final data were taken in the range of 25–80% completion of the reaction. Variation in temperature before attainment of equilibrium was thereby eliminated. The rate curves obtained are shown in Fig. 1 and the rate constants and approximate energies of activation are given in Table III.

Ann Arbor, Mich.

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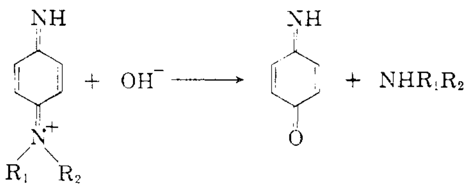
The Mechanism of Dye Formation in Color Photography. VII. Intermediate Bases in the Deamination of Quinonediimines[1]

By L. K. J. Tong, M. Carolyn Glesmann and R. L. Bent

Received May 5, 1959

The deamination of certain oxidized derivatives of *p*-phenylenediamines in aqueous solutions proceeds through stable intermediates which have been postulated as the addition products with OH^-. Some equilibrium constants for this reaction were measured spectrophotometrically. The addition compounds appear to be inert in the formation of indoaniline dyes.

It has been shown earlier in this series[2,3] that quinonediimines, formed by oxidation of *p*-amino-N,N-dialkylanilines, undergo a deamination of the substituted amino group to form quinonemonoimines according to the equation



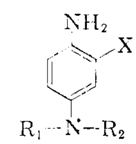
In the cases reported earlier, the rate of this reaction was a linear function of the OH^- concentration. Certain amines containing hydroxyalkyl substituents on the tertiary nitrogen, however, follow a more complicated rate law. The analysis of this rate law has led to a more detailed understanding of the SN2 deamination reaction and is reported in the present paper.

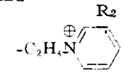
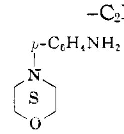
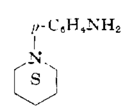
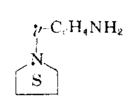
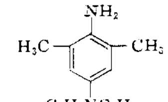
As before, the reaction rates are measured by determination of the yields at various times of the indoaniline dye and the indophenol dye which are formed by coupling of the quinonediimine or the quinonemonoimine, respectively, with α-naphthol, depending on whether or not deamination takes place. The deaminations of the quinonediimines derived from the amines in Table I, like those of the four compounds discussed earlier,[2] are directly proportional to the OH^- concentration over the whole measured range from *p*H 8.0 to 12.0. The rates are given in Table I as $\log k_1/(OH^-)$, *i.e.*, deamination rates for unit OH^- activity. The values of the earlier measurements are repeated, in italics, for comparison.

The deamination rates of quinonediimines derived from the amines listed in Table II when plotted against *p*H, Fig. 1, tend toward limiting values and actually reach these in several cases. Then even drastic increases in *p*H up to 0.375 *N* KOH do not further raise the deamination rate. Such changes in dependence are often indicative of the formation of more or less stable intermediates, but diamines with high oxidation potentials might exhibit a non-linear log *k* vs. *p*H plot because of

Table I

Second-order Rate Constants $k_1/(OH^-)$ for Elimination of the Dialkylamine



Number	Compound X	R₁	R₂	$\log k_1/(OH^-)$
1	CH_3	C_2H_5		5.35
2	H	C_2H_5	$-C_2H_4SO_3^{\ominus}$	4.51
3	H	C_2H_5	$-C_2H_4NHCOCH_3$	4.42
4	H	CH_3	$-CH_3$	4.40
5	Cl	C_2H_5	$-C_2H_5$	*4.34*
6	H	C_2H_5	$-C_2H_4OCH_3$	*4.30*
7	H	C_2H_5	$-C_2H_5NHSO_2CH_3$[a]	4.30
8	H	C_2H_5	$-C_2H_5$	*3.99*
9	CH_3	C_2H_5	$-C_2H_4SO_3^{\ominus}$	*3.83*
10	CH_3	C_2H_5	$-C_2H_4N(CH_3)SO_2CH_3$	*3.78*
11	CH_3	C_2H_5	$-C_2H_4NHSO_2CH_3$[a]	*3.64*
12	CH_3	C_2H_5	$-C_3H_6SO_3^{\ominus}$	3.46
13	C_2H_4OH	C_2H_5	$-C_2H_5$	3.36
14	CH_3	C_2H_5	$-CH_2COO^{\ominus}$	3.35
15	CH_3	$-CH_2COO^{\ominus}$	$-CH_2COO^{\ominus}$	3.24
16	CH_3	C_2H_5	$-C_2H_5$	*3.22*
17	CH_3	C_2H_5	$-C_2H_4N^{\ominus}SO_2CH_3$[a]	*2.48*
18	H	C_2H_5	$-C_2H_4N^{\ominus}SO_2CH_3$[a]	*2.34*
19	$-OCH_3$	C_2H_5	$-C_2H_5$	2.03
20				5.00
21				4.10
22				3.78
23				2.34

[a] Data from references 2 and 3 are included for comparison. Compounds 17 and 18 are the same as compounds 11 and 7 after ionization.

(1) For Part VI, see L. K. J. Tong and M. Carolyn Glesmann, This Journal, **79**, 4310 (1957).

(2) L. K. J. Tong, *J. Phys. Chem.*, **58**, 1090 (1954).

(3) L. K. J. Tong and M. Carolyn Glesmann, This Journal, **78**, 5827 (1956).

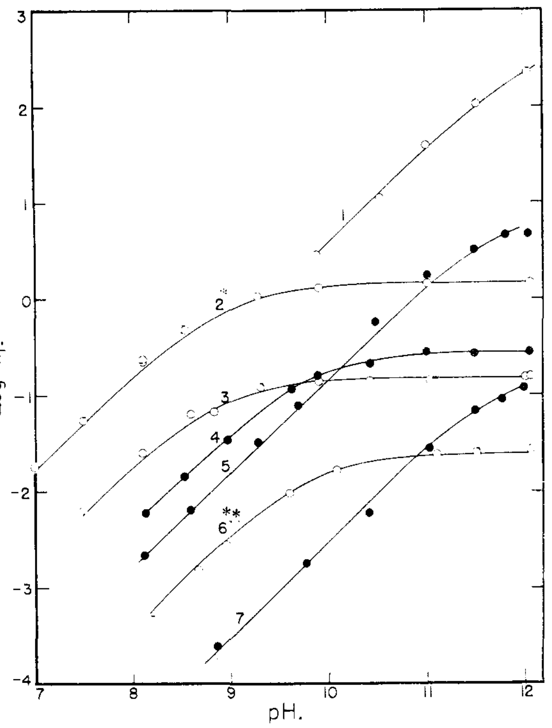
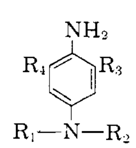


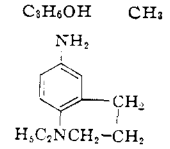
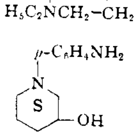
Fig. 1.—pH dependence of first-order rate constants for elimination of the tertiary amines from the following compounds: 1, N-(4-aminophenyl)-3-hydroxypiperidine (31); **2**, 4-amino-N,N-bis-(β-hydroxyethyl)-3-methylaniline (26) *log k_1 displaced 1 unit upward; **3**, 4-amino-N-ethyl-N-(β-hydroxyethyl)-aniline (25); **4**, 4-amino-3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline (28); **5**, 4-amino-3-methyl-N-ethyl-N-(3-hydroxypropyl)-aniline (29); **6**, 4-amino-N,N-bis-(β-hydroxyethyl)-3,5-dimethylaniline (27) **log k_1 displaced 1 unit downward; **7**, 6-amino-1-ethyl-1,2,3,4-tetrahydroquinoline (30).

incomplete oxidation. In order to exclude this possibility, the data shown for pH 12 in Fig. 1 were checked by oxidizing the amines with varying amounts of excess ferricyanide with no change in the results.

