[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

ANTIMALARIALS.[1] SOME NEW SECONDARY AND TERTIARY ARYLMETHYLAMINES

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Received January 6, 1947

In the course of the investigation of the antimalarial activity of the substituted α-phenyl-β-dialkylaminoethanols (1) attention was given to the evaluation of a variety of substituents on the nitrogen. In this connection a number of new secondary benzylalkylamines were made and used in condensations with nuclear substituted α-bromoacetophenones, especially the para-chloro derivative; these amines, listed in Table I, were made from the corresponding aromatic aldehydes by condensation with the appropriate primary amines to the Schiff bases (a few of which are listed in Table II), and by subsequent hydrogenation with Raney nickel (*cf.* ref. 2–7). One secondary amine, N-(α-butylbenzyl)-methylamine (XII) was made by the addition of butylmagnesium halide to benzalmethylamine.

The N-benzyl derivative of novalamine (XXXVII) and the analogous N-

$$C_6H_5CH_2NH\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2CH_2N(C_2H_5)_2$$

XXXVII (SN-3942)[3]

benzyl-N-(3-diethyl- and 3-dibutylaminopropyl)amines, were made for use as secondary amines in the synthesis of amino alcohols; the novalamino compound (XXXVII) was itself tested against avian malaria (Q = < 0.3).[4]

A second aspect of the studies in this field was the interest in some of these compounds themselves as possible antimalarials. This interest was stimulated by reports of the slight activity shown by a few individual compounds of this type, for example, benzyltetradecylamine and *p*-methylbenzyldodecylamine (8). This led to the synthesis of the tertiary arylmethyl amines listed in Table III which include six *para*-halogenobenzyl compounds and six α-naphthyl-

[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 University of Virginia.

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[3] 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 have been tabulated in the Monograph (8).

[4] These tests, A-1, as described in the Survey Monograph (8), were carried out at the National Institute of Health under the direction of Dr. G. Robert Coatney.

TABLE I

SECONDARY (ARYLMETHYL)AMINES. $ArCH_2NHR$

	ArCH₂-	R-	PREP.[a] METHOD	YIELD %	B.P. C°/MM.	n_D^{20}	M.P. C° HYDROCHLORIDE
I	$C_6H_5CH_2$-	*i*-propyl-	DFJ	93	66–68/1	1.5029	195
II	$C_6H_5CH_2$-	*s*-butyl-	AFH	95	84–86/2	1.5023	143–145
III	$C_6H_5CH_2$-	*n*-octyl-	BEG	83	156–157/13	1.5068	—
IV	$C_6H_5CH_2$-	*n*-dodecyl-	DG[b]	70	185–190/2	—	201–202.5
V	$C_6H_5CH_2$- (2,3)	cyclohexyl-	CFG[c]	56	209–210/98[h]	$1.5290^{23°}$	252–253
VI	*ortho* $ClC_6H_4CH_2$-	CH_3-	CEJ	—	83–84/2	1.5405[h]	—
VII	*para* $ClC_6H_4CH_2$-	CH_3-	BEJK	85	118–121/23	—	194–195
VIII	*para* $CH_3OC_6H_4CH_2$-	CH_3-(7)	—[d]	75	88–96/2	—	—
IX	*para* $CH_3OC_6H_4CH_2$-	*n*-butyl-	—[e]	82	147–151/2[h]	$1.508^{25°}$	—
X	α-furyl-CH_2-	ethyl-(4,5)	CEG[i]	49	73–75/25	—	120–121
XI	α-naphthyl-CH_2-	CH_3- (6)	—[f]	93	—	—	187–188
XII	$C_6H_5CHCH_2CH_2CH_2CH_3$ |	CH_3-	—[g]	61	242–243	—	144–145

[a] The letters indicate conditions and procedures described in the experimental section.

[b] A 0.07-mole run. There was formed a considerable amount of di-*n*-dodecylamine which was isolated and identified.

[c] A small amount (3 ml.) of concentrated ammonium hydroxide was added to the 3-mole reduction mixture.

[d] Reduction was with Raney nickel at about 1400 lbs. per sq. in. at room temperature.

