cymene with 0.8 g. of 10% palladium-on-charcoal. The warm solution was filtered from catalyst, and on cooling colorless needles of VI slowly crystallized: yield 0.7 g.; m. p. 158–160°. Recrystallization from acetic acid diluted with a little water, or from 95% ethanol, gave needles of m. p. 162–163°. The identity of the product was demonstrated by analysis and by mixed melting point with an authentic sample.[6]

10-Methoxy-1,2-benzanthracene (VIII).—Two grams of compound IV was methylated in methanolic alkali, using dimethyl sulfate as alkylating agent. The oil obtained in this manner could not be crystallized so it was refluxed in 50 cc. of *p*-cymene with 1.0 g. of 20% palladium-on-charcoal for twenty-four hours. The catalyst was filtered off and the filtrate concentrated to dryness. The residue was triturated with Skellysolve B and several successive 50-cc. portions of Skellysolve B were distilled from the product, which solidified to give 0.45 g. of yellow crystals of m. p. 104–106°. Two recrystallizations from Skellysolve B gave colorless platelets of m. p. 109.5–110.5°. The identity of this product was established by analysis and by mixture melting point with an authentic specimen.[6]

10-Hydroxy-1,2-benzanthracene (IX).—Two grams of compound IV was heated with a mixture of 2 g. of sodium chloride, 10 g. of zinc chloride and 4 g. of zinc dust at 270–300° for twenty minutes, according to the method of Clar.[7] The product could not be purified so it was refluxed for twenty-four hours in 20 cc. of *p*-cymene with 1.5 g. of 10% palladium-on-charcoal. Filtration and cooling gave 0.3 g. of yellow crystals of m. p. 148–154°. Two recrystallizations from benzene gave golden yellow leaflets, m. p. 153–155° (lit.[8] m. p. 154–155.5°).

Direct dehydrogenation of compound IV in refluxing *p*-cymene, without previous zinc dust treatment, gave IX (in a much poorer yield) contaminated with a large amount of the bimolecular dehydrogenation product X.

The Bimolecular Dehydrogenation Product X.—Two grams of compound IV was heated in an oil-bath at 230–240° for three hours with 0.3 g. of 10% palladium-on-charcoal. The cooled residue was taken up in 100 cc. of 95% ethanol and filtered. The filtrate was concentrated to dryness to give a solid residue, consisting of a mixture of a deep green and a colorless product. Recrystallization did not result in purification so the solid was sublimed at a bath temperature of 145° and under a vacuum of 0.2 mm. The sublimed, dark colored material could not be purified but the non-volatile residue consisted of 0.3 g. of colorless material of m. p. 230–235° (dec.). Recrystallization from 50 cc. of 95% ethanol gave fine colorless needles of m. p. 241–244° (dec.).

Anal. Calcd. for $C_{36}H_{22}O_2$ (compound X): C, 88.86; H, 4.56. Found: C, 88.90; H, 4.71.

Acknowledgments.—The help of Dr. William Sidon in the preparation of starting materials is gratefully acknowledged. For the microanalyses, the author is indebted to Mr. E. F. Shelberg, chief microanalyst, Abbott Laboratories.

Summary

The application of a novel cyclization reaction to the synthesis of oxygenated benzanthracene derivatives has been studied. A modification in the preparation of the important intermediate, ethyl γ-phenylacetoacetate, is reported.

NORTH CHICAGO, ILLINOIS RECEIVED JULY 17, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Some N-(2-Diethylaminoethyl)-anilines[1]

