[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY, SCHOOL OF MEDICINE]

Syntheses of Certain Derivatives of Phenylalanine and of Auramine in Studies of Antimalarial Action[1]

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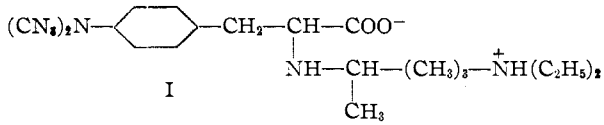
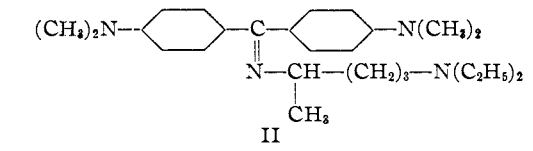
In the course of studies of the biochemical action of antimalarial drugs,[2] it became desirable to synthesize certain compounds with substituent dimethylaminophenyl groupings. Such compounds included N-(4-diethylamino-1-methylbutyl)-β-(*p*-dimethylaminophenyl)-alanine

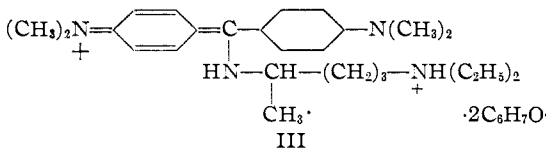


I

the ethyl ester thereof, N^4-[4,4'-*bis*-(dimethylamino)-benzohydrylidene]-N^1,N^1-diethyl-1,4-pentanediamine ("Novalauramine"), II, the dicitrate, III



II

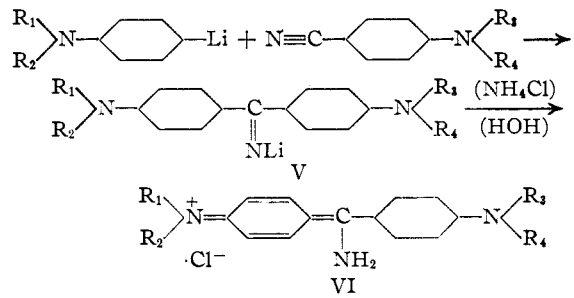


III

and a number of related substances.[3]

Compound I was prepared by hydrogenation in ethanolic solution in the presence of a platinum catalyst of a mixture of the appropriate ketonic acid and 4-diethylamino-1-methylbutylamine, $(C_2H_5)_2NCH_2CH_2CH_2CH(CH_3)NH_2$, IV. By the same method the corresponding derivative of phenylalanine was prepared for comparison. Such a reductive condensation was not attained in the presence of catalytic platinum, palladium or nickel under various conditions with *p*-dimethylaminophenylglyoxylic acid[4] in place of the arylpyruvic acids.

Compound II was synthesized by condensation of auramine base and the amine, IV. Various related imines were formed similarly by means of heating analogs of auramine with IV in excess until evolution of ammonia ceased. A satisfactory method of synthesis of the auramines on a laboratory scale appears not to have been recorded. This program necessitated the development of a new method, consisting essentially of the appropriate condensation of a *p*-dialkylaminophenyllithium with a *p*-dialkylaminobenzonitrile followed by controlled hydrolysis with aqueous ammonium chloride. The process is depicted schematically as



V

VI

Details of the several preparations and of the fabrication of necessary intermediates are presented.[3,5]

Experimental

N-(4-Diethylamino-1-methylbutyl)-β-(*p*-dimethylaminophenyl)-alanine (I)

***p*-Dimethylaminophenylpyruvic Acid.**—By alkaline hydrolysis in aqueous ethanol of the red azlactone, m. p., 220°, prepared from *p*-dimethylaminobenzaldehyde and hippuric acid according to Hellerman, Lindsay, Weisiger and Ramsdell,[7] there was provided α-benzoylamino-*p*-dimethylaminocinnamic acid, m. p., 229°.[7] A mixture of the latter acid, 62.5 g. (0.2 mole) with 505 g. of potassium hydroxide (85% potassium hydroxide) in 2.5 l. of water was refluxed for two and one-half hours, cooled to 15° and treated with 750 ml. of concentrated hydrochloric acid, the temperature being maintained below 25°. From the mixture, at 15°, benzoic acid was removed by filtration; the filtrate was brought to *p*H 5 by the addition of concentrated potassium hydroxide solution, filtered for removal of a slight yellow precipitate, and then treated with 3.5 l. of barium hydroxide solution, which had been saturated at room temperature and clarified by filtration through "Supercel." The mixture was cooled and allowed to stand for one hour, after which the barium salt was collected. The salt from two preparations conducted simultaneously was suspended in 700 ml. of water and the *p*H adjusted to 3.6 by the addition of 25% sulfuric acid. The precipitated barium sulfate was removed by filtration through "Supercel." The clear filtrate was concentrated under reduced pressure to a paste that was dried in a

(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 Johns Hopkins University.

