rather than in the usual 9,10 and 12,13 positions. Furthermore, ordinary 9,10–12,13-linoleic acid would have yielded the C_6 monobasic acid when oxidized, but no such acid was recovered. Therefore, it seems likely that the linoleic acid of hair fat bears the same relation to 6,7-oleic acid as ordinary linoleic acid bears to 9,10-oleic acid. In any case the double bonds are separated by a CH_2 group since the acid is alkali isomerizable to the conjugated form.

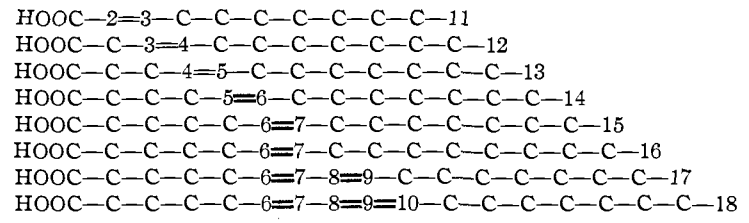


Fig. 3.—Position of double bonds.

Acids Other than the Normal Series.—In the C_7 and C_{11} fractions there were traces of acids which were insoluble in cold hexane. The amounts were insufficient for purification. Microanalyses on the crude hexane soluble and insoluble fractions were obtained.[16] The hexane soluble portion of the C_7 fraction was a monobasic acid as judged from the equivalence of its molecular weight in camphor to its neutralization equivalent. Its carbon and hydrogen contents were those of a C_7 saturated monobasic acid, presumably straight-chained.

The hexane insoluble C_7 acid was likewise a monobasic acid. High carbon and low hydrogen contents clearly indicated an aromatic nucleus and the boiling point of the methyl ester limited the choice to benzoic acid, a common preservative in cosmetic preparations. The proportion present in the total free fatty acid fraction is on the order of 0.02–0.03%.

The C_{11} fraction, in addition to a presumably normal saturated fatty acid and traces of an unsaturated acid, contained a hexane insoluble substance having a molecular weight much higher than its neutralization equivalent and carbon and hydrogen contents suggestive of a saturated dibasic acid having eight carbon atoms, probably suberic acid. Its content in the total free fatty acid fraction does not exceed 0.05%.

(16) Microanalyses by T. S. Ma, Department of Chemistry, University of Chicago.

Summary

The free fatty acid fraction of human hair fat has been examined and found to contain normal saturated and unsaturated fatty acids, ranging in chain length from 7 to 22 carbon atoms. The normal saturated and unsaturated fatty acids having odd carbon contents appear to have been obtained from a natural source for the first time. The 6,7 position appears to be the characteristic location of the double bond in the unsaturated acids, although some 8,9 and other isomers are present. The unique character of most of the acids precludes the possibility of extensive extraneous origin.

WHITING, INDIANA RECEIVED JANUARY 20, 1947

[CONTRIBUTION FROM THE LABORATORIES OF G. D. SEARLE AND COMPANY]

1-Dialkylaminoalkylaminoisoquinolines[1]

BY RICHARD A. ROBINSON

As our part of the current intensive search for new antimalarial drugs[2] we undertook the synthesis of basically alkylated aminoisoquinolines, a field in which other groups had not shown an interest.[2a] Although this field, in our hands, proved to be unproductive as a source of active antimalarial drugs, several interesting chemical syntheses were achieved, and they will be discussed here and in succeeding papers.

We have synthesized basically alkylated 1-aminoisoquinolines (II) in which variations were made in two directions: (1) variations in the side chain of otherwise unsubstituted dialkylaminoalkylaminoisoquinolines, and (2) the further substitution of 1-(γ-diethylaminopropylamino)-isoquinoline with chloro or methoxyl groups.

The basic side chains were introduced through the reaction of 1-chloroisoquinolines (I) with the desired dialkylaminoalkylamine. The 1-chloroisoquinolines were synthesized by a variety of methods which, in their final step, depended on the conversion of an isoquinoline N-oxide (III), or an isocarbostyril derivative (IV) to the corresponding 1-chloroisoquinoline by the action of phosphorus oxychloride. 1-Chloroisoquinoline was prepared from isoquinoline. Isoquinoline was first converted to isocarbostyril according to the procedure of Chichibabin and Kursanova[3] and the latter substance reacted with phosphorus oxychloride to give 1-chloroisoquinoline.[4]

7-Methoxy-1-chloroisoquinoline and 1,7-dichloroisoquinoline were derived from the known 7-methoxyisoquinoline which was prepared as described by Fritsch.[5] 7-Methoxyisoquinoline was converted to its N-oxide derivative which reacted with phosphorus oxychloride to yield 7-methoxy-1-chloroisoquinoline. This method was suggested

(1) Presented before the organic division of the American Chemical Society, Sept., 1946.

