[COMMUNICATION FROM THE KODAK RESEARCH LABORATORIES]

Chemical Constitution, Electrochemical, Photographic and Allergenic Properties of *p*-Amino-N-dialkylanilines[1]

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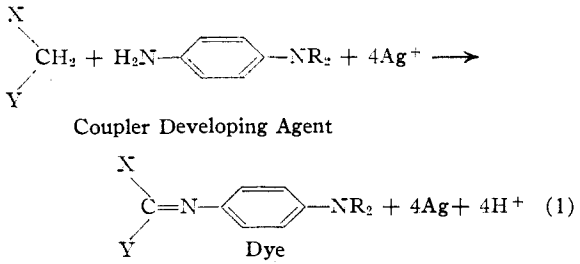
The ability of color-forming developing agents of the *p*-amino-N-dialkylaniline type to release electrons was measured by their polarographic half-wave potentials. These become more positive when electron-releasing groups are introduced at the tertiary nitrogen or in the position ortho to the primary amino group in the benzene ring, and the reverse holds for electron-attracting groups. The sequence of half-wave potentials can be explained on the basis of the inductive or mesomeric effects of the groups involved, though in several instances the size of the mesomeric effect would not have been anticipated. Solvation may be the cause of deviations. Steric factors are present. They become dominant if the substituents are introduced in the position ortho to the tertiary amino group. Ring closure involving the tertiary nitrogen and the ortho carbon atom in the benzene ring counteracts the steric hindrance. Steric hindrance is also found if six-membered rings are closed between the two non-aromatic substituents on the tertiary nitrogen. Formation of five-membered rings has the opposite effect. A close relationship exists between the half-wave potentials and the abilities of the developing agents to reduce silver halide and to form dyes in coupling development. Some deviations from this relationship are observed and explained. It was found that certain substituents diminish the allergenic properties of *p*-amino-N-dialkylanilines, and a hypothesis is suggested which explains their action. *p*-Amino-N-dialkylanilines were generally prepared by reduction of the corresponding nitro- or nitroso-N-dialkylanilines. Where these could not be made, and for convenience in other cases, the *p*-(2,5-dichlorophenylazo)-N-dialkylanilines were used because of their ease of preparation and purification, and their stability. Methods were worked out for the introduction of side chains and functional groups by stepwise synthesis or as entities.

Introduction

The dyes in color photographic processes such as Kodachrome, Ektachrome, Kodacolor, Agfacolor, Ansco Color, etc., are formed by oxidative condensation of compounds containing active methylene or methine groups (couplers) with photographic developing agents[3] as shown, for instance, in Equation (1).



Coupler Developing Agent

Dye (1)

Inasmuch as the developer reacts more rapidly with silver halide grains which have been exposed to light than with unexposed silver halide, reduction of silver ion and dye formation take place preferentially in the exposed regions of the photographic layers. Of the main types of developing agents, hydroquinones, catechols, *p*- and *o*-aminophenols and *p*-phenylenediamines, the unsymmetrical dialkyl derivatives of the latter provide the best color-forming developing agents because of the desirable light absorption and the relatively high stability of their azomethine and indoaniline dyes. However, *p*-amino-N-dialkylanilines are, as a class, weak developing agents, requiring long processing times even in solutions of high alkalinity (pH > 10.5). Moreover, these compounds afflict some individuals with a *sensitization dermatitis* similar to that caused by poison ivy. The present paper describes an investigation of *p*-amino-N-dialkylanilines which was undertaken in order to understand and to overcome these deficiencies. The *p*-amino-N-dialkylanilines are listed in Table I, together with identifying numbers used throughout this paper and with the data on *half-wave potentials, development rates, coupling efficiencies and allergenic activities.* Some additional compounds for which no half-wave potentials or quantitative development rates were determined but allergenic activities can be given are listed in Section V, with their identifying numbers.

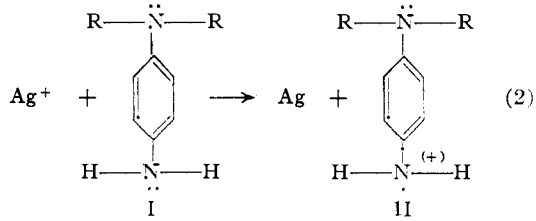
(1) Communication No. 1385 from the Kodak Research Laboratories.

(2) Deceased.

(3) R. Fischer and H. Siegrist, *Phot. Korr.*, **51**, 18–22 (1914); J. S. Friedman, "History of Color Photography," American Photographic Publishing Co., Boston, Mass., 1944.

Discussion

I. General.—The elementary process of photographic development is the reduction of silver ion to silver, the electron being supplied by the developer (Eq. 2).



(2)

The free-energy change of the oxidation of the developing agent can be determined by measuring the oxidation potential, or, more conveniently, the *polarographic half-wave potential*, $E_{1/2}$, of the developing agent.[4] The greater the free energy of the process, *i.e.*, the greater the tendency of the developing agent to release electrons, the more *positive* is its oxidation half-wave potential according to the Lewis–Randall convention.[5] According to the transition state theory, the rate of development is a function of the free-energy change of the formation of the transition state, $\Delta F^{\neq}$. If we assume that $\Delta F^{\neq}$ is proportional to the free energy change of the reaction, ΔF, the logarithm of the rate of development should be linearly related to the half-wave potential, $E_{1/2}$, *i.e.*, we can expect

(4) D. B. Julian and W. R. Ruby, THIS JOURNAL, **72**, 4719 (1950).

(5) G. N. Lewis and M. Randall, "Thermodynamics," McGraw-Hill Book Co., Inc., New York, N. Y., 1923, p. 389.

TABLE I

Number[a]	Compound	$E_{1/2}$ (mv.) *vs.* H electrode at *p*H 11.0[b]	Development rate $1/t$ (min.$^{-1}$)	Allergenic activity	Coupling efficiency
24	4-Amino-2-acetamido-N-diethylaniline	−390	0.0014		0
9	4-Amino-2-methyl-N-diethylaniline	−341	.0038		0
8	4-Amino-2-methyl-N-dimethylaniline	−329			+
11	4-Amino-2,5-dimethyl-N-diethylaniline	−321	.0096		0
49	N-(4-Aminophenyl)-morpholine	−315	.0012	Low	+
23	2,4-Diamino-N-diethylaniline	−305	.029		0
51	N-(4-Aminophenyl)-piperazine	−304	.013		+
50	N-(4-Amino-3-methylphenyl)-morpholine	−298	.01		++
42	4-Amino-N-ethyl-N-carbamylmethylaniline	−290	.037		++
18	4-Amino-2-methoxy-N-diethylaniline	−287	.032		+
17	4-Amino-3-chloro-N-diethylaniline	−271	.091	Moderate	++
43	4-Amino-3-methyl-N-ethyl-N-carbamylmethylaniline	−256	.093	Low	++
47	N-(4-Aminophenyl)-piperidine	−254	.054	Low	++
32a	4-Amino-N-ethyl-N-(β-methoxyethyl)-aniline	−253			++
35	4-Amino-N-ethyl-N-(β-acetamidoethyl)-aniline	−251	.16		++
39	4-Amino-N-ethyl-N-(N′-methyl-β-methylsulfonamidoethyl)-aniline	−247	.15	Low	++
33	4-Amino-N-ethyl-N-(β-ethoxyethyl)-aniline	−242	.15		++
48	N-(4-Amino-3-methylphenyl)-piperidine	−240	.12		++
19	4-Amino-2-methoxy-5-methyl-N-diethylaniline	−239	.13		++
1	4-Amino-N-dimethylaniline	−235	.30		++
44	4-Amino-N-ethyl-N-tetrahydrofurfurylaniline	−233	.20		++
2	4-Amino-N-methyl-N-ethylaniline	−231	.34		++
4	4-Amino-N-methyl-N-(*n*-butyl)-aniline	−229	.37		++
3	4-Amino-N-methyl-N-(*n*-propyl)-aniline	−225	.44		++
40	4-Amino-3-methyl-N-ethyl-N-(N′-methyl-β-methylsulfonamidoethyl)-aniline	−222	.39	Low	++
5	4-Amino-N-diethylaniline	−222	.44	Mod. to high	++
14	4-Amino-3-(methylsulfonamidomethyl)-N-diethylaniline	−221	.21		++
36	4-Amino-N-ethyl-N-(β-methylsulfonamidoethyl)-aniline	−219	.18	Low	++
13	4-Amino-3-hydroxymethyl-N-diethylaniline	−219	.29	Low	++
6	4-Amino-N-ethyl-N-(*n*-propyl)-aniline	−217	.58		++
15	4-Amino-3-(β-acetamidoethyl)-N-diethylaniline	−211	.36	Low	++
14a	4-Amino-3-(β-hydroxyethyl)-N-diethylaniline	−211			++
14b	4-Amino-3-(β-aminoethyl)-N-diethylaniline	−210			++
31	4-Amino-N-ethyl-N-(β-hydroxyethyl)-aniline	−206	.42		++
7	4-Amino-N-di-(*n*-propyl)-aniline	−204	.53		++
34	4-Amino-N-ethyl-N-(β-aminoethyl)-aniline	−204	.50		+
30	4-Amino-3-methyl-N-methyl-N-(β-methylsulfonamidoethyl)-aniline	−204	.37		++
10a	4-Amino-3-ethyl-N-diethylaniline	−203			++
16a	4-Amino-3-(N′-methyl-β-methylsulfonamidoethyl)-N-diethyl-aniline	−202	.45	Low	++
46	1-(4-Aminophenyl)-pyrrolidine	−202	.83	High[c]	++
45	4-Amino-3-methyl-N-ethyl-N-tetrahydrofurfurylaniline	−201	.67		++
16	4-Amino-3-(β-methylsulfonamidoethyl)-N-diethylaniline	−200[d]	.43	Low to mod.	++
26	4-Amino-3-acetamido-N-diethylaniline	−199	.31		++
37	4-Amino-3-methyl-N-ethyl-N-(β-methylsulfonamidoethyl)-aniline	−190	.38	Low to mod.	++
10	4-Amino-3-methyl-N-diethylaniline	−190	.80	Mod. to high	++
54	6-Amino-1-(β-methylsulfonamidoethyl)-1,2,3,4-tetrahydro-quinoline	−188	1.0	Low to mod.	++
32	4-Amino-3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline	−188	0.67		++
53	6-Amino-1-ethyl-1,2,3,4-tetrahydroquinoline	−182	1.42		++
41	4-Amino-3-ethoxy-N-ethyl-N-(N′-methyl-β-methylsulfonamido-ethyl)-aniline	−176	0.13	Low	++
52	5-Amino-1-(β-methylsulfonamidoethyl)-2,3-dihydroindole	−169	2.0	Low to mod.	+
12	4-Amino-3,5-dimethyl-N-diethylaniline	−167	1.0		+
38	4-Amino-3-ethoxy-N-ethyl-N-(β-methylsulfonamidoethyl)-aniline	−165	0.29	Low	++
21	4-Amino-3-methoxy-N-diethylaniline	−159	.27		++
22	4-Amino-3-ethoxy-N-diethylaniline	−153	.71	High	++

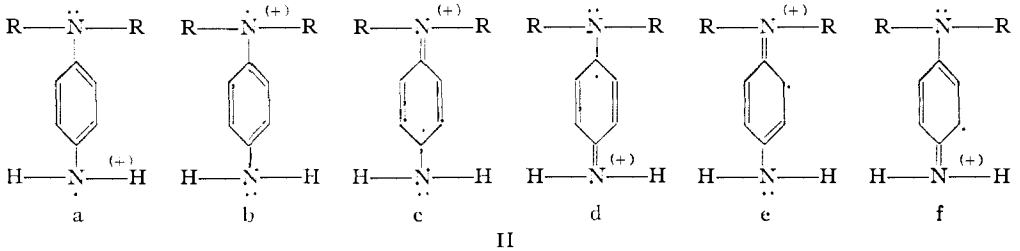
TABLE I (*Continued*)

Number[a]	Compound	$E_{1/2}$ (mv.) *vs.* H electrode at *p*H 11.0[b]	Development rate $1/t$ (min.$^{-1}$)	Allergenic activity	Coupling efficiency
55	9-Aminojulolidine	−142	2.5	High	++
29	4-Amino-3-dimethylamino-N-diethylaniline	−110	2.2		++
27	4-Amino-3-methylsulfonamido-N-diethylaniline	− 81	1.7		+
25	3,4-Diamino-N-diethylaniline	− 58	3.3		0
28	4-Amino-3-ethylamino-N-diethylaniline	− 17	2.5		++
20	4-Amino-3-hydroxy-N-diethylaniline	+ 62	2.5		+[e]

[a] Refers to location in Table IX of the experimental section. [b] Half-wave potentials determined with stationary platinum microelectrode. [c] Observed with 1-(4-amino-3-methylphenyl)-pyrrolidine. [d] The accuracy of this determination is lower than usual (see Section 1A). [e] Dye not typical.

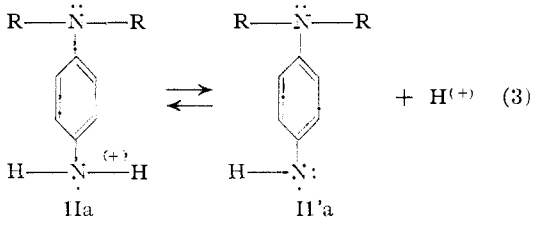
the developing agent to be the more active, the more positive $E_{1/2}$.[6]

The primary oxidation product of a *p*-amino-N-dialkylaniline (I) is a semiquinone ion (II) (Eq. 2) stabilized by resonance of the principal structures (IIa-f). For reasons of convenience,



II

the resonance hybrid is represented in the following discussion by IIa. The semiquinone ion is involved in several equilibria, namely, electrolytic dissociation (Eq. 3), disproportionation and dimerization.[7a,b,c] The resonance hybrid of the



semiquinone requires that the three substituents on the nitrogen, including the benzene ring, lie in one plane.[7c] If this configuration is prevented by steric conditions, formation of the semiquinone will be inhibited and the half-wave potentials will be less positive than in the absence of steric hindrance.

II. Half-wave Potentials.—Table II shows that the half-wave potentials are shifted to more positive values when both of the *aliphatic groups attached to the nitrogen atom* of *p*-amino-dimethylaniline *are lengthened* symmetrically, in agreement with the higher electron-releasing inductive effect of the longer chains; going from compound 1 to 5 and from 5 to 7, the shift amounts to 13 and 18 mv., respectively. If only one of the aliphatic groups is lengthened so that the two aliphatic groups attached to the tertiary nitrogen atom become different (series 1, 2, 3 and 5, 6), the increment for CH_2 is in no case larger than 6 (2, 3). It appears that the more balanced substitution is more efficient in facilitating the release of electrons by the tertiary amino group than the unsymmetrical substitution. When the propyl group (3) is lengthened to a butyl group (4) while the other substituent remains methyl, $E_{1/2}$ even becomes less positive.

Table III shows the *effect* of various *groups* replacing H in methyl *attached to the tertiary nitrogen*. The other substituent on the nitrogen is, in all cases, ethyl. The figures in column 2 refer to *p*-amino*anilines*, those in column 3 to *p*-amino-*m*-*toluidines*, and those in column 4 to *p*-amino-*m*-*phenetidines*. In compounds 42 and 43, H of the methyl group is directly replaced by an electron-attracting group, with the result that the half-wave potential of 42 is considerably less positive than that of the parent compound 2. Comparison of 42 with 5, and of 43 with 10 shows that a similar relation holds in the toluidine series. The electron attraction must be transmitted to the tertiary nitrogen by an inductive effect because of the blocking of a mesomeric effect by the intervening CH_2 group.

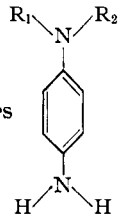
The active substituent in all other compounds of Table III replaces a β-hydrogen in ethyl. The effect of $-NHCOCH_3$ and of $-N(CH_3)SO_3CH_3$ in compounds 35, 39, 40 and 41, respectively, may be understood as an electron-attracting inductive effect caused by the positive end (N) of the acylamino and sulfonamido groups. This effect is more than compensated in compounds 36, 37 and 38, where the electrolytic dissociation at *p*H 11 of $NHSO_2CH_3$ to $N^{(-)}SO_2CH_3$ reverses the polarity of the N atom. The half-wave potentials of the ethers, 32a, 33, 44 and 45, agree with the expectation that ether oxygen has a higher electron-attracting inductive effect than hydrogen.

(6) C. E. K. Mees, "Theory of the Photographic Process," The Macmillan Co., New York, N. Y., 1942, p. 470.

(7) (a) S. Granick, L. Michaelis and M. P. Schubert, *Science*, **90**, 422 (1939); L. Michaelis, M. P. Schubert and S. Granick, THIS JOURNAL, **61**, 1981 (1939); (b) J. E. LuValle, D. B. Glass and A. Weissberger, *ibid.*, **70**, 2223 (1948); (c) L. Michaelis and M. P. Schubert, *Chem. Revs.*, **22**, 437 (1938); L. Michaelis, *Ann. N. Y. Acad. Sci.*, **XL** Art. 2, 64 (1940).

TABLE II[a]

EFFECT ON $E_{1/2}$ OF DIFFERENT ALKYL GROUPS



R_2 = H + CH_2 · · · ⟶

R_1 = H + CH_2 · · ·

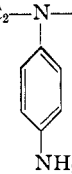
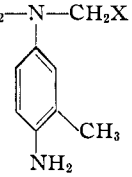
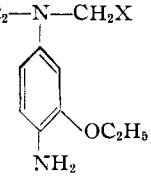
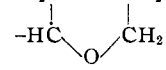
↓

H_3C CH_3 N −235 (1)	H_3C C_2H_5 N −231 (2)	H_3C $C_3H_7(n)$ N −225 (3)	H_3C $C_4H_9(n)$ N −229 (4)
H_3C C_2H_5 N −231 (2)	H_5C_2 C_2H_5 N −222 (5)	H_5C_2 $C_3H_7(n)$ N −217 (6)	
		$H_7C_3(n)C_3H_7(n)$ N −204 (7)	

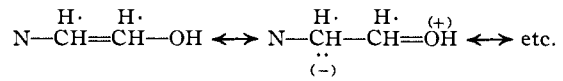
[a] Identification numbers of the compounds are added in parentheses in this and other tables.