BY MARK A. STAHMANN AND ARTHUR C. COPE

Most antimalarial drugs contain one or more relatively weakly basic groups and in addition an alkylamino side chain which is more strongly basic. For example, 8-aminoquinolines of the Plasmochin type, similarly substituted 4-aminoquinolines, and Atebrin have a strong basic center in the side chain and weaker basic centers provided by the heterocyclic nitrogen and the secondary amino group attached to the heterocyclic nucleus. These common structural features suggest that the presence of these basic centers is associated with the antimalarial activity of the compounds. Some evidence in this direction is furnished by the observation that the toxic effects of Atebrin and quinine to certain microörganisms may be overcome or antagonized by small amounts of several polybasic amines, notably spermine and spermidine.[2] In such experiments the basic centers of the polybasic amines presumably compete with those of the antimalarial drugs for the same enzyme surface, and provide the enzyme with some degree of protection from inactivation by combination with the drugs. It appears possible, therefore, that the antimalarial drugs function by inactivating an essential enzyme of the malaria parasite by combining with the enzyme, and that the basic groups of the drugs are involved in this combination. Enzymatic processes are known which depend upon combination of the enzyme with basic centers in the substrate. For example, the hydrolysis of peptides by aminopeptidases depends upon the presence of a basic center (the α-amino group) in the peptide.[3] Such a process might be blocked by a basic antimalarial drug which could combine with and inactivate the enzyme.

As part of a study of the relationship of chemical structure to antimalarial activity directed along the lines indicated above, we have prepared a series of N-(2-diethylaminoethyl)-anilines (I) and N,N-bis-(2-diethylaminoethyl)-anilines (II). These

$ArNHCH_2CH_2N(C_2H_5)_2$ (I) $ArN(CH_2CH_2N(C_2H_5)_2)_2$ (II)

compounds were investigated to determine whether such simple aromatic amines with alkylamino side chains have antimalarial properties. They

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts Institute of Technology.

(2) Silverman and Evans, *J. Biol. Chem.*, **154**, 521 (1944).

(3) See Johnson and Berger, *Advances in Enzymol.*, **2**, 69 (1942).

TABLE I

N-(2-DIETHYLAMINOETHYL)-ANILINES (I) AND N,N-BIS-(2-DIETHYLAMINOETHYL)-ANILINES (II)

ArNHCH₂CH₂N(C₂H₅)₂ (I) Ar	Survey number (SN—)[a]	Yield, %	Boiling point, °C.	Mm.	$n^{25}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
Phenyl[b]	14,154	88	126–127	3	1.5251	$C_{12}H_{20}N_2$	74.9	74.8	10.5	10.6	14.6	14.5		
p-Chlorophenyl[c]	14,153	69	161–162	6	1.5373	$C_{12}H_{19}N_2Cl$	63.6	63.5	8.4	8.4	12.4	12.4	15.6	15.8
m-Chlorophenyl	14,147	88	151–153	3	1.5370	$C_{12}H_{19}N_2Cl$	63.6	63.3	8.4	8.4	12.4	12.4	15.6	15.7
o-Chlorophenyl[d]	14,152	48	116–117	5	1.5364	$C_{12}H_{19}N_2Cl$	63.6	63.3	8.4	8.4	12.4	12.4	15.6	15.9
2,4-Dichlorophenyl	14,149	24	158–159	3	1.5436	$C_{12}H_{18}N_2Cl_2$	55.2	55.4	6.9	7.1	10.7	10.8	27.2	27.2
2,5-Dichlorophenyl[e]	14,150	19	148–149	2	1.5438	$C_{12}H_{18}N_2Cl_2$	55.2	55.0	6.9	7.1	10.7	11.0	27.2	26.9
2,4,6-Trichlorophenyl	14,148	4	160–162	3	1.5461	$C_{12}H_{17}N_2Cl_3$	48.7	49.0	5.8	5.9	9.5	9.3	36.0	35.8
2-Methoxy-4-chlorophenyl	14,722	34	151–152	1	1.5373	$C_{13}H_{21}N_2OCl$	60.8	61.0	8.2	8.3	10.9	10.9	13.8	13.8
p-Iodophenyl[f]	14,851	42	180–181	4	1.5789	$C_{12}H_{19}N_2I$	45.3	45.3	6.0	6.0	8.8	8.8	39.9	39.6
p-Nitrophenyl[g]	14,848	15	227–228	8	1.6401	$C_{12}H_{19}N_3O_2$	60.7	61.0	8.1	8.4	17.7	17.6		
p-Diethylaminophenyl	14,850	35	159–160	2	1.5306	$C_{16}H_{29}N_3$	72.9	72.8	11.1	11.0	16.0	15.7		
α-Naphthyl	14,849	77	156–157	1	1.5886	$C_{16}H_{22}N_2$	79.3	79.3	9.2	9.2	11.6	11.6		
ArN(CH₂CH₂N(C₂H₅)₂)₂ (II) Ar														
Phenyl[h]	14,163	29	174–177	6	1.5137	$C_{18}H_{33}N_3$	74.2	74.5	11.4	11.3	14.4	14.4		
p-Chlorophenyl	14,160	13	180–182	1	1.5227	$C_{18}H_{32}N_3Cl$	66.3	66.0	9.9	9.9	12.9	13.0	10.9	10.8
m-Chlorophenyl	14,159	10	167–169	1	1.5208	$C_{18}H_{32}N_3Cl$	66.3	66.0	9.9	9.8	12.9	12.9	10.9	10.6
p-Diethylaminophenyl	14,852	30	201–211	4	1.5201	$C_{22}H_{42}N_4$	72.9	72.8	11.7	11.7	15.5	15.4		