[e] Reduction was with Raney nickel at about 1800 lbs. per sq. in. at 165° (10 hrs.).

[f] Made from α-(chloromethyl)naphthalene (*cf.* Ref. 6). The product was crystallized from isopropanol.

[g] See experimental part.

[h] Not analyzed.

[i] Prepared by James A. Freek.

TABLE II

SCHIFF BASES. $ArCH{=}NR$

	Ar-	R-	B.P. C°/MM.	n_D^{20}	PREP.[a] METHOD	YIELD %
XIII	C_6H_5-	*i*-propyl-	64/1	—	A	83[b]
XIV	C_6H_5-	*s*-butyl-	86–88/3	1.5211	A	92[b]
XV	C_6H_5-	*n*-octyl-	142–143/2	1.5136	A	85
XVI	C_6H_5-	*n*-dodecyl-	167/1	1.5022	D	80
XVII	*ortho* ClC_6H_4-	CH_3-	78–80/2	1.5660	C	85[b]
XVIII	*para* ClC_6H_4-	CH_3-	69–71/2	—	B	93
XIX	*para* $CH_3OC_6H_4$-	CH_3-	113–115/14	—	B	83[b]
XX	*para* $CH_3OC_6H_4$-	*n*-butyl-	126–127/3.5	—	A	73[b]

[a] The letters refer to the procedures for preparing the Schiff bases, which are outlined in the experimental part.

[b] These compounds were not analyzed, but were reduced directly, to the secondary amines.

TABLE III

TERTIARY (ARYLMETHYL)AMINES. $ArCH_2N\begin{matrix}R\\ \diagup\\ \diagdown\\ R'\end{matrix}$

	SN	Ar-	R	R′	Q[a]	PREP.[a] METHOD	YIELD[b] %	B.P.C°/MM.	n_D^{20}	M.P. HYDROCHLORIDE
XXI	7110	C_6H_5-	$C_6H_5CH_2$-	*n*-decyl-	<0.03	H	—	216–217/0.5	1.5253	—
XXII	7518	C_6H_5-	$C_6H_5CH_2$-	myristyl-	<0.03	I	—	216–217/2	1.5130	—
XXIII	7916	C_6H_5-	$C_6H_5CH_2$-	$C_6H_5CH_2CH_2$-	<0.03	J	72	—	—	201–203
XXIV	7111	*p*-ClC_6H_4-	*n*-octyl-	*n*-octyl-	0.06	BD	—	225–226/0.5	1.4903	—
XXV	7516	*p*-ClC_6H_4-	*n*-nonyl-	*n*-nonyl-	<0.03	BD	—	234–235.5/0.5	1.4889	—
XXVI	7515	*p*-ClC_6H_4-	-N-tetrahydroquinolyl-		<0.06	BE	73	—	—	54–55[c]
XXVII	7919	*p*-BrC_6H_4-	*n*-octyl-	*n*-octyl-	0.03+	BD	—	228–229/0.5	1.5003	—
XXVIII	6549	*p*-BrC_6H_4-	$C_6H_5CH_2$-	cyclohexyl-	<0.06	AE	65	—	—	67–68[c]
XXIX	8115	*p*-BrC_6H_4-	*p*-$CH_3OC_6H_4CH_2$-	*n*-butyl-	<0.03	BD	—	215.5/0.5	1.5629	—
XXX	6972	*p*-BrC_6H_4-	$C_6H_5CH_2$-	$C_6H_5CH_2$-	<0.03	BG	52	—	—	203–204[d]
XXXI	7987	α-naphthyl-	ethyl-	ethyl-	<0 08	BDG[f]	48	—	—	217–218
XXXII	8344	α-naphthyl-	*n*-amyl-	*n*-amyl-	<0.06	BDF[g]	57	187–188/1	1.5395	—
XXXIII	7986	α-naphthyl-	$C_6H_5CH_2$-	CH_3-(6)	<0.03	BCG[f]	96	—	—	223–225[e]
XXXIV	8116	α-naphthyl-	$C_6H_5CH_2$-	$C_6H_5CH_2$-	<0.03	BDG[g]	80	—	—	192–194
XXXV	7521	α-naphthyl-	*p*-$ClC_6H_4CH_2$-	CH_3-	<0.03	BDG[f]	—[h]	—	—	208–209
XXXVI	8476	α-naphthyl-	*p*-$CH_3OC_6H_4CH_2$-	CH_3-	<0.03	—[f,i]	87	—	—	188–190

[a] See experimental part under the heading "The arylmethyl tertiary amines."

