

It is ambiguous to discuss the lifetime of a growing chain in a non-steady state system with bimolecular termination. Nevertheless, it is interesting to illustrate the order of magnitude of the lifetime of a growing chain in a particular polymerization, *i.e.*, the one used earlier as an example for calculations. Thus, it took 24 min. to reduce the concentration of the growing chain from 0.5 millimolar to 0.25 millimolar. Of course, the average lifetime increases with decrease of concentration and is dependent upon all the other variables which change the value of $k_t$.

In the catalyst system used by Ludlum, Anderson and Ashby,[30] the growing sites were demonstrated to be very longlived. The stability could be attributed to the lower valence state of Ti. Herman and Nelson[31] suggested that the alkyls of Ti(II) are relatively stable. In addition, their catalyst system is heterogeneous, in which case bimolecular termination is necessarily more difficult.

**Acknowledgment.**—The author is indebted to the members of the Central Research Division at the Research Center, Hercules Powder Co., for discussions and assistance in the preparation of this paper. Mrs. M. Korden's assistance in carrying out most of the experimental work is also appreciated.

(30) D. B. Ludlum, A. W. Anderson and C. E. Ashby, THIS JOURNAL, **80**, 1380 (1958).

(31) D. F. Herman and W. K. Nelson, *ibid.*, **75**, 3877, 3882 (1953).

WILMINGTON, DEL.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Anomalous $pK_a$ Values of Some Substituted Phenylethylamines[1]

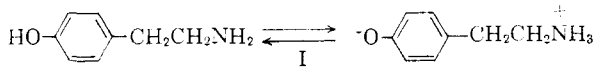
BY MURRAY M. TUCKERMAN, J. RICHARD MAYER AND FREDERICK C. NACHOD

RECEIVED JULY 15, 1958

The $pK_a$ values of some substituted phenylethylamines having pressor activity were determined. The seemingly anomalous lower $pK_a$ values for some secondary amines in contrast to the corresponding primary amines are discussed. Some of the physiological consequences are briefly considered.

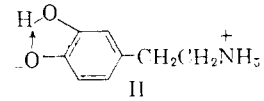
During an investigation of methods of separation and determination of arterenol (nor-epinephrine) and epinephrine, it was found that this pair of primary and secondary amines had the same $pK_a$ value, within the limits of experimental error. This unanticipated result led to the determination of $pK_a$ values for other pairs of pressor phenylethylamines listed in Table I. Two pairs of primary amine and corresponding N-methylamine are reported in which the primary amine has a greater $pK_a$ value than the secondary amine. An explanation of the observed values is given below.

**The Primary Amines.**—The parent compound for this series, 2-phenylethylamine, has a $pK_a$ value of 9.78. The substitution of a *p*-hydroxyl group in the benzene ring lowers the $pK_a$ to 9.22. Since an inductive effect in this case would have to operate through an ethylene chain the more likely cause of decreased base strength may be attributed to zwitterion formation (I).

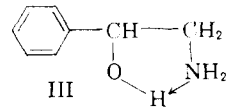


I

The further decrease in $pK_a$ to 8.93 which results when a second hydroxyl group is introduced in the *m*-position (II) can be explained in terms of an increased opportunity for zwitterion formation and stabilization of the zwitterion by hydrogen bonding.



II



III

If in the parent compound a benzylic hydrogen is replaced by an hydroxyl group, a $pK_a$ value of 8.90 is observed which is lower than that of either I or II. *A priori* this lowered basicity may be due to the inductive effect of the hydroxyl group or the presence of hydrogen bonding (III).

The observed hydrogen bonding in the ethanolamines[2] would favor this latter view. It is interesting that this effect is of greater importance in lowering basicity than zwitterion formation.

When both a *p*-hydroxyl group and a benzylic hydroxyl group are present (IV), the observed $pK_a$ is 8.81. Since the inductive effect of a *p*-hydroxyl group would tend to develop a fractional positive charge on the benzylic carbon atom, which in turn increases the acidity of the benzylic hydroxyl group, it is clear that the resulting strengthening of the hydrogen bridge would further reduce the basicity of the nitrogen atom.