[a] The Survey Number (SN—) refers to the number by which the compound will be identified in the forthcoming monograph (ref. 4). [b] Dihydrochloride, m. p. 122–124°. *Anal.* Calcd. for $C_{12}H_{20}N_2 \cdot 2HCl$: C, 54.3; H, 8.4; N, 10.6; Cl, 26.7. Found: C, 54.4; H, 8.6; N, 10.4; Cl, 26.7. Clemo and Perkin, *J. Chem. Soc.*, **125,** 1809 (1924), have prepared the base and report b. p. 163° (17 mm.). [c] Dihydrochloride, m. p. 132–133° (very hygroscopic). *Anal.* Calcd. for $C_{12}H_{19}N_2Cl \cdot 2HCl$: C, 48.1; H, 7.1; N, 9.3; Cl, 35.5. Found: C, 48.0; H, 7.3; N, 9.3; Cl, 35.5. [d] Monohydrochloride, m. p. 141–143°. *Anal.* Calcd. for $C_{12}H_{19}N_2Cl \cdot HCl$: C, 54.8; H, 7.7; N, 10.6; Cl, 26.9. Found: C, 54.9; H, 7.8; N, 10.5; Cl, 26.9. [e] Monohydrochloride, m. p. 164–165°. *Anal.* Calcd. for $C_{12}H_{18}N_2Cl_2 \cdot HCl$: C, 48.4; H, 6.4; N, 9.4; Cl, 35.7. Found: C, 48.3; H, 6.3; N, 9.7; Cl, 35.8. [f] The residue in the distilling flask decomposed suddenly near the end of the distillation. [g] This compound is a dark red liquid with a brilliant dark blue fluorescence. [h] English Patent 292,615 (*Chem. Zentr.*, **101,** 1697 (1930)) gives b. p. 160° (4 mm.) for this compound.

failed to show activity in avian malaria at dose levels at which they were not toxic to the host,[4] and accordingly within the limits investigated the arylamino group cannot replace the 4- or 8-aminoquinoline or 9-aminoacridine nucleus without loss of useful antimalarial activity.

The mono- and disubstituted aniline derivatives which were synthesized and are listed in Table I were prepared from the corresponding primary aromatic amines by alkylation with 2-diethylaminoethyl chloride hydrochloride suspended in benzene in the presence of an excess of potassium carbonate. A small amount of copper bronze powder was added as a catalyst.[5] N-(2-Diethylaminoethyl)-aniline was prepared in 70–72% yield in the absence of the catalyst, and in 78–88% yield under similar conditions in the presence of copper bronze, which was therefore added in subsequent alkylations.