(1a) Henry Strong Denison Scholar for 1946–1947.

(2) (a) M. R. Bovarnick, A. Lindsay and L. Hellerman, *J. Biol. Chem.*, **163**, 523, 535 (1946); (b) L. Hellerman, A. Lindsay and M. R. Bovarnick, *ibid.*, **163**, 553 (1946).

(3) See the Experimental Part.

(4) H. Staudinger and H. Stockmann, *Ber.*, **42**, 3489 (1909).

(5) Antimalarial activity with respect to infections of *P. lophurae* in ducks appeared in the case of Compound III, SN-12,710-6029. The several analogs of III described in this preliminary exploration were reported as inactive (ref. 6).

(6) The Survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph, edited by F. Y. Wiselogle.

(7) Flavoenzyme studies, to be published; *cf.* ref. 2b.

vacuum over phosphorus pentoxide; yield, 50 g. (60%); dec. pt., 140–140.5°. Recrystallization from acetone and petroleum ether gave a yellow powder, turning pink at 120° and melting (dec.) at 141°. The acid decomposes during standing at room temperature for two to four months.

Anal.[8] Calcd. for $C_{11}H_{13}O_3N$: C, 63.7; H, 6.3; N, 6.8. Found: C, 63.5; H, 6.3; N, 7.1.

Phenylhydrazone.—One gram of the acid, dissolved in a little hot water, was treated with a solution of 2 g. of phenylhydrazine hydrochloride; a product formed that was collected and recrystallized from acetone–water; thickets of fine needles, dec. pt., 174°.

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.4; H, 6.8; N, 14.1. Found: C, 68.4; H, 6.6; N, 14.2.

Compound I (SN-11,527).[6]—*p*-Dimethylaminophenylpyruvic acid, 21 g. (0.1 mole), and 63 g. (0.4 mole) of 4-diethylamino-1-methylbutylamine[9] were dissolved in 200 ml. of absolute ethanol; there was added 1 g. of platinum catalyst[10] and the mixture was shaken with hydrogen (pressure, 30 pounds) for an hour, during which the theoretical amount of hydrogen was absorbed. The catalyst was collected; from the filtrate ethanol was removed by vacuum distillation (and excess IV at 3 mm.) and the residual viscous liquid was treated with acetone, whereupon a white solid appeared. This was collected, washed thoroughly by trituration with acetone, and dried in a vacuum over calcium chloride and chipped paraffin; yield 22 g. (60%) of white powder dec. at 187–189°. That the product contained no appreciable quantity of a salt of initial amine was proved in a test with nitrous acid by the Van Slyke method for amino-N; it was observed also that 4-diethylamino-1-methylbutylamine in the standard apparatus yields in ten minutes or less the calculated amount of nitrogen.

Anal. Calcd. for $C_{20}H_{35}N_3O_2$: C, 68.7; H, 10.1; N, 12.0. Found: C, 67.7; H, 10.2; N (Dumas), 12.0, (Micro-Kjeldahl), 12.0.

Ethyl Ester of Compound I.[11]—A solution of 20 g. of Compound I in 300 ml. of dry ethanol at 0° was saturated with dried hydrogen chloride gas. The flask was stoppered tightly and stored at room temperature for two days, after which the solvent and the hydrogen chloride were removed in a vacuum. The residue was dissolved in 200 ml. of iced water; 75 ml. of ether, some crushed ice, and a cold solution of 15 g. of sodium hydroxide in 50 ml. of water was added; extraction with ether was completed, and the ether extracts dried over anhydrous sodium sulfate. After the ether was removed under reduced pressure, the residual oil was distilled at 3 mm.; 18 g. (83%) of light yellow oil came over at 206°.