[b] Of good material but not necessarily brought to analytical purity.

[c] Melting point of the base.

[d] The base melts about at room temperature; it was filtered (cold) and converted into the hydrochloride.

[e] B and B. (6), 225°.

[f] From α-(chloromethyl)naphthalene.

[g] From α-(bromomethyl)naphthalene.

[h] The yield was nearly quantitative.

[i] No solvent was used. Reaction occurred quickly with tempe ature rise, and after standing, cooling, digesting with ether, and filte ing off the secondary amine hydrochloride, the product was isolated from the filtrate.

methyl derivatives; the molecular weight in each case was brought to a fairly high level by means of appropriate alkyl groups on the nitrogen. The introduction of halogens into the phenyl nucleus was expected to increase activity as it does in so many other types (8), and the choice of the α- rather than the β-naphthyl series was based on the higher antimalarial activities of the corresponding α-naphthyl amino alcohols (9).

The preparation of the tertiary amines involving at least one arylmethyl group was usually accomplished by the action of the appropriate arylmethyl halide on an available secondary amine, using in some cases a secondary arylmethylamine from Table I. In the synthesis of the α-naphthylmethyl compounds, naphthalene was chloromethylated by a variation of the Darzens and Lévy method (10). It was found impractical to use unpurified material, however, since the condensation with secondary amines was slow and apparently allowed secondary reactions to interfere seriously. The more reactive bromomethyl compound was made by the hydrobromic-acetic acid method (11), and much better results were achieved in these condensations.

The results of screening tests against avian malaria were disappointing in that only two compounds showed slight activity against *gallinaceum* in the chick (8). *p*-Chlorobenzyldioctylamine showed Q = 0.06 as compared with the Q = 0.25 in the case of α-(4-chlorophenyl)-β-dioctylaminoethanol (1).

EXPERIMENTAL[5, 6]

The Schiff bases in most cases (A) were made by adding the primary amine dropwise with stirring into benzaldehyde or the appropriate derivative, with continued stirring for at least 4–24 hours, separating from the water formed, and fractionally distilling the product under reduced pressure. In a few cases (B) a cooled mixture of benzene, the aldehyde, and primary amine hydrochloride was treated dropwise with a slight excess of the calculated amount of concentrated sodium hydroxide, and allowed to stand for two hours. In one case (C) a 25% aqueous methylamine solution was used (overnight). Often the Schiff base thus obtained was not further purified or characterized and was used directly in the reduction to the secondary amine. In one case (D) the condensation was run in ether as the solvent to dissolve the reactants (one hour).

Hydrogenation of the Schiff bases. (For literature, see Ref. 12). Raney nickel was used as catalyst and hydrogenation was usually run at room temperature and atmospheric pressure. In some cases (A) no solvent was used, and in others 95% ethanol, in (B) the very small amounts necessary for introduction of the catalyst, or in larger amounts (C) on the order of 1–2 volumes. In one case a small amount of absolute ethanol was used (D). The reductions were usually slow when the reduction was run in (E) one molar or (F) larger scale. Some reductions (G) required 12–24 hours for absorption of the calculated amount of hydrogen, others required longer, from (H) two or three days, to (I) five days, or longer (J). The products were always fractionally distilled under reduced pressure, and in some cases were then converted into the hydrochlorides.

It is interesting to note that Raney nickel caused elimination of only a very small amount of the *para* halogen, as was shown in the case of 4-chlorobenzylmethylamine, where after one typical reduction (K) an aliquot portion of the solution was treated with silver nitrate

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[5] All melting points are corrected.

[6] A number of the microanalyses were carried out by Misses C. H. Vondra, Geraldine Alley and Mrs. Joyce B. Caliga.

and the resulting precipitate of silver halide was filtered and determined quantitatively; this demonstrated that reductive elimination of the *para* chlorine had occurred to the extent of 3.8%.