The monoalkylanilines were the principal products when somewhat more than two moles of the primary aromatic amines were treated with one mole of 2-diethylaminoethyl chloride hydrochloride. Yields of the alkylation products were lower for *p*- and *o*-substituted anilines than for aniline, and in the group of chloroanilines decreased progressively in the sequence *m*-, *p*-, *o*-, di- and trichloroaniline. The N,N-bis-(2-diethylamino-ethyl)-anilines were prepared by alkylation of the primary aromatic amines with a large excess of 2-diethylaminoethyl chloride hydrochloride. In most cases the intermediate monoalkylanilines were not isolated. With aniline itself, the yield was practically the same when N-(2-diethylaminoethyl)-aniline was isolated and realkylated. Attempts to prepare the dialkylanilines in which the aryl group was 2,4,6-trichlorophenyl, 4-nitrophenyl and α-naphthyl gave only the monoalkylanilines. Reduction of the basicity of the nitrogen and steric hindrance both should be at a maximum in 2,4,6-trichloroaniline, among the amines which were alkylated. In this case, the yield of the monoalkylaniline was only four per cent. and none of the dialkylaniline was isolated.

Experimental[6]

N-(2-Diethylaminoethyl)-anilines (I).—A suspension of 0.6 mole of the primary aromatic amine, 0.4 mole (69 g.) of 2-diethylaminoethyl chloride hydrochloride, 0.9 mole (125 g.) of anhydrous potassium carbonate, 2 g. of copper bronze powder and 350 ml. of benzene was heated under reflux and stirred with a Hershberg stirrer for eleven hours. The reaction mixture was then cooled, 500 ml. of 10% aqueous sodium hydroxide solution was added, and the mixture was extracted with two 300-ml. portions of ether. The ether extracts were combined, washed with water and saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue was fractionated through a Widmer column with a six-inch spiral. The forerun consisted largely of the primary aromatic amine which was used in excess; if this amine was a solid, most of it was separated by crystallization or distillation through a Claisen type still head before the residue was fractionated. The second fraction, which contained the N-(2-diethylaminoethyl)-aniline, was refractionated. In some cases, a small amount of the N,N-bis-(2-diethylaminoethyl)-aniline was obtained as a higher boiling fraction.

(4) Pharmacological data will be cited in a forthcoming monograph prepared by the Survey of Antimalarial Drugs.

(5) Kermack and Wright, *J. Chem. Soc.*, 1121 (1935).

(6) Melting and boiling points are uncorrected.

The hydrochlorides listed in the footnotes to Table I were prepared by dissolving the bases in dry ether and adding slowly with stirring an ether solution containing slightly more than two equivalents of hydrogen chloride. The salts were purified by recrystallization from an anhydrous alcohol ether mixture. They proved to be somewhat hygroscopic and consequently most of the compounds were submitted as the bases for pharmacological testing.

N,N-Bis-(2-diethylaminoethyl)-anilines (II).—A suspension of 0.3 mole of the primary aromatic amine, 0.7 mole (120 g.) of 2-diethylaminoethyl chloride hydrochloride, 1.2 moles (166 g.) of anhydrous potassium carbonate, 2 g. of copper bronze powder and 350 ml. of benzene was heated under reflux with stirring as described above for twenty-four hours. An additional 0.3 mole (52 g.) of 2-diethylaminoethyl chloride hydrochloride was then added and the stirring and heating were continued for an additional twelve hours. The reaction mixture was then cooled, aqueous sodium hydroxide was added and the mixture was extracted with ether as described in the preceding section. The ether extracts were dried, the ether was removed, and the residue was fractionated. A forerun consisting largely of the N-(2-diethylaminoethyl)-aniline distilled first, followed by the higher boiling N,N-bis-(2-diethylaminoethyl)-aniline.

We are indebted to Mr. S. M. Nagy and Mrs. C. K. Fitz for analyses.

Summary

A number of N-(2-diethylaminoethyl)-anilines (I) and N,N-bis-(2-diethylaminoethyl)-anilines (II) have been prepared by the alkylation of primary aromatic amines with diethylaminoethyl chloride. These compounds have been tested for activity in avian malaria.