TABLE III

EFFECT ON $E_{1/2}$ OF SUBSTITUENTS ATTACHED TO THE *t*-ALKYLAMINO GROUP

X =	H_5C_2—N—CH_2X 	H_5C_2—N—CH_2X 	H_5C_2—N—CH_2X 
$-CONH_2$	−290 (42)	−256 (43)	
$-CH_2OCH_3$	−253 (32a)		
$-CH_2NHCOCH_3$	−251 (35)		
$-CH_2N(CH_3)SO_2CH_3$	−247 (39)	−222 (40)	−176 (41)
$-CH_2OC_2H_5$	−242 (33)		
	−233 (44)	−201 (45)	
−H	−231 (2)		
$-CH_3$	−222 (5)	−190 (10)	−153 (22)
$-CH_2NHSO_2CH_3$	−219 (36)	−190 (37)	−165 (38)
$-CH_2OH$	−206 (31)	−188 (32)	
$-CH_2NH_2$	−204 (34)		

The position of compounds 31 and 34 relative to the parent substance 5 cannot be the result of an inductive effect which would attract electrons toward the -OH and $-NH_2$ groups. The observed effect in the opposite, positive, direction corresponding to about 16 mv. is difficult to understand. It may indicate that an electron-releasing mesomeric effect of these groups is superimposed upon their inductive effect and relayed to the carbon attached to the tertiary nitrogen (C_1). This would increase the electron density at the carbon atom, C_1, and counteract the inductive effect of $-C_2H_4OH$ and $-C_2H_4NH_2$, respectively. The mechanism of second-order hyperconjugation[8] has been suggested in order to explain how a mesomeric effect can be relayed through an aliphatic two-carbon chain. In our case, one might assume that the following structures contribute to the resonance hybrid and increase the electron density at the carbon atom, C_1, and therefore on the nitrogen.



The $-OC_2H_5$ group in 33 shifts the half-wave potential by 20 mv. to a more negative value than that of the parent substance 5. It would appear that the mesomeric electron-releasing mechanism of second-order hyperconjugation does not operate as effectively with $-C_2H_4OC_2H_5$ as with $-C_2H_4OH$. The half-wave potential of the methyl ether, 32a, is more negative than of the ethyl ether in accordance with the greater electron-attracting effect of CH_3O as compared with C_2H_5O.[9] The tetrahydrofuryl derivative, 44, has a half-wave potential

(8) E. Berliner and F. Berliner, THIS JOURNAL, 71, 1195 (1949).

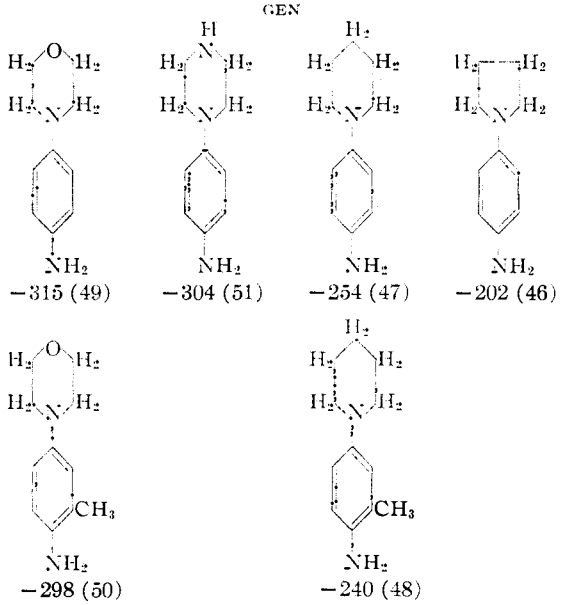
(9) See pK of methoxy and ethoxy acetic acids and Hammett's σ values; L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 188.

intermediate between those of the parent compound, 5, and 33.

The introduction of CH_3 or of OC_2H_5 in position 3 of the benzene nucleus renders the half-wave potential more positive (see Table III) but the observations made with the derivatives of aniline are, in general, confirmed by those with *m*-toluidine and with *m*-phenetidine. Why the difference between OH and H becomes insignificant with the toluidine derivatives 32 and 10 remains unexplained, but the identity of their half-wave potentials still shows the presence of an electron-releasing effect in 32 which compensates for the inductive electron attraction by OH.

TABLE IV

EFFECT ON $E_{1/2}$ OF CYCLIZATION ON THE TERTIARY NITROGEN



Ring closure of the *substituents* on the *tertiary nitrogen* to give derivatives of piperidine, piperazine and morpholine (Table IV) shifts the half-wave potentials to more *negative* values. Taking as the basis of comparison *p*-aminodiethyl*aniline*, the shift amounts to −32, −82 and −93 mv., respectively. In the *toluidine* series, only the derivatives of piperidine and morpholine were studied. Compared with *p*-aminodiethyl-*m*-toluidine, the shift in half-wave potential amounts to 50 and 108 mv., respectively. The effect of the ring closure shows that the formation of the quinonoid system requires more energy for the six-membered cyclic compounds than for the open-chain derivatives. The shift of half-wave potentials with $-CH_2-$, $-NH-$ or $-O-$ as ring members is in agreement with the known electronegativity of these ring members. At variance with the effect of the six-membered ring, the presence of a five-membered ring in *p*-amino-N-phenylpyrrolidine shifts the half-wave potential by 20 mv. to more positive values as compared with *p*-amino-N-diethylaniline; *i.e.*, the five-membered ring facilitates the formation of the resonance system IIa–f. These observations, which are in agreement with the rates of autoxidation and the photographic data (see below), can be understood as follows:

It was mentioned above that in the structures IIa–f the three atoms linked to the nitrogen lie in the plane of the benzene ring while in the reduced *p*-phenylenediamine this restriction is not imposed on the constellation[10] of the molecule. The most stable form of a hydrogenated six-membered homocyclic ring is the chair form, where none of the valencies is much deflected from the tetrahedral bond angle, and the hydrogen atoms are staggered so that the coulomb interaction of neighboring hydrogen atoms is at a minimum.[11,12] In a model of N-phenylpiperidine, with pyramidal nitrogen, the two rings cannot rotate freely against each other with the heterocyclic ring in the chair form or in the boat form, because of some interference between the hydrogen atoms adjacent to the nitrogen–benzene bond, Fig. 1 (A). Thus, the constellation closest to coplanarity of the rings is hindered. The interference between the hydrogen atoms persists to about the same degree in a model with tetracovalent nitrogen (for which a model of aromatic carbon was used), Fig. 1 (B), which is present in the oxidized compound. The energy required for the formation of the oxidized forms of the piperidine, piperazine and morpholine derivatives is, therefore, higher than for the open-chain compounds. This explains the shift of the half-wave potentials to more negative values by cyclization to a six-membered ring.

In contrast to the six-membered ring, a hydrogenated five-membered ring is almost planar.[11] The model of phenylpyrrolidine with pyramidal nitrogen, Fig. 1 (C), shows strong steric interference between the hydrogen atoms adjacent to the nitrogen–benzene bond, but a model with tetracovalent nitrogen which is present in the oxidized compound, Fig. 1 (D), shows no steric interference between those hydrogens. The molecule will, therefore, tend to assume a shape in which the nitrogen is tetracovalent. Thus, the conditions for formation of the oxidized compound are even more favorable for the pyrrolidine derivative than for the *p*-aminodialkylanilines with open alkyl groups. The latter can assume constellations in which the hydrogen atoms adjacent to the nitrogen–benzene bond interfere with each other, although these constellations can be avoided without distorting the valence angles on the tertiary nitrogen by rotation about the bond between alkyl carbon and tertiary nitrogen, and about C–C links of aliphatic groups larger than methyl.

Table V shows the *effect of substituents in position 3* on the half-wave potential of *p*-aminodiethylaniline. In the first thirteen compounds, 17 to 12, the active substituent is attached directly to the benzene nucleus. Besides the inductive effect, it can therefore exhibit the ordinary mesomeric effect on the nitrogen in position 4. The sequence of the substituents in an arrangement proceeding from the most negative to the most positive half-wave potential agrees, with the exception of $NHSO_2CH_3$, OH and $N(CH_3)_2$, with the inductive and mesomeric

(10) "Constellation" refers to "those forms of the molecules which result from free rotation about single bonds" [V. Prelog, *J. Chem. Soc.*, 423 (1950)].

(11) K. S. Pitzer, *Science*, **101**, 672 (1945).

(12) V. Prelog, *J. Chem. Soc.*, 420 (1950).

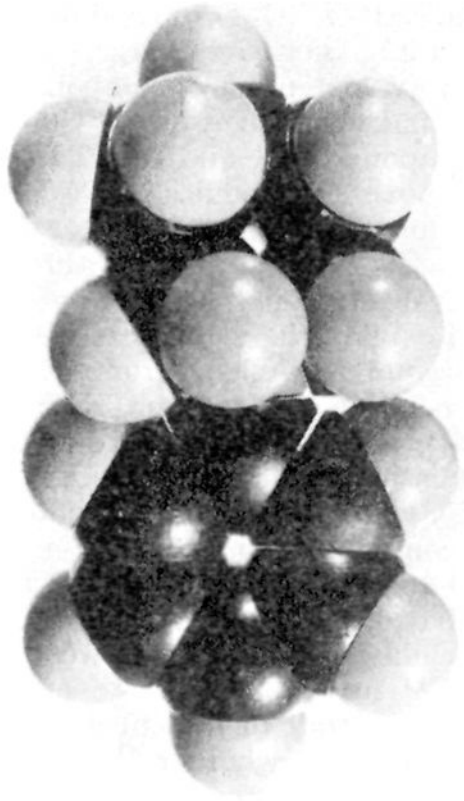


Fig. 1A.

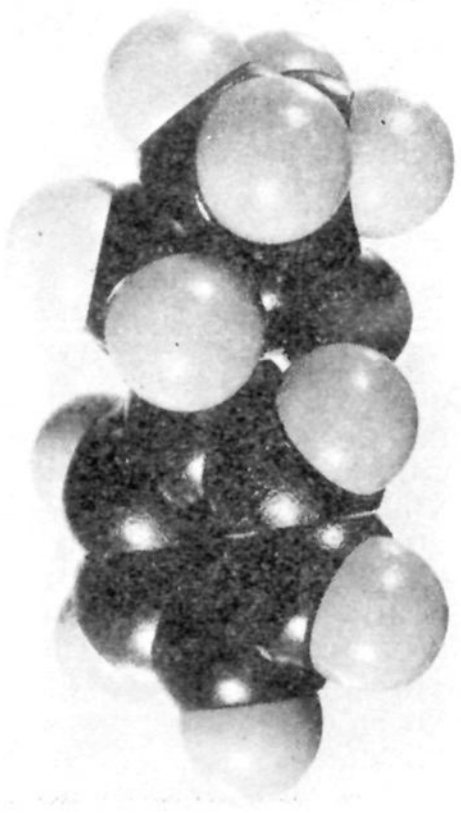


Fig. 1C.

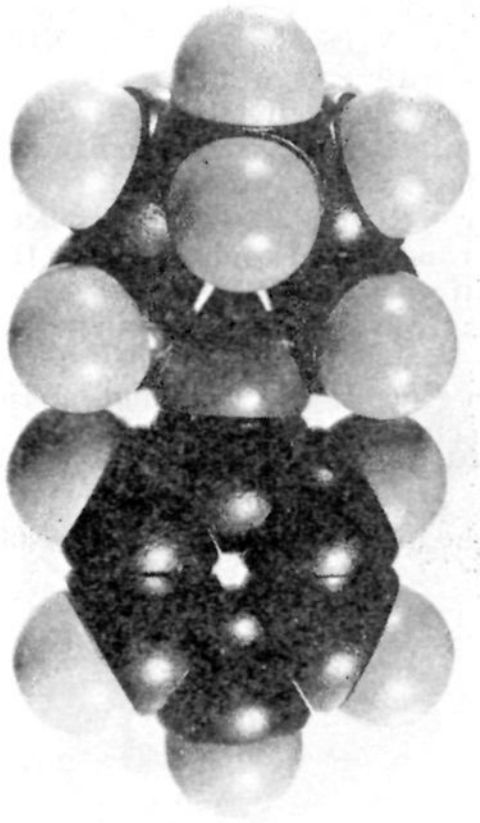


Fig. 1B.

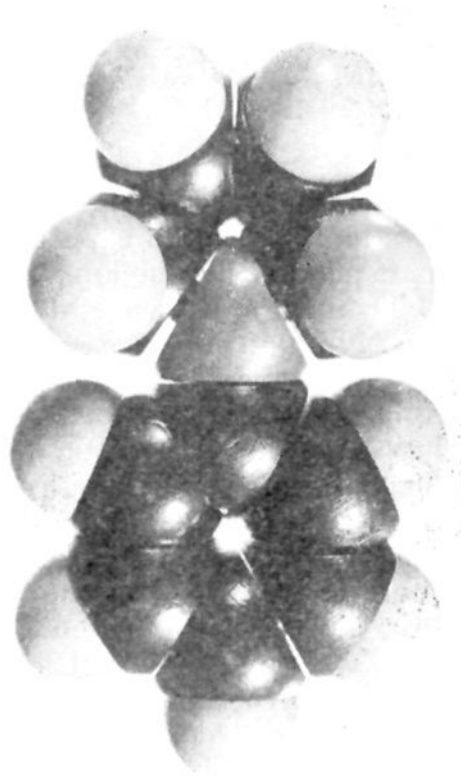


Fig. 1D.

Fig. 1.—Fisher–Taylor–Hirschfelder models of N-phenylpiperidine (1A and 1B) and N-phenylpyrrolidine (1C and 1D).

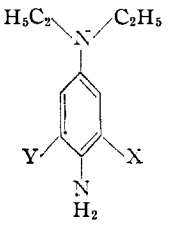
effects to be expected from other data.[13] Introduction of one methyl group in position 3 of the *p*-aminodialkylaniline shifts the half-wave potential by 32 mv. to more positive values, to which a second methyl group in position 5 adds another 23 mv. Ethyl, 10a, has a smaller electron-releasing effect than methyl, which shows that the shift of the half-wave potential to more positive values by the latter group is due, at least in part, to hyperconjugation, *i.e.*, a mesomeric effect. The sequence is in agreement with the effects of substituents in positions 2 or 4 on the reduction potentials of the 1,4- or the 1,2-naphthoquinone systems, respectively.[14] Fieser's values for the systems referred to the unsubstituted compounds as zero and, with signs changed to conform with the Lewis–Randall convention,[4] are listed in Table V, columns 5 and 6.

(13) A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1949; J. R. Johnson in Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 1844, 1848.

(14) L. F. Fieser and M. Fieser, THIS JOURNAL, **57**, 491 (1935).

TABLE V

EFFECT ON $E_{1/2}$ OF SUBSTITUENTS ORTHO TO THE PRIMARY AMINO GROUP



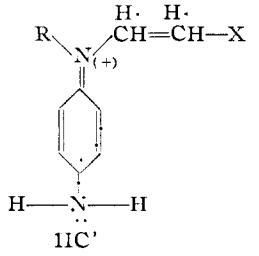
No.	Y	X	$E_{1/2}$	Potentials of naphthoquinones[14] 1,4-	1,2-
17	H	Cl	−271	− 24	
5	H	H	−222	0	
10a	H	C_2H_5	−203		
26	H	$NHCOCH_3$	−199	+ 67	+ 30
10	H	CH_3	−190	+ 76	+ 44
21	H	OCH_3	−159	+131	+143
22	H	OC_2H_5	−153		
29	H	$N(CH_3)_2$	−110	+181	
27	H	$NHSO_2CH_3$	− 81		
25	H	NH_2	− 58	+210	+251
28	H	NHC_2H_5	− 17		+279
20	H	OH	+ 62	+128	
12	CH_3	CH_3	−167		
14	H	$CH_2NHSO_2CH_3$	−221		
13	H	CH_2OH	−219		
15	H	$CH_2CH_2NHCOCH_3$	−211		
14a	H	CH_2CH_2OH	−211		
14b	H	$CH_2CH_2NH_2$	−210		
16a	H	$CH_2CH_2N(CH_3)SO_2CH_3$	−202		
16	H	$CH_2CH_2NHSO_2CH_3$	−200		

The fact that the substituents, $NHSO_2CH_3$ (27) and OH (20), shift the potential more toward positive values than one would expect for the neutral groups is explained by the ionization of these groups at *p*H 11 and the presence of formal negative charges on N or O in conjugation with the aromatic system. Scale models show possibilities for steric interference between the substituents in position 3 and the NH_2 group in position 4. These effects are, in general, not large enough to upset the expected sequence of the half-wave potentials,[13] though they will have to be considered when more quantitative correlations are attempted than in the present paper. The dimethylamino group, however, shifts the half-wave potential by about 100 mv. less toward positive values than would be expected from the known mesomeric effect of this group. The $N(CH_3)_2$ and NH_2 groups interfere sterically when the methyl groups and the hydrogen atoms lie in the plane of the benzene nucleus and their electron-releasing interaction is therefore diminished.

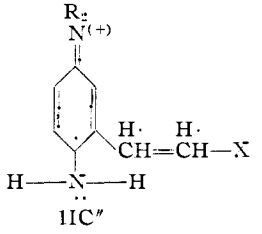
Comparison of compounds 13 and 10 shows that OH when substituted in CH_3 shifts the potential to more negative values by 29 mv., in agreement with the expected electron-attracting inductive effect, *i.e.*, the electron-releasing effect of CH_3 is lost by substitution of OH. The group, $NHSO_2CH_3$, substituted in methyl (14) has about the same effect as OH, indicating that the inductive electron-attracting effect of the two substituents is about equal. One would expect the methylsulfonamido group to exert a stronger electron-attracting inductive effect than hydroxyl because of the strongly electron-attracting sulfonyl group but, again, dissociation at *p*H 11 of the $NHSO_2CH_3$ group endows the nitrogen atom with a formal negative charge.

The half-wave potentials of compounds 14 and 13 are about equal while there is a 13 mv. difference between compounds 36 and 31 (Table III). As mentioned above, the potential of 31 may be more positive because of a mesomeric effect of OH which is relayed to the tertiary nitrogen through second-order hyperconjugation. A lowering of this effect in 13 would explain the identity of $E_{1/2}$ for 14 and 13. If a second methylene group is inserted between the benzene nucleus and $NHSO_2CH_3$ (16), the half-wave potential becomes more positive by 21 mv. It is not changed by methylation of the nitrogen (16a), but the half-wave potential of the acetamido compound, 15, is 9 mv. more negative than that of 16a. The effect of $NHCOCH_3$ in 15 is similar to that of OH and NH_2 in 14a and 14b, respectively, while the difference between OH or NH_2 and $NHCOCH_3$ in 31, 34 and 35 is over 40 mv.

That the magnitude of the effect of substituents varies, depending on whether they are attached, through C_2H_4, to the tertiary nitrogen in position 1 or to the ring in position 3, deserves some discussion. The half-wave potentials of the parent compounds, 5 and 10a, are −222 and −203 mv., respectively. Substitution of a hydrogen in the β-position of the ethyl group by $NHCOCH_3$, $N(CH_3)SO_2CH_3$, $NHSO_2CH_3$, OH and NH_2, results in derivatives with $E_{1/2}$ −251, −247, −219, −206 and −204 mv., respectively, if C_2H_4 is attached to the nitrogen. If C_2H_4 is attached to the ring, the corresponding values are −211, −202, −200, −211 and −210 mv. The differences between derivatives and parent compounds for the N-ethylene derivatives are −29, −25, +3, +16 and +18 mv., respectively, and for the ring-ethylene compounds, −8, +1, +3, −8 and −7 mv., respectively. In general, the compounds are more sensitive to the effect of the substituents in the N-ethyl group, which may be due to the greater susceptibility of the contributing structures IIC′ than of IIC″ for the mesomeric effects of the substituents.