Anal. Calcd. for $C_{22}H_{39}N_3O_2$: C, 70.0; H, 10.4; N, 11.1. Found: C, 70.5; H, 10.5; N, 11.0.

N-(4-Diethylamino-1-methylbutyl)-β-phenylalanine, $C_6H_5CH_2CH[NHCH(CH_3)CH_2CH_2CH_2\overset{+}{N}H(C_2H_5)_2]COO^-$ (SN-11, 526).—This was prepared in a manner similar to the procedure for Compound I. The reaction mixture consisted of phenylpyruvic acid,[12] 6.8 g. (0.0415 mole), 4-diethylamino-1-methylbutylamine, 25 g. (0.158 mole), 60 ml. of ethanol and 0.3 g. of platinum catalyst.[10] The residual crude product after removal of volatile liquids from the reaction mixture was stored in the ice-chest with 125 ml. of acetone, collected and dissolved in a minimal quantity of hot water; the solution was treated with 300 ml. of acetone and allowed to stand at 5°; platelets, dried in a vacuum over calcium chloride and chipped paraffin; yield, 9.2 g. (70%); m. p. with decomposition, 173°.

Treatment of the product with strong alkali yielded no ether-extractable amine. The product gave no nitrogen when shaken with nitrous acid in the Van Slyke apparatus.

Anal. Calcd. for $C_{18}H_{30}N_2O_2$: C, 70.5; H, 9.9; N, 9.1. Found: C, 69.8; H, 9.8; N, 9.4.

Auramine Derivatives: Dicitrate, III, and Certain Analogs

Compound II.[13]—A mixture of 14.3 g. (0.054 mole) of pure, dry auramine base (prepared from auramine O)[14] and 14.8 g. (0.093 mole) of 4-diethylamino-1-methylbutylamine, contained in a 60-ml. distilling flask, was heated under reflux at 115–120° for six and one-half hours, moisture being excluded. Most of the ammonia was evolved during the first three hours. Excess IV was distilled at 3 mm., and evacuation continued while the bath was held at 120° for several hours; there remained the calculated quantity of a thick oil (II), hydrolysis of a sample of which with hot hydrochloric acid yielded Michler ketone (96.3%) and IV (75%, recovered as dithiocarbamate semihydrate).

"Novalauramine," II, in ethanol solution was found to be reducible to a leuco product by the action of sodium amalgam. The reductant was obtained as an oil which like leucoauramine was readily hydrolyzable by acids; in aqueous-ethanolic solution it exhibited even at *p*H 6.4 a deep blue color.[15]

Compound III (Dicitrate).—To a cool solution of 6.1 g. of II in 50 ml. of absolute ethanol was added two mol. equivalents of citric acid monohydrate in 40 ml. of warm ethanol, after which ether was added slowly; a gum appeared, from which the supernatent fluid was decanted. The gum was dissolved in 100 ml. of ethanol, and ether was added slowly during cooling. The product was washed *thoroughly* by trituration with ether, collected rapidly, and dried in a vacuum over phosphorus pentoxide and chipped paraffin; yield, 11 g. (94%) of a bright yellow-orange, very hygroscopic solid. *Anal.* (b), Table I.

4-Dimethylamino-4′-di-*n*-butylamino- and 4,4′-Tetrabutyldiamino Analogs of Compounds II and III.—The necessary ketimines were obtained from the salts, VI, prepared by the method described below. In the condensation with IV, a ketimine was refluxed with 2 1/2 to 3 mol. equivalents of amine for six hours, in an atmosphere of nitrogen, the bath temperature being increased gradually from 120 to 150°. Excess amine was removed as described for II. The products were obtained in excellent yield. *Anal.* (a), Table I.

The preparation of dicitrates was best effected by treatment of the aforementioned condensation products in ether solution with two mol. equivalents of citric acid in ether solution (*e.g.*, 20 g. of the dimethylaminodibutylamino product in 100 ml. of anhydrous ether with 17.1 g. of citric acid hydrate in 2500 ml. of ether). The products were thoroughly washed with ether, collected *rapidly* on sintered glass funnels, and dried in a vacuum. *Anal.* (c) and (d), Table I.

p-Dibutylaminobenzonitrile (VII)

This nitrile was required as an intermediate in various preparations. It was obtained through the following steps.