TABLE II

ACID-BASE EQUILIBRIUM CONSTANTS (K) AND SPECIFIC REACTION RATES FOR ELIMINATION OF THE DIALKYLAMINES (k_1')



Number	R_1	R_2	R_3	R_4	log K	logk_1'
24	C_2H_4OH	C_2H_4OH	H	H	5.88	−1.1
25	C_2H_5	C_2H_4OH	H	H	5.10	−0.86
26	C_2H_4OH	C_2H_4OH	CH_3	H	5.05	− .86
27	C_2H_4OH	C_2H_4OH	CH_3	CH_3	4.22	− .5
28	C_2H_5	C_2H_4OH	CH_3	H	4.18	− .6
29	C_2H_5	C_3H_6OH	CH_3	H	2.7[a]	+ .8
30					2.24	− .7
31					<1.9[a]	+ 2.7

[a] Log K derived from deamination rate studies.

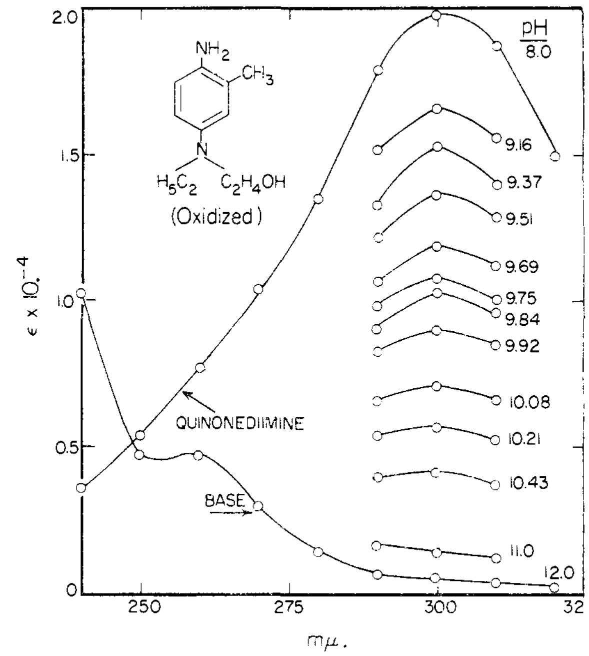


Fig. 2.—Extinction coefficient for oxidized 4-amino-3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline (28) at pH indicated.

For further information about possible intermediates, solutions of the quinonediimine from 4-amino-3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline were examined photometrically. This quinonediimine reaches the limiting deamination rate at pH 11, with a half-time of 7 sec. Photometric measurements of fresh solutions at pH 8.0 and 12.0, respectively, 0.8 sec. after adjustment of the pH to these values, resulted in the curves shown in Fig. 2 for the full range of wave length. The change in ϵ, 2×10^4 at 300 mμ, reveals the existence of at least two species in these solutions. The extinctions for intermediate values of pH shown in Fig. 2 follow a quantitative relationship shown in Fig. 3 indicating that these species are in equi-

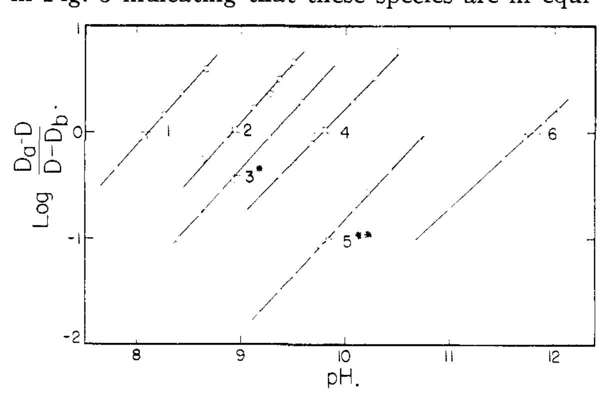


Fig. 3.—Equilibrium constants for base formation: 1, 4-amino-N,N-bis-(β-hydroxyethyl)-aniline (24); **2**, 4-amino-N-ethyl-N-(β-hydroxyethyl)-aniline (25); **3**, 4-amino-N,N-bis-(β-hydroxyethyl)-3-methylaniline (26) *log $(D_a - D)/(D - D_b)$ displaced 0.4 unit downward; **4**, 4-amino-N,N-bis-(β-hydroxyethyl)-3,5-dimethylaniline (27); **5**, 4-amino-3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline (28) **log $(D_a - D)/(D - D_b)$ displaced 1.0 unit downward; **6**, 6-amino-1-ethyl-1,2,3,4-tetrahydroquinoline (30).

librium. Similar measurements of other quinonediimines with limiting values of deamination rates confirmed these results. In order to ascertain that the compounds under consideration have the oxidation state of quinonediimines, a given quantity of diamine was oxidized at pH 8 with increasing amounts of ferricyanide. The densities at 300 mμ, measured after each addition and plotted against the amount of oxidant, had a sharp break at the point where two equivalents of oxidant had been added, the increase in density beyond this point being due to excess ferricyanide.

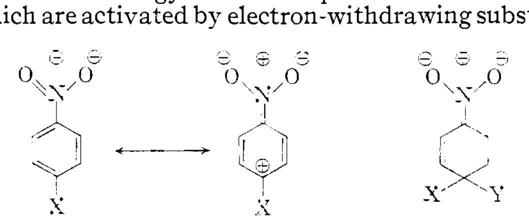
In Fig. 3 is plotted a function of the densities at 300 mμ at pH 8.0 (D_a), at pH 12.0 (D_b) and at the intermediate values of pH given on the abscissa (D) which should be linear with pH if only two molecular species in equilibrium with OH^- are involved. The linearity shown confirms the conditions just stated for the systems under investigation. The slope of unity further reveals that the equilibrium reaction involves either elimination of one H^+ or addition of one OH^-. A mechanism which satisfies these conditions and the general kinetics and which appears chemically plausible is given by the scheme

$$\mathrm{QDI}^+ + \mathrm{OH}^- \overset{K}{\rightleftharpoons} (\mathrm{QDIOH}) \xrightarrow{k_1'} \mathrm{QMI} + \text{amine}$$

We assume that the equilibrium between QDI^+, OH^- and the base (QDIOH) is rapidly attained and that the cleavage into quinonemonoimine and amine is the rate-determining step. If K is small, the concentration of the base is small and is proportional to (OH^-); if K is very large and practically all of QDI^+ is present as the base, an increase of (OH^-) has only little effect on the concentration of the base. Hence, inasmuch as the base is the intermediate for the deamination reaction, the deamination rate becomes independent of pH if K is large and if the pH is high enough to convert the quinonediimine practically completely to the base.

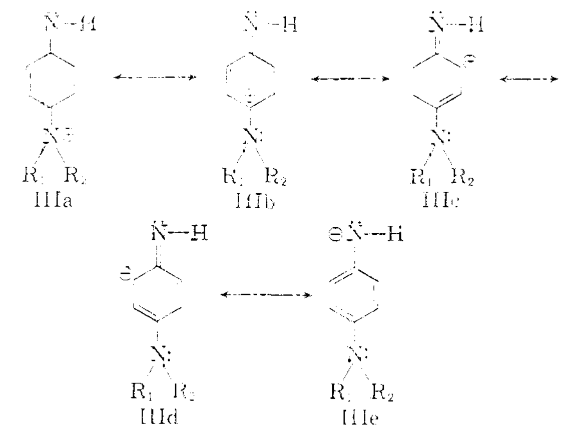
The first-order rate constant of the cleavage reaction of the base to form quinonemonoimine and amine, k_1', can be determined directly if the compounds are present almost completely as the bases. For the systems revealing a tendency toward limiting deamination rates, k_1' can be calculated using the constant K. All but the most obvious conventional methods used in these calculations are discussed in the next section.