IIC′



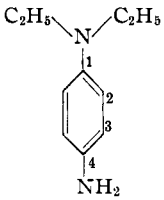
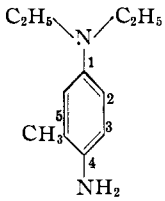
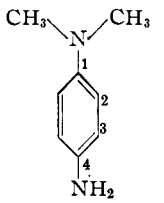
IIC″

It must be kept in mind that half-wave potentials are determined in a polar solution and that they may be affected by the solvation of the reduced and oxidized forms of the developing agents. These factors are not taken into consideration in the present paper. They may be responsible for anomalies which are encountered when the observed half-wave potentials are explained on the basis of the electronic structures of the *p*-aminodialkylanilines only.

Steric hindrance becomes dominant when *substituents* are introduced in position 2, *i.e.*, in ortho-po-

TABLE VI

EFFECT ON $E_{1/2}$ OF SUBSTITUENTS IN POSITIONS 2 OR 3 TO THE TERTIARY AMINO GROUP

	X	$E_{1/2}$ (X in 3)	$E_{1/2}$ (X in 2)	Δ_3	Δ_2	$\Delta_{2,3}$
	H	−222(5)	−222(5)			
	$NHCOCH_3$	−199(26)	−390(24)	+ 23	−168	191
	CH_3	−190(10)	−341(9)	+ 32	−119	151
	NH_2	− 58(25)	−305(23)	+164	− 83	247
	OCH_3	−159(21)	−287(18)	+ 63	− 65	128
	H	−190(10)	−190(10)			
	CH_3	−167(12)	−321(11)	+ 23	−131	154
	OCH_3		−239(19)		− 49	
	H		−235(1)			
	CH_3		−329(8)		− 94	

sition to the dialkylamino group.[7c] Table VI gives the half-wave potentials of these compounds (column 3) in comparison with the corresponding 3-substituted derivatives (column 2). Column 4 shows the difference in $E_{1/2}$ between the parent compounds (5, 10 and 1, respectively) and the 3-substituted derivative, Δ_3, and demonstrates a shift to more positive values with all substituents listed. The same substituents when in position 2 cause a shift to more negative values, as compared with the unsubstituted parent compounds. This is shown by the differences, Δ_2, in column 5. In discussing the different effects of substituents in positions 2 and 3, one must keep in mind that position 2 is ortho to a tertiary amino group while position 3 is ortho to a primary amino group. However, the differences in the effect of identical substituents on the half-wave potentials, depending on whether they are introduced in position 2 or 3, are much larger than would be explained by the difference in the electronic effects between the primary and tertiary amino groups. This difference is, therefore, neglected in the following, and we attribute the difference between columns 2 and 3 ($\Delta_{2,3}$) to the steric interference of the substituents in question with NR_2 and NH_2, respectively. Since deviations from coplanarity which do not influence the inductive effect will greatly alter the mesomeric effect, no simple relation can be expected between the size and shape of groups, as shown by scale models, and $\Delta_{2,3}$. This explains, for instance, why the $\Delta_{2,3}$ value is greater for NH_2 than for $NHCOCH_3$. The NH_2 group has a much larger electron-releasing mesomeric effect than $NHCOCH_3$ and the electron-releasing effect of the former is, therefore, more affected by steric interference than that of $NHCOCH_3$, in spite of the greater size of the latter group.

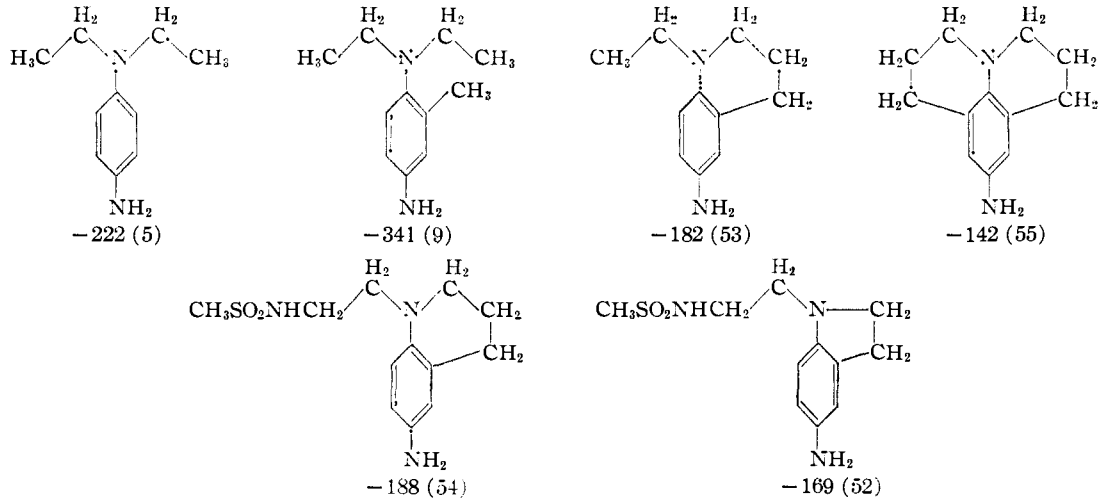
The values for compounds 10, 11 and 12, in comparison with the values for 5, 9 and 10, show that $\Delta_{2,3}$ is not appreciably affected by the presence of an additional methyl group in position 5. Although the second CH_3 group *ortho* to the NH_2 group has a smaller effect on $E_{1/2}$ than the first (23 mv. *vs.* 32 mv.), this difference is compensated by a larger shift of $E_{1/2}$ to negative values by CH_3 in position 2 in the xylene derivative (11) than in the toluene compound (9). On the other hand, the difference between the methoxy compound and the parent substance is greater for the derivative of aniline (18) than of toluidine (19). Interference of CH_3 with $N(CH_3)_2$ (8) is, as would be expected, smaller than with $N(C_2H_5)_2$ (9).

While the introduction of methyl in position 2 of *p*-amino-N-diethylaniline (9) renders the half-wave potential less positive by 119 mv., this effect is more than compensated by ring closure leading to 6-amino-N-ethyl-1,2,3,4-tetrahydroquinoline (53), (Table VII), whose half-wave potential is 40 mv. more positive than that of *p*-amino-N-diethylaniline. We attribute the effect of the ring closure to the nearly coplanar arrangement of the substituents on the tertiary nitrogen which increases the ease of formation of the semiquinone. Formation of a third ring system in 9-aminojulolidine (55) results in a further shift of the half-wave potential to a more positive value. As in *p*-amino-N-diethylaniline, substitution of a β-hydrogen in the ethyl group by $NHSO_2CH_3$ (54) has only a small effect on the half-wave potential. Comparison of this compound with the corresponding dihydroindole derivative (52) shows that formation of a hydrogenated five-membered ring shifts the half-wave potential to an even more positive value than that of a hydrogenated six-membered ring, in agreement with the greater planarity of the five-membered ring.

Both the five- and six-membered rings might in-

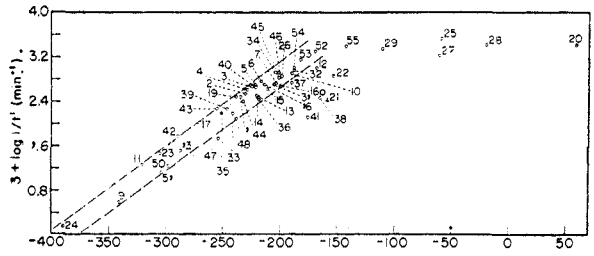
TABLE VII

EFFECT ON $E_{1/2}$ OF RING CLOSURE BETWEEN N-ALKYL AND THE ORTHO POSITION



fluence $E_{1/2}$ through a Mills–Nixon effect.[15] The five-membered ring would be expected to decrease the contribution of the benzenoid structure with the double bond between carbon atoms 1 and 2. It would, therefore, render the reduced form less stable, make its oxidation easier and shift the half-wave potential to a more positive value. This would be in agreement with the observations, but the six-membered ring would operate in the opposite manner and shift $E_{1/2}$ to more negative instead of more positive values.

III. Development Rates.—The relation between half-wave potential ($E_{1/2}$) and *development rate* ($1/t'$) is shown by Fig. 2; $t' = t - t_0$ where t_0 is the induction period. In this figure, the logarithms of the development rates are plotted against the half-wave potentials for all the compounds tested, with the exception of N-(*p*-aminophenyl)-morpholine. This latter compound gave excessively high fog, and development rate determinations with it are not considered reliable.



$E_{1/2}$, mv., *vs.* H electrode at *p*H 11.0.

Fig. 2.—$E_{1/2}$ *vs.* log development rate.

The two parallel broken lines separated by approximately 0.4 log unit include between them most of the data points. For the majority of the compounds tested, therefore, a linear relation holds between the logarithm of the development rate and the half-wave potential within a variation of ±0.2 log unit and over a range of reaction rates that varies 1000-fold. Since the rate of a chemical reaction is an exponential functional of the free energy of activation, the observed relation implies that the half-wave potentials are approximately proportional to the activation energies of development of this series of compounds. Similar correlations between reaction rates and oxidation–reduction potentials have been observed previously, and a theoretical basis for expecting such a relation exists when conditions are such that the total free-energy change of the reaction, ΔF, is proportional to the free-energy change of the formation of the transition state, $\Delta F^{\pm}$.[16]

There are some exceptions to the general relation found for the present series of developing agents: (1) Compounds with potentials more positive than about −170 mv. give rates lower than would be predicted. However, the rate of development by these compounds is so high that the rate of diffusion rather than of reaction becomes limiting. Hence, the measured rates do not represent the rates of the chemical reaction. (2) The four compounds which contain alkoxy groups in the 3-position of the benzene nucleus, 21, 22, 38 and 41, develop at rates lower than would be expected from the general relation. These alkoxy groups exert a strong electron-releasing mesomeric effect toward the ring with which they are in conjugation, provided that ring, oxygen and CH_2 are coplanar. Interference with the coplanarity will diminish the mesomeric effect of the alkoxy groups. The lower development rates may, therefore, be caused by interference with the coplanarity arising in the adsorption of the development agent to the silver or silver halide surface. This implies that the *p*-aminodialkylanilines are in contact with the silver halide grain in a region close to, and possibly identical with, the primary amino group. The latter can, therefore, be considered as the probable location in the molecule where the electron detaches itself, and the following considerations lend further support to this suggestion.

The $C_{arom.}$–N linkage has a dipole moment of about 1.5 *D*. The *p*-aminodialkylaniline molecule in aqueous solution will, therefore, be surrounded by oriented water molecules, and the polarized

(15) R. T. Arnold and H. E. Zaugg, THIS JOURNAL, **63**, 1317 (1941).

(16) C. H. Gershinowitz, *J. Chem. Phys.*, **4**, 363 (1936).

layer so formed will facilitate the passage of the electron. Since the aromatic nucleus is probably less hydrated than the polar and exposed amino groups, the latter are more likely the points at which the electron leaves the molecule. Moreover, it appears more likely for steric reasons that the electron leaves the primary amino group than the tertiary amino group.

Rates of oxidation, k, at *p*H 11.6 are available for some of the compounds.[7b] Table VIII shows that they are the higher, the more positive the half-wave potentials, but that log *k* increases more rapidly than if it were proportional to $E_{1/2}$ as the latter becomes more positive. It must be borne in

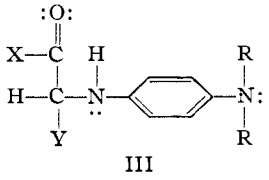
TABLE VIII

HALF-WAVE POTENTIALS AND RELATIVE RATES OF AUTOXIDATION (*k*)

	$E_{1/2}$, *p*H 11.0	*k*, *p*H 11.5	log *k*	$-\log k / E_{1/2} \times 10^3$
N-(4-Aminophenyl)-morpholine (49)	−315	3	0.48	1.5
N-(4-Amino-3-methylphenyl)-morpholine (50)	−298	4	0.60	2.0
N-(4-Aminophenyl)-piperidine (47)	−254	11	1.04	4.1
N-(4-Amino-3-methylphenyl)-piperidine (48)	−240	40	1.60	6.7
4-Amino-N-dimethylaniline (1)	−235	100	2.00	8.5
4-Amino-N-diethylaniline (5)	−222	210	2.32	10.5
N-(4-Aminophenyl)-pyrrolidine (46)	−202	610	2.79	26.4
4-Amino-3-methyldiethylaniline (10)	−190	195	2.29	12.1

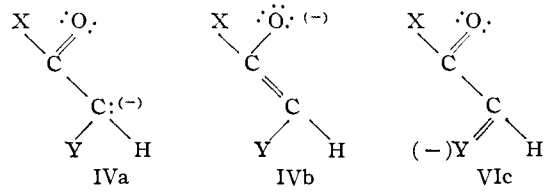
mind that the analogy between the mechanism of the establishment of a polarographic potential and the mechanism of photographic development is closer than between the former process and the autoxidation of the developing agent. The polarographic half-wave potential depends on the free-energy change of the transfer of electrons from the respective compound through the surface of the electrode into an electron sink established by the applied potential. In photographic development, the developing agent transfers electrons through the silver surface into an electron sink maintained by the silver ions of the silver halide grain. The autoxidation rates, however, depend largely on the equilibria between the compound in its reduced, totally oxidized and semiquinonoid states, each of which participates in ionization and dismutation equilibria. Thus, the mechanism of autoxidation is more complex than that of photographic development, as shown by the complicated *p*H dependence of the former and the simple proportionality with *p*H of the latter.[17]

IV. Coupling Efficiencies.—In the absence of kinetic data, only a few statements can be made about the mechanism of the *formation of azomethine dyes.* The *leuco* dye (III) is the first non-radical product of the oxidative condensation. It can be



III

assumed that III is oxidized to the dye by the silver ion in solution or, in photographic development, by the semiquinone of the developing agent or by the silver bleach bath.[18] The formation of III is, therefore, the relevant step in the condensation of *p*-aminodialkylanilines and compounds with active methylene or methine groups (couplers). It takes place in alkaline solution, and the anion of the coupler appears to be the reactive species. The most important structures contributing to the resonance hybrid of the anion of the open-chain coupler containing an activating CO group are represented by IVa, b and c, and include a structure (IVa) without a C=C double bond.



IVa IVb VIc

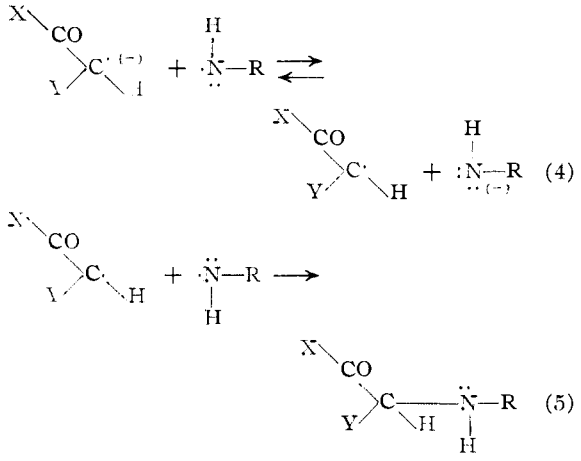
With respect to the developing agent, it can be excluded that the reduced form of the *p*-aminodialkylaniline reacts with the coupler anion to form a complex which is then oxidized, because color formation can proceed at a high rate even though the oxidizing agent (silver halide) and the coupler are immobilized in different locations of a photographic emulsion. It can also be excluded that, in general, a *p*-nitrosodialkylaniline is an intermediate in the reaction; the nitroso compounds do not react or react very sluggishly under conditions where freshly oxidized developing agent forms dye in a good yield.[18] The first oxidation product of *p*-aminodialkylaniline which is likely to undergo condensation is the semiquinone. At the *p*H in question (10), it is present in an equilibrium between the semiquinone cation (IIa) and the neutral semiquinone (II'a). If either undergoes condensation with the anion of the coupler to form the leuco dye, an electron must be removed. The most likely acceptor is a second equivalent of the semiquinone which is reduced to *p*-aminodialkylaniline in the process. The formation of the leuco dye would thus require a triple collision between one coupler particle and two semiquinone particles. Since this is rather improbable, other possibilities must be considered.

The triple collision will be avoided if the dimer and not the monomeric semiquinone enters into the reaction. The former might disproportionate in the reaction, so that the leuco dye is formed in the collision between one coupler anion and one quinhydrone particle, yielding as a by-product one molecule of reduced developing agent. In another mechanism, which also avoids a triple collision, the semiquinone may first react with the coupler anion and oxidize the latter to a free radical leading to the equilibrium (Eq. 4), and the coupler radical may then react with more semiquinone to form the leuco dye (III) (Eq. 5).[19] The developer semiquinone and also the free radical of the coupler should dimerize to a certain extent with formation of N–N and C–C linkages, respectively. The azo dyes which are formed as by-products of the condensation re-

(17) T. H. James, *PSA Journal*, **16B**, 83 (1950).

(18) A. Weissberger and H. D. Porter, THIS JOURNAL, **65**, 732 (1943).

(19) J. E. LuValle and A. Weissberger, *ibid.*, **69**, 1568 (1947); L. Michaelis, *Chem. Revs.*, **16**, 243 (1935).



(4)

(5)

actions[20] may be the result of a dimerization of the semiquinone to the hydrazo compound and oxidation of the latter. The yellow bands of the chromatograms (see Experimental Section Ic) are characteristic of these azo dyes. The formation of dimerized coupler would be difficult to establish because of the high reactivity of the dimerized coupler with oxidized developing agent.[21] If the condensation of coupler and developer to the dye is inhibited, both side reactions gain in importance but, in general, the condensation (Eq. 5) should prevail because of the greater polarization of the transition state complex, *i.e.*, for reasons similar to those causing alternation in copolymerizations.[22]

A reaction of totally oxidized quinone diimine, $\ddot{H}N{=}C_6H_4{=}NRR$, with IV, though not excluded, is less likely than the reaction of the semiquinone or quinhydrone, because high dye yields were obtained in many cases where a considerable part of the quinone diimine, if formed, would probably have been lost.[22a]

The experimental conditions for the dye formation were so chosen that abundant oxidizing agent and coupler were present for the dye formation with a developing agent of medium activity, for instance, *p*-aminodialkylaniline, within the reaction time of twenty minutes. In those cases where the dye yield was low, formation of silver during this time showed the progress of the oxidation of the *p*-aminodialkylaniline, and an extension of the reaction time to several hours did not increase the yield of the azomethine dye. A low dye yield, therefore, does not indicate failure of the developing agent to be oxidized but rather that the condensation to the dye proceeds so slowly that the oxidized developing agent is lost by side reactions. Of these, reference has been made above to the dimerization, but other reactions may play a role, depending on the nature of the *p*-aminodialkylaniline. Thus, it has been observed that compounds whose half-wave potentials are more positive than that of *p*-amino-N-diethylaniline because of the presence of electron-releasing substituents on the tertiary nitrogen, when oxidized, tend to undergo cleavage reactions involving the tertiary amino groups. This may lead to additional breaks in the current voltage curves which are characteristic for the oxidation of the cleavage products, for instance, with compound 46, and/or to low dye yields.