***p*-Di-*n*-butylaminobenzaldehyde.**[16,17]—In a 4-liter beaker was heated at 100° for one-half to three-quarters of an hour a mixture of 306 g. of dibutylaniline (1.49 mole),

(8) Microanalyses, C, H and N (Dumas), by Arlington Laboratories.

(9) The amine used in these preparations either had been purified through the dithiocarbamate by the method of R. G. Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 431 (1944), or rectified at 1 to 3 mm. and assayed by the dithiocarbamate method (found, 97%).

(10) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 452.

(11) The dicitrate salt of this compound is designated SN-12,709-6029.

(12) "Organic Syntheses," Coll. Vol. II, p. 519 (1943).

(13) See the Introduction.

(14) v. L. Semper, *Ann.*, **381**, 234 (1911); (b) C. Graebe, *Ber.*, **20**, 3264 (1887).

(15) *Cf.* 14b and R. Möhlau, M. Heinze and R. Zimmermann, *Ber.*, **35**, 375 (1902).

(16) Compare F. Ullmann and U. Frey, *Ber.*, **37**, 858 (1904); T. Ingvaldsen and L. Baumann, *J. Biol. Chem.*, **41**, 146 (1920).

(17) Several new compounds have been designated as *p*-substituted on the basis of the methods of preparation and also certain interrelationships demonstrated herein.

TABLE I

ANALYSES, p-$R_2N—C_6H_4—C(=N—CH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2)—C_6H_4—NR'_2$-$p'$

	R	R'	SN	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
a	CH_3	C_4H_9		$C_{32}H_{52}N_4$	78.0	10.6	11.4	77.8	10.8	11.6
	Dicitrates, *e. g.*, Cpd. III									
b	CH_3	CH_3	12,710	$C_{38}H_{56}N_4O_{14}$	57.6	7.1	7.1	58.0	7.5	7.2
c	CH_3	C_4H_9	9971	$C_{44}H_{68}N_4O_{14}$	60.2	7.8	6.4	59.5	7.9	6.8
d	C_4H_9	C_4H_9	14,369	$C_{50}H_{80}N_4O_{14}$	62.0	8.3	6.6	61.3	8.3	6.3
	Related ketimines, $R_2N—C_6H_4—C(=NH)C_6H_4—NR'_2$									
e[a]	CH_3	C_4H_9		$C_{23}H_{33}N_3$	78.6	9.5	12.0	77.8	9.7	12.1
f[a]	C_4H_9	C_4H_9		$C_{29}H_{45}N_3$			9.6			9.7
	Ketones, $R_2N—C_6H_4—CO—C_6H_4—NR'_2$									
g	CH_3	C_4H_9		$C_{23}H_{32}N_2O$	78.4	9.1	7.9	78.7	9.5	8.4
h	C_4H_9	C_4H_9		$C_{29}H_{44}N_2O$	79.8	10.2	6.4	79.7	9.9	6.8

[a] Obtained directly, and not further purified. See text.

300 ml. of concentrated hydrochloric acid, and 126 ml. of 40% formaldehyde. To the hot solution was added p-nitrosodimethylaniline hydrochloride, freshly prepared from 150 g. of dimethylaniline (1.24 mole) and washed with 300 ml. of cold 5 M hydrochloric acid. Gentle warming of the mixture on a steam-bath initiated a vigorous reaction that was allowed to proceed unabated to its conclusion. The hot mixture was added to 2 kg. of cracked ice; cold 50% sodium hydroxide was added until the red color was discharged. The oily product was extracted with ether, the ether extracts dried with anhydrous potassium carbonate and filtered, and the ether removed under reduced pressure. The residual oil was treated with 500 ml. of water, 500 ml. of glacial acetic acid and 250 ml. of 40% formaldehyde, and the mixture stirred for two hours, after which 600 ml. of water was added, and a lower red layer drawn off and discarded. The upper yellow layer was taken up in 600 ml. of ether, washed with sodium bicarbonate solution to remove acid, and with water. The ether solution was dried with potassium carbonate, filtered, and the solvent evaporated. The residual liquid was fractionated in a vacuum; yield, 149 g. of a light-yellow liquid, b.p. 176–179° (1.5 mm.).