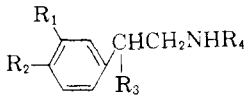
This concept of hydrogen bond strengthening by the operation of an inductive effect is supported

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society, 134th National Meeting, Chicago, Ill., September 8, 1958.

(2) E. D. Bergmann, E. Gil-Av and S. Pinchas, THIS JOURNAL, **75**, 68 (1953).

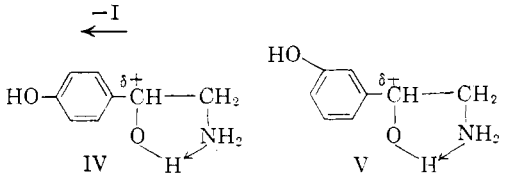
TABLE I

SUMMARY OF $pK_a$ VALUES OF SOME SYMPATHOMIMETIC AMINES



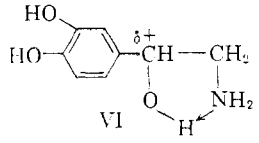
| | | | | | | Effect of structural change from H | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $pK_a$ | $R_4 = CH_3$ | $R_3 = OH$ | $R_1 = OH$ | $R_2 = OH$ | $R_1,R_2 =$ OH | $R_1,R_3 =$ OH | $R_2,R_3 =$ OH |
| 1 | H | H | H | H | 9.78 | | | | | | | |
| 2 | H | H | H | $CH_3$ | 10.31 | +0.53 | | | | | | |
| 3 | H | H | OH | H | 8.90 | | −0.88 | | | | | |
| 4 | H | H | OH | $CH_3$ | 9.31 | + .41 | −1.00 | | | | | |
| 5 | H | OH | OH | H | 8.81 | | −0.41 | | −0.09 | | | −0.97 |
| 6 | H | OH | OH | $CH_3$ | 8.62 | − .19 | − .74 | | − .69 | | | −1.69 |
| 7 | OH | H | OH | H | 8.67 | | | −0.23 | | | −1.11 | |
| 8 | OH | H | OH | $CH_3$ | 8.89 | + .22 | | − .42 | | | −1.42 | |
| 9 | H | OH | H | H | 9.22 | | | | − .56 | | | |
| 10 | H | OH | H | $CH_3$ | 9.36 | + .14 | | | − .95 | | | |
| 11 | OH | OH | H | H | 8.93 | | | − .29 | | −0.85 | | |
| 12 | OH | OH | H | $CH_3$ | 8.78 | − .15 | | − .58 | | −1.53 | | |
| 13 | OH | OH | OH | H | 8.58 | | − .35 | − .23 | − .09 | −0.32 | −0.64 | |
| 14 | OH | OH | OH | $CH_3$ | 8.55 | − .03 | − .23 | − .07 | − .34 | −0.76 | −0.81 | |

by the fact that in the corresponding *m*-hydroxy compound (V) where one would expect a greater inductive effect and a correspondingly lower basicity, the $pK_a$ is 8.67.



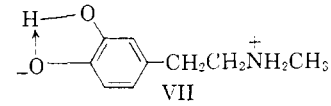
IV V

The introduction of a third hydroxyl group to give arterenol, 2-(3,4-dihydroxyphenyl)-2-hydroxyethylamine (VI), lowers the $pK_a$ to 8.58. In terms of the above effects it would appear that an additional degree of hydrogen bond stabilization has resulted due to an increased inductive effect operating as in V.



VI

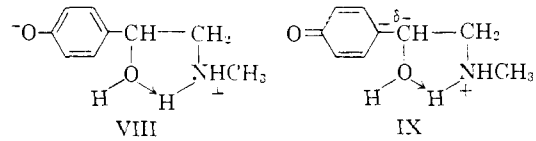
**The Secondary Amines.**—The observed $pK_a$ for N-methyl-2-phenylethylamine is 10.31—a value which reflects the expected inductive effect of a methyl group. The introduction of a *p*-hydroxyl group lowers the $pK_a$ to 9.36 thus paralleling the results for the primary amine. However the magnitude of the change (−0.95) is larger than for the primary amine (−0.56). This apparently is due to the greater intrinsic basicity of the nitrogen atom in the secondary amine which favors zwitterion formation. The degree to which zwitterion formation occurs is therefore dependent upon the availability of protons and the base strength of the nitrogen atom. This is illustrated in the case of N-methyl-2-(3,4-dihydroxyphenyl)-ethylamine (VII) whose $pK_a$ is 8.78. This value is as expected less than that of the 4-hydroxy compound and furthermore is *less* than that of the corresponding primary amine II. In this case the formation of zwitterions would be particularly favored in view of the presence of a secondary amino nitrogen, two phenolic hydroxyl groups, and further stabilization of the zwitterion by hydrogen bonding.