The mechanism of the deamination can be understood in analogy to nucleophilic substitutions[4] which are activated by electron-withdrawing substituents, as shown for the nitro group by Ia and Ib. For Y^- as the entering nucleophilic reagent, the intermediate II has been postulated. The resonating structures of the diimine undergoing deamination can be written as III. The principal difference between structures III and I is the formal positive charge, which may account for the higher activity of the diimines toward nucleophilic reagents.



Ia Ib II

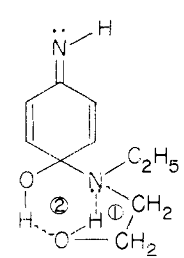
(4) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951).



IIIa IIIb IIIc IIId IIIe

Negative ions may attack any of the positions indicated with a positive charge. The addition of OH^- will, however, remain undetected unless the addition product is a stable base or undergoes an irreversible reaction which leads to a stable product. The quantitative yields of indophenol dyes show the absence of side reactions at high pH. A deficit in dye yield reveals the formation of non-coupling products at lower pH. As shown below, information on the kinetics of the reaction which causes the deficit suffices for the present discussion. With respect to the chemistry of the side-reaction it may be pointed out, however, that non-coupling by-products may be formed by reactions of structures which become possible, or are activated, by addition of a proton to III. Willstätter[5] has shown that in strongly acidic solution the imino group of oxidized p-phenylenediamine is eliminated; the reactive species is probably a protonated diimine.

The stability of the bases of diimines containing N-hydroxyalkyl groups can be explained by formation of a double ring system through intramolecular hydrogen bonding, as shown by IV. It is



IV

apparent from this structure that the stability of rings 1 and 2 depends on whether or not the position of the two OH groups permits formation of 5- or 6-membered rings. Moreover, the formation of this ring system is more probable if two instead of one β-hydroxyethyl groups are present. This is borne out by a comparison of compound

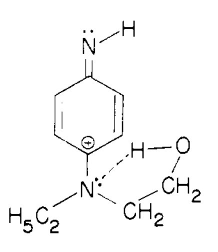
(5) R. Willstätter and E. Mayer, *Ber.*, **37**, 1505 (1904).

24 with compound 25, and 26 with 28. The small values of K for compounds 31 and 13 can be attributed to the inability of these substances to form intramolecular hydrogen bonds. Evidence that the stability of bases with substances having N-hydroxyalkyl groups is not caused primarily by the inductive effect of the OH group is given by the absence of detectable bases in other compounds containing electronegative groups, such as compounds 1, 5, 6, 10, 13, 14. The suggestion that single, hydrogen-bonded rings are insufficient to stabilize the bases comes from the fact that several compounds, 2, 6, 9, 12, 14, with stronger basic groups than β-hydroxyethyl but without hydrogen to form the second ring with the nitrogen, did not show the tendency to form bases. Compound 30, which cannot form a hydrogen bond with the added OH^-, forms a base which is highly unstable with respect to cleavage to the diimine. The C–N bond, however, being a covalent bond in the ring, is slow to break, as shown by the small k_1'. The effect of the $-C_2H_4N(H)SO_2CH_3$ group, in compound 11, in stabilizing the base could not be determined because the proton dissociates at pH 10. The absence of the base below this pH limits the log K to <4.

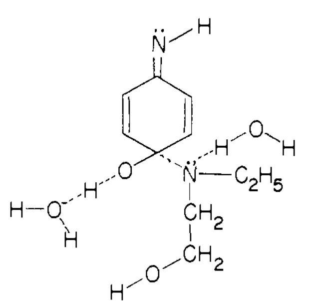
The C_2H_4OH group on the tertiary nitrogen increases the stability of the bond with the entering OH^- (large K) and of the ring carbon–N bond (small k_1') as shown by the results in Table II. The data for all compounds for which K could be determined follow a continuous trend with the exception of 6-amino-1-ethyl-1,2,3,4-tetrahydroquinoline (8). The hydroquinoline system has a stabilizing effect on the base but more with respect toward deamination than toward dissociation, and its effect on dissociation does not reach the magnitude of the stabilization by the double ring system IV.

There is evidence that the $-C_2H_4OH$ group not only stabilizes the base but activates the diimine for nucleophilic attack in general; the rate of coupling with 2-(3-disulfobenzamido)-5-methylphenol was found to be 7×10^3 with compound 16 and 1.9×10^5 with compound 26, and similar effects have been observed for the oxidative sulfonation of these compounds.[6]

Hydrogen bonding to the nitrogen atom probably favors structures IIIb, IIIc, IIId and IIIe over structure IIIa. With such hydrogen bonding, structure III would become V.



V



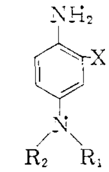
VI

(6) L. K. J. Tong and M. Carolyn Glesmann, unpublished data.

Table III shows the effect of N substitution on the specific rate constant (k_3') for the reaction of diimines at lower pH which leads to non-coupling products. The $-C_2H_4N(H)SO_2CH_3$ groups accelerate the reaction compared to –H and $-C_2H_5$, while $-C_2H_4N(CH_3)SO_2CH_3$ has no effect; $-C_2H_4NHCOCH_3$, which does not markedly stabilize the base (Table I), has very little effect.

TABLE III

SPECIFIC RATE CONSTANTS FOR THE FORMATION OF NON-COUPLING PRODUCT FROM OXIDIZED DIAMINES (k_3')



Number	X	R_1	R_2	$k_3' \times 10^3$
8	H	C_2H_5	C_2H_5	0.5
32	H	H	H	0.5
25	H	C_2H_5	$-C_2H_4OH$	19.0
6	H	C_2H_5	$-C_2H_4OCH_3$	0.7
7	H	C_2H_5	$-C_2H_4NHSO_2CH_3$	70.0
3	H	C_2H_5	$-C_2H_4NHCOCH_3$	1.0
16	CH_3	C_2H_5	C_2H_5	0.5
10	CH_3	C_2H_5	$-C_2H_4N(CH_3)SO_2CH_3$	0.5
28	CH_3	C_2H_5	$-C_2H_4OH$	5.0
11	CH_3	C_2H_5	$-C_2H_4NHSO_2CH_3$	15.0
29	CH_3	C_2H_5	$-C_3H_6OH$	0.4

The decrease in the specific rate constant, k_1', brought about by substituting $-C_2H_4OH$ for $-C_2H_5$ on nitrogen, indicates that the hydroxylated group stabilizes the base more than the activated complex, possibly because the complex, as represented by VI, has no intramolecular hydrogen-bonding and, therefore, derives no increased stability from the hydroxyl group.

Calculations

Plots of log k_1 *vs.* pH for the diimines in Table I are linear up to pH 12 and do not reveal formation of intermediate bases; the average slopes were 1.02 ± 0.02. To calculate log $k_1/(OH^-)$ (Table I), log k_1 was obtained graphically at pH 12, and log (OH^-) at this pH was taken as -2.00. If we make the plausible assumption that the deamination proceeds *via* the base even though its concentration may be small, $k_1/(OH^-)$ in Table I becomes $k_1'K$, with an upper limit for log K of 1.5 since more than 25% conversion to the base would certainly be kinetically detected.

The equilibrium constant K is obtained by plotting log $(D_a - D)/(D - D_b)$ *vs.* pH (Fig. 3); D_a is the density at 300 mμ of the diimine (pH 7–8), D_b is the density of the base (pH 11, 12 or in KOH solution), and D is the density at the intermediate pH indicated. From the pH value, $(pH)_{1/2}$, where the expression just given is zero, the equilibrium constant K (Table II, column 3) is calculated as $\log K = -\log k_w - (pH)_{1/2}$, $-\log k_w$ being taken as 14.00. Although the precision of $\pm$ 0.02 log unit is indicated, the accuracy of log K is estimated at ± 0.1 because of possible systematic errors. The quinonediimines 29 and 31 were too unstable for absorption measurements and the K-values were selected to fit the data of deamination rates.