Anal. Calcd. for $C_{15}H_{23}NO$: N, 6.0. Found: N, 6.5.

p-Di-n-butylaminobenzaldoxime.—The above aldehyde, 105 g. (0.45 mole), hydroxylamine hydrochloride, 39.3 g. (0.57 mole) in saturated aqueous solution, and sodium hydroxide, 22.6 g. (0.57 mole) in a little water, were added to 700 ml. of 95% ethanol; the mixture was refluxed for three hours, then cooled, and diluted with 2 liters of water. The precipitated oil crystallized when cooled. The product was collected, washed with water, and dried over phosphorus pentoxide. The product (110 g.) was recrystallized from 275 ml. of ligroin (b. p. 60–90°); yield 86 g. (77%); m.p. (thrice recrystallized), 68–72°.

Anal. Calcd. for $C_{15}H_{24}N_2O$: C, 72.5; H, 9.7; N, 11.3. Found: C, 72.7; H, 9.7; N, 11.1.

Nitrile, VII.—A solution of 86 g., of the above oxime in 440 ml. of acetic anhydride was refluxed at 135–140° for four hours, moisture being excluded. After removal of 300 ml. of solvent under 20 mm., the cooled residue was poured upon 150 g. of cracked ice; cold sodium hydroxide was added until the pH of the mixture was 8. The oil was extracted with ether, dried over potassium carbonate, the ether removed under reduced pressure, and the residual oil fractionated in a vacuum; yield, 68 g. (85%) of a light-orange liquid, b.p. 176–179° (2 mm.).

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.2; H, 9.6; N, 12.2. Found: C, 78.1; H, 9.7; N, 12.2.

p-Dibutylaminobenzoic Acid.[17]—A mixture of 4 g. of nitrile, VII, 12 ml. of concentrated hydrochloric acid, and 2 ml. water was refluxed for four hours. The mixture was cooled, and a solid product collected, washed with water and recrystallized from ethanol–water. The product was dissolved in dilute sodium hydroxide, the solution decolorized by treatment with 2 g. of carbon, and the acid recovered after filtration and acidification; the product, recrystallized from ethanol–water, melted at 115°; yield, 2 g.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.3; N, 5.6. Found: C, 72.7; H, 9.4; N, 6.0.

N⁴-(4-Dibutylamino-4′-methoxybenzohydrylidene)-N¹,N¹-diethyl-1,4-pentanediamine, Dicitrate (IX)

p-Methoxyphenylmagnesium iodide was prepared from 18.3 g. of p-iodoanisole and 1.9 g. of magnesium in 30 ml. of dry ether, the usual precautions being observed. Reaction proceeded normally and was complete in three hours. A solution of 14.1 g. of p-dibutylaminobenzonitrile in 40 ml. of ether was added during fifteen minutes, the mixture refluxed for forty-five minutes, and allowed to stand at room temperature for fifteen hours. The mixture was treated with ice and 60 g. of ammonium chloride,[18] and the product promptly extracted with ether. The ethereal solution was dried, treated with dried hydrogen chloride, and the gummy salts worked up for free imine in the usual manner. *Anal.* of crude 4-methoxy-4′-di-n-butylaminobenzophenoneimine. Calcd. for $C_{22}H_{30}N_2O$: C, 78.1; H, 8.9; N, 8.3. Found: C, 77.2; H, 9.1; N, 7.8.

Dicitrate, IX (SN-13,647).—The above ketimine, 12.5 g., was treated with 20 g. of IV, according to the general method already described, and the product (18 g.) in 100 ml. of ether was shaken with 11 g. of citric acid hydrate in 1 liter of ether. The salt was obtained according to the general procedure. It was decidedly hygroscopic. Samples of the dicitrate were treated with excess standard alkali, and the base extracted and recovered. *Anal.* Calcd. for $C_{31}H_{49}N_3O \cdot 2\,C_6H_8O_7$: base, 55.5; acid, 44.5. Found: base, 54; acid, 41. From the base, after hydrolysis, there was recovered 77% of IV, as the dithiocarbamate.

Anal. Calcd. for $C_{43}H_{65}N_3O_{15}$: C, 59.8; H, 7.6; N, 4.9. Found: C, 59.8; H, 8.0; N, 5.3.