VII

The situation exists therefore in this pair of secondary and primary amines (VII and II) that an inherently more basic center is attenuated by zwitterion formation to a greater extent than a less basic center. Therefore the secondary amine displays a lower $pK_a$ than the primary amine.

The substitution of an hydroxyl group on the benzylic carbon of N-methyl-2-phenylethylamine lowers the $pK_a$ to 9.31. This change of −1.00 unit is comparable to the corresponding change of −0.88 unit observed for the primary amine. The introduction of a *m*-hydroxyl group into N-methyl-2-hydroxy-2-phenylethylamine further reduces the $pK_a$ to 8.89. These changes are interpretable in terms of the above concepts. When, however, a *p*-hydroxyl group is substituted into N-methyl-2-hydroxy-2-phenylethylamine, a marked decrease in $pK_a$ to 8.62 occurs. This difference (−0.69) is considerably larger than that observed in the primary amine (−0.09) and suggests that a fundamental change has taken place. For this compound we postulate structure VIII which involves a hydrogen bridge unlike that of the primary amine.



VIII IX

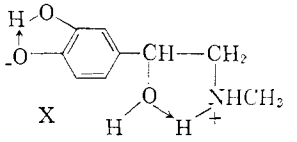
The $\overset{+}{N}$—H···O hydrogen bridge involved here would be expected to be more stable than an N···H—O system by virtue of the greater lability of the proton and the opportunity for resonance. It derives a further degree of stabilization by the increased electron density on the benzylic oxygen as a result of the fractional negative charge placed

on the benzylic carbon atom in the resonating zwitterion IX.

It would appear that both a *p*-hydroxyl group and an N-methyl group are prerequisite to the formation of this kind of hydrogen bond. This is the second example in this series when a secondary amine is less basic than the corresponding primary amine—in this case by reason of a unique hydrogen bond in the secondary amine.

In comparing the corresponding *m*-hydroxy secondary and primary amines it is seen that the normal order exists—the secondary amine having a $pK_a$ of 8.89 and the primary, 8.67.

Finally, in the case of epinephrine (X), zwitterion formation is further enhanced by additional hydrogen bonding as before, the $pK_a$ being 8.55.



It will be seen therefore that two different types of hydrogen bonding have been proposed for arterenol and epinephrine—each one imposing a different configuration upon the respective molecules.

## Discussion

The fact that the $pK_a$ values of the pair, arterenol and epinephrine, are identical would preclude that the ratio of ionic and non-ionic species of each in a buffer system such as blood could be affected in favor of one or the other catechol amine. Hence the body has no mechanism to sort out the two amines on the basis of their electrochemical properties since the $pK_a$ values are delicately balanced by the mutual interaction of the five above-mentioned effects. Yet in certain stress conditions (*e.g.*, hemorrhagic shock) the output and subsequently the concentration of epinephrine may increase 400 to 500% with a lesser increase of the desmethyl analog.[3] The identity of base strength in this pair re-emphasizes that physiological action must be based primarily on morphological differences[4] and not on physicochemical properties. It further strengthens the receptor mechanism concept based on the marked difference in physiological action[5] of each of the optical isomers, where no gross physico-chemical differences can be postulated.

If the relative ratio of the two catecholamines in the body is coupled by an enzymatic methylation reaction and their relative production is a function of biological age,[6] one can further speculate that no marked activation energy can be associated with the methylation or de-methylation reactions.