Deamination rates were calculated from the analysis of the butyl acetate extracts of the "blue" indoaniline dye and the "red" indophenol dye. Both the quinonediimine and its base (by reverting to the quinonediimine) form the "blue" dye with α-naphthol, while the quinonemonoimine produces the "red" dye. The symbols (T_a), (T_b), (M) and (Y), respectively, are the concentrations of quinonediimine, its base, quinonemonoimine, and the non-coupling product in the aqueous solution where the reaction takes place; and (B) and (R) are the concentrations of the "blue" and "red" dyes in the butyl acetate extract. It has been found that the decrease in blue dye follows first-order kinetics over the entire *p*H range: $d(B)/dt = -k(B)$. Since (B) is proportional to the sum $(T_a) + (T_b)$, it follows that

$$\frac{d[(T_a) + (T_b)]}{dt} = -k[(T_a) + (T_b)] \qquad (1)$$

In the lower *p*H range, where a non-coupling product, Y, is formed besides the quinonemonoimine, M, the ratio of their concentrations, (Y)/(M), was found to be constant throughout a given reaction, suggesting that

$$d(M)/dt = k_1[(T_a) + (T_b)] \qquad (2)$$

and

$$d(Y)/dt = k_3[(T_a) + (T_b)] \qquad (3)$$

where $k_1 + k_3 = k$.

In order to resolve k into k_1 and k_3, relation (4) was used

$$\frac{-d(M)}{d[(T_a) + (T_b)]} = \frac{-d(R)}{d(B)} = \frac{k_1}{k_1 + k_3} \qquad (4)$$

The values of k_1 and k_3[7] in Table IV were determined graphically by plotting (B) *versus* (R) and using eq. (4). As shown in Table IV, k_3 is negligible in most cases. Where k_3 has a finite small value compared to k_1, k_3 was calculated with eq. (4) for the lowest *p*H. The other k_3 values listed were calculated by equation (5)

$$k_3 = \frac{k_3'(T_a)}{(T_a) + (T_b)} \qquad (5)$$

This dependence is verified by the results shown in Fig. 4.

As reported before,[8] coupling rates of active methine compounds with diimines which do not form stable bases are proportional to the product of the concentrations of the diimine and the coupler anion (C^-).

$$d(dye)/dt = k_{coup}(T_a)(C^-) \qquad (6)$$

It was of interest to determine whether with diimines which form stable bases the latter contribute to the coupling rate. Figure 5 shows the *p*H-dependence of the second-order coupling rate constants for three substances of this type; the coupler used was 5-methyl-2-(3,5-disulfobenzamido)-phenol (VII).

The calculation of the rate constants (k_{coup}) was based on the total concentration of oxidized diimines, $(T_a) + (T_b)$. The curves drawn were

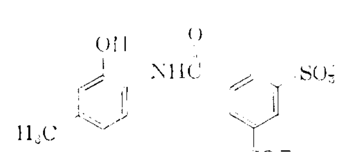
(7) To avoid confusion, the subscripts used to designate the rate constants in reference 2 were retained. Values of k_2 for deamination of the monoimine are negligible in the present determinations.

(8) L. K. J. Tong and M. Carolyn Glesmann, This Journal, **79**, 583 (1957).

Table IV

First-order Rate Constants for the Elimination of Dialkylamines (k_1), and for the Reaction Leading to Non-coupling Products (k_3)

*p*H	k_1, sec.$^{-1}$	k_3, sec.$^{-1}$	*p*H	k_1, sec.$^{-1}$	k_3, sec.$^{-1}$
4-Amino-3-methyl-N-ethyl-N-(β-hydroxyethyl)aniline (28)			4-Amino-N,N-bis-(β-hydroxyethyl)-3,5-dimethylaniline (27)		
12.05	0.282	Negl.	12.05	0.274	Negl.
11.50	.270	Negl.	11.50	.258	Negl.
11.00	.276	Negl.	11.10	.248	Negl.
10.43	.216	Negl.	10.08	.167	Negl.
9.90	.161	Negl.	9.61	.095	Negl.
9.63	.111	0.002	8.95	.0276	Negl.
8.97	.035	.0042	8.67	.0157	Negl.
8.53	.0143	.0046	8.19	.00467	Negl.
8.12	.0059	.0048			
4-Amino-3-methyl-N-ethyl-N-(3-hydroxypropyl)-aniline (29)			4-Amino-N-ethyl-N-(β-hydroxyethyl)-aniline (25)		
12.04	5.86	Negl.	12.06	0.157	Negl.
11.80	4.61	Negl.	12.01	.152	Negl.
11.49	3.29	Negl.	11.03	.145	Negl.
11.01	1.73	Negl.	10.42	.150	Negl.
10.49	0.580	Negl.	9.91	.139	0.001
9.69	.078	Negl.	9.30	.118	.005
9.28	.031	Negl.	8.83	.068	.010
8.59	.0063	Negl.	8.60	.066	.010
8.11	.0022	Negl.	8.10	.025	.016
			7.50	.0064	.018
4-Amino-N,N-bis-(β-hydroxyethyl)-3-methylaniline (26)			6-Amino-1-ethyl-1,2,3,4-tetrahydroquinoline (30)		
12.07	0.147	Negl.	(0.5 *M* KOH)	0.147	Negl.
11.01	.147	Negl.	12.12	.127	Negl.
9.90	.131	Negl.	12.00	.122	Negl.
9.23	.108	Negl.	11.79	.092	Negl.
8.52	.0479	0.0046	11.49	.067	Negl.
8.54	.0474	.0046	11.03	.028	Negl.
8.10	.0228	.0052	10.40	.006	0.0003
8.10	.0224	.0052	9.77	.00178	.0003
7.50	.0057	.0061	8.86	.00025	.0003
7.02	.0018	.0063			
4-Amino-N,N-bis-(β-hydroxyethyl)-aniline (24)			N-(4-Aminophenyl)-3-hydroxypiperidine (31)		
12.10	0.084	Negl.	12.04	226	Negl.
11.57	.078	Negl.	11.52	104	Negl.
11.10	.078	Negl.	11.00	40.1	Negl.
10.55	.075	Negl.	10.53	11.1	Negl.
9.84	.088	Negl.	9.87	2.81	Negl.
9.60	.083	Negl.			
9.19	.082	Negl.			
8.99	.076	0.009			
8.87	.056	.016			
8.78	.071	.012			
8.60	.066	.019			
8.54	.059	.024			
8.40	.061	.025			
8.09	.044	.032			
8.04	.035	.044			
8.01	.045	.043			
7.80	.038	.046			
7.53	.021	.045			



VII

calculated with the equation

$$k_{coup} = k'_{coup}\frac{(T_a)}{(T_a) + (T_b)} \qquad (7)$$

the concentration ratio calculated from the equilibrium constants in Table II and k'_{coup}, the specific