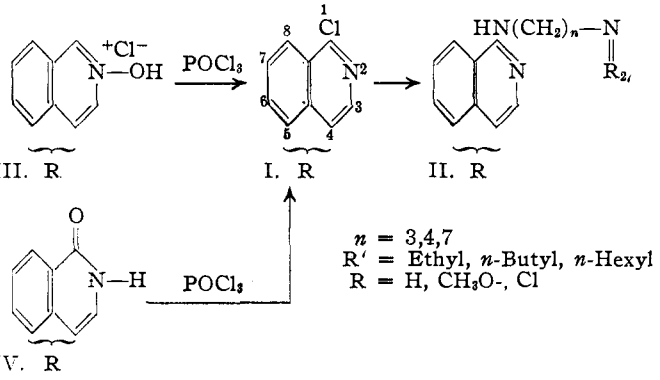
(2) This work was undertaken in coöperation with the Survey of Antimalarial Drugs of the National Research Council. The results of antimalarial screening tests on the compounds here reported will be found in "Antimalarial Drugs 1941–45," Edwards Brothers, Ann Arbor, Michigan, 1946.

(2a) Drake and Peck, THIS JOURNAL, **68**, 1309 (1946), have recently reported several chloro derivatives of 1-(δ-diethylaminoisobutylamino)-isoquinoline. None of their compounds was duplicated in this work.

(3) Chichibabin and Kursanova, *J. Russ. Phys.-Chem. Soc.*, **62**, 1211 (1930).

(4) Gabriel and Colman, *Ber.*, **33**, 985 (1900).

(5) Fritsch, *Ann.*, **286**, 1 (1895).



by Meisenheimer's[6] synthesis of 4-chloroquinoline. In going from 7-methoxyisoquinoline to 1,7-dichloroisoquinoline the following transformations were made: (1) demethylation, (2) preparation of 7-aminoisoquinoline by the Bucherer reaction, (3) preparation of 7-chloroisoquinoline by the diazo reaction and (4) conversion of 7-chloroisoquinoline to 1,7-dichloroisoquinoline by way of the amine oxide.

The 1,5-dichloroisoquinoline was derived from 1-chloroisoquinoline. By nitration a nitro-1-chloroisoquinoline was obtained which was converted to amino-1-chloroisoquinoline by catalytic reduction. For proof of structure of the amino-1-chloroisoquinoline the 1-chloro group was removed by hydrogenation in the presence of Raney nickel and sodium hydroxide. The aminoisoquinoline obtained was identical with 5-aminoisoquinoline whose structure has been determined independently by Tyson[7] and Andersag.[8] The amino-1-chloroisoquinoline, which was therefore the 5-amino-1-chloro-isoquinoline, was converted to 1,5-dichloroisoquinoline by the diazo reaction.

5-Methoxy-1-chloroisoquinoline was derived from isoquinoline-5-sulfonic acid. This acid was prepared according to the procedure of Claus and Seeleman.[9] Its structure has been established by Tyson.[7] Weisgerber[10] has reported a hydroxyisocarbostyril which he obtained in small quantities from the conversion of isoquinoline-5-sulfonic acid to 5-hydroxyisoquinoline by caustic fusion. We found that 5-hydroxyisocarbostyril was formed exclusively when the fusion was made with technical potassium hydroxide flakes at 220–230°. 5-Hydroxyisocarbostyril readily gave an *o*-methyl ether which was smoothly converted to 5-methoxy-1-chloroisoquinoline by the action of phosphorus oxychloride.