In compound 12, methyl groups occupy the two positions *ortho* to the primary amino group. While there is little or no steric interference with the *oxidation process*—the methyl groups shift the half-wave potentials by 55 mv. to more positive values—a scale model of the *dye* shows that steric hindrance of its formation can be expected and the observed dye yield is low. Compounds 24, 9, 23 and 11 formed appreciable amounts of silver in the coupling experiments but no dye, showing that the steric factors which shift the half-wave potentials to more negative values altogether prevent the dye formation. Compounds 27 and 25, though forming magenta dyes rapidly in test-tube experiments, give little or no dye in the standard test, because the dye first formed undergoes ring closure with formation of azine dyes of different color. The low dye yields with compounds 34 and 52 seem to be connected with decomposition reactions which involve a cleavage of the tertiary amino group.

V. Allergenic Activities.—The allergenic properties of the compounds, as determined by topical application, are summarized in column 4 of Table I. All compounds of high allergenic potency have relatively positive half-wave potentials, and it can be assumed that their potency is related to their reducing action, or, rather, to their oxidation to semiquinones and quinones which, by condensation with body proteins, may form antigens. However, it was possible to reduce the allergenic potency of *p*-aminodialkylanilines by substitution with certain groups[23] and still retain the desirable relatively positive oxidation potentials, as shown by compounds 36, 16, 16a, 15, 37, 54, 41, 52 and 38 in Table I. In addition to these compounds, 4-amino-3-ethoxy-N-ethyl-N-(β-acetamidoethyl)-aniline (35a) and 6-amino-7-methyl-1-(β-methylsulfonamidoethyl)-1,2,3,4-tetrahydroquinoline (54a) showed low allergenic activity.

It was observed at an early stage of this investigation that sulfonamido and carbonamido groups are particularly effective in reducing the allergenic activity. The work was guided by the concept that these groups might decrease the penetration of the *p*-aminodialkylanilines into the skin by decreasing the lipoid-solubility and perhaps by increasing the affinity for the keratin of the upper skin layers, and, therefore, be less potent skin allergens. Increased solubility in aqueous alkali does not, by itself, seem to be responsible for the effect because carbonamido and N-methylsulfonamido groups are allergy-reducing but their introduction does not increase the solubility of the respective *p*-aminodialkylanilines in aqueous alkali over that of the parent substances.

However, other factors may be responsible for depressing the allergenic potency. According to recent studies, lipoid-solubility is not apparently essential for the penetration of materials through

(20) R. Gerbaux, *Bull. soc. chim. belges*, **58**, 498 (1949).

(21) P. W. Vittum, private communication.

(22) C. Walling, THIS JOURNAL, **71**, 1930 (1949).

(22a) R. Willstätter and E. Mayer, *Ber.*, **37**, 1494 (1904); L. Michaelis, M. P. Schubert and S. Granick, THIS JOURNAL **61**, 1981 (1939).

(23) A. Weissberger, U. S. Patent 2,193,015 (1940).

the skin,[24] since many water-soluble materials penetrate with ease, and the effect of the allergy-reducing groups might be attributed, by analogy with Landsteiner's views, to the fact that the modified compounds react less readily with proteins or that the protein-developer conjugate does not possess the proper spatial configuration (Pauling) to allow it to induce antibody formation.

On the other hand, it may be pointed out in favor of our explanation that some compounds which were made allergenically less potent by sulfonamido groups and tested by means of subcutaneous injection, were found to be strongly allergenic under these circumstances. Moreover, hydroquinone, which is not very allergenic and water-soluble, becomes highly allergenic when chains are introduced in the ring to yield compounds which, by analogy, can be assumed to be considerably more lipoid-soluble than the parent substance. The allergenic properties do not become marked until the aliphatic chain reaches a length which appears sufficient to produce this change in solubility, as shown by the fact that toluhydroquinone and *s*-amylhydroquinone are low in allergenic potency like the parent substance, while *s*-dodecylhydroquinone is considerably allergenic and the monoalkylhydroquinones with *s*-C_{14}, C_{18} and C_{20} chains proved to be highly allergenic in our tests with animals.

Experimental

I. **Measurements. A. Half-Wave Potentials** (D. B. Julian, W. R. Ruby).—The oxidation potentials of the developing agents were determined from polarographic current–voltage curves. A platinum microelectrode was used as the polarizable electrode since the dropping mercury electrode is not applicable over a large portion of the voltage range required for these compounds, as described in a previous paper.[4] The half-wave potentials determined from the current–voltage curves are identical with oxidation–reduction potentials if the system under test is thermodynamically reversible.[25] Because of the instability of the "totally oxidized form" of these compounds, the diimines, it is difficult to prove the reversibility of the systems by the usual criteria. However, an analysis of the current–voltage curves for a number of substituted *p*-phenylenediamines has shown good agreement with the theoretical values of slope for a two-electron reaction.[4]

Two or more determinations were made in all cases in solutions well buffered with phosphate (5×10^{-2} *M*) for *p*H 11. In general, the values for half-wave potentials are reliable to at least ±4 mv. Better accuracy has been obtained in those cases where four or more determinations have been made. The *p*H was checked at the completion of the determination, using a Beckman Model G meter. The concentration of the developing agent was 5×10^{-4} *M*. The potentials are reported as oxidation potentials *vs.* the standard hydrogen electrode, following the sign convention of Lewis and Randall.[5]

B. **Development Rates** (T. H. James).—Black-and-white development rates were determined for a simple motion-picture type emulsion under the following conditions: The developing agent was used in 0.0025 *M* solution made up in an atmosphere of oxygen-free nitrogen and from component solutions which had been deaerated by passage of nitrogen. The developing agent was dissolved in a dilute hydrochloric acid solution, and this solution was thoroughly deaerated before mixing it with the deaerated alkaline component. The solutions were buffered at *p*H 11 with a carbonate–bicarbonate buffer and contained *M*/300 KBr. All development rates were determined at 20 ± 0.05°. The apparatus was essentially that previously described[26] and nitrogen was used for agitation. The photographic material was exposed on the Eastman IIb positive sensitometer with a maximum exposure of log *E* 2.05.

The rate data were determined as the reciprocals of the time in minutes required to attain an optical density of 0.2 above fog. The exposure used was log *E* 1.75. When the development curve showed an induction period, the calculated rates were corrected by subtracting from the time, *t*, needed to obtain the density of 0.2, a time, t_0, corresponding to the length of the induction period as determined by extrapolation of the density–time of development curve to zero density.

C. **Coupling Efficiency** (J. C. Dessloch, F. C. Duennebier, P. W. Vittum).—In order to compare the coupling efficiencies of the different *p*-aminodialkylanilines, the yields of the azomethine dyes formed with 2-cyanoacetylcoumarone under standard conditions were estimated after chromatographic purification from the *length of the adsorbed magenta bands* developed under similar conditions, and the *densities of the dye solutions* which were obtained by elution of the bands. This method is only approximate, inasmuch as extinction coefficients and the adsorptivities of the dyes are not known and no allowance could be made for differences in these properties of the various dyes. A solution of 0.0003 mole of 2-cyanoacetylcoumarone (m.p. 147–149°) in 40 ml. of 2% ammonium hydroxide was placed in a three-necked flask fitted with delivery tube, bubbler and stirrer. The apparatus was flushed with nitrogen, and, with stirring, 0.0002 mole of developer in 15 ml. of water was added. Twelve milliliters of 0.1 *N* silver nitrate (50% excess) was added dropwise over a period of ten minutes, and the mixture stirred under nitrogen twenty minutes longer. The reaction mixture was filtered with the aid of Celite and the dye extracted from both aqueous liquor and solid material with ethyl acetate. The ethyl acetate solution was washed with three portions of water, and evaporated to dryness. In a typical chromatographic examination, the crude dye from 4-amino-3-ethoxy-N-diethylaniline was taken up in a mixture of one part of acetone and two parts of cyclohexane, adsorbed on a column of Doucil,[27] and developed with fresh solvent. Three bands could be distinguished: a small red band; a main magenta band; a small yellow band. The length of the magenta band was measured; the band was separated from the rest of the column, the dye eluted with acetone, and, after evaporation of the acetone, taken up in *n*-butyl acetate. The density of this solution was determined spectrophotometrically. According to the results, the developers were graded as follows: 0, indicating no coupling; +, slight coupling; ++, good coupling.

D. **Biological Assays** (D. W. Fassett, J. H. Sterner).—The biological assays were modifications of the Landsteiner[28] techniques, in which it was shown that skin sensitization could be readily produced in the guinea pig by such simple chemicals as *p*-phenylenediamine and dinitrochlorobenzene. The routine modification utilized a topical application of the sensitizing and test doses, and a new scoring system was developed.

Ten drops of a 0.1 molar solution of the freshly prepared base (dissolved in a 1:1:3 mixture of acetone, dioxane and olive oil) was dropped on the clipped skin of the lower back of white male guinea pigs. Twenty-four hours later, the hair at this area was removed by a barium sulfide depilatory, and readings for primary irritation were made, under uniform fluorescent lighting, of the amount of redness and swelling of the skin compared with the normal areas. The grading of *redness* was as follows: 0, normal; 1 slight, just detectable; 2, moderate, easily seen; 3, definite deep red, usually hot, not hemorrhagic; 4, dark red, may show hemorrhagic areas, usually accompanied by marked swelling and increase in heat of skin.

The degree of *swelling* of the skin was determined by picking up a fold of skin about one centimeter in length and feeling it between thumb and forefinger. The grading was as follows: 0, normal; 1, slight, just detectable; 2, moderate, easily felt; 3, marked, difficult to pick up a fold of skin, often visible without feeling the skin.

(24) H. O. Calvery, J. H. Draize and E. P. Laug, *Physiol. Dev.*, **26**, 495 (1946); M. Polak and A. M. Mom, *J. Investigative Dermatol.*, **13**, 125 (1949).

(25) O. H. Müller, *J. Chem. Ed.*, **18**, 65 (1941); *Cold Spring Harbor Symposium Quant. Biol.*, **7**, 59 (1939).

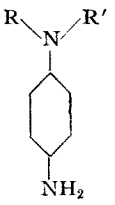
(26) T. H. James, *J. Phys. Chem.*, **43**, 701 (1939).

(27) Sodium-aluminum silicate, obtained from Philadelphia Quartz Co.

(28) K. Landsteiner, "The Specificity of Serological Reactions," Harvard University Press, Cambridge, Mass., 1944, pp. 197–210.

TABLE IX

4-AMINO-N-DIALKYLANILINES



No.[a]	Name	R	R	Substituent	Intermediate[a]	Base M.p., b.p., °C.	Mm.	Method, yield, %	Salt[b] m.p., °C.	Method, yield, %	Analyses,[c] % Calcd.	Found
1	4-Amino-N-dimethylaniline[d,7b]	CH_3	CH_3						½ H_2SO_4		C 51.9	52.2
									> 235°		H 7.0	7.1
											N 15.1	15.6
2	4-Amino-N-methyl-N-ethylaniline	CH_3	C_2H_5		Nitroso	B. 99-102	1	4	½H_2SO_4	1a	N 14.1	14.2
								45	225–228 dec.			
3	4-Amino-N-methyl-N-(*n*-propyl)-aniline	CH_3	C_3H_7-*n*		Nitroso	B. 104-106	1	4	½H_2SO_4	1a	C 56.4	56.6
								64	222-224 dec.	66	H 7.6	8.0
											N 13.1	13.2
4	4-Amino-N-methyl-N-(*n*-butyl)-aniline	CH_3	C_4H_9-*n*		Nitroso	B. 114-116	1	4	½H_2SO_4	1a	C 58.1	58.4
								78	208–211 dec.	80	H 8.0	8.4
											N 12.3	12.5
5	4-Amino-N-diethylaniline[7b]	C_2H_5	C_2H_5						HCl		C 58.5	58.7
									233.5		H 8.3	8.3
											N 13.7	13.7
6	4-Amino-N-ethyl-N-(*n*-propyl)-aniline	C_2H_5	C_3H_7-*n*		Nitroso	B. 105-107	1	4	½H_2SO_4	1a	N 12.3	12.1
								52	205-208 dec.	77		
7	4-Amino-N-di-(*n*-propyl)-aniline[7b,29]	*n*-C_3H_7	C_3H_7-*n*						H_2SO_4		C 49.6	49.3
									120–123		H 7.6	7.4
											N 9.7	9.6
8	4-Amino-2-methyl-N-dimethylaniline[7b,30]	CH_3	CH_3	2 CH_3					2HCl		N 12.6	12.7
									186–189 dec.			
9	4-Amino-2-methyl-N-diethylaniline[3]	C_2H_5	C_2H_5	2 CH_3	Azo			7	H_2SO_4	3a	C 47.8	47.3
									215–220 dec.	72	H 7.3	7.1
											N 10.1	10.1
											S 11.6	11.5
10	4-Amino-3-methyl-N-diethylaniline[7b]	C_2H_5	C_2H_5	3-CH_3					HCl		C 61.5	61.5
									263		H 8.9	8.9
											N 13.0	13.0
10a	4-Amino-3-ethyl-N-diethylaniline	C_2H_5	C_2H_5	3-C_2H_5	Azo			7	HCl	3c	C 62.9	62.9
									226.5-227.5	47	H 8.8	9.1
											N 12.3	12.3
11	4-Amino-2,5-dimethyl-N-diethylaniline	C_2H_5	C_2H_5	2,5-CH_3	Azo			7	3/2H_2SO_4	3a	C 42.5	42.8
									167–168	65	H 6.8	7.0
											N 14.1	13.7
12	4-Amino-3,5-dimethyl-N-diethylaniline	C_2H_5	C_2H_5	3,5-CH_3	Nitroso			5	HCl	3c	N 12.2	12.2
					Azo			7	263–264	81	Cl 15.5	15.7
13	4-Amino-3-hydroxymethyl-N-diethylaniline[32]	C_2H_5	C_2H_5	3-CH_2OH	Azo	B. 180	6	7	H_2SO_4-H_2O	3b	N 9.0	9.1
									102–103	72		
14	4-Amino-3-methylsulfonamidomethyl-N-diethylaniline	C_2H_5	C_2H_5	3-$CH_2NHSO_2CH_3$	Azo			7	HCl	3a	N 13.6	13.7
									196–197	89	Cl 11.5	11.8
14a	4-Amino-3-(β-hydroxyethyl)-N-diethyaniline	C_2H_5	C_2H_5	3-CH_2CH_2OH	Azo			7	2HCl	3a	C 51.2	51.0
									191–192	79	H 7.8	7.8
											Cl 25.3	25.2

TABLE IX (*Continued*)

No.[a]	Name	R	R	Substituent	Intermediate[a]	Base M.p., b.p., °C.	Mm.	Method, yield, %	Salt[b] m.p., °C.	Method, yield, %	Analyses,[c] % Calcd.	Found
14b	4-Amino-3-(β-aminoethyl)-N-diethylaniline	C_2H_5	C_2H_5	3-$CH_2CH_2NH_2$	Compound 15				3HCl	2c	C 45.5	45.2
									230	73	H 7.6	7.6
											Cl 33.6	33.5
											N 13.3	13.2
15	4-Amino-3-(β-acetamidoethyl)-N-diethylaniline	C_2H_5	C_2H_5	3-$CH_2CH_2NHCOCH_3$	Nitroso	B. 195–200	2	4	2HCl	1b	C 52.0	52.1
								84	190–192 dec.	70	H 7.1	7.9
											N 13.0	13.1
16	4-Amino-3-(β-methylsulfonamidoethyl)-N-diethylaniline	C_2H_5	C_2H_5	3-$CH_2CH_2NHSO_2CH_3$	Nitroso	B. 220–230	2	4	HCl	1a	C 48.5	48.8
								67	218–219	85	H 7.5	7.4
											N 13.1	13.0
16a	4-Amino-3-(N'-methyl-β-methylsulfonamidoethyl)-N-diethylaniline	C_2H_5	C_2H_5	3-$CH_2CH_2N(CH_3)SO_2CH_3$	Azo			7	H_2SO_4 138–140	3a 52	C 42.3 H 6.9 N 10.6 S 16.1	42.1 6.7 10.3 16.1
17	4-Amino-3-chloro-N-diethylaniline[33]	C_2H_5	C_2H_5	3-Cl	Azo			7	HCl 230–232 dec.	3c 58	C 51.1 H 6.8 N 11.9	51.6 6.9 11.9
18	4-Amino-2-methoxy-N-diethylaniline	C_2H_5	C_2H_5	2-OCH_3	Azo			7	$^1/_2H_2SO_4$ 183–185	3c 78	C 54.3 H 7.8 N 11.5	54.0 7.8 11.2
19	4-Amino-2-methoxy-5-methyl-N-diethylaniline	C_2H_5	C_2H_5	2-OCH_3-5-CH_3	Azo	-$NHCOCH_3$ m. 128–129		8 55	2HCl 228 dec.	2a 79	Cl 25.3	25.5
20	4-Amino-3-hydroxy-N-diethylaniline	C_2H_5	C_2H_5	3-OH	Azo			7	HCl 201–203	3a 57	N 12.9 Cl 16.4	12.9 16.3
21	4-Amino-3-methoxy-N-diethylaniline	C_2H_5	C_2H_5	3-OCH_3	Azo			7	HCl 208–209.5	3c 79	C 57.2 H 8.2 N 12.1 Cl 15.4	56.8 8.3 11.9 15.6
22	4-Amino-3-ethoxy-N-diethylaniline	C_2H_5	C_2H_5	3-OC_2H_5	Nitroso	B. 146–148	8	4 54	$^1/_2H_2SO_4 \cdot H_2O$ 144–146	1c 43	C 52.4 H 8.4 N 10.2	52.8 8.1 10.2
23	2,4-Diamino-N-diethylaniline	C_2H_5	C_2H_5	2-NH_2	Nitro			6	2HCl 235 dec.	3c 76	Cl 28.2	28.2
24	4-Amino-2-acetamido-N-diethylaniline	C_2H_5	C_2H_5	2-$NHCOCH_3$	Nitro	M. 103–104 (hexane)		6 79			C 65.0 H 8.6 N 19.0	65.2 8.5 19.4
25	3,4-Diamino-N-diethylaniline	C_2H_5	C_2H_5	3-NH_2	Nitro			6	H_2SO_4 203–205	3a 79	C 43.3 H 6.9 S 11.5	43.1 6.9 11.6
26	4-Amino-3-acetamido-N-diethylaniline	C_2H_5	C_2H_5	3-$NHCOCH_3$	Nitro	M. 100–101 (benzene)		6 83			C 65.1 H 8.6	65.2 8.7
27	4-Amino-3-methylsulfonamido-N-diethylaniline[34]	C_2H_5	C_2H_5	3-$NHSO_2CH_3$	Nitroso Azo			5 7	HCl 232	3a 88	C 45.0 H 6.8 N 14.3	45.0 7.0 13.9
28	4-Amino-3-ethylamino-N-diethylaniline	C_2H_5	C_2H_5	3-NHC_2H_5	Nitro			6	Mixture approximating H_2SO_4-$^1/_2H_2O$ 178–180 dec.	3d 43	C 45.8 H 7.6 S 10.2	45.8 7.4 10.9
29	4-Amino-3-dimethylamino-N-diethylaniline	C_2H_5	C_2H_5	3-$N(CH_3)_2$	Nitro			6	$H_2SO_4 \cdot H_2O$ 107–109	3d 68	C 44.6 H 7.7 S 9.9	44.7 7.7 10.2
30	4-Amino-3-methyl-N-methyl-N-(β-methylsulfonamidoethyl)-aniline	CH_3	$CH_2CH_2NHSO_2CH_3$	3-CH_3	Nitroso			5	H_2SO_4 184–185.5	3a 67	N 11.8	12.0