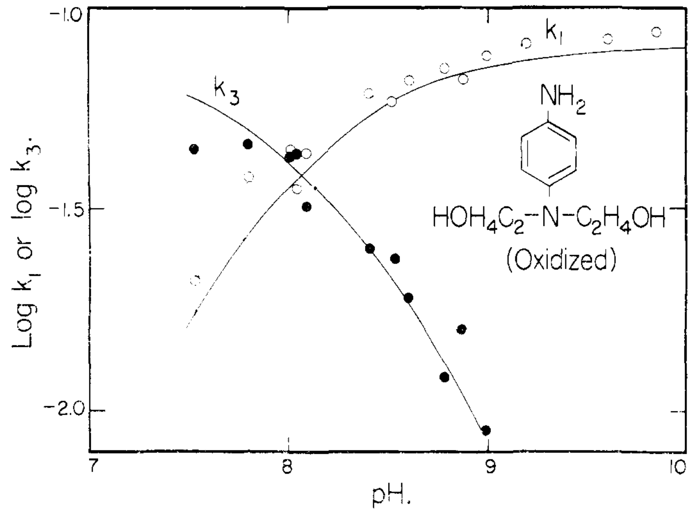


Fig. 4.—pH dependence of first-order rate constants. Formation of non-coupling products (k_3) and elimination of tertiary amine (k_1) from oxidized 4-amino-N,N-bis-(β-hydroxyethyl)-aniline (24). Curves calculated, points observed.

rate constant, chosen to fit the data. The implication of eq. 7 is that not the base but only the diimine couples. Although the differences between the plotted points and the curves at the extremes appear to be greater than the random experimental error, systematic errors in coupling rates are inherently larger than in equilibrium measurements and in deamination rates because coupling rate measurements are more sensitive to such factors as extinction coefficients of the dyes and flow characteristics of the stream containing the reaction mixtures. The general agreement between the measured points and the curves therefore appears to justify the conclusion that the bases do not contribute to the observed coupling rates.

Measurements

All experiments were carried out at 25 ± 0.1°. The buffers were prepared by mixing the appropriate volumes of KH_2PO_4, K_2HPO_4, K_3PO_4 solutions to give a constant ionic strength of 0.375 in the final solutions. The pH of the solutions was measured with a Beckman model G pH meter and a glass electrode.

The compounds $K_3Fe(CN)_6$, KCl and the phosphates used for buffers were reagent grade; n-butyl acetate, glacial acetic acid and α-naphthol were Eastman White Label Grade. Triton X-100 was obtained from Rohm and Haas.

The ultraviolet absorbance (240–350 mμ) *of the oxidized p-phenylenediamines* in buffers ranging from pH 7 to 12 was measured within 0.8 sec. after oxidation by the following technique: The solutions of p-phenylenediamines (2×10^{-4} M), $K_3Fe(CN)_6$, (2×10^{-3} M), and phosphate buffer (μ = 0.75) were mixed in the jet mixer[9] in a volume ratio of 1:1·2, respectively. A short Tygon tube of small internal diameter connected the outlet of the mixing machine to a hypodermic syringe needle, which extended through a rubber cap to the bottom of a 1-cm. rectangular quartz cell. A second hole in the cap served as an outlet for the solution. While the solution was flowing at a constant velocity and after a steady state had been attained, the absorbance of the reaction mixture was measured in the Beckman model DU spectrophotometer with a hydrogen lamp as light source. Absorptions due to buffer, $K_3Fe(CN)_6$, $K_4Fe(CN)_6$, were either corrected using the known extinction coefficients of these materials or canceled by adding them to the reference solution in the Beckman spectrophotometer. The average age of the solution flowing in the cell was 0.8 sec. after mixing as determined by carrying out a reaction of known rate. At high pH, the absorbance was corrected for deamination based on the known rate and the extinction coefficient of the product.

Coupling rates with 2-(3,5-disulfobenzamido)-5-methylphenol were measured by the continuous flow method with compounds 25 and 26. The stop method was used with compound 30. The dyes with compounds 25 and 26 obeyed Beer's law within the concentration range used. Triton X-100 was added to the acid stop in the reaction with compound 30 to allow the use of Beer's law. No Triton was added during the coupling reaction to avoid complications.

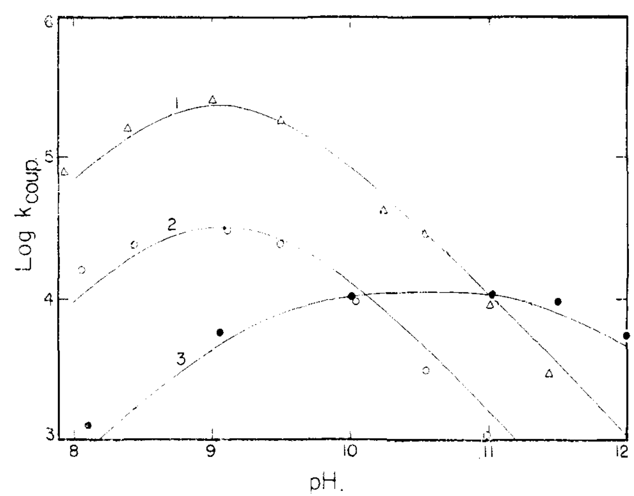


Fig. 5.—Second-order rate constants (moles/liter sec.) of the coupling of 2-(3,5-disulfobenzamido)-5-methylphenol (VI1) with the oxidation products of the following diamines: **1**, 4-amino-N-ethyl-N-(β-hydroxyethyl)-aniline (25); **2**, 4-amino-N,N-bis-(β-hydroxyethyl)-3-methylaniline (26); **3**, 6-amino-1-ethyl-1,2,3,4-tetrahydroquinoline (30). Curves were calculated from equilibrium constants in Table II, the dissociation constant of the coupler $= 5.9 \times 10^{-10}$, and the following specific rate constants; $\log k'_{coup.}$ = 6.16, 5.28 and 4.08 for curves 1, 2, 3, respectively. Points are observed.

Deamination rates were determined as described before.[2] For rapid deamination reactions, the jet mixer was used with the stop method. For the most rapid reactions, the mixing chamber was adjusted to permit observation of a reaction time of one millisec. For slow reactions, requiring reaction times longer than one sec., the solutions

(9) W. R. Ruby, *Rev. Sci. Instruments*, **26**, 460 (1955).

were mixed manually with syringes. For compound 1, 4-amino-3-methyl-N-ethyl-N-β-(1-pyridinium)-ethyl aniline chloride, the undeaminated dye remained completely in the aqueous phase and the deaminated dye was extracted into the butyl acetate.

Preparations

For compounds 3, 4, 5, 6, 7, 8, 10, 11, 13, 16, 17, 18, 19, 20, 21, 22, 23, 25, 28 and 30, see ref. 10. For 9, see ref. 3. **4-Amino-N-ethyl-3-methyl-N-[β-(1-pyridinium)-ethyl]-aniline Chloride Hydrochloride** (1, Table I)[11] was prepared by the following reactions starting from N-ethyl-N-(β-chloroethyl)-3-methylaniline (I).[10]

N-Ethyl-3-methyl-N-[β-(1-pyridinium)-ethyl]-aniline Chloride (II).—Compound I (100 g., 0.506 mole) and 500 ml. of dry pyridine were refluxed for 70 hr. The mixture was diluted with 2 liters of acetone and then with anhydrous ether–acetone (1:1) until precipitation occurred. Crystallization was induced by seeding and completed by cooling and addition of 3 liters of anhydrous ether in portions; yield of crude 131 g. (94%), m.p. 70–71°. The crude was recrystallized from absolute ethanol using Darco. After dilution with 9 volumes of acetone, it was precipitated with anhydrous ether; m.p. 72–73°, light yellow crystals.

Anal. Calcd. for $C_{16}H_{21}ClN_2$: C, 69.4; H, 7.7; N, 10.1. Found: C, 69.4; H, 7.6; N, 9.8.

N-Ethyl-3-methyl-4-nitroso-N-[β-(1-pyridinium)-ethyl]-aniline Chloride Hydrochloride (III).—Compound II (75 g., 0.271 mole) was dissolved in 128 ml. of concentrated hydrochloric acid and 120 ml. of water. Sodium nitrite (19.5 g., 0.030 mole) in 75 ml. of water was added to the cooled solution in 15 min. After about 15 min. it was diluted with 1500 ml. of absolute ethanol. The filtered solution was evaporated *in vacuo* to a residue to which 800 ml. of absolute alcohol was added. The alcohol solution was filtered and diluted with 800 ml. of acetone to precipitate 62 g. (67%) of the nitroso compound; recrystallization from absolute alcohol–acetone containing a little concentrated hydrochloric acid gave a greenish-yellow powder (dec. above 140°).