## Experimental

The $pK_a$ values listed in Table I were determined in a manner similar to that given by Parke and Davis[7] in an approximately $5 \times 10^{-6}$ *M* aqueous solution. The essentials of this method are: (1) obtaining a correction curve by titrating standard alkali potentiometrically into a measured volume of solvent; (2) dissolving the sample in the same quantity of solvent as in (1) and titrating potentiometrically with the standard alkali; (3) subtracting the correction curve from the compound curve; (4) determining the maximum for $\Delta$ ml. titrant/$\Delta$ *p*H by use of the second derivative of the corrected curve and interpolating between measured values in a manner analogous to the potentiometric determination of end-points as given by Lingane.[8]

(3) U. S. von Euler, *Brit. Med. J.*, **I**, 105 (1951); R. J. Humphreys and W. Raab, *Proc. Soc. Exptl. Biol. Med.*, **74**, 302 (1950).

(4) Interestingly, the isopropyl arterenol has a $pK_a$ of 8.64 indicating a slightly higher value than arterenol or epinephrine. This can be explained as a somewhat lesser contribution of the hydrogen bond owing to crowding by the isopropyl group.

(5) A. M. Lands, F. P. Luduena and B. F. Tullar, *J. Pharmacol. Exptl. Therap.*, **111**, 469 (1954); F. P. Luduena, L. von Euler, B. F. Tullar and A. M. Lands, *Arch. intern. pharmacodynam.*, **111**, 392 (1957).

(6) R. E. Coupland, *J. Endocrinol.*, **9**, 194 (1953).

(7) T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1915).

(8) J. J. Lingane, "Electroanalytical Chemistry," Interscience Publishers, Inc., New York, N. Y., 1953, p. 70.

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[CONTRIBUTION FROM THE ILLINOIS STATE GEOLOGICAL SURVEY]

# Aromatic Fluorine Compounds. VIII. Plant Growth Regulators and Intermediates[1,2]

BY G. C. FINGER, M. J. GORTATOWSKI,[3] R. H. SHILEY AND R. H. WHITE

RECEIVED JUNE 5, 1958

The preparation and properties of 41 fluorophenoxyacetic acids, 4 fluorophenoxypropionic acids, 2 fluorobenzoic acids, several indole derivatives, and a number of miscellaneous compounds are described. Data are given for many intermediates such as new fluorinated phenols, anisoles, anilines and nitrobenzenes. Most of the subject compounds are related to a number of well-known herbicides or plant growth regulators such as 2,4-D, 2,4,5-T and others.

Chlorinated plant growth regulators have been studied extensively, whereas very little information is available on the fluoro[4-10] or mixed fluoro-halogen[11-13] analogs. A large number of fluorinated derivatives were synthesized for testing for

(1) This research was supported in part by contract with the U. S. Army Chemical Corps, Fort Detrick, Frederick, Md., through the University of Illinois. The research was the responsibility of the State Geological Survey.

(2) Published by permission of the Chief of the Illinois State Geological Survey.

(3) Formerly Special Research Assistant.

(4) F. D. Jones (to Am. Chem. Paint Co.), U. S. Patent 2,390,951 (1945).

(5) H. E. Thompson, C. P. Swanson and A. G. Norman, *Botan. Gaz.*, **107**, 476 (1946).

(6) M. S. Newman, W. Fones and M. Renoll, THIS JOURNAL, **69**, 718 (1947).

(7) C. E. Minarik, D. Ready, A. G. Norman, H. E. Thompson and J. F. Owings, Jr., *Botan. Gaz.*, **113**, 135 (1951).

(8) J. C. Crane and R. Bondeau, *Plant Physiol.*, **26**, 136 (1951).

(9) L. J. Edgerton and M. B. Hoffman, *Proc. Am. Soc. Hort. Sci.*, **62**, 159 (1953).

(10) N. P. Buu-Hoi, V. Q. Yen and N. D. Xuong, *J. Org. Chem.*, **23**, 189 (1958).

(11) M. W. Bullock and S. W. Fox, THIS JOURNAL, **73**, 5155 (1951).

(12) O. L. Hoffman, S. W. Fox and M. W. Bullock, *J. Biol. Chem.*, **196**, 437 (1952).

(13) R. L. Wain, *Nature*, **172**, 710 (1953).