Synthesis of Auramine and Certain Analogs

Auramine.—There were observed the general precautions used in the preparation of Grignard reagents; reaction mixtures were stirred mechanically, and the air in the apparatus displaced by dry nitrogen, a slight positive pressure of the latter being maintained. To 1.00 g. (0.144 mole) of lithium shavings, and 50 ml. of anhydrous ether was added slowly 14.5 g. (0.073 mole) of dry p-bromodimethylaniline in 50 ml. ether; reaction[19] was initiated

(18) (a) Compare C. Moureu and G. Mignonac, *Compt. rend.*, **156**, 1801 (1913); *Ann. chim.*, **14**, 322 (1930); (b) R. L. Garner and L. Hellerman, THIS JOURNAL, **68**, 823 (1946).

(19) Compare K. Ziegler and H. Colonius, *Ann.*, **479**, 135 (1930); E. Müller and T. Töpel, *Ber.*, **72**, 273 (1939); H. Gilman, E. A. Zoellner and W. M. Selby, THIS JOURNAL, **54**, 1957 (1932); **55**, 1252 (1933); H. Gilman, W. Langham and F. W. Moore, *ibid.*, **62**, 2327 (1940).

by warming, and regulated by the rate of addition of the bromo-compound; then the mixture was refluxed for one-half hour and to the cooled solution of *p*-dimethylaminophenyllithium was added during vigorous stirring 10.5 g. (0.073 mole) of *p*-dimethylaminobenzonitrile in 50 ml. of dry ether and the mixture was refluxed for one-half hour, and allowed to stand at room temp. for sixteen hours. The mixture was shaken with ice and 100 ml. of iced, saturated ammonium chloride solution.[20] A canary-yellow solid precipitated; it was collected, washed with water, and dried in a vacuum; yield, 19 g.; m.p., above 270° (*Anal.* $C_{17}H_{22}N_3Cl \cdot H_2O$: Calcd.: base, 83.1; Cl, 11.0. Found: base, 86; Cl (Volhard), 10.8).

Of the hydrochloride, 4 g. was dissolved in 50 ml. ethanol (95%), and the solution treated at 0° with 1 g. of sodium hydroxide in 10 ml. of water. Upon addition of 200 ml. of iced water there was obtained a slightly orange solid, which was collected at once, washed, and dried in a vacuum; yield, 3.05 g.; m. p., 134° (recorded,[14] 136°).

From 2.55 g. of this auramine base, there was obtained, after hydrolysis with dilute hydrochloric acid and treatment of the solution with dilute alkali, 2.33 g. (91%) of Michler ketone; m.p. 175°, and m.p. of a mixture with known 4,4'-tetramethyldiaminobenzophenone, 173–174°.

Compound (e), Table I.—The method was precisely similar to that described above (auramine), reactants being lithium, 1.06 g. (0.153 mole), *p*-bromodimethylaniline, 15.2 g. (0.076 mole), and *p*-dibutylaminobenzonitrile, 17.5 g. (0.076 mole). No precipitate formed here after the addition of nitrile to the lithio-compound. Yield of canary yellow salt was 19 g.; m.p., 235°; yield from a second run with 1.85 g. of lithium and proportionate amounts of the other reactants was 42 g.

Of the hydrochloride, 49 g. was dissolved in 350 ml. of ethanol and the solution treated at 0° with 13 g. of sodium hydroxide in 100 ml. water; the imine was precipitated promptly by the addition of 400 ml. of iced water and taken up in benzene; the benzene solution was dried at once over sodium sulfate and benzene removed in a vacuum, and the residue was heated finally under 2 mm. at 100°; yield, 42 g. *Anal.* Table I.

Compound (f), Table I.—The initial reactants were lithium, 1.11 g. (0.16 mole), *p*-bromodibutylaniline (described below), 22.7 g. (0.08 mole) and *p*-dibutylaminobenzonitrile, 18.4 g. (0.08) mole. The crude ketimine was obtained similarly to the method given in the preceding reaction. *Anal.* Table I.

4-Dimethylamino-4'-di-*n*-butylaminobenzophenone.[17] **Preparation A.**—The dicitrate, compound (c) of Table I (5.0 g.) was treated with excess sodium hydroxide and the base extracted with ether. The ether was removed and the residue was refluxed with 50 ml. of 2 *N* hydrochloric acid for one and one-half hours. After alkalinization of the mixture, extraction with ether and removal of ether, there remained 2.1 g. of ketone which was crystallized from ethanol–water, and recrystallized from ethanol; m.p., 78–78.5° (cor.), and unchanged by admixture with ketone from Preparation B.