Anal. Calcd. for $C_{16}H_{21}Cl_2N_3O$: C, 56.1; H, 6.18; N, 12.3; Cl, 20.7. Found: C, 55.6, 55.9; H, 6.6, 6.6; N, 12.2; Cl, 20.3.

4-Amino-N-ethyl-3-methyl-N-[β-(1-pyridinium)-ethyl]-aniline Chloride Hydrochloride (1).—To the nitroso compound (10 g., 0.0292 mole) dissolved in 150 ml. of absolute ethanol containing 2 ml. of concentrated hydrochloric acid was added 2.0 g. of 10% palladium-on-charcoal and the mixture was shaken under 45 lb. of hydrogen for 45 min. After addition of 50 ml. of water, it was filtered using Super-Cel. The filtrate evaporated at room temperature *in vacuo* gave an oil. Absolute ethanol (50 ml.) was added and the solution again evaporated. The oil, upon treatment with a little absolute ethanol containing a small amount of ether, crystallized; yield 6.7 g. (70%). Two grams was slurried in 20 ml. of boiling absolute ethanol and the minimum amount of concentrated hydrochloric acid (approx. 25 drops) to effect solution added. The solution was filtered and cooled; yield 1.4 g. (70%) of bright yellow crystals (no m.p.)

Anal. Calcd. for $C_{16}H_{23}Cl_2N_3$: C, 58.5; H, 7.1; N, 12.8; Cl, 21.6. Found: C, 58.4, 58.0; H, 7.2, 7.1; N, 12.5; Cl, 21.2.

4-Amino-N-ethyl-N-(β-sulfoethyl)-aniline (2, Table I) was prepared in the same way as described for the 3-methyl homolog (9).[3] The resultant amino acid was recrystallized from distilled water, and was dried in a vacuum desiccator; m.p. 268–269° dec., immersed at 260°. Speed is essential to prevent oxidation.

Anal. Calcd.: C, 49.2; H, 6.55; N, 11.48. Found: C, 49.6; H, 6.4; N, 11.4.

4-Amino-N-ethyl-3-methyl-N-(3-sulfopropyl)-aniline Hydrochloride (12, Table I) was prepared by the following reactions:

3-Chloropropanesulfonic Acid, Sodium Salt (I).—A solution of 252 g. (2 moles) of sodium sulfite in 1200 ml. of water was added dropwise over a period of 2.5 hr. to 315 g. (2 moles) of 1-bromo-3-chloropropane (Eastman Organic Chemicals) in 1200 ml. of 95% ethanol and 400 ml. of water, with heating and stirring. Heating and stirring were continued for a further 3.5 hr. and the reaction mixture concentrated to dryness under reduced pressure. The residue was dissolved in about 5300 ml. of 95% alcohol, filtered hot and chilled. The solid was filtered and washed with cold ethanol; yield 128 g. (35%).

3-Hydroxypropanesulfonic Acid Sultone (II) was prepared by hydrolysis of I.[12]

N-Ethyl-3-methyl-N-(3-sulfopropyl)-aniline (III).—A mixture of 3.93 g. (0.0291 mole) of N-ethyl-3-methylaniline (see later), 50 ml. of dry benzene and 3.55 g. (0.0291 mole) of II was refluxed for 8 hr. on a steam-bath. After chilling, the precipitate was filtered, washed with dry benzene, slurried with 75 ml. of acetone, and dried in air; yield 5.25 g. (70%).

Anal. Calcd.: C, 56.0; H, 7.4; N, 12.45. Found: C, 56.3; H, 7.3; N, 12.2.

N-Ethyl-3-methyl-4-nitroso-N-(3-sulfopropyl)-aniline (IV).—Nitrosation of III was carried out as with compounds 2 and 9 (Table I). The free amino acid did not precipitate and it was neutralized with sodium hydroxide before reduction.

4-Amino-N-ethyl-3-methyl-N-(3-sulfopropyl)-aniline Hydrochloride (12).—The sodium salt of IV was reduced catalytically at 50 p.s.i. in 20 ml. of water, 150 ml. of ethanol and 1.5 g. of 10% palladium-on-charcoal. The filtrate was concentrated to dryness and extracted with 75 ml. of 95% ethanol, filtered hot, and again concentrated. It was extracted with a mixture of 55 ml. of acetone and 40 ml. of 95% ethanol, and again concentrated to dryness. The gummy product was converted to the hydrochloride by heating with 50 ml. of concentrated hydrochloric acid in 25 ml. of water and evaporated to dryness. The residue was dissolved in 35 ml. of 95% ethanol, filtered, and the salt of the developer was precipitated with ether. The alcohol–ether treatment was repeated. Finally, the material was dissolved in absolute alcohol, filtered and concentrated to dryness. The solid was broken up and thoroughly dried in a vacuum desiccator; yield of the aniline hydrochloride, 1.4 g. (45%). The material was slightly hygroscopic. *Anal.* Calcd.: C, 46.6; H, 6.8; S, 10.38. Found: C, 46.0; H, 7.0; S, 11.6.

4-Amino-N-carboxymethyl-N-ethyl-3-methylaniline dihydrochloride (14, Table I) was prepared by the following series of reactions:

N-Ethyl-3-methylaniline (I).—The pure secondary aniline was obtained by reducing 3-methylacetanilide with lithium aluminum hydride, as described in the literature for similar compounds.[13] The powdered amide was added in portions to a suspension of the hydride (large excess) in ether under reflux. Refluxing was continued for a further 6 hr.

N-Carbethoxymethyl-N-ethyl-3-methylaniline (II).—A mixture of 51 g. (0.378 mole) of I, 63.1 g. (0.378 mole) of ethyl bromoacetate (Eastman Organic Chemicals), 400 ml. of 95% ethanol, 200 ml. of water and 31.8 g. (0.378 mole) of sodium bicarbonate was refluxed on a mantle for 17 hr. After the alcohol had been removed, the product was extracted with ether, dried and concentrated. The fraction boiling at 152–156° (10 mm.) was collected; yield of II, 68 g. (81.5%).

N-Carbethoxymethyl-4-(2,5-dichlorophenylazo)-N-ethyl-3-methylaniline (III).—The azo dye was prepared by coupling II with diazotized 2,5-dichloroaniline, as described previously.[10] It is important to use purified dichloroaniline. The over-all yield of IV was 70 g. (78.5%), m.p. 152.5–153.5°.

Anal. Calcd.: C, 57.8; H, 5.33. Found: C, 58.1; H, 5.5.

4-Amino-N-carbethoxymethyl-N-ethyl-3-methylaniline Hydrochloride (IV).—Compound III, 7.88 g., was reduced catalytically using 200 ml. of absolute ethanol and Raney nickel. The catalyst was filtered off, one equivalent of concentrated hydrochloric acid was added and the solution concentrated to dryness. The residue was dissolved in 30

(10) R. L. Bent, *et al.*, This Journal, **73**, 3100 (1951).

(11) Prepared by H. J. Osborn, of these Laboratories.

(12) J. Willems, *Bull. soc. chim. Belges*, **64**, 425 (1955).

(13) R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 495.

ml. of hot acetone and chilled, and a little ether was added. The yield of IV was 3.8 g. (70%), m.p. 171.5–173.5° dec. (immersed at 160°).

Anal. Calcd.: C, 57.1; H, 7.7; N, 10.33. Found: C, 56.9; H, 7.9; N, 10.7.