N-(1-Phenylpentyl)methylamine (XII). (*cf.* Ref. 13). A solution of 0.444 mole of *n*-butylmagnesium bromide in 300 ml. of absolute ether and 300 ml. of toluene was distilled until the temperature of the residual mixture reached 100°; 37.4 g. (0.314 mole) of benzalmethylamine in an equal volume of toluene was added over fifteen minutes with refluxing, and refluxing was continued for an additional fifteen minutes. Upon hydrolysis, extraction

TABLE IV

ANALYSES

	EMPIRICAL FORMULA	CRYSTALLIZED FROM	CALC'D C(N)	FOUND C(N)	CALC'D H	FOUND H
I	$C_{10}H_{15}N$	—	$^{N}9.39$	9.47	—	—
	$C_{10}H_{15}N\cdot HCl$	isopropanol	64.68	64.58	8.68	8.39
II	$C_{11}H_{17}N$	—	$^{N}8.58$	8.53	—	—
	$C_{11}H_{17}N\cdot HCl$	butanone	$^{N}7.01$	7.25	—	—
III	$C_{15}H_{25}N$	—	82.13	81.86	11.49	11.58
IV	$C_{19}H_{33}N\cdot HCl$	—	$^{N}4.49$	4.37	—	—
VII	$C_8H_{10}ClN\cdot HCl$	ether[a]	$^{N}7.29$	7.19	—	—
XII	$C_{12}H_{19}N\cdot HCl$	ether-EtOH	$^{N}6.56$	6.43	—	—
XV	$C_{15}H_{23}N$	—	82.89	83.25	10.66	10.33
XVI	$C_{19}H_{33}N$	—	$^{N}5.12$	4.90	—	—
XVIII	C_8H_8ClN	—	$^{N}9.12$	8.74	—	—
XXI	$C_{24}H_{35}N$	—	$^{N}4.15$	4.09	—	—
XXII	$C_{28}H_{43}N$	—	$^{N}3.56$	3.64	—	—
XXIII	$C_{22}H_{23}N\cdot HCl$	EtOH-ether	$^{N}4.15$	4.41	—	—
XXIV	$C_{23}H_{40}ClN$	—	$^{N}3.83$	3.84	—	—
XXV	$C_{25}H_{44}ClN$	—	$^{N}3.55$	3.84	—	—
XXVI	$C_{16}H_{16}ClN$	isopropanol	$^{N}5.43$	5.38	—	—
XXVII	$C_{23}H_{40}BrN$	—	$^{N}3.41$	3.53	—	—
XXVIII	$C_{20}H_{34}BrN$	ethanol	$^{N}3.91$	4.30	—	—
XXIX	$C_{19}H_{24}BrNO$	—	62.98	62.98	6.68	6.79
XXX	$C_{21}H_{20}BrN\cdot HCl$	abs. EtOH	$^{N}3.48$	3.46	—	—
XXXI	$C_{15}H_{19}N\cdot HCl$	CH_3OH-ether	72.12	72.44	8.07	7.73
XXXII	$C_{21}H_{31}N$	—	$^{N}4.71$	4.94	—	—
XXXIV	$C_{25}H_{23}N\cdot HCl$	isopropanol	$^{N}3.75$	3.96	—	—
XXXV	$C_{19}H_{18}ClN\cdot HCl$	isopropanol	$^{N}4.22$	4.34	—	—
XXXVI	$C_{20}H_{21}NO\cdot HCl$	acetone-ether	$^{N}4.27$	4.54	—	—

[a] Precipitated from ether by ethereal hydrogen chloride.

[N] Those analyses carrying this designation are for nitrogen.

with ether, and drying over sodium sulfate with Norit treatment, the oil which was obtained was distilled under reduced pressure; 34.6 g. (61%); b.p. at atmospheric pressure, 242–243°. It was converted into the hydrochloride from ether.