Preparation B.—From 0.97 g. of lithium, 20 g. of *p*-bromodibutylaniline and 10.2 g. of *p*-dimethylaminobenzonitrile there was prepared by the general method the ketimine hydrochloride, which was washed with water and with ether. A mixture of this salt, 100 ml. of water, 50 ml. of ethanol and 2.8 ml. of concentrated hydrochloric acid was refluxed for two hours. After alkalinization, the product was extracted with two 50-ml. portions of benzene and the extracts were dried over sodium sulfate. After removal of benzene, the residue was distilled at 3 mm., and collected, in the range, 290–300°. Crystallization was induced after the viscous product was precipitated from ethanol–water; m.p. of product twice recrystallized from ethanol, 78°; yield, 8.6 g. *Anal.* (g), Table I.

4,4'-Tetrabutyldiaminobenzophenone.[17]—This ketone was prepared from the dicitrate, compound (d), Table I, similarly to the method described under Preparation A, above; after several recrystallizations from ethanol–water, m.p., 60.2 (cor.). *Anal.* (h), Table I.

***p*-Bromo-di-*n*-butylaniline.**[17]—Bromine, 68.5 g. (0.43 mole) in 50 ml. of glacial acetic acid was added slowly (during one and one-half hours) to 88 g. (0.43 mole) pure dibutylaniline in 250 ml. of acetic acid, vigorously stirred and cooled in ice water, the temperature being kept below 15°. The reaction mixture was diluted with water to 750 ml.; there formed a white solid that was collected, suspended in water and treated with excess sodium hydroxide, giving an oily product. (More of the crude product was obtained by alkalinization of the acid aqueous mother liquor.) The base was extracted with benzene, and the extract was washed with water and dried over sodium sulfate. The solvent was distilled, and the residual oil fractionated in a vacuum; b. p., at *ca.* 2 mm., 156–158°; yield, 104 g. (85%).

Anal. Calcd. for $C_{14}H_{22}NBr$: N, 4.9; Br. 28.1. Found: N, 5.0; Br, 28.7.

An ether solution of *p*-dibutylaminophenyllithium, prepared under nitrogen from 0.64 g. lithium and 13.1 g. of the bromo-compound according to the general method, was poured over 50 g. of solid carbon dioxide (12 lumps, ether-washed). After the Dry Ice had disappeared, 100 g. of ice, 50 ml. of water and 15 ml. of concentrated hydrochloric acid were added to the deep blue mixture. After alkalinization and extraction with ether, the residual aqueous layer was boiled with charcoal (Darco), filtered and acidified; the resulting precipitate was collected, washed with water, and recrystallized from ethanol–water; yield, less than 1 g.; m.p., 114–115°, and unchanged when admixed[17] with dibutylaminobenzoic acid, previously prepared from dibutylaminobenzonitrile.

Summary

1. There have been synthesized, in connection with studies of antimalarial agents, N-(4-diethylamino-1-methylbutyl)-β-(*p*-dimethylaminophenyl)-alanine and the ethyl ester thereof; N-(4-diethylamino-1-methylbutyl)-β-phenylalanine; and the dicitrates of (a) N^4-[4,4'-*bis*-(dimethylamino)-benzohydrylidine]-N^1,N^1-diethyl-1,4-pentanediamine, ("Novalauramine"), (b) the 4-dimethylamino-4'-di-*n*-butylamino- and (c) 4,4'-tetrabutyldiamino- analogs thereof, and (d) N^4-(4-dibutylamino-4'-methoxybenzohydrylidine)-N^1,N^1-diethyl-1,4-pentanediamine.

2. In connection with the syntheses, there were prepared *p*-dimethylaminophenylpyruvic acid, *p*-N,N-di-*n*-butylaminobenzaldehyde, *p*-dibutylaminobenzonitrile, *p*-dibutylaminobenzoic acid, *p*-bromo-N,N-di-*n*-butylaniline, 4-dimethylamino-4'-di-*n*-butylaminobenzophenone and 4,4'-tetrabutyldiaminobenzophenone.

3. A new method for the synthesis of auramine and certain analogs is described.

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(20) The formation of auramine salt in satisfactory yield, under the conditions, undoubtedly is favored by the stability of the resonating dye ion; compare ref. 18.