6-Methoxy-1-chloroisoquinoline was prepared in the following way. 6-Methoxytetrahydroisoquinoline prepared according to the procedure of Helfer[11] was dehydrogenated by means of Raney nickel. The resulting 6-methoxyisoquinoline was then converted to its 1-chloro derivative by way of the amine oxide. 1,3-Dichloroisoquinoline was prepared from homophthalimide according to the procedure of Gabriel.[12]

The γ-dialkylaminopropylamines required in this work were prepared from acrylonitrile and dialkylamines as described by Whitmore and co-workers.[13] The γ-diethylaminobutyronitrile required for the synthesis of δ-diethylaminobutylamine, was prepared according to Untermohler and Hamilton.[14]

Acknowledgment.—We are indebted to Mr. John W. Cusic, Mr. W. M. Selby, Dr. Viktor Papesch and Dr. Miles R. McCorkle for some of the synthetic work and to Miss Evelyn Schuber and Miss Viola Stoll for the analytical work.

Experimental

1-(γ-Diethylaminopropylamino)-isoquinoline Dihydrochloride.—Thirty-five grams of γ-diethylaminopropylamine and 16.3 g. of 1-chloroisoquinoline (m. p. 37°) were heated to 135–140° for ten minutes. The temperature of the mass was raised to reflux point (175–180°) during twenty-five minutes and held at this point ten minutes. The product was then isolated in the usual way. The dihydrochloride, prepared by adding hydrogen chloride to an ethereal solution of the base, crystallized well from aqueous acetone.

6-Methoxy-isoquinoline.—Twenty-six grams of 6-methoxytetrahydroisoquinoline, 35 g. of active Raney nickel and 200 g. of naphthalene (practical grade, freshly distilled), were heated to 200 ± 5° (under air-condenser) for one hour. Rapid stirring was maintained. The catalyst and naphthalene were then removed and a dry ethereal solution of the organic bases prepared. A small amount of carbon bisulfide (depending on the quantity of precipitate formed) was added to remove traces of unchanged tetrahydroisoquinoline as the dithiocarbamate. The 6-methoxyisoquinoline was then precipitated as the hydrochloride.

6-Methoxyisoquinoline N-Oxide.—Forty grams (0.25 mole) of 6-methoxyisoquinoline was added slowly to 0.328 mole of phthalyl per-acid in 1300 ml. of dry ether at −6 to −8° and stirred for ninety minutes. The mixture was stored in an ice-box overnight. The perphthalate, an oily substance, was washed by decantation with ether. The oil was permitted to warm up to room temperature (the temperature rose to 45° due to exothermic effect). After standing overnight the product was mostly crystalline. The product was warmed with 420 ml. of ethanol containing excess hydrogen chloride. The hydrochloride crystallized from the ethanol solution.

7-Chloroisoquinoline N-Oxide.—Hydrogen peroxide, 41.14 g. of 30% solution (0.36 mole) and 200 ml. of glacial acetic acid were kept at the temperature of the steam-bath one hour. To this solution (at room temperature) was added, all at once, 47 g. (0.29 mole) of 7-chloroisoquinoline. This solution was heated on the steam-bath for one hour (a test should show complete solubility in very dilute alkali). The acetic acid was removed at 20–30 mm. pressure and the crystalline residue stored in a vacuum desiccator over potassium hydroxide for thirty-six hours. Absolute alcohol, 100 ml., was added and then one equivalent of ethereal hydrogen chloride. The amine oxide hydrochloride (difficultly soluble in alcohol) separated. The product was washed with alcohol and dried at 60°.

(6) Meisenheimer, *Ber.*, **59**, 1848 (1926); Bachmann and Cooper, *J. Org. Chem.*, **9**, 302 (1944).
(7) Tyson, THIS JOURNAL, **61**, 183 (1939).
(8) Andersag, *Med. u. Chem.*, **2**, 377 (1934).
(9) Claus and Seeleman, *J. prakt. Chem.*, [2] **52**, 1 (1895).
(10) Weisgerber, *Ber.*, **47**, 3175 (1914).
(11) Helfer, *Helv. Chim. Acta*, **7**, 945 (1924).
(12) Gabriel, *Ber.*, **19**, 1655 (1886).
(13) Whitmore, *et al.*, THIS JOURNAL, **66**, 725 (1944).
(14) Untermohler and Hamilton, *ibid.*, **63**, 156 (1941).