TABLE IX (*Continued*)

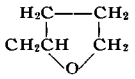
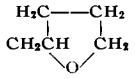
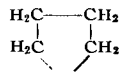
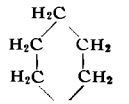
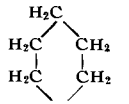
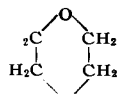
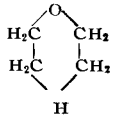
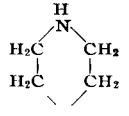
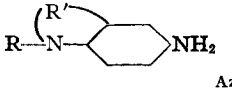
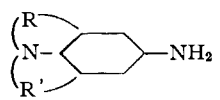
No.[a]	Name	R	R'	Substituent	Intermediate[a]	Base M.p., b.p., °C.	Mm.	Method, yield, %	Salt[b] m.p., °C.	Method, yield, %	Analyses,[c] % Calcd.	Found
31	4-Amino-N-ethyl-N-(β-hydroxyethyl)-aniline[35]	C_2H_5	CH_2CH_2OH		Nitroso	B. 148–160	1	4	$1/2H_2SO_4 \cdot H_2O$	1a	N 11.3	11.4
								90	179–180	74		
32	4-Amino-3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline[35]	C_2H_5	CH_2CH_2OH	3-CH_3	Nitroso	B. 148	2	4	$H_2SO_4 \cdot H_2O$	1a	N 9.0	9.0
								53	150–153	78		
32a	4-Amino-N-ethyl-N-(β-methoxyethyl)-aniline	C_2H_5	$CH_2CH_2OCH_3$		Azo			7	$1/2H_2SO_4$	3a	C 54.3	54.5
									187–189	81	H 7.8	8.1
											N 11.5	11.4
33	4-Amino-N-ethyl-N-(β-ethoxyethyl)-aniline	C_2H_5	$CH_2CH_2OC_2H_5$		Nitroso	B. 163 168	7	4	2HCl	1b	C 51.2	51.6
								36	198–199 dec.	64	H 7.8	8.1
											Cl 25.2	25.1
											N 10.0	10.6
34	4-Amino-N-ethyl-N-(β-aminoethyl)-aniline	C_2H_5	$CH_2CH_2NH_2$		Compound 35				2HCl	2b	C 47.6	48.0
									>250	50	H 7.5	7.5
											N 16.7	16.8
35	4-Amino-N-ethyl-N-(β-acetamidoethyl)-aniline	C_2H_5	$CH_2CH_2NHCOCH_3$		Nitroso	B. 190–195	1	5	2HCl	1b	N 14.3	14.4
								86	177–180	26		
35a	4-Amino-3-ethoxy-N-ethyl-N-(β-acetamidoethyl)-aniline	C_2H_5	$CH_2CH_2NHCOCH_3$	3-OC_2H_5	Nitroso			5	$H_2C_2O_4$	3a	N 11.8	11.8
										76		
36	4-Amino-N-ethyl-N-(β-methylsulfonamidoethyl)-aniline[23]	C_2H_5	$CH_2CH_2NHSO_2CH_3$		Nitroso	M. 67.5–68.5[e]		5	2HCl	3a	C 40.0	39.6
									200 dec.	75	H 6.4	6.5
											N 12.7	12.5
									H_2SO_4	1d	C 37.2	37.3
									153–155	85	H 5.9	5.8
37	4-Amino-3-methyl-N-ethyl-N-(β-methylsulfonamidoethyl)-aniline[23]	C_2H_5	$CH_2CH_2NHSO_2CH_3$	3-CH_3	Nitroso	M. 91–91.5[e]		4, 5	H_2SO_4	1d, 3a	N 11.4	11.1
								See also ref. 45	168–169	92, 91	S 17.3	17.2
									$3/2H_2SO_4 \cdot H_2O$[36]		C 33.0	32.8
									125–130		H 6.0	6.1
											N 9.6	9.7
38	4-Amino-3-ethoxy-N-ethyl-N-(β-methylsulfonamidoethyl)-aniline	C_2H_5	$CH_2CH_2NHSO_2CH_3$	3-OC_2H_5	Nitroso			5	$H_2C_2O_4$	3a	C 46.0	45.6
									87.5–90	78	H 6.4	6.8
											N 10.7	10.7
39	4-Amino-N-ethyl-N-(N'-methyl-β-methylsulfonamidoethyl)-aniline	C_2H_5	$CH_2CH_2NSO_2CH_3$ | CH_3		Nitroso	B. 205	1	4	$1/2H_2SO_4$	1a	C 45.0	45.4
									182	91	H 6.9	6.9
											N 13.1	13.4
40	4-Amino-3-methyl-N-(N'-methyl-β-methylsulfonamidoethyl)-aniline	C_2H_5	$CH_2CH_2NSO_2CH_3$ | CH_3	3-CH_3	Nitroso	M. 85–86		4, 5	$1/2H_2SO_4 \cdot H_2O$	3a	N 11.9	12.1
								74	148.5–150	82		
41	4-Amino-3-ethoxy-N-ethyl-N-(N'-methyl-β-methylsulfonamidoethyl)-aniline	C_2H_5	$CH_2CH_2NSO_2CH_3$ | CH_3	3-OC_2H_5	Nitroso			5	$H_2C_2O_4$	3a	N 10.4	10.6
									149–151	77		
42	4-Amino-N-ethyl-N-carbamylmethylaniline[37]	C_2H_5	CH_2CONH_2		Nitroso			5	HCl	3a	C 52.2	52.6
									252–253 dec.	57	H 7.0	7.4
											N 18.3	18.7
43	4-Amino-3-methyl-N-ethyl-N-carbamylmethylaniline[37]	C_2H_5	CH_2CONH_2	3-CH_3	Azo	M. 127–128		9			C 63.8	64.1
								79			H 8.2	8.4
											N 20.0	20.5
44	4-Amino-N-ethyl-N-tetrahydrofurfurylaniline	C_2H_5			Azo	B. 156–159	1	9	$1/2H_2SO_4$	1a	C 58.0	58.2
								54	165–169 dec.		H 7.8	7.2
											N 10.4	10.4
45	4-Amino-3-methyl-N-ethyl-N-tetrahydrofurfuryl-aniline[38]	C_2H_5		3-CH_3	Nitroso	B. 171–173	3	4	$1/2H_2SO_4$	1a	N 9.9	9.9
								Poor	136–138			

TABLE IX (*Continued*)

No.[a]	Name	R	R′	Substituent	Intermediate[a]	Base M.p., b.p., °C.	Mm.	Method, yield %	Salt[b] m.p., °C.	Method, yield %	Analyses,[c] % Calcd.	Found
46	N-(4-Aminophenyl)-pyrrolidine[7b]								$^1/_2H_2SO_4$ >255		C 56.9 H 7.1 N 13.3 S 7.6	57.4 7.2 13.2 7.5
47	N-(4-Aminophenyl)-piperidine[7b,39]								$^1/_2H_2SO_4$ >250		N 12.4	12.3
48	N-(4-Amino-3-methylphenyl)-piperidine[7b]			3-CH_3					H_2SO_4 179.5–180.5		N 9.7	9.7
49	N-(4-Aminophenyl)-morpnoline[7b,40]								$^1/_2H_2SO_4 \cdot H_2O$ 250 dec.		N 11.4	11.4
50	N-(4-Amino-3-methylphenyl)-morpholine[7b]			3-CH_3					$^1/_2H_2SO_4$ 214–215.5	3a 54	C 54.8 H 7.1 N 11.6	55.0 7.2 11.4
51	N-(4-Aminophenyl)-piperazine[41]				Nitro	M. 119–120.5		6 72			C 67.7 H 8.5 N 23.7	67.7 8.5 23.3
												
52	5-Amino-1-(β-methylsulfonamidoethyl)-2,3-dihydroindole	CH_3SO_2 C_2H_4NH	CH_2CH_2		Azo			7	$^1/_2H_2SO_4$ 235	3a 79	N 13.8	13.5
53	6-Amino-1-ethyl-1,2,3,4-tetrahydroquinoline[42]	C_2H_5	$CH_2CH_2CH_2$		Azo			7	$^1/_2H_2SO_4$ 252	3a 86	C 58.6 H 7.6 N 12.4	58.4 7.4 12.3
54	6-Amino-1-(β-methylsulfonamidoethyl)-1,2,3,4-tetrahydroquinoline	CH_3SO_2 C_2H_4NH	$CH_2CH_2CH_2$		Azo	M. 115–117		7	$^1/_2H_2SO_4$ 179–182	3a 91	N 13.2	13.2
54a	6-Amino-7-methyl-1-(β-methylsulfonamidoethyl)-1,2,3,4-tetrahydroquinoline	CH_3SO_2 C_2H_4NH	$CH_2CH_2CH_2$	7-CH_3	Azo	M. 150–152		3a 67	$^1/_2H_2SO_4 \cdot H_2O$ 205–212	7 71	N 12.0	12.0
												
55	9-Aminojulolidine	$CH_2CH_2CH_2$	$CH_2CH_2CH_2$		Azo			7	$^1/_2H_2SO_4$ 242 dec.	3a 82	N 11.8	11.5

[a] The position of the compound in this table will be used to locate intermediates in Tables X, XI, XII and XIII, and in the methods of preparation. [b] The salt is not necessarily that described in any prior references. [c] Analytical data are those of the salt unless otherwise indicated. [d] Eastman Grade was recrystallized from a mixture of 5 volumes of water and ethanol (Darco). [e] The salt may be neutralized with ammonium hydroxide.

The *total score* equals the sum of redness and swelling and ranges from zero for no irritation, to seven for severe irritation. This is called the *initial reading* and is a measure of any simple or primary irritating property which may be present. The solution is applied again at the same area 48 and 96 hours after the first application without obtaining further readings.

After a three-week interval (a period determined by experiment to be adequate for the development of sensitization), the same procedure is repeated, this time on the right shoulder area. An additional test may be made seven days later, using the left shoulder area. The difference between the initial reading for primary irritation and an average of the two final readings is considered a measure of the degree of skin sensitization induced. Skin sensitizers of *high* activity, such as *p*-phenylenediamine (which is run with every group of unknowns, as a control or standard), usually give final values between four and seven, compared with initial values usually below one. We have designated as compounds of *low* activity, those which give up to two times the initial value, and of moderate activity those which show somewhere between two and four times the initial value.

Tests by this method with a large number of compounds used in the processing of photographic materials have shown that it is very useful in differentiating the highly potent sensitizing agents, which might affect a large percentage of individuals exposed, from those of low potency which affect only an occasional person. Following the development of the animal-experiment data, a series of patch tests was performed on human subjects with those compounds of photographic interest which showed low to moderate sensitizing properties. As in the animal tests, a sequence of sensitizing applications, a three-week latent period and a test application were made on groups of fifty to one hundred subjects. As an arbitrary criterion, substances showing no greater sensitizing potency than metol (N-methyl-*p*-aminophenol) were considered satisfactory for general photographic processing purposes. The results of the animal experiments, the human patch test studies and the observed experience with the materials in plant use (as judged by the incidence of dermatitis) have given a remarkably good correlation. Compounds which have yielded varying experimental values, such as 4-amino-3-methyl-N-diethylaniline (10), should be regarded as potent skin sensitizers.

II. **Preparations** (R. L. Bent, D. B. Glass, J. M. Snell, J. R. Thirtle).—In order to avoid repetition of individual procedures, the preparation of 4-amino-N-dialkylanilines is described in the following paragraphs by means of general procedures and tables. The arrangement which proved most economical and lucid is to begin with the final products and to work back from these to the starting materials which are available commercially or are described in the literature.

A. 4-Amino-N-dialkylanilines. 1. **Salts.**—4-Amino-N-dialkylanilines are, as a rule, susceptible to aerial oxidation and the compounds were, therefore, in the majority of cases transformed into the more stable salts, as shown in Table IX, the nature and amount of acid being so chosen as to obtain crystalline products. The presence or absence of water leading to hydrates or to anhydrous salts, respectively, afforded another variable. In some cases, moisture absorbed from the air was sufficient for the formation of the hydrates. Precipitations and purifications of the salts were carried out by the following methods, to which reference is made in Table IX.

Method 1. a.—Compounds 2, 3, 4, 6, 16, 31, 32, 39, 44, 45: The distilled 4-amino-N-dialkylaniline is dissolved in about three volumes of absolute alcohol or 95% ethanol (Compound 44) by warming if necessary, and the theoretical quantity of acid for the monohydrochloride, hemisulfate, sulfate, sesquisulfate or oxalate in five volumes of absolute alcohol is added. The solution is cooled, scratched and seeded if necessary. After thorough chilling, the salt is collected and washed with cold absolute alcohol and dried in a vacuum desiccator over sulfuric acid. The salts may be recrystallized from absolute alcohol.

b.—Compounds 15, 33, 35: The distilled 4-amino-N-dialkylaniline is treated as in **a** except that a 5% excess over 2 moles of concentrated hydrochloric acid is added. The salt crystallizes and is recrystallized from *n*-butanol (Compound 33) or is thrown out of solution as a gum by five volumes of acetone. The supernatant liquid is decanted and the gum washed with acetone. The gum is dissolved in 2.5 volumes of boiling absolute alcohol and allowed to stand several hours at room temperature, then overnight at 0°. The white crystals are collected and washed with absolute alcohol containing a trace of concentrated hydrochloric acid.

c.—Compound 22: Treated as in **a** but the amine is dissolved in two volumes of absolute alcohol and the theoretical amount of acid for the hemisulfate is added in ten volumes of absolute alcohol followed by a volume of ether twice that of the resulting solution. The hemisulfate hydrate precipitates out on scratching. The product is collected and washed with acetone.

d.—Compounds 36, 37: The crystalline free base (footnote *e*, Table IX) is dissolved in a mixture of an equal weight of water and the theoretical amount of sulfuric acid. The solution is then diluted with ten volumes of absolute alcohol, while scratching and cooling. After standing overnight, the crystals are collected and washed with cold absolute alcohol.

Method 2. a.—Compound 19: A solution of 0.1 mole of the amide, obtained by acetylation after reduction of the azo dye (Method 8), in 50 cc. of water and 50 cc. of concentrated hydrochloric acid is refluxed for two hours, then concentrated to a sirup under reduced pressure. The residue is dissolved in 150 cc. of absolute alcohol and again concentrated to a sirup. This residue is dissolved in 200 cc. of absolute alcohol and concentrated until the salt begins to crystallize. The mixture is chilled overnight and the crystals are collected and dried *in vacuo*.

b.—Compound 34: The N-(β-acetamidoethyl)-derivative (Compound 35) is treated as in **a** except that the final solution containing 100 cc. of absolute alcohol is not concentrated.

c.—Compound 14b: Compound 15 was heated at reflux with four volumes of concentrated hydrochloric acid for seventeen hours. The acid was removed under vacuum and an equal volume more was added and distilled off. The residue was treated with an equal volume of absolute alcohol and concentrated under a vacuum until crystallization started. The mixture was chilled and the crystals washed with absolute alcohol, triturated with ten volumes of hot absolute alcohol, and dried over sulfuric acid.

Method 3. a.—Compounds 9, 11, 14, 14a, 16a, 20, 25, 27, 30, 32a, 35a, 36, 37, 38, 40, 41, 42, 46, 50, 52–55.—The filtered alcoholic solution of the 4-amino-N-dialkylaniline obtained by catalytic reduction of the nitroso, nitro or azo derivative (Methods 5, 6, 7) is treated with the theoretical quantity of acid for the monohydrochloride, dihydrochloride, hemisulfate, sulfate, sesquisulfate or oxalate in five volumes of absolute alcohol. Crystallization is induced, if necessary, as described in 1-**a**. Compounds 20 and 27 are purified by washing with acetone; the others may be recrystallized, if necessary, from alcohol or alcohol and water, and dried over sulfuric acid *in vacuo*.

b.—Compound 13: Treated as in **a** but the sulfuric acid is added in 95% alcohol. The solution is allowed to stand at room temperature for three days. The crystals are collected, washed with 95% alcohol and dried at 45°.

c.—Compounds 10a, 12, 17, 18, 21, 23: Treated as in a but ether or acetone is added carefully until crystallization starts. After standing at 0° overnight, the crystals are collected and washed with cold acetone.

(29) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 116 (1915); P. Karrer, *Ber.*, **48**, 1398 (1915).

(30) A. Bernthsen, *ibid.*, **25**, 3128 (1892); L. F. Fieser and H. T. Thompson, THIS JOURNAL, **61**, 376 (1939).

(31) J. Rohner, German Patent 193,211 (1907).

(32) J. B. Dickey and J. G. McNally, U. S. Patent 2,273,564 (1942).

(33) German Patent 197,035 (1908).

(34) V. Tulagin, U. S. Patent 2,414,491 (1947); A. Weissberger, U. S. Patent 2,449,919 (1948).

(35) British Patent 460,580 (1937); Canadian Patent 369,777 (1937); U. S. Patent 2,108,243 (1938) (I. G.).

(36) Supplied by Tennessee Eastman Corporation.

(37) British Patent 541,328 (1941).

(38) J. B. Dickey and J. G. McNally, U. S. Patent 2,364,350 (1944).

(39) E. Lellman and W. Geller, *Ber.*, **21**, 2281 (1888).

(40) H. A. Lubs, U. S. Patent 2,004,763 (1935); C. B. Kremer, M. Meltsner and L. Greenstein, THIS JOURNAL, **61**, 2552 (1939).

(41) (a) V. Prelog and Z. Blažek, *Collection Czechoslov. Chem. Commun.*, **6**, 211 (1934) [*C. A.*, **28**, 5824 (1934)]; (b) *ibid.*, **8**, 377 (1936) [*C. A.*, **31**, 1949 (1937)]; (c) D. Kohlbach, *Arhiv. Hem. Farm.*, **11**, 99 (1937) [*C. A.*, **33**, 2897 (1939)].

(42) W. D. Peterson, U. S. Patent 2,196,739 (1940).

d.—Compounds 28, 29; Treated as in **a** but 7 cc. of water is added to the filtrate (for 0.1 mole run) and the salt is drowned out with ether. The gummy solid is dissolved in hot absolute alcohol and chilled overnight. The tacky crystals are recrystallized from absolute alcohol.