The arylmethyl tertiary amines were made by the interaction of one equivalent of the arylmethyl- or alkyl-halide and two equivalents of the appropriate secondary amine in (A) benzene or (B) ether as solvent, either with refluxing (C) until the precipitation of the halogen as the secondary amine hydrohalide was complete (10–15 hours), or allowing the mixture to stand for a much longer time at room temperature (D). The secondary amine

hydrochloride was filtered off and served as indication of the progress and completion of the reaction. Evaporation of the solvent gave the tertiary amine which, if it was a solid, was crystallized (E), or, if not, was distilled (F), or converted into the hydrochloride (G).

In the case of the benzylamine condensations with (H) decyl and (I) myristyl iodides the reactions were run in xylene under refluxing for two hours. In one case (J) the product was obtained by the interaction of a 2:1:2 equivalent mixture of benzyl bromide, β-phenylethylamine, and aqueous sodium carbonate with shaking for twenty-four hours (the crude base in this case boiled at 206–211° at 3 mm.).

α-(Bromomethyl)naphthalene was made by a modification of the method of Darzens and Lévy (10, 11) using 30% hydrogen bromide in concentrated acetic acid. Naphthalene (130 g.) was added with stirring to a solution of 40 g. of paraformaldehyde in 400 ml. of 30% hydrobromic-acetic acids and the mixture was heated for eighteen hours at 55°. Extraction with benzene and washing with sodium carbonate and with water, drying, and distilling, gave a cut of 123 g. (55%) boiling at 150–155° (1 mm.); it crystallized upon cooling.

N-Benzyl-N-(4-diethylaminopentyl)amine (XXXVII) was made by allowing 68.4 g. (0.4 mole) of benzyl bromide to react with 126 g. (0.8 mole) of novalamine in 200 ml. of ether. The ether solution was decanted from the resinous precipitate of hydrobromides, was washed with water, dried, and evaporated. The oil thus obtained, on fractional distillation at 4.5 mm., gave cuts totaling 46 g. of boiling range 142.5–149° and n_D^{20} 1.4982–1.4989. The dihydrochloride was precipitated from ether (with decantation of this solvent) and crystallized several times from absolute ethanol; hygroscopic; softens at 85–87° and melts at 142–144°.

Anal. Calc'd for $C_{16}H_{28}N_2 \cdot 2HCl$: C, 59.80; H, 9.41; Cl^-, 22.07.
Found: C, 59.00; H, 9.32; Cl^-, 21.91.

In a second preparation, benzaldehyde was condensed with novalamine (Procedure A) and the Schiff base, N-benzal-N-(4-diethylaminopentyl)amine, was obtained as an oil [b.p. 155.5° (14 mm.); n_D^{20} 1.5180] (not analyzed), and was hydrogenated to the secondary amine with Raney nickel (Procedure B); this product was identified as the dihydrochloride.

N-Benzyl-N-(3-di-n-butylaminopropyl)amine. The crude Schiff base obtained by allowing an equimolar mixture of benzaldehyde and γ-dibutylaminopropylamine to stand overnight, separating from water generated, and washing with saturated sodium chloride solution, was hydrogenated with Raney nickel (Procedure B); yield 39%; redistillation gave a boiling range of 169–170° (6 mm.); n_D^{23} 1.4920–1.4923.

Anal. Calc'd for $C_{18}H_{32}N_2$: N, 10.13. Found: N, 10.21.

N-Benzyl-N-(3-diethylaminopropyl)amine was made by condensing 53 g. of benzaldehyde with 65 g. of γ-diethylaminopropylamine (shaking overnight), separating from the water generated, and hydrogenating with Raney nickel at 100° and a pressure of 1900 lbs. per sq. in. Fractionation at 4 mm. pressure gave 62.5 g. of product boiling at 132–134°. Redistillation gave the boiling point 129° (3.5 mm.); n_D^{25} 1.5010.

Anal. Calc'd for $C_{14}H_{24}N_2$: N, 12.72. Found: N, 12.99.

SUMMARY

Eight new arylmethyl secondary amines have been synthesized by Raney nickel hydrogenation of Schiff bases, for use in the synthesis of α-dialkylaminomethylbenzyl alcohols.

Three N-benzyl-N-(dialkylaminoalkyl)amines are reported.

Fifteen new arylmethyl tertiary amines were made from primary and secondary amines by condensation with arylmethyl or alkyl halides; these were made for the purpose of antimalarial tests.

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