TABLE I

ISOQUINOLINE DERIVATIVES[a]

No.	Substituents	M. p., °C.	Yield, %	Formula	Water, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
1	1-(γ-Diethylaminopropylamino)-	oil		$C_{16}H_{23}N_3$		74.67	74.8	9.01	9.12				
	(Dihydrochloride)[b]	125	88	$C_{16}H_{25}Cl_2N_3$	3.31					12.72	12.51	21.47	20.7
2	1-(α-Diethylaminobutylamino)-												
	(Dihydrochloride)[b,c]	90	85	$C_{17}H_{27}Cl_2N_3$	8.55	59.3	58.7	7.91	8.29	12.20	11.80	20.59	20.22
3	1-(α-Diethylamino-α-methyl-												
	butylamino)-			$C_{18}H_{27}N_3$		75.74	76.0	9.54	9.25				
	(Dihydrochloride)[b,d]	95–100	80	$C_{18}H_{29}Cl_2N_3$	9.7					11.73	11.41	19.79	19.15
4	1-(γ-Dibutylaminopropylamino)-												
	(Dihydrochloride)[b,e]	135	85	$C_{20}H_{33}Cl_2N_3$	4.87	62.16	62.7	8.35	8.7	10.88	10.21	18.35	18.27
5	1-(γ-Dihexylaminopropylamino)-												
	(Dihydrochloride)[f]	163	80	$C_{24}H_{41}Cl_2N_3$		65.14	65.2	9.34	9.1	9.5	9.43	16.03	15.96
6	1-[γ-(γ-Diethylaminopropyl-												
	amino)-propylamino]-[g]												
	(Trihydrochloride)[b,h]	140	60	$C_{19}H_{38}Cl_3N_4$	2.9	53.8	52.7	7.85	8.4	13.22	12.72	25.09	24.47
7	5-Methoxy-1-(γ-diethylamino-												
	propylamino)-												
	(Dihydrochloride)[i]	231	85	$C_{17}H_{27}Cl_2N_3O$		56.67	56.76	7.55	7.91	11.66	11.43	19.68	19.61
8	6-Methoxy-1-(γ-diethylamino-												
	propylamino)-												
	(Dihydrochloride)[i]	184	85	$C_{17}H_{27}Cl_2N_3O$		56.67	56.0	7.55	7.38	11.66	11.31	19.68	19.45
9	7-Methoxy-1-(γ-diethylamino-												
	propylamino)-	oil		$C_{17}H_{28}N_3O$		71.05	70.7	8.77	8.66	14.62	14.90		
	(Dihydrochloride)[b,j]	120	80	$C_{17}H_{27}Cl_2N_3O$	5.3					11.66	11.4	19.68	19.85
10	5-Chloro-1-(γ-diethylamino-												
	propylamino)-	oil		$C_{16}H_{22}ClN_3$		65.85	66.2	7.6	7.69	12.15	11.89		
	(Dihydrochloride)[i]	227	75	$C_{16}H_{24}Cl_3N_3$								29.16	28.57
												Cl^- 19.44	19.62
11	7-Chloro-1-(γ-diethylamino-												
	propylamino)-												
	(Dihydrochloride)[b]	161	80	$C_{16}H_{24}Cl_3N_3$	4.18	52.68	52.45	6.63	6.89			29.16	28.92
												Cl^- 19.44	19.34
12	3-Chloro-1-(γ-diethylamino-												
	propylamino)-	oil		$C_{16}H_{22}ClN_3$		65.85	65.4	7.6	7.82	12.15	11.93		
	(Dihydrochloride)[b,k]	125	75	$C_{16}H_{24}Cl_3N_3$	4.72							Cl^- 19.44	19.18
13	1-(ω-Diethylaminoheptylamino)-	oil	80	$C_{20}H_{31}N_3$		76.63	76.6	9.97	9.95	13.4	13.71		
14	6-Methoxy-												
	(Hydrochloride)	216	95	$C_{10}H_{10}ClNO$		61.42	60.92	5.15	5.06	7.16	6.9	18.13	18.12
	(Picrate)	225		$C_{16}H_{12}N_4O_8$						14.43	14.1		
15	1,5-Dihydroxy-[l]	282	90	$C_9H_7NO_2$						8.69	8.57		
16	5-Methoxy-1-hydroxy-[m]	220	50	$C_{10}H_9NO_2$						8.00	7.99		
17	5-Methoxy-1-chloro-[n]	137	100	$C_{10}H_8ClNO$		62.02	62.0	4.16	4.2	7.24	7.13	18.31	18.2
18	6-Methoxy-1-chloro-[o]	77	70	$C_{10}H_8ClNO$		62.02	62.18	4.16	4.14	7.24	7.0	18.31	18.25
							61.88		4.08				
19	7-Methoxy-1-chloro-[p]	76	75	$C_{10}H_8ClNO$		62.02	62.37	4.16	4.15	7.24	7.14	18.31	18.58
							62.39						
20	6-Methoxy-N-oxide-												
	(Hydrochloride)	197	40	$C_{10}H_{10}ClNO_2$		56.74	56.6	4.76	4.75	6.62	6.27	16.75	16.68
21	1,7-Dichloro-[q]	138	90	$C_9H_5Cl_2N$		54.58	54.71	2.55	2.71	7.07	6.92	35.8	35.78
											6.77		
22	1,5-Dichloro-[r]	147	50	$C_9H_5Cl_2N$								35.81	35.48
23	1-Chloro-5-nitro-[s]	187	80	$C_9H_5ClN_2O_2$						13.43	13.05		
24	1-Chloro-5-amino-[t]	180	75	$C_9H_7ClN_2$						15.69	15.47	19.85	19.16
25	7-Chloro-[u]	45	75	C_9H_6ClN								21.67	21.72
26	7-Chloro-N-oxide-												
	(Hydrochloride)	218	97	$C_9H_7Cl_2NO$		50.03	49.98	3.27	3.34			32.82	32.08
												Cl^- 16.41	16.37
27	7-Amino-[v]	204	95	$C_9H_8N_2$		74.97	74.7	5.59	5.45	19.44	19.02		