4-Amino-N-carboxymethyl-N-ethyl-3-methylaniline Dihydrochloride (14).—Compound IV (2.35 g., 0.00862 mole) was hydrolyzed by refluxing with 20 ml. of concentrated hydrochloric acid and 55 ml. of water for 7 hr. The solution was concentrated to dryness, and the sticky solid slurried with 50 ml. of acetone, decanted, and the procedure repeated with another 50 ml. of acetone. The solid was dried thoroughly in a vacuum desiccator; yield of 14, 2 g. (82%), m.p. dec. at 150°. Analysis indicated a mixture of the monohydrochloride and dihydrochloride.

4-Amino-N,N-bis-(carboxymethyl)-3-methylaniline hydrochloride (15, Table I) was prepared by the following series of reactions:

N,N-Bis-(carbethoxymethyl)-3-methylaniline (I).—A mixture of 107 g. (1 mole) of *m*-toluidine, 334 g. (2 moles) of ethyl bromoacetate (Eastman Organic Chemicals), 184.5 g. (2.2 moles) of sodium bicarbonate, 1200 ml. of 95% ethanol and 500 ml. of water was refluxed on a mantle for 60 hr. The alcohol was removed and the oil extracted with ether. The ether was dried, concentrated, and distilled. The first fraction, b.p. 160–170° (10 mm.), consisted of the N-carbethoxymethyl-3-methylaniline (m.p. 66.5–67.5°, after recrystallization). The fraction, b.p. 150–165° (1 mm.), was collected and then redistilled slowly using a 1-ft. column; yield of I, b.p. 135–143° (1 mm.), 77 g. (27.5%).

Anal. Calcd.: C, 68.4; H, 7.77. Found: C, 68.6; H, 8.0.

N,N-Bis-(carbethoxymethyl)-4-(2,5-dichlorophenylazo)-3-methylaniline (II).—The coupling of diazotized dichloroaniline with I was done as previously described; yield of II from 60 g. (0.215 mole) of I, after recrystallization from 95% ethanol, 31.5 g. (32.5%), m.p. 118–119.5°.

Anal. Calcd.: C, 55.6; H, 5.08; N, 9.4. Found: C, 55.6; H, 5.2; N, 9.7.

4-Amino-N,N-bis-(carbethoxymethyl)-3-methylaniline Hydrochloride (III).—The azo dye II was reduced in the same manner as described for compound 14. The yield of III from 4.52 g. (0.01 mole) of II was 2.85 g. (85%), m.p. 162–166°, with shrinking and softening. Analysis indicated a mixture of mono- and dihydrochlorides had formed.

4-Amino-N,N-bis-(carboxymethyl)-3-methylaniline Hydrochloride (15).—The ester III was hydrolyzed, as described for compound 14. The yield of compound 15 was nearly quantitative. The light-tan powder decomposed at 135°. Analysis showed a mixture of mono- and dihydrochlorides.

4-Amino-N,N-bis-(β-hydroxyethyl)-aniline Sulfate (24, Table II) was prepared by the following series of reactions:

N,N-Bis-(β-hydroxyethyl)-4-nitroaniline (I).—A mixture of 78.75 g. (0.5 mole) of 1-chloro-4-nitrobenzene and 105 g. (1 mole) of 2,2′-iminodiethanol (Eastman Organic Chemicals) was heated in an oil-bath for 4.5 hr. (temperature of bath, 130–140°). The warm reaction mixture was poured into 500 ml. of cold water, the solid was filtered, washed with water, dried and then slurried with ether; yield of I, after recrystallization from aqueous ethanol, 25 g. (22%), m.p. 103–104°.

4-Amino-N,N-bis-(β-hydroxyethyl)-aniline Sulfate (24).—The nitroaniline I was reduced catalytically using ethanol and 10% palladium-on-charcoal; yield of 24, b.p. 201–205° (1 mm.), obtained from 22.6 g. (0.1 mole) of I was 14.9 g. (76%). The distillate solidified in the receiver, m.p. 87–88°.

Anal. Calcd.: C, 61.2; H, 8.16. Found: C, 61.0; H, 8.4.

The free base (14.55 g.) was converted to the sulfate by dissolving it in 60 ml. of absolute ethanol and adding one equivalent of concentrated sulfuric acid in 20 ml. of ethanol; yield of 24, m.p. 172–173° with effervescence, 11.5 g. (53%).

4-Amino-N,N-bis-(β-hydroxyethyl)-3-methylaniline (26, Table II) was prepared by the following reactions:

N,N-Bis-(β-hydroxyethyl)-3-methylaniline (I).—The practical material from Eastman Organic Chemicals (listed as 2,2′-*m*-tolyliminodiethanol) was distilled under reduced pressure, and a fraction, b.p. 160–165° (1 mm.), was collected. The pure product had m.p. 65–67°.

N,N-Bis-(β-hydroxyethyl)-3-methyl-4-nitrosoaniline (II).—Nitrosation of I was carried out in the normal manner; yield of II, obtained from 78 g. (0.4 mole) of I, after recrystallization from 1700 ml. of benzene and 450 ml. of acetone, was 52 g. (58%), m.p. 109–110°.

4-Amino-N,N-bis-(β-hydroxyethyl)-3-methylaniline (26).—Reduction of II was carried out using ethanol and palladium-on-charcoal. The filtrate was concentrated to dryness. After crystallization first from 1600 ml. of acetonitrile and then from 600 ml. of 95% ethanol, 47 g. of 26, m.p. 113–114° (56%), was obtained from 83.5 g. of the crude free base. Speed is important to prevent decomposition. *Anal.* Calcd.: C, 62.8; H, 8.56; N, 13.3. Found: C, 62.8; H, 8.5; N, 13.5.

4-Amino-N,N-bis-(β-hydroxyethyl)-3,5-dimethylaniline (27, Table II)[14] was prepared by the following reactions:

N,N-Bis-(β-hydroxyethyl)-3,5-dimethylaniline (I).—A mixture of 100 g. (0.826 mole) of 3,5-dimethylaniline (Eastman Organic Chemicals) and 88.1 g. (2 moles) of ethylene oxide was placed in a steel reaction vessel and heated, with shaking, at 150° for 16 hr. The reaction mixture was extracted with ethanol, concentrated to dryness, and distilled. The fraction, b.p. 160–172° (3 mm.), 136 g., was collected (m.p. 94–98°); yield of I, after recrystallization from 1500 ml. of a 50:50 benzene–ligroin mixture (ligroin, b.p. 65–76°), 97 g. (56%), m.p. 103–104°. *Anal.* Calcd.: C, 68.85; H, 9.15; N, 6.69. Found: C, 68.8; H, 9.0; N, 6.8.

N,N-Bis-(β-hydroxyethyl)-3,5-dimethyl-4-nitrosoaniline (II).—Nitrosation of I was carried out in the normal manner. From 20.93 g. (0.1 mole) of I was obtained 17.75 g. of II. This was recrystallized from 200 ml. of acetone, and 800 ml. of benzene was added when the mixture was cool; final yield of II, 6.65 g. (29%), light-brown solid, m.p. 150–152°.

4-Amino-N,N-bis-(β-hydroxyethyl)-3,5-dimethylaniline (27).—Reduction of II was carried out as with compound 26. The product was recrystallized from water; yield of 27 from 6.65 g. (0.0279 mole) of II was 4.92 g., light-brown solid (78.5%), m.p. 110–112°.

Anal. Calcd.: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.0; H, 8.7; N, 12.4.