2. Bases.—The last step in the preparation of 4-amino-N-dialkylanilines is, in every case, a reduction, either of a nitroso, a nitro or an azo compound. The choice of intermediate depends on the ease with which the latter can be obtained and reduced. If nitroso compounds could be easily obtained and reduced, they were chosen as intermediates. In other cases, the preparations were conducted by way of the nitro compounds or, if these were not available, of the azo compounds. The azo dyes were also chosen when it was desirable to keep a stable intermediate in stock.

Treatment of dialkylanilines with nitrous acid can result not only in *p*-nitroso and *p*-nitro compounds, but also in other mononitro and dinitro products, and in the elimination of an alkyl group and formation of N-nitroso derivatives.[43] In experiments with 1-alkyl-1,2,3,4-tetrahydroquinolines, it appeared to us that the heterocyclic ring might be opened by the nitrous acid.

In the preparation of azo dyes as intermediates, a diazonium salt should be used which is reactive enough to give good yields of well-crystallizing azo compounds and which, after reduction, forms an amine which can be easily separated from the desired product. Azo compounds from *p*-nitroaniline which were used in early work are undesirable because *p*-phenylenediamine is the second product of the reduction. Diazotized 2,5-dichloroaniline[44] reacts readily with dialkylanilines and the resulting azo dyes are easily purified by recrystallization. After reduction, the 2,5-dichloroaniline is so weak a base that the *p*-aminodialkylaniline can be precipitated by addition of the theoretical amount of mineral acid without salt formation of the dichloroaniline.

(A) **From Nitroso Compounds.**—Nitroso compounds are most frequently reduced by zinc and hydrochloric acid and the amines are isolated by distillation (Method 4). This method is generally satisfactory for compounds boiling below 200° at 1 mm. Some relatively volatile compounds, however, are too unstable even at a lower temperature to be prepared in this way. For convenience in these cases as well as some others, the nitroso compounds are reduced catalytically in alcoholic solution and the salts of these amines isolated by addition of an acid to the filtered reduction mixture (Method 5).

Method 4.—Compounds 2, 3, 4, 6, 15, 16, 22, 31, 32, 33, 37, 39, 40, 45: One mole of the nitroso compound is dissolved in one liter of water and 600 cc. of concentrated hydrochloric acid, or the solution as obtained in Method 10b is diluted with 700 cc. of water and 600 cc. of concentrated hydrochloric acid. To this solution is added gradually, with stirring, about 300 g. of zinc dust at 20° (ice-bath). When the reaction mixture is colorless, the excess zinc dust is removed and the filtrate is treated with excess 50% sodium hydroxide or with excess ammonium hydroxide.[45] The oil is extracted into benzene or chloroform, dried over potassium carbonate or sodium sulfate, concentrated to a low volume, then vacuum-distilled. The desired fraction is collected over a 5 to 20° range at 1 to 10 mm., then refractioned over a narrow range.

Method 5.—Compounds 12, 27, 30, 34, 35, 35a, 36, 37, 38, 40, 41, 42: Up to 0.2 mole of 4-nitrosodialkylaniline obtained by Method 10 is shaken with Raney nickel catalyst in 25 to 150 cc. of absolute alcohol at 70–80° under 45 p.s.i. of hydrogen. Reduction is usually complete in ten to thirty minutes. The catalyst is removed by filtration and the salt formed by Method 3, or the filtrate is concentrated and the residue recrystallized (Compound 40) or distilled and treated as in Method 1b (Compound 35).

(B) **From Nitro Compounds. Method 6.**—Compounds 23, 24, 25, 26, 28, 29, 44, 51: Up to 0.2 mole of the nitro compound is reduced with hydrogen and catalyst as described above. The filtrate is treated by Method 3 to form the salt, concentrated under reduced pressure, and the residue distilled at 1–10 mm. (Compound 44; salt by Method 1a), or concentrated, leaving a crystalline product which can be recrystallized from hexane or benzene (Compounds 24, 26, 51).

(C) **From Azo Compounds. Method 7. 2,5-Dichlorophenylazo.**—Compounds 9, 10a, 11, 12, 13, 14, 14a, 16a, 17, 18, 20, 21, 27, 32a, 52–55: Catalytic reduction is effected as above and the salt is precipitated from the filtrate by Method 3, or the amine may crystallize from the reduction mixture on cooling (Compound 54a).

Method 8. *p*-Nitrophenylazo.—Compound 19: Catalytic reduction is effected as described above. The filtrate is concentrated under reduced pressure and up to 100 cc. (for 0.2 mole run) of acetic anhydride is added, with stirring and cooling. Several drops of concentrated sulfuric acid are added and the mixture is heated on a steam-bath for thirty minutes. The excess acetic anhydride is destroyed by stirring with 600 cc. of water. The solution is neutralized with sodium hydroxide, then 200 cc. of concentrated hydrochloric acid is added, and the N,N'-diacetyl-*p*-phenylenediamine is removed by filtration. The filtrate is made alkaline with 50% sodium hydroxide, chilled thoroughly and insoluble 4-acetamidodialkylaniline collected and washed. The acetamido compound is hydrolyzed and converted to the salt as described in Method 2a.

Method 9. *p*-Sulfophenylazo.—Compounds 43, 44: The solution of the *p*-sulfophenylazo derivative of the dialkylaniline is prepared as described in Method 14. Solid sodium hydrosulfite is added in small portions (together with water, if precipitation of the dye occurs) until all the red color disappears. The solution is made alkaline with 50% sodium hydroxide and the product is (a) extracted with ether, dried over magnesium sulfate, concentrated, and the residue distilled at low pressure (Compound 44; salt by Method 1), or (b) collected as a solid, washed with water and recrystallized from water containing a little alcohol.

B. **Intermediates** (1) **Nitroso Compounds.**—The simplest method for making the intermediates from which 4-amino-N-dialkylanilines are obtained is that of nitrosation. The reaction is usually complete within one-half hour. The nitroso compound may be isolated by making the reaction mixture alkaline, or, because of the unstable nature of many nitroso compounds of this type, may be reduced directly to the corresponding *p*-phenylenediamine compound. When a minimum of water has been used in the nitrosation reaction, the hydrochloride of the nitroso derivative may crystallize from the reaction mixture on standing at low temperature.

Some less readily nitrosated compounds may take longer (as much as several hours) to react completely. Side reactions, however, make it desirable to end the reaction as soon as possible.[43] In Table X are listed the nitroso derivatives which were made in this work. Where no yield is indicated, the nitroso derivative was reduced without isolation directly to the dialkyl *p*-phenylenediamine. Moreover, the indicated yields are not entirely proportional to the extent of nitrosation, since isolation and purification introduced difficulties.

Method 10. 4-Nitrosodialkylanilines.—Compounds 2, 3, 4, 6, 12, 15, 16, 22, 27, 30–33, 35–42, 45: A solution of one mole of dialkylaniline in one liter of water and 250 cc. of concentrated hydrochloric acid is cooled to 0° and nitrosated by the addition of 69 g. (1.0 mole) of sodium nitrite in 200 cc. of water, keeping the temperature at 0–5°. The mixture is stirred at 0–5° for thirty minutes, then treated in one of the following ways:

a.—The mixture is made alkaline with ammonium hydroxide and stirred at 0–5° until crystallization occurs or a gummy solid persists. The material is recrystallized from 150 to 400 cc. of 95% alcohol, and cooled to 5° before filtering. The crystals are washed with cold 95% alcohol and dried in air. (Compounds 2, 12, 16, 27, 30, 35–42.)

b.—The hydrochloride of the nitroso compound may precipitate in some quantity. More hydrochloric acid and water are added and reduction to the developing agent is effected by zinc dust by Method 4. (Compounds 3, 4, 6, 15, 16, 22, 31–33, 45.)

(2) **Nitro Compounds.**—In preparing 4-nitrodialkylanilines, we have used either the condensation of nitrohalobenzene with a secondary amine or selective reaction of 3,4-dinitrodialkylanilines with ammonia and amines. The first method has been applied especially to the intermediates in which the secondary amine was heterocyclic. Only one

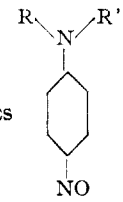
(43) H. H. Hodgson and D. E. Nicholson, *J. Chem. Soc.*, 470 (1941).

(44) E. Noelting and E. Kopp, *Ber.*, **38**, 3506 (1905).

(45) Compounds 37 and 40, which form soluble sodium salts, crystallize when ammonium hydroxide is used. The crystals are collected, washed with water, dried and recrystallized from water or a benzene-ligroin mixture.

TABLE X

4-NITROSO-N-DIALKYLANILINES

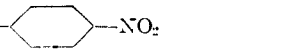


Compound[a] number	R	R'	Substituent	Method	Yield, %	M.p., °C.	Analyses, % Calcd.	Found	Ref.
2	CH_3	C_2H_5		10a					43, 46
3	CH_3	C_3H_7-*n*		10b					47
4	CH_3	C_4H_9-*n*		10b					48
6	C_2H_5	C_3H_7-*n*		10b					
12	C_2H_5	C_2H_5	3,5-CH_3	10a	44	103–104	N 13.6	13.7	
15	C_2H_5	C_2H_5	$CH_2CH_2NHCOCH_3$	10b					
16	C_2H_5	C_2H_5	$CH_2CH_2NHSO_2CH_3$	10a, b	65 as ·HCl 100 from ·HCl	81–82.5	N 14.0	14.3	
22	C_2H_5	C_2H_5	3-OC_2H_5	10b					49
27	C_2H_5	C_2H_5	3-$NHSO_2CH_3$	10a, b	71	81–82[b] 109–111	N 15.5	15.7	34
30	CH_3	$CH_2CH_2NHSO_2CH_3$	3-CH_3	10a	83	133–134	N 15.5	15.9	
31	C_2H_5	CH_2CH_2OH		10b					35
32	C_2H_5	CH_2CH_2OH	3-CH_3	10b					35
33	C_2H_5	$CH_2CH_2OC_2H_5$		10b					
35	C_2H_5	$CH_2CH_2NHCOCH_3$		10a	83	106–107	N 17.9	17.6	
35a	C_2H_5	$CH_2CH_2NHCOCH_3$	3-OC_2H_5	10a	100	141–142	N 15.0	14.6	
36	C_2H_5	$CH_2CH_2NHSO_2CH_3$		10a	83	106–107	N 15.5	15.3	
37	C_2H_5	$CH_2CH_2NHSO_2CH_3$	3-CH_3	10a	75	121–122	N 14.7	14.3	
38	C_2H_5	$CH_2CH_2NHSO_2CH_3$	3-OC_2H_5	10a	85	112–113			
39	C_2H_5	$CH_2CH_2N(CH_3)SO_2CH_3$		10a	78	93–94	N 14.7	14.7	
40	C_2H_5	$CH_2CH_2N(CH_3)SO_2CH_3$	3-CH_3	10a	51	74–76	N 14.0	13.6	
41	C_2H_5	$CH_2CH_2N(CH_3)SO_2CH_3$	3-OC_2H_5	10a	61	111–112			
42	C_2H_5	CH_2CONH_2		10a	89	168–169	N 20.3	20.8	
45	C_2H_5	$CH_2\overline{CHCH_2CH_2CH_2O}$	3-CH_3	10b					

[a] Refers to location of reduced compound in Table IX. [b] Polymorphism.

TABLE XI

4-NITRO-N-DIALKYLANILINES



Compound No.[a]	X	Substituent	Yield, %	M.p., °C.	Analyses, % Calcd.	Found	Ref.
23	$(C_2H_5)_2N$	2-NO_2	85	78–80			50
23	$(C_2H_5)_2N$	2-NH_2	32	204–205 (hydrochloride)			51
24	$(C_2H_5)_2N$	2-$NHCOCH_3$	77	49–50.5	N 16.7	16.2	
25	$(C_2H_5)_2N$	3-NO_2	56	94–96			52
25	$(C_2H_5)_2N$	3-NH_2	92	136–137			53
26	$(C_2H_5)_2N$	3-$NHCOCH_3$	90	94–95[54]	N 16.7	16.4	
28	$(C_2H_5)_2N$	3-NHC_2H_5	95	78–80			53
29	$(C_2H_5)_2N$	3-$N(CH_3)_2$	92	63.5–64.5			53
51	$HN(-CH_2CH_2-)_2N-$		72	129–130			41, 55, 57

[a] Refers to position in Table IX.

(46) J. C. Cain, *Seventh Int. Congr. Appl. Chem., London*, 1909; *J. Soc. Chem. Ind.*, **28**, 696 (1909).

(47) R. Stoerner and V. F. von Lepel, *Ber.*, **29**, 2110 (1896).

(48) J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, **117**, 103 (1920), isolated the nitroso compound as a greenish-blue liquid.

(49) German Patent 300,253 (1917) (*Chem. Zentr.*, **88**, II, 579 (1917)).

(50) P. van Romburgh, *Rec. trav. chim.*, **2**, 40 (1883).

(51) H. Burton and C. S. Gibson, *J. Chem. Soc.*, 2387 (1927).

(52) (a) A. Hantzsch, *Ber.*, **43**, 1662 (1910), dinitrated diethylaniline; (b) based on the method of H. Swann, *J. Chem Soc.*, **117**, 1 (1920); see also H. H. Hodgson and E. W. Smith, *ibid.*, 1508 (1931).

(53) P. van Romburgh, *Rec. trav. chim.*, **42**, 804 (1923).

(54) Melting point was first 70–71° but changed to 94–95° on standing at 45°.

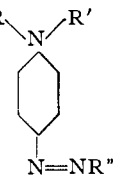
(55) A. Schmidt and G. Wickmann, *Ber.*, **24**, 3237 (1891).

dialkylaniline proper was made by this method, namely, 2,4-dinitrodiethylaniline. The second method was used to make developing agents having an amino or amido group in the 3-position. The 4-nitrodialkylanilines are listed in Table XI.

Method 11. a. 2-Acetamido-4-nitro-N-diethylaniline.—Compound 24: A mixture of 12.6 g. (0.052 mole) of 2-amino-4-nitro-N-diethylaniline hydrochloride, 4.9 g. (0.06 mole) of sodium acetate, 9.5 cc. of acetic anhydride and 25 cc. of glacial acetic acid was heated on a steam-bath for four hours, with stirring. The excess acetic anhydride was hydrolyzed and the reaction mixture made alkaline with ammonium hydroxide. The mixture was extracted with benzene and the extract evaporated to dryness. The residue crystallized on standing, giving 12.3 g. (95%), m.p. 48–

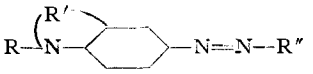
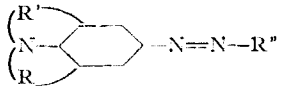
TABLE XII

4-ARYLAZO-N-DIALKYLANILINES



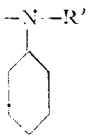
Compound No.[a]	R	R'	Substituent	R"	Method	Yield, %	M.p., °C.	Analyses, % Calcd.	Found
9	C_2H_5	C_2H_5	2-CH_3	2,5-Dichlorophenyl	15	48	71–73	Ref. 31	
10a	C_2H_5	C_2H_5	3-C_2H_5	2,5-Dichlorophenyl	15	83	87.5–88.5	C 61.6	61.2
								H 6.0	6.2
								N 12.0	12.1
11	C_2H_5	C_2H_5	2,5-CH_3	2,5-Dichlorophenyl	15	71	93–94.5	N 12.0	12.3
12	C_2H_5	C_2H_5	3,5-CH_3	2,5-Dichlorophenyl	15	72	164–165	N 12.0	12.2
13[58]	C_2H_5	C_2H_5	3-CH_2OH	2,5-Dichlorophenyl	15	82	128–128.5	N 11.9	11.5
14	C_2H_5	C_2H_5	3-$CH_2NHSO_2CH_3$	2,5-Dichlorophenyl	15	73	144–145	N 13.3	13.1
14a	C_2H_5	C_2H_5	3-CH_2CH_2OH	2,5-Dichlorophenyl	15	77	110.5–111.5	C 59.0	58.6
								H 5.8	6.0
								N 11.5	11.8
16a	C_2H_5	C_2H_5	3-$CH_2CH_2N(CH_3)SO_2CH_3$	2,5-Dichlorophenyl	15	74	143–144	C 52.5	52.5
								H 5.7	5.4
								N 12.2	12.1
								Cl 15.5	15.8
17	C_2H_5	C_2H_5	3-Cl	2,5-Dichlorophenyl	15	78	135–136	N 11.8	11.8
18	C_2H_5	C_2H_5	2-OCH_3	2,5-Dichlorophenyl	15	43.5	67–70	C 58.0	57.9
								H 5.4	5.4
								N 11.9	12.1
19	C_2H_5	C_2H_5	2-OCH_3-5-CH_3	*p*-Nitrophenyl	13	70	116–117	N 16.4	16.2
20	C_2H_5	C_2H_5	3-OH	2,5-Dichlorophenyl	15	43	153–155	C 56.8	56.6
						22	157–158	H 5.0	5.0
								O 4.7	5.1
21	C_2H_5	C_2H_5	3-OCH_3	2,5-Dichlorophenyl	15	65	140.5–142	C 58.0	57.5
								H 5.4	5.6
								N 11.9	12.0
27	C_2H_5	C_2H_5	3-$NHSO_2CH_3$	2,5-Dichlorophenyl	15	80	135–136	C 49.2	49.5
								H 4.8	5.0
32a	C_2H_5	$C_2H_4OCH_3$		2,5-Dichlorophenyl	15	64	77.5–79	C 57.9	57.4
								H 5.4	5.5
43	C_2H_5	CH_2CONH_2	3-CH_3	*p*-Sulfophenyl	14				
44	C_2H_5	$CH_2CHCH_2CH_2CH_2O$		*p*-Sulfophenyl	14				

TABLE XII (*Continued*)

Compound No.[a]	R	R'	Substituent	R"	Method	Yield, %	M.p., °C.	Analyses, % Calcd.	Found
									
52	$CH_3SO_2NHCH_2CH_2$	CH_2CH_2		2,5-Dichlorophenyl	15	89	144–146	N 13.6	13.1
53	C_2H_5	$CH_2CH_2CH_2$		2,5-Dichlorophenyl	15	65	128–129	N 12.6	12.8
54	$CH_3SO_2NHCH_2CH_2$	$CH_2CH_2CH_2$		2,5-Dichlorophenyl	15	83	149–150	N 13.1	13.3
54a	$CH_3SO_2NHCH_2CH_2$	$CH_2CH_2CH_2$	7-CH_3	2,5-Dichlorophenyl	15	31	183–184	N 12.7	12.4
									
55[59]	$CH_2CH_2CH_2$	$CH_2CH_2CH_2$		2,5-Dichlorophenyl	15	48	147–148	N 12.1	12.3

[a] Refers to position in Table IX.