CAMBRIDGE, MASSACHUSETTS RECEIVED AUGUST 20, 1946

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

The Condensation of Aldehydes and Amines with Nitrogenous Five-atom Ring Systems[1]

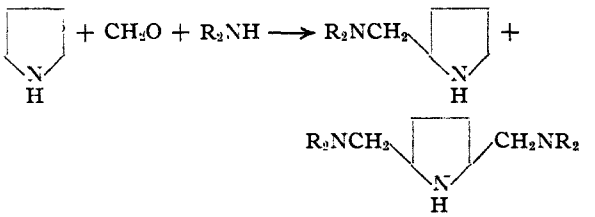
BY G. BRYANT BACHMAN AND LOWELL V. HEISEY[2]

The condensation of aldehydes and amines with compounds containing an active hydrogen atom has proved to be a widely applicable method of introducing aminomethyl groups.[3]

As applied to heterocyclic compounds, three types of active hydrogen atoms may be involved: (1) those directly attached to the nucleus, as in antipyrine[4] and indole[5]; (2) those attached to the α-carbon of an alkyl group attached to the ring, as in α-picoline[6] and quinaldine[7]; and (3) those attached to side chains where the activation is provided by some group other than the ring, as in 2-acetothienone[8] or 2-acetylfuran.[8]

The published observations on Mannich bases derived from each of these types are rather limited in scope and the behaviors of many of the simpler ring systems under the usual conditions of the condensation are unknown. We have undertaken to prepare a series of compounds of type (1) for the purpose of studying the generality of the reaction in the heterocyclic series, of determining the most active hydrogen in various ring systems, and of studying the pharmacological activity of these types of nitrogeneous material.

Pyrrole condenses with formaldehyde and secondary amines according to the equation



With dimethyl- or diethylamine colorless, high-boiling liquids are obtained which are stable only under vacuum in sealed containers. These liquids possess strong, characteristic and rather pleasant odors. The products from the higher aliphatic amines, such as di-*n*-butylamine, decompose on attempted vacuum distillation.

While only disubstituted products are obtained with aliphatic amines under various conditions, piperidine and morpholine readily give either mono or disubstituted pyrroles according to the ratio of reactants used. These products are white, crystalline, relatively stable solids and are formed in 85–95% yields. N-Methylaniline and thialdine do not react.

The Mannich condensation may proceed by any one or all of three different mechanisms[3]

(A) $R{-}H + CH_2O \longrightarrow R{-}CH_2OH$
$RCH_2OH + R'_2NH \longrightarrow RCH_2NR'_2 + H_2O$

(B) $R'_2NH + CH_2O \longrightarrow R'_2NCH_2OH$
$R'NCH_2OH + R{-}H \longrightarrow RCH_2NR'_2 + H_2O$

or (C) $R{-}H + CH_2O + R'_2NH \longrightarrow RCH_2NR'_2 + H_2O$

where C represents a mechanism involving different (but unspecified) intermediates from those shown in A and B. A trimolecular reaction for C is conceivable but improbable without supporting kinetic evidence. In our experience the best

(1) Read before the Organic Section at the Atlantic City meeting of the American Chemical Society, April, 1946.

(2) From the M.S. thesis of Lowell V. Heisey, Purdue University, October, 1944.

(3) For a review see Blicke, "The Mannich Reaction," Vol. I, Chapter 10, of "Organic Reactions," R. Adams, editor-in-chief, John Wiley and Sons, Inc., New York, N. Y., 1942.

(4) Mannich and Krosche, *Arch. Pharm.*, **250**, 647 (1912).

(5) Kuhn and Stein, *Ber.*, **70**, 567 (1937).

(6) Tetral Hoan Fou, *Compt. rend.*, **192**, 1212 (1931).

(7) Kermack and Muir, *J. Chem. Soc.*, 3089 (1931).

(8) Levy and Nisbet, *ibid.*, 1053 (1938).