[a] In the preparation of 1 through 13 the reaction between the diamine and the 1-chloroisoquinoline occurred in the temperature range 150–200°. [b] The dihydrochlorides frequently contained water although in some cases they crystallized as the anhydrous salt. Due to difficulty in handling the dried substances the analyses were made on the hydrates and corrected to anhydrous values. The melting points are for the hydrated substances. [c] Purified by recrystallization from isopropanol in which it is moderately soluble. [d] Soluble in ethanol, difficultly soluble in acetone. [e] Easily soluble in acetone, recrystallized from *i*-propanol. [f] Purified by recrystallization from acetone. [g] Prepared from 1-chloroisoquinoline and γ-(γ-diethylaminopropylamino)-propylamine. [h] Recrystallized from isopropanol and ethanol. [i] Recrystallized from isopropanol in which it is difficultly soluble. [j] Recrystallized from isopropanol or isopropanol–acetone, moderately soluble in isopropanol. [k] Soluble in ethanol, recrystallized from ethanol–acetone. [l] Prepared by fusion of isoquinoline-5-sodium sulfonate with technical potassium hydroxide at 220–230° for fifteen minutes. [m] Prepared from (15) by methylation with methyl iodide. [n] Prepared from (16) by the action of phosphorus oxychloride. [o] Prepared from (20) by the action of phosphorus oxychloride. [p] Prepared from 7-methoxyisoquinoline-N-oxide by the action of phosphorus oxychloride. [q] Prepared from (26) by the action of phosphorus oxychloride. [r] Prepared from (24) by the diazo reaction. [s] Prepared by nitration of 1-chloroisoquinoline in sulfuric acid at 5–8°. [t] Prepared from (23) by hydrogenation in the presence of Raney nickel at 25° and three atmospheres pressure. [u] Prepared from (27) by the diazo-reaction. [v] Prepared from 7-hydroxyisoquinoline by the Bucherer reaction.

5-Aminoisoquinoline.—One and eight-tenths grams of amino-1-chloroisoquinoline (prepared from 1-chloroisoquinoline by nitration and reduction), 0.9 g. of sodium hydroxide, 1 g. of Raney nickel and 0.05 g. of chloroplatinic acid in 150 cc. of ethanol was hydrogenated at forty pounds pressure. One mole of hydrogen was absorbed in four hours. One and one-half grams of aminoisoquinoline which melted unsharply at 125° was obtained. After recrystallization from benzene, the product melted at 132°. When it was mixed with 5-aminoisoquinoline there was no depression of the melting point.

Summary

Several 1-dialkylaminoalkylaminoisoquinolines are described.

Several chloro and methoxy derivatives of 1-(γ-diethylaminopropylamino)-isoquinoline are described.

Several methoxy and chloro derivatives of 1-chloroisoquinoline are described.