4-Amino-N-ethyl-N-(3-hydroxypropyl)-3-methylaniline sulfate (29, Table II) was prepared by the following reactions:

N-Ethyl-N-(3-hydroxypropyl)-3-methylaniline (I).—A mixture of 135 g. (1 mole) of N-ethyl-*m*-toluidine, 139 g. (1 mole) of 3-bromopropanol (Eastman Organic Chemicals), 800 ml. of 95% ethanol and 250 ml. of water was refluxed on a mantle for 60 hr. After concentration, the oily layer was extracted with ether. The ether extracts were dried, filtered, concentrated, and the residue was distilled under reduced pressure; yield of I, b.p. 176–180° (15 mm.), 129 g. (67%). *Anal.* Calcd.: C, 74.6; H, 9.84. Found: C, 74.2; H, 9.7.

4-(2,5-Dichlorophenylazo)-N-ethyl-N-(3-hydroxypropyl)-3-methylaniline (II).—Azo coupling of I was carried out as previously described. The crude azo dye did not readily become crystalline; final yield of II, obtained from 19.3 g. (0.1 mole) of I, after recrystallization from acetonitrile, 18.5 g. (50.5%), m.p. 92–94°.

Anal. Calcd.: C, 59.0; H, 5.74; N, 11.48. Found: C, 58.6; H, 5.5; N, 11.6.

4-Amino-N-ethyl-N-(3-hydroxypropyl)-3-methylaniline Sulfate (29).—Reduction of the azo dye was carried out with Raney nickel as catalyst. The free base was distilled under reduced pressure, and a fraction collected with b.p. 149–152° (1 mm.); yield of 29 from 18.5 g. (0.0505 mole) of II, 5.9 g. (56%).

Anal. Calcd.: C, 69.2; H, 9.61; N, 13.45. Found: C, 69.0; H, 9.4; N, 13.9.

The sulfate was formed by adding one equivalent of sulfuric acid to an alcoholic solution of the free base, m.p. 155–156°.

Anal. Calcd.: C, 47.0; H, 7.18. Found: C, 47.5; H, 6.9.

N-(4-Aminophenyl)-3-hydroxypiperidine hemisulfate (31, Table II)[15] was prepared by the following series of reactions:

(14) Prepared by A. E. Anderson, of these Laboratories.

(15) Prepared by W. C. Firth, Jr., of these Laboratories.

N-(4-Nitrophenyl)-3-hydroxypiperidine (I).—Fifty grams (0.5 mole) of 3-hydroxypiperidine (Aldrich Chemical Co.) and 39.8 g. (0.25 mole) of *p*-nitrochlorobenzene (Eastman Organic Chemicals) were heated on a steam-bath for 5.5 hr. The material was warmed with 250 ml. of water, cooled, filtered, and again treated with 250 ml. of water. The solid was recrystallized from 100 ml. of 95% ethanol and again from 75 ml. of ethanol; yield of I was 24.6 g. (45%), m.p. 126.5–128.5°. *Anal.* Calcd.: C, 59.7; H, 6.3; N, 12.65. Found: C, 59.6; H, 6.5; N, 12.9.

N-(4-Aminophenyl)-3-hydroxypiperidine Hemisulfate (31).—Reduction of I was carried out using 10% palladium-on-charcoal and absolute alcohol. One equivalent of concentrated sulfuric acid was added to the filtrate, and the solid was filtered and dried in a vacuum desiccator; yield of 31 from 10 g. of I, 8.4 g. Recrystallization of 2 g. of the salt from 95% ethanol gave 1 g. of 31, m.p. >240° with dec. (38.2%). *Anal.* Calcd.: C, 54.75; H, 7.1. Found: C, 55.0; H, 7.1.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Reaction of Cholestenolone Acetates with Ethanedithiol

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Two γ-acetoxy-α,β-unsaturated ketones of the cholestane series were found to react with ethanedithiol in an anomalous fashion to give products other than the normal ethylenethioketals. Structural elucidation of anomalous compounds A-F could not be accomplished by chemical means, and ultraviolet spectroscopy afforded only limited guidance. However, nuclear magnetic resonance spectroscopy provided an unequivocal basis for evaluation of structures and configurations tentatively deduced from considerations of mechanism and led to reasonable solutions of all problems encountered.

In a study of the condensation of ketones with ethanedithiol in the presence of boron fluoride etherate,[3] it was noted that Δ^4-cholestene-6β-ol-3-one, which is easily isomerized by acids to cholestane-3,6-dione,[4] reacts with ethanedithiol to give the same product as this diketone, namely, the bisethylenethioketal **9**, m.p. 220°. The corresponding acetate **1**, however, gave an anomalous isomeric product, m.p. 131°, which we shall designate compound A. Koji Nakanishi found Δ^4-cholestene-3β-ol-6-one acetate to give another product for which no obvious formula was available. In the first phase of the present work (C. Y.), attempts to clarify the issue by condensation of the two α-acetoxy-$\Delta^{\alpha,\beta}$-ketones with ethanedithiol or β-mercaptoethanol under a variety of conditions led, rather, to expansion of the problem by isolation of four more anomalous sulfur compounds. Desulfurization, substantially the only chemical reaction available, afforded little evidence of structure, and ultraviolet absorption characteristics alone did not solve the problem.

Work on the problem was later resumed (T. G.) with guidance from nuclear magnetic resonance spectroscopy. Although the n.m.r. data do not indicate uniquely applicable structures, the combination of n.m.r. and ultraviolet characterization provided useful clues and also afforded a valuable gauge for checking formulas suggested by mechanistic considerations. We shall present first the interpretations eventually arrived at and then report the spectroscopic evidence supporting the structures.

Compound A is regarded as the unsaturated β-mercaptoethylthiomonoketal **5**. The conditions for its formation are about the same as for formation of the 3,6-bisketal **9**, and A is converted into the latter compound on further treatment with ethanedithiol and boron fluoride etherate. Like **9** it yields cholestane on desulfurization, at least on reaction with reactive Raney nickel; saturation of a double bond has been observed in other instances.[3] Compound A is the only one of the six anomalous products which gives a positive test for the sulfhydryl group with sodium azide and iodine.[5] The mechanism suggested involves initial formation of the carbonium ion **2**, and this accommodates the fact that Δ^4-cholestene-6α-ol-3-one acetate likewise yields compound A. The bisketal **9** has also been obtained from 4α-acetoxy-Δ^5-cholestene-3-one **4**.[6] The carbonium ion **3** immediately derived from **4** is destabilized by the adjacent carbonyl group and probably gives place to the more stable conjugated ion **2**, which then affords **6**, **5** and **9** as before.

The second anomalous product derived from **1**, compound B, was obtained with use of one equivalent of ethanedithiol and contains only two atoms of sulfur. An analogous product, compound C, was obtained by reaction of **1** with β-mercaptoethanol. Since C reacts with Raney nickel to form cholestenone (**12**), the oxygen can be placed at C_3 as in **11**, and compound B can be assigned the similar formula (**10**). These formulas account for the dienic ultraviolet absorption, λ266 mμ for C and λ 292 mμ for B. On the assumption that a sulfur atom attached to a double bond has a bathochromic effect of 30 mμ,[7] the values calculated[8] are 264 and 294 mμ. The formation of the S_2-product **10** is accounted for on the supposition

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(2) Recipient of a Fulbright travel grant on leave from Nagoya University, Nagoya, Japan.

(3) L. F. Fieser, THIS JOURNAL, **76**, 1945 (1954).

(4) L. F. Fieser, *ibid.*, **75**, 4377 (1953).

(5) F. Feigl, "Spot Tests," Vol. II, Elsevier Press, Houston, Tex., 1954, p. 164.

(6) L. F. Fieser and R. Stevenson, THIS JOURNAL, **76**, 1728 (1954).

(7) J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *ibid.*, **73**, 1528 (1951), report that testosterone 3-benzyl thioenol ether absorbs at 268 mμ; the enol acetate absorbs at 239 mμ.

(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 16–18.