TABLE XIII

SUBSTITUTED ANILINES 

Cpd. No.[a]	No.	R	R'	Substituent	Intermediate	Method	B.p., m.p., °C.	Mm.	Yield, %	Analyses, % Calcd.	Found	Ref.
					$CH_3NHC_6H_5$	16b(1)	B. 95–98	10	60			63
					$CH_3NHC_6H_5$	16b(1)	B. 114–116	12	66			48, 63
					$C_2H_5NHC_6H_5$	16b(1)	B. 100–104	11	40			63
3	1	CH_3	n-C_3H_7	3-C_2H_5	3-Ethylaniline	16a	B. 112–115	11	68			
4	2	CH_3	n-C_4H_9	2,5-CH_3	2,5-Xylidine	16a	B. 107–110	20	40	N 7.9	7.5	
6	3	C_2H_5	n-C_3H_7	3,5-CH_3	3,5-Xylidine	16a	B. 119–120	12	83			
10a	3a	C_2H_5	C_2H_5	3-CH_2Br	3-$(C_2H_5)_2NC_6H_4CH_2OH$[58]	21b	Hydrobromide M. 162–164		77	N 4.3	4.4	
11	4	C_2H_5	C_2H_5	3-$CH_2N(CO)_2C_6H_4$	6	22[64]	M. 86–88		83	N 9.1	8.9	
12	5	C_2H_5	C_2H_5	3-CH_2NH_2	7	23b	B. 84	0.5	75	N 15.7	15.0	
14	6	C_2H_5	C_2H_5	3-$CH_2NHSO_2CH_3$	8	25b	Sodium salt M. 88		79	N 10.1	9.8	
14	7	C_2H_5	C_2H_5	3-CH_2COOH	11	33	B. 160–165	1	37b	N 6.8	6.9	
14	8	C_2H_5	C_2H_5	3-CH_2CH_2OH	9a	34	B. 100–103	1	81	N 7.3	7.3	
14	9	C_2H_5	C_2H_5	3-CH_2CN		27	B. 132–135	2	83			65
14a	9a	C_2H_5	C_2H_5	3-CH_2CN	10	16a	B. 125–130	2	89	N 14.9	15.0	
14a	9b	C_2H_5	C_2H_5	3-$CH_2CH_2NH_2$	11	24	B. 148–150	10	100			
15	10	H	H	3-$CH_2CH_2NHCOCH_3$	12	25a	Not purif.		100			
15	11	C_2H_5	C_2H_5	3-$CH_2CH_2NHSO_2CH_3$	12	25b	Hydrochloride M. 181–182.5		98 (Base)	N 9.1	9.1 Hydrochloride	
15	12	C_2H_5	C_2H_5	3-$CH_2CH_2N(CH_3)SO_2CH_3$	14	26a	B. 150–155	0.05	61			[c]
15	13	C_2H_5	C_2H_5	3-Cl	*m*-Chloroaniline	16a	B. 113–114	6	86			66
16	14	C_2H_5	C_2H_5	2-OCH_3	*o*-Anisidine	16a	B. 95–98	8	21			
16a	14a	C_2H_5	C_2H_5									
17	15	C_2H_5	C_2H_5									
18	16	C_2H_5	C_2H_5									

TABLE XIII (*Continued*)

Cpd. No.[a]	No.	R	R'	Substituent	Intermediate	Method	B.p., m.p., °C.	Mm.	Yield, %	Analyses, % Calcd.	Found	Ref.
19	17	C_2H_5	C_2H_5	2-OCH_3-5-CH_3	Cresidine	16a	B. 121–122	18	78	N 7.3	7.2	
21	18	C_2H_5	C_2H_5	3-OCH_3	*m*-Anisidine	16a	B. 120–124	8	65			67
27	19	C_2H_5	C_2H_5	3-$NHSO_2CH_3$	3-$(C_2H_5)_2N$-$C_6H_4NH_2$	25b	Hydrochloride M. 182–183		80 (Base)	N 10.0 Hydrochloride	10.4	
30	20	CH_3	$C_2H_4NH_2$	3-CH_3	3-$CH_3NHC_6H_4CH_3$	16b(2)	B. 125–126	6	38			
30	21	CH_3	$C_2H_4NHSO_2CH_3$	3-CH_3	20	25b	M. 55–59		76			
31	22	C_2H_5	C_2H_4OH		$C_2H_5NHC_6H_5$	18	B. 165–167	22	100			68
32	23	C_2H_5	C_2H_4OH	3-CH_3	3-$C_2H_5NHC_6H_4CH_3$	18	B. 117–119	1.5	94			
32a	23a	C_2H_5	$C_2H_4OCH_3$		$C_2H_5NHC_6H_5$	16b(1)	B. 123–125	13	51			69
33	24	C_2H_5	$C_2H_4OC_2H_5$		$C_2H_5NHC_6H_5$	16b(1)	B. 110–115	3	82			
35	25	C_2H_5	C_2H_4Cl		22	21a	B. 127	10	93			70
35	26	C_2H_5	$C_2H_4N(CO)_2C_6H_4$		25	22	M. 81–82		82			
35	27	C_2H_5	$C_2H_4NH_2$		26	23a	B. 120–121	5	90			71
					41	24	B. 120–121	5	82			
35	28	C_2H_5	$C_2H_4NHCOCH_3$		27	25a	M. 93.5–94.5		100 (crude)			
35a	28a	C_2H_5	$C_2H_4NHCOCH_3$	3-OC_2H_5	36	25a	M. 96–97		77			
36	29	C_2H_5	$C_2H_4NHSO_2CH_3$		27	25b	M. 49–50		84	N 11.6	12.0	
37	30	C_2H_5	C_2H_4Cl	3-CH_3	23	21a	B. 100–102	2	90			
37	31	C_2H_5	$C_2H_4N(CO)_2C_6H_4$	3-CH_3	30	22	M. 88–90		90	N 9.1	9.2	
37	32	C_2H_5	$C_2H_4NH_2$	3-CH_3	31	23a	B. 120	3	82	N 15.7	15.1	
					43	24	B. 120	3	94			
37	33	C_2H_5	$C_2H_4NHSO_2CH_3$	3-CH_3	32	25b	B. 194–195	1	86			
38	34	C_2H_5	$COCH_3$	3-OC_2H_5	*m*-Phenetidine	28	B. 158–159	10	50			
38	35	C_2H_5	H	3-OC_2H_5	34	29	B. 125–127	7	95	N 8.5	8.3	72
38	36	C_2H_5	$C_2H_4NH_2$	3-OC_2H_5	35	16b(2)	B. 181–183	18	40			
38	37	C_2H_5	$C_2H_4NHSO_2CH_3$	3-OC_2H_5	36	25b	Not purif.		89			
39	38	C_2H_5	$C_2H_4N(CH_3)SO_2CH_3$		35	16b(4)	Not purif.		99			
					29	26a	Not purif.		60			
40	39	C_2H_5	$C_2H_4NSO_2CH_2$ with CH_3	3-CH_3	33	26a	Not purif.		88			
41	40	C_2H_5	$C_2H_4NSO_2CH_3$ with CH_3	3-OC_2H_5	37	26b	Not purif.		60			
42	41	C_2H_5	CH_2CN		$C_2H_5NHC_6H_5$	19	B. 133–134	6	75			
42	42	C_2H_5	CH_2CONH_2		41	20	M. 113.5–115		73			
43	43	C_2H_5	CH_2CN	3-CH_3	3-$C_2H_5NHC_6H_4CH_3$	19	B. 107	1	79	N 16.1	16.1	
43	44	C_2H_5	CH_2CONH_2	3-CH_3	43	20	M. 124–125		56			
44	45	C_2H_5	$CH_2C{=}CHCH{=}CH{-}O$		$C_2H_5NHC_6H_5$	16b(3)	B. 125–126	3	65			
44	46	C_2H_5	$CH_2{-}CH{-}CH_2{-}CH_2{-}CH_2{-}O$		45	31[73]	B. 128–130	3	57			74
45	47		$=CH{-}C{=}CH{-}CH{=}CH{-}O$	3-CH_3	*m*-$H_2NC_6H_4CH_3$	30	B. 130–132	3	70	N 7.6	7.4	

TABLE XIII (*Continued*)

Cpd. No.[a]	No.	R	R'	Substituent	Intermediate	Method	B.p., m.p., °C.	Mm.	Yield, %	Analyses, % Calcd.	Found	Ref.
45	48	H	$CH_2CH(-CH_2-CH_2-CH_2-O-)$	3-CH_3	47	31	B. 132	3	75			
45	49	C_2H_5	$CH_2CH(-CH_2-CH_2-CH_2-O-)$	3-CH_3	48	17	B. 125–128	3	61	(See also ref. 76)		
52	50	H	CH_2-CH_2		Indole	32	B. 94.5 Hydrochloride M. 222–224	8	71			75, 79
52	51	H $CH_3SO_2NC_2H_4$	CH_2-CH_2		50	16b(4)	M. 70–71		95	N 11.7	11.9	
54	52	$CH_3SO_2NC_2H_4$	$CH_2CH_2CH_2$		Tetrahydroquinoline	16b(4)	M. 51–53		86	N 11.0	10.9	
54a	53	H $CH_3SO_2NC_2H_4$	$CH_2CH_2CH_2$	7-CH_3	7-Methyltetrahydro-quinoline	16b(4)	B. 223 Hydrochloride M. 185–186	1.5	57	N 10.4	10.4	

[a] Refers to position in Table IX. [b] The nitrile was impure, accounting for the low yield. [c] Prepared also by an alternate series of reactions. No. 12 gave N-*p*-tosyl, m.p. 108.5–109.5°, N-methyl-N-*p*-tosyl, b.p. 210–212°, N-methyl, b.p. 164–165° (18 mm.), then No. 14a by Method 25b. The procedures for acylation,[61] alkylation[61] and hydrolysis,[62] were modified from those in the literature.

49.5°. Recrystallization from a mixture of hexane and benzene gave 9.9 g. (77%), m.p. 49–50.5°.

b. 3-Acetamido-4-nitro-N-diethylaniline.—Compound 26: A solution of 13 g. (0.06 mole) of 3-amino-4-nitro-N-diethylaniline, 25 cc. of acetic anhydride and 30 cc. of glacial acetic acid was heated on a steam-bath for two hours. The excess anhydride was hydrolyzed and the solution cooled, scratched and chilled. The yield was 14 g. (90%), m.p. 94–95°.[54]

Method 12. N-(4-Nitrophenyl)-piperazine.—Compound 51: A mixture of 25.8 g. (0.3 mole) of anhydrous piperazine[56] and 9.5 g. (0.06 mole) of *p*-chloronitrobenzene was heated in a stoppered citrate bottle, which was completely immersed in a steam-bath for sixteen hours. The mixture was melted into 300 cc. of slightly alkaline water. The yellow precipitate was collected and, while still moist, extracted with two 100-cc. portions of hot benzene. The solution was dried superficially over Drierite, filtered and diluted with 600 cc. of petroleum ether. The bright yellow crystals were collected and washed with petroleum ether, giving 9.0 g. (72%), m.p. 129–130°.[57]

(3) Azo Compounds.—The value of azo dyes as intermediates for the preparation of 4-amino-N-dialkylanilines has been discussed above. Table XII lists the compounds prepared for this purpose.

Method 13. *p*-Nitrophenylazo Compounds.—Compound 19: One mole of *p*-nitroaniline is dissolved in a boiling mixture of 300 cc. of concentrated hydrochloric acid and 300 cc. of water, and poured onto 2 kg. of ice, with stirring. A solution of 1 mole of sodium nitrite in 150 cc. of water is added all at once and the solution stirred at 0–5° for one-half hour. One mole of the amine is added to the diazonium solution and 2.8–3 moles of sodium acetate in 400 cc. of water is added gradually, with stirring. The azo dye is washed with water and crystallized from glacial acetic acid and from 95% alcohol.

Method 14. *p*-Sulfophenylazo Compounds.—Compounds 43, 44: Sulfanilic acid (1 mole) and sodium nitrite (1 mole) are dissolved in 1250 cc. of ice-cold water and poured into an ice-cold solution of 125 g. of sulfuric acid and 760 cc. of water. The diazonium salt is filtered off and washed with a little water, then stirred into a solution of one mole of dialkylaniline in about one liter of glacial acetic acid. The azo compound is not isolated but reduced after thirty minutes to the corresponding *p*-phenylenediamine developing agent by Method 9.

(56) Water was removed from the hexahydrate by co-distillation with benzene. The crystals were collected after cooling and were washed with petroleum ether.

(57) This agrees with that reported by A. Schmidt and G. Wickmann[55] but varies from that (135°) reported by V. Prelog and Z. Blažek,[41] who used a ring-closure method for preparation.

(58) The *m*-diethylaminobenzyl alcohol was supplied by Dr. Lee Davy, of Tennessee Eastman Corporation.

(59) Julolidine was prepared as described in "Org. Syn.," Vol. 26, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 40.

(60) Some of the heterocyclic amines described here give very poor yields of dye in the presence of nitrous acid.

(61) W. H. Carothers, C. F. Bickford and G. J. Hurwitz, THIS JOURNAL, **49**, 2908 (1927).

(62) H. Lecher and F. Graf, *Ann.*, **445**, 61 (1925).

(63) S. Komatsu, *Mem. Coll. Sci. and Eng. Kyoto Imp. Univ.*, **3**, 371 (1912) [*C. A.*, **7**, 1020 (1913)].

(64) No. 6 was converted to the free base and extracted into chloroform. The solution was then treated as in Method 22, the chloroform, of course, distilling off.

(65) C. F. Koelsch, THIS JOURNAL, **65**, 437 (1943).

(66) See also German Patent 105,103 (*Chem. Zentr.*, **71**, I, 238 (1900)).

(67) W. R. Brown and F. A. Mason, *J. Chem. Soc.*, 1269 (1933), by alkylation of *m*-diethylaminophenol.

(68) See also W. Laun, *Ber.*, **17**, 675 (1884) and German Patent 163,043 (*Chem. Zentr.*, **76**, II, 1062 (1905)).

(69) French Patent 758,079 (1934).

(70) H. Dehnert, German Patent 650,259 (1937).

(71) *Cf.* also J. von Braun, *Ber.*, **70**, 979 (1937).

(72) A. M. Hjort, E. J. de Beer, J. S. Buck and W. S. Ide, *J. Pharmacol.*, **55**, 152 (1935).

(73) Method 31 used, with absorption of two moles of hydrogen.

(74) See also R. Paul, *Compt. rend.*, **221**, 412 (1945); *Bull. soc. chim. France*, **12**, 827 (1945); R. Paul and S. Tchelitcheff, *Compt. rend.*, **221**, 560 (1945); *Bull. soc. chim. France*, **14**, 341 (1947).

Method 15. 2,5-Dichlorophenylazo Compounds.—Compounds 9, 10a, 12–14a, 16a, 17, 20, 32a, 52–55: One mole (162 g.) of 2,5-dichloroaniline is diazotized by the method of Noelting and Kopp,[44] and a little sulfamic acid is added to destroy the excess nitrous acid.[60] The diazonium solution at 0° is added to a solution of one mole of a dialkylaniline or N-alkyl heterocyclic compound in an equal weight of glacial acetic acid or in a solution of 100 cc. of concentrated hydrochloric acid and 500 cc. of water. Sodium acetate is then added, with vigorous stirring, until the *p*H is about 5. After one-half hour in an ice-bath, the crude dye is collected either by filtration or by decantation of the aqueous phase and crystallized from about four liters of 95% alcohol. The product is recrystallized from 95% alcohol or a smaller amount of acetone.

In Table XIII are listed the dialkylanilines which do not appear earlier or to which reference has not been made. The numbers in column 2 are used to designate intermediates (column 6) when possible. Unless otherwise indicated, Eastman White Label chemicals were used.

Method 16. Alkyl Halide. a. From 1° anilines—with Alkyl Iodide or Bromide.—A mixture of one mole of the aniline with 2.1 moles of the alkyl iodide or bromide, 1.2 moles of sodium carbonate, 400 cc. of 95% alcohol and 100 cc. of water is refluxed vigorously on a steam-bath five to sixteen hours. The alcohol is removed under reduced pressure and 400 cc. of water is added. The product is extracted into 250 cc. of ether, the extract is washed with water, dried over sodium sulfate and concentrated to an oil which is distilled under reduced pressure.

b.—From Monoalkylanilines. (1) **General Reaction.**—The monoalkylaniline is treated as in **a** but with 1.1 mole of simple or substituted alkyl iodide or bromide and 0.6 mole of sodium carbonate or 1.2 moles of sodium bicarbonate.

(2) **With β-Bromoethylamine Hydrobromide.**—A mixture of 1.34 moles of the alkylaniline and 0.67 mole of β-bromoethylamine hydrobromide is stirred and heated in an oil-bath, the temperature being raised slowly to 145° during one and three-quarter hours. A vigorous reaction occurs at about 115° with a temperature rise of about 50°. The reaction mixture is stirred for two hours longer at 145°, cooled and 400 cc. of 10% sodium hydroxide is stirred over the solid reaction mixture. The oil is separated and the aqueous layer extracted with ether. The ether solution is combined with the oil, dried over sodium hydroxide pellets and concentrated. The residue is fractionally distilled under vacuum. The best yield obtained was 80% based on the bromo compound, or 40% based on the alkylaniline.

(3) **With Furfuryl Chloride.**—A mixture of 15.5 g. (0.133 mole) of furfuryl chloride[76] and 32.7 g. (0.27 mole) of N-ethylaniline was warmed gently to start the reaction, then cooled in running water to control the vigor of the reaction. Finally, the mixture was heated in a steam-bath for thirty minutes and poured into water. After neutralization with ammonium hydroxide, the amines were extracted with ether, dried, concentrated and distilled under vacuum. The product, N-ethyl-N-furfurylaniline, weighed 17.5 g. (65% based on furfuryl chloride), b.p. 125–126° (3 mm.).

(4) **With β-(Methylsulfonamido)-ethyl Bromide.**[77]—One mole of the N-alkylaniline or cyclic secondary amine, one mole (202 g.) of β-(methylsulfonamido)-ethyl bromide, 1.1 moles (92 g.) of sodium bicarbonate, 190 cc. of water and 500 cc. of 95% ethyl alcohol are refluxed on a steam-bath for at least two hours, but preferably overnight. The alcohol and most of the water are removed under reduced pressure and the residue is shaken with water and enough acetic acid added (less than 10 cc.) to make a neutral mixture. The tertiary amine usually crystallizes on shaking or standing. If not, the amine may be taken up in ether, dried and distilled under reduced pressure.

Method 17. Alkyl Sulfate.—Tetrahydrofurfuryl-*m*-toluidine (194 g., 1.0 mole) and ethyl sulfate (154 g., 1.0 mole) were mixed in a flask fitted with an air-cooled reflux condenser and warmed gently on a steam-bath. When the reaction started, the flask was immediately immersed in cold water. When the reaction had moderated, the mixture was heated on the steam-bath for one hour and poured into cold water. The mixture was made alkaline with ammonium hydroxide and the amine taken up in ether. The ethereal solution was concentrated and the residue distilled under vacuum.