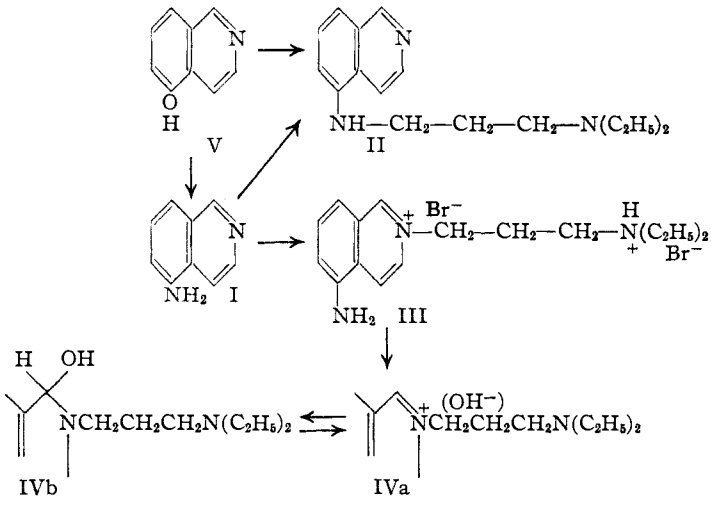
CHICAGO, ILLINOIS RECEIVED FEBRUARY 3, 1947

[CONTRIBUTION FROM THE LABORATORIES OF G. D. SEARLE AND COMPANY]

5-(γ-Diethylaminopropylamino)-isoquinoline[1]

BY RICHARD A. ROBINSON

As outlined in the preceding paper[2,3] we have undertaken the synthesis of basically alkylated aminoisoquinolines as a contribution to the search for new antimalarial drugs. The synthesis of the 1-dialkylaminoalkylaminoisoquinolines was readily accomplished through the reaction of 1-chloroisoquinoline derivatives with dialkylaminoalkyl amines. Such a simple synthesis was not effective for the introduction of a dialkylaminoalkylamino side chain at position 5. In this connection various attempts to bring about a transformation between 5-iodoisoquinoline and dialkylaminoalkylamines were made without success. The problem of preparing a 5-(γ-diethylaminopropylamino)-isoquinoline was therefore approached by other methods. The most obvious method, the aminoalkylation of 5-aminoisoquinoline (I)



was tried under a broad range of conditions. Despite numerous modifications of the known alkylation procedures, no condition was ever found which would produce a 5-(dialkylaminoalkylamino)-isoquinoline in satisfactory yield. Under neutral or slightly acid conditions (*p*H 4–5) alkylation by means of γ-diethylaminopropyl bromide attacks preferentially the ring nitrogen thereby producing an isoquinolinium salt (III). The isoquinolinium compound was characterized through the strongly basic properties of its base form (IVa) (an aqueous solution is alkaline to phenolphthalein) and by the demonstration of the presence of a primary amino group by a diazotization and coupling reaction.

The *p*H value of a tenth normal solution of 5-aminoisoquinoline hydrochloride (*p*H = 2.4) indicated that aminoalkylation might take place under more acidic conditions. A trial was accordingly made in the *p*H range 2.8 to 3.2. The 5-aminoisoquinoline was chiefly unattacked, but in this case 6% of the 5-(γ-diethylaminopropylamino)-isoquinoline (II) was obtained. This indicates that aminoalkylation of the 5-amino group could probably be accomplished under very strictly defined conditions. However, the desired product was obtained by another method and further study of the aminoalkylation procedure was not deemed necessary.

Other unsuccessful attempts at aminoalkylation included the reaction of 5-aminoisoquinoline with dialkylaminoalkanols and dialkylaminoalkylamines at elevated temperatures with the hope that alkylation would take place through the elimination of water and ammonia, respectively. Such was not the case. The reaction of 5-formylaminoisoquinoline with γ-diethylaminopropyl-sodium oxide according to German Patent 650,491 also failed to yield the desired product. Various attempts to condense 5-diethylaminopentanone-2 and 5-aminoisoquinoline were unsuccessful. It was hoped that a 5-(δ-diethylaminoisobutylamino)-isoquinoline could be obtained in this way. An indirect ap-

(1) Presented before the organic division of the Am. Chem. Soc., Sept., 1946.

(2) This work was undertaken in coöperation with the Survey of Antimalarial Drugs of the National Research Council. The results of antimalarial screening tests on the compounds here reported will be found in "Antimalarial Drugs 1941–1945," Edwards Brothers, Ann Arbor, Michigan, 1946.

(3) Paper I, THIS JOURNAL, **69**, 1939 (1947).