Method 18. Ethylene Oxide.—The 2° aniline (1.0 mole) and ethylene oxide (1.2 moles) are mixed in a cold high-pressure bomb. The bomb is sealed and heated, with shaking or stirring, at 130–135° for one to two hours. The contents are removed and fractionally distilled under vacuum.

Method 19. Bisulfite, Formaldehyde, Sodium Cyanide.—To a suspension of 104 g. (1.0 mole) of sodium bisulfite in 100 cc. of water is added 80 cc. of formalin. The mixture is stirred slowly and kept at 45–50°, first by cooling and later by warming. Then one mole of the 2° aniline is added and the mixture is stirred until a clear solution results (*ca.* one-half hour). The solution is allowed to cool to 40°, and a solution of 50 g. (1.0 mole) of sodium cyanide in 100 cc. of water is added. After the solution is stirred at 65° for twenty minutes, the upper layer is separated and distilled under reduced pressure.

Method 20. Preparation of Carbamylanilines.—To 400 cc. of concentrated sulfuric acid was added one mole of the nitrile, dropwise with stirring, the temperature being kept at 25° by cooling (ice-bath). The reaction mixture was stirred slowly at 25–30° until a test portion gave no turbidity when diluted with water (three and one-half hours). The solution was then poured onto 1 kg. of ice, with vigorous stirring. The solution was made alkaline with 1.1 liters of concentrated ammonium hydroxide, the temperature being kept at 25° by means of an ice–salt-bath. The mixture was cooled to 0° and the precipitate collected, washed with water and dried in air. Yield of crude product, melting over a 2° range, was 95%. Recrystallization from 400 cc. of benzene, treating with Filtercel, raised the melting point about 12°.

Method 21. Haloalkylanilines. a.—Preparation of N-Alkyl-N-(β-chloroethyl)-anilines.—A slight excess (169 g., 1.1 moles) of phosphorous oxychloride was placed in a one-liter flask equipped with a stirrer and cooled with running water. One mole of the N-alkyl-N-(β-hydroxyethyl)-aniline was added at such a rate that the temperature stayed at about 45°. (There was a slight induction period.) The mixture was stirred at 90° for one hour and then poured onto ice. The solution was made alkaline with concentrated ammonium hydroxide and the product taken up in 300 cc. of ether. The ethereal solution was washed with 200 cc. of dilute sodium chloride, dried over magnesium sulfate, and concentrated. The residue was distilled under reduced pressure.

b. Preparation of *m*-Diethylaminobenzyl Bromide Hydrobromide.—A solution of 35.8 g. (0.2 mole) of *m*-diethylaminobenzyl alcohol in 227 cc. (2.0 moles) of 48% hydrobromic acid was refluxed overnight. The excess acid was removed under vacuum on a steam-bath. The residue weighed 57 g. (88%), and, though probably satisfactory for further use, was, however, washed with 25 cc. of absolute alcohol, dissolved in 100 cc. of hot absolute alcohol, treated with decolorizing carbon and chilled. The crystals were collected, washed with two 50-cc. portions of absolute alcohol and with 100 cc. of ether. Yield was 41 g. (63.4%) of white crystals, melting at 162–164°. The filtrate was worked up to yield 8.1 g. more product. The total yield was thus 49.1 g. (77%).

Method 22. Preparation of Phthalimides.—A mixture of one mole of potassium phthalimide and one mole of N-alkyl-N-(β-chloroethyl)-aniline was heated at 175–180° for twenty-four hours, stirring during the early stages of the reaction. The mixture was cooled and the organic material dissolved in 200 cc. of hot acetone. The acetone solution

(75) *Cf.* F. E. King, J. A. Barltrop and R. J. Walley, *J. Chem. Soc.*, 277 (1945).

(76) W. R. Kirner, THIS JOURNAL, **50**, 1955 (1928).

(77) β-(Methylsulfonamido)-ethyl bromide: A solution of 513 g. (2.5 moles) of β-bromoethylamine hydrobromide in 250 cc. of water was stirred and treated dropwise with 343.8 g. (3.0 moles) of methanesulfonyl chloride and 220 g. of sodium hydroxide in 800 cc. of water, the temperature being kept at 0–5° and the *p*H slightly on the alkaline side. After one hour longer, 6.5 cc. of concentrated hydrochloric acid was added (congo red). The crystals were collected at 0° and washed quickly with cold water. The moist crystals were taken up in two liters of ether, dried over anhydrous sodium sulfate, and cooled to 20°. When crystallization started, the mixture was diluted with two liters of petroleum ether (b.p. 30–35°).

The crystals were collected at 5° and dried in air. The yield was 371 g. (73.5%) of glistening white plates melting at 47–49°. This material is satisfactory for use but recrystallization from a mixture of benzene and ligroin (4:1) gives a 90% or better recovery, melting at 49–50°. *Anal.* Calcd. for $C_2H_8BrNO_2S$: Br, 39.6. Found: Br, 39.8.

was poured into 600 cc. of water, with stirring. After one hour, the crystals were collected and washed with water. The moist product was recrystallized from 400 cc. of 95% ethyl alcohol.

Method 23. Cleavage of Phthalimides. a. With Hydrobromic Acid.—A mixture of one mole of the phthalimidoalkylaniline and one liter of 48% hydrobromic acid was refluxed for three hours. The phthalic acid was filtered from the cooled mixture and washed with water. The filtrate and washings were combined and concentrated to a low volume under reduced pressure. The residue was dissolved in water and made strongly alkaline with 40% sodium hydroxide solution. The amine was extracted into ether. The ethereal solution was dried over solid sodium hydroxide and evaporated, and the residue distilled under reduced pressure.

b. With Hydrazine Hydrate.—To a solution of one mole of phthalimidoalkylaniline in 1150 cc. of hot 95% ethyl alcohol was added 61.8 g. (1.05 moles) of 85% hydrazine hydrate. The reaction mixture was heated under reflux for one hour and cooled. After the addition of 340 cc. of concentrated hydrochloric acid, the reaction mixture was heated at 80°, with stirring for thirty minutes, followed by addition of 450 cc. of water. The mixture was cooled to 20° and the phthalhydrazide was collected and washed with water (yield 94%). The filtrate and washings were concentrated to 350–450 cc. and the small amount of precipitate was filtered off and washed with water. The filtrate and washings were combined and made alkaline with 40% sodium hydroxide, while being cooled. The mixture was treated with 450 cc. of ether and the solid filtered off. The ethereal solution was washed with water, dried over magnesium sulfate, and concentrated. The residue was distilled under reduced pressure.

Method 24. Reduction of Nitriles.—A mixture of two moles of the nitrile, 250 cc. of liquid ammonia (150 cc. of methanol was used also in some reductions) and about 15 g. of Raney nickel catalyst was placed in a 1200-cc. hydrogenation bomb. Hydrogenation occurred in about eight hours at 110–115° and 1500–2000 p.s.i. The catalyst was filtered off, methanol being used to rinse the bomb and catalyst. After concentration to remove the methanol, the residue was vacuum-distilled.

Method 25. Acylation of Amines. a. With Acetic Anhydride.—The amine (0.5 mole) is added to 75 cc. of acetic anhydride, with cooling (below 75°) and stirring. The mixture is then heated on the steam-bath for thirty minutes and the excess acetic anhydride is decomposed by 500 cc. of water.[78] On cooling, the amide crystallizes, is collected, washed with water and dried. More amide may be recovered from the filtrate by evaporation of the latter to dryness and extracting the residue with ether.

b. With Methanesulfonyl Chloride. (1) General Reaction.—A mixture of one mole of the amine and one liter of water is cooled to 10°. The mixture is stirred vigorously while 115 g. (1 mole) of methanesulfonyl chloride and a solution of 40 g. (1 mole) of sodium hydroxide in 200 cc. of water are added simultaneously at such a rate that the temperature does not rise above 10° (ice-bath). The reaction mixture is stirred forty-five minutes longer at 10°. The following subsequent steps may be taken:

(2) Modifications.—(a) Compound 36: The sulfonamide crystallizes and is recrystallized from 95% ethyl alcohol. (b) Compounds 16, 16a, 37, 38: The oily sulfonamide is taken up in 750 cc. of ether or chloroform, washed with water, dried over sodium sulfate and the solvent distilled off. The residue is distilled (Compound 37), nitrosated directly by Method 10 or azo-coupled by Method 15 (Compound 16a). (c) Compound 14: The reaction mixture is acidified with 25 cc. of concentrated hydrochloric acid and azo-coupled by Method 15, or the reaction mixture is treated with 52.5 cc. (1 mole) of 50% sodium hydroxide. The sodium salt of the sulfonamide is collected on a suction funnel, and washed with a solution of 75 cc. of 50% sodium hydroxide in 500 cc. of water. After one hour on the suction funnel, the salt is washed with dry acetone.

Method 26. Alkylation of Sulfonamides. a. With Alkyl Sulfate.—A mixture of 0.3 mole of the sulfonamide and 600 cc. of water containing 28.8 g. (0.72 mole) of sodium hydroxide is warmed and stirred until solution occurs. The solution is cooled to 35° and 45.3 g. (0.36 mole) of dimethyl sulfate is added during ten minutes, the temperature being kept at 35 ± 1°. After stirring for one and one-half hours longer and then standing for two hours, the amide is extracted with ether. The ethereal solution is washed with 5% sodium hydroxide and then with water. The solution is dried over sodium hydroxide pellets and evaporated. The residue is nitrosated by Method 10.

b. With Alkyl Iodide.—The sodium salt of N-ethyl-N-(β-methylsulfonamidoethyl)-*m*-phenetidine was prepared by adding a solution of 12 g. (0.3 mole) of sodium hydroxide in 50 cc. of water to 72.5 g. (0.25 mole) of the sulfonamide. The mixture was stirred and warmed until solution occurred, then cooled, with stirring, and kept at 0° overnight. The precipitate was collected and washed with dry ether (yield 88%).

A solution of 9.3 g. (0.03 mole) of the sodium salt in 50 cc. of absolute ethanol was treated with 5.0 cc. of methyl iodide. The mixture was refluxed for one and one-quarter hours, filtered and concentrated to a sirup under reduced pressure. The sirup was shaken with water and ether. The ether layer was separated, washed with 5% sodium hydroxide and water and dried over sodium hydroxide pellets. A solid was filtered off (probably sodium salt of unreacted amide) and the ether distilled off under reduced pressure. The residue was nitrosated by Method 10.

Method 27. Preparation of *m*-Aminophenylacetonitrile. a. *m*-Nitrobenzyl Bromide.—Bromine (740 ml., 2360 g., 14.8 moles) was added, dropwise, to 2020 g. (14.8 moles) of *m*-nitrotoluene in a three-necked flask equipped with a powerful stirrer and a reflux condenser. The flask was arranged in an oil-bath at 130–140° and illuminated with a No. 2 photoflood lamp. The addition required seven hours. The reaction mixture was stirred at 135° until no more hydrogen bromide was evolved. The cooled mixture was taken up in two liters of ether and the resulting solution washed with two liters of water. The ethereal solution was dried over sodium sulfate, decanted and evaporated under vacuum. The residue was a mixture of *m*-nitrotoluene, *m*-nitrobenzyl bromide and *m*-nitrobenzal bromide. This residue was allowed to stand two days, whereupon a mass of crystals had formed. These were separated from the liquid by decanting the latter. The crystals melted at 95–100° and were probably impure *m*-nitrobenzal bromide (739 g.). The decanted liquid was fractionated through a ten-inch Vigreux column at 1–2 mm. and the fraction distilling at 122–150° was collected (925 g.). This material was again distilled through the same column at 7–8 mm., giving 683 g. (21%) of material distilling between 153.5 and 156.5° (about 95% of this came over between 153.5 and 154.5°). A sample of the product, recrystallized from ethanol, melted at 58°.

b. *m*-Nitrophenylacetonitrile.—Sodium cyanide, 49 g. (1 mole), was dissolved in 80 ml. of warm water and diluted with 280 ml. of 95% alcohol. This solution was cooled to 20° and 173 g. (0.8 mole) of *m*-nitrobenzyl bromide was added. The mixture was stirred, warmed to 40° and the exothermic reaction allowed to proceed with the temperature held at 60–65° by external cooling. The reaction mixture was refluxed for one hour on a steam-bath and the alcohol was removed under reduced pressure. The residue was partitioned between water and ether. The ether layer was separated, washed with water, dried over sodium sulfate and concentrated. The crude dry product weighed 122 g. (94%). This material was distilled at 3 mm., yielding 100 g. (77%) of material distilling at 160–165°.

m-Nitrophenylacetonitrile in yields of 62–64% was also prepared from *m*-nitrobenzyl chloride (now available at Eastman Kodak Company).

c. *m*-Aminophenylacetonitrile.—A solution of 610 g. (2.7 moles) of stannous chloride in 700 ml. of concentrated hydrochloric acid was arranged for stirring and cooling. The *m*-nitrophenylacetonitrile, 146 g. (0.9 mole), was added in large chunks at such a rate that the temperature rose to 40°, where it was maintained by cooling. When the exothermic reaction subsided (45 min.), the mixture was stirred for two hours. The solution was cooled in a salt–ice-bath, diluted with one kg. of ice, and made alkaline with two liters of 40% sodium hydroxide, the temperature being kept below 35°. The amine was extracted with two 500-ml. portions of ether and the extract was washed with water and dried over sodium sulfate. The ether was

(78) The solution at this point may be made acid with 125 cc. of concentrated hydrochloric acid and nitrosated as described in Method 10.

removed and the residue distilled, yielding 99 g. (83%), b.p. 132–135° (2 mm.).

Method 28. Preparation of N-Ethyl-*m*-acetophenetide.—A mixture of 397 g. (2.9 moles) of *m*-phenetidine and 452 g. (2.9 moles) of ethyl iodide was allowed to stand in a water-bath at 35° while the temperature rose to about 50° during thirty minutes. The vigorous exothermic reaction which set in was moderated with cold water. The mixture stood at 45° overnight, and was then made fluid by stirring over it 250 cc. of 40% sodium hydroxide in 500 cc. of water. The bases were extracted into ether and dried over sodium hydroxide pellets. After concentration, the oil was distilled. The yield of the mixed 1, 2, and 3° amines was 460 g., b.p. 145–147° (18 mm.).

The mixture of amines was added to 275 cc. of acetic anhydride, with stirring and cooling (50°). The reactants were heated on a steam-bath for one-half hour, the excess acetic anhydride was decomposed by 400 cc. of water and the solution made alkaline with 40% sodium hydroxide. The oil was taken up in ether, dried over sodium sulfate and concentrated. The residue was fractionally distilled twice, yielding 422 g. (70%) of N-ethyl-*m*-acetophenetide, b.p. 105–110° (1 mm.).

Method 29. N-Ethyl-*m*-phenetidine.—A mixture of 289 g. (1.4 moles) of N-ethyl-*m*-acetophenetide, 200 cc. of water and 200 cc. of concentrated hydrochloric acid was refluxed overnight. The reaction mixture was cooled, made alkaline with 40% sodium hydroxide and extracted with ether. The ethereal solution was dried over sodium hydroxide pellets and evaporated. The residue was distilled under reduced pressure, giving 219 g. (95%), b.p. 125–127° (7 mm.).

Method 30. N-Furfural-*m*-toluidine.—A mixture was made of 360 g. (3.75 moles) of furfural and 401 g. (3.75 moles) of *m*-toluidine. Heat was generated and the water formed was removed. Distillation at reduced pressure gave 485 g. (70%), b.p. 130–132° (3 mm.).

Method 31. N-Tetrahydrofurfuryl-*m*-toluidine.—Four hundred and eighty-five grams (2.62 moles) of N-furfural-*m*-toluidine was reduced by Raney nickel catalyst and hydrogen at 1600 p.s.i. and 60°. After one molar equivalent of hydrogen had been absorbed, the reaction was slower and the temperature was raised to 115°. The last molar equivalent was absorbed very slowly at 120°. The reduced compound was filtered and distilled; yield 378 g. (75%), b.p. 140–142° (4 mm.).

A preparation in which the Schiff base reaction mixture was reduced without further purification gave a yield of 55%, b.p. 132° (3 mm.).

Method 32. 2,3-Dihydroindole.[79]—One hundred grams (0.86 mole) of indole in 250 cc. of absolute alcohol was reduced by Raney nickel catalyst and hydrogen at 2000 p.s.i. and 80–100° in about seven hours. The catalyst was filtered off, and the filtrate and washings (about 700 cc.) were treated with 71 cc. (0.86 mole) of concentrated hydrochloric acid, cooled to 20° and diluted with one liter of ether. The white crystals of 2,3-dihydroindole hydrochloride were collected and washed with ether; yield 94 g. (71%), m.p. 222–224°.

The hydrochloride (99 g., 0.64 mole) was dissolved in 200 cc. of water and 35 cc. of 50% sodium hydroxide was added, with cooling. The aqueous layer was drawn off and the oil was shaken with 25 cc. of ether and 25 cc. of water. After separation, and continued extractions with ether, the ethereal solution was dried over sodium sulfate. The solution was concentrated and the dihydroindole was distilled at 105.5° (14 mm); 94.5° (8 mm.); yield 68.4 g. (90.3%); $n^{29}D$ 1.5880.

Method 33. *m*-Diethylaminophenylacetic Acid.—A solution of 37.7 g. (0.2 mole) of *m*-diethylaminophenylacetonitrile, 40 cc. of concentrated hydrochloric acid and 40 cc. of water was heated at reflux overnight. The reaction mixture was concentrated under vacuum and the residue dissolved in 100 cc. of water and made definitely alkaline with 20 cc. of 50% sodium hydroxide. The solution was extracted with two 50-cc. portions of ether, acidified with 40 cc. of glacial acetic acid and extracted with three 70-cc. portions of ether. The latter ether solution was concentrated and the residue distilled, giving 15.4 g. (37.2%), b.p. 160–165° (1 mm.) (see *b*, Table XIII).

Method 34. *m*-Diethylaminophenethyl Alcohol.—To a stirred solution-suspension of 3.8 g. (0.1 mole) of lithium aluminum hydride in 100 cc. of dry ether was added, dropwise over a period of one-half hour, a solution of 14.7 g. (0.071 mole) of *m*-diethylaminophenylacetic acid in 50 cc. of dry ether. Refluxing was continued for one hour longer, then 10 cc. of water was added dropwise, followed by 150 cc. of 10% sulfuric acid slowly. Stirring was continued to break up the solid. The ether layer was removed and the aqueous layer made alkaline with ammonium hydroxide. The mixture was filtered and the solid material was washed with ether. The filtrate was extracted with ether and the ether solutions were combined, dried over sodium sulfate and concentrated. The residue was distilled and 11.1 g. (81%), b.p. 100–103° (1 mm.), was collected.

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(79) F. E. King, J. A. Barltrop and R. J. Walley[75] reported a quantitative yield of dihydroindole boiling over a 5° range at 10 mm. Under the same conditions, we always obtained a mixture requiring fractional distillation. The preparation of the hydrochloride greatly simplified the purification and the product distilled with no range.