[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. I.[1,2] AMINO ALCOHOLS DERIVED FROM 1,2,3,4-TETRAHYDROPHENANTHRENE

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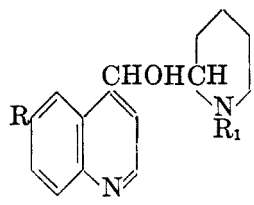
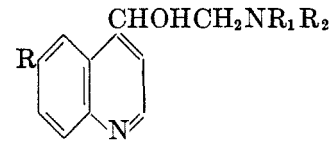
The most widely used and most effective antimalarials are at present quinine and Atabrine. Both the natural and the synthetic product are schizonticides, checking only the clinical symptoms of malaria. Plasmochin, less frequently used, appears to be the best known gametocide. A true causal prophylactic, attacking the parasite in the sporozoite-phase or shortly thereafter, has not been found as yet.

In January 1939, the Unit of Chemotherapy of the National Institute of Health was assigned the task of searching for new antimalarials with consideration of all three aspects of the chemotherapy of malaria, *i.e.*, the attack by chemicals of schizonts, gametocytes, and sporozoites. Atabrine and Plasmochin, the two outstanding antimalarials developed by the I. G. Farbenindustrie A.-G. of Germany, are structurally characterized by the aminodialkylaminoalkane side chain and a condensed aromatic-heterocyclic ring system. Whether a true causal prophylactic will have similar structural features appears doubtful. So far none of the active schizonticides or gametocides derived from acridine or quinoline have exhibited such an effect. Since the advent of these two synthetic drugs intensive efforts have been made by chemists, particularly in Great Britain, France, and Russia, to replace or improve them. This was attempted by changing, principally through minor variations, their structural features.

Attempts, however, to find substitutes for the natural product quinine, by adhering more closely to the alkaloid as a structural model, date back much further. These earlier efforts involved principally the synthesis of compounds of the two types I and II. In both structures the important feature of the alkaloid, *i.e.*, the amino alcohol grouping is retained.



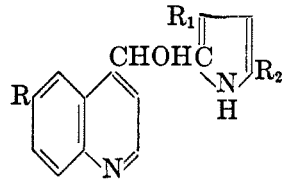
I



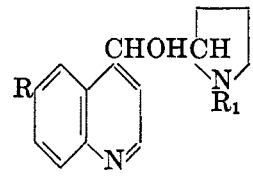
II

[1] The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health.

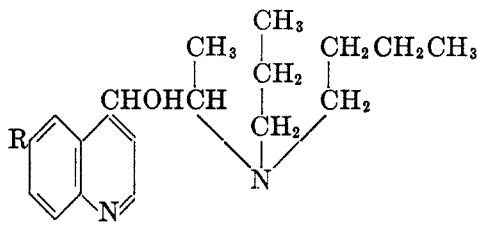
[2] Studies in the Phenanthrene Series XXVI. [Communication XXV, *J. Org. Chem.*, **5**, 313 (1940)].



Ia



Ib



III

R = H or Alkoxyl
R_1, R_2 = H or Alkyl

Thus Ruzicka and associates set forth to synthesize compounds of type I and Ib (1, 2, 3, 4). Karrer (5) prepared representatives of Ia, while Kaufmann (6) and Rabe (7, 8, 9) and their associates centered their synthetic efforts upon type II. Compounds of the latter type were then also prepared in the laboratories of the I. G. Farbenindustrie A.-G. (10). None of these efforts led to any chemotherapeutic success. It was eventually left to Ainley and King (11) to find in a series of compounds of type I, two members which showed a definite plasmodicidal effect in avian malaria. King and Work (12) then extended their searches for antimalarials, preparing compounds of type II. By increasing the size of the amino group, they succeeded in finding three members in that series which showed marked activity in avian malaria.

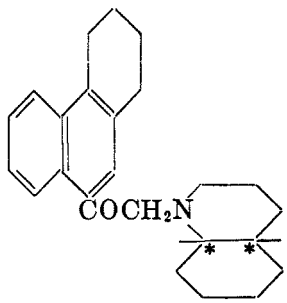
In the first stages of our search for new antimalarials, we had decided to prepare amino alcohols of type II carrying the side chain—$CHOHCH(R_1)N(R_2R_3)$, and R_1, R_2, R_3 to be chosen in such manner that this portion could formally be considered a "quinuclidine with two C—C bonds disrupted"[3] (*e.g.*, III). While this work was under way it was largely anticipated by the paper of King and Work (12). In the meantime we also had submitted to antimalarial testing a considerable number of amino alcohols derived chiefly from phenanthrene, which had been prepared by Mosettig and co-workers[4] during the years 1929–1939 in attempting to find compounds with central narcotic properties. Surprisingly, a large percentage of these showed a significant plasmodicidal activity (*P. cathemerium*, *P. relictum*, *P. gallinaceum*, and *P. knowlesi*). We, therefore, immediately decided to exploit this field thoroughly, including also analogous derivatives of naphthalene and anthracene. It is obvious that by introducing one or more other substituents (*e.g.*, alkoxyl or halogen) into the nucleus, by partial saturation of the aromatic system, and by changes in the alkamine side

[3] Mosettig and Schmehl, unpublished results.

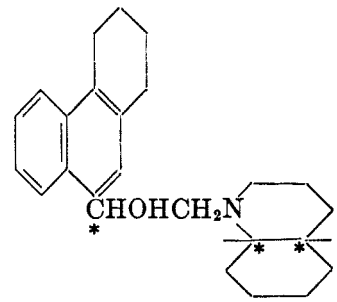
[4] See for Bibliography: "Studies on Drug Addiction," Small, Eddy, Mosettig, and Himmelsbach, Pub. Health Rep., Suppl., No. 138, 1938.

chain itself, the number of possible variations, even in one series only, becomes exceedingly large. As the work went on, however, the speedily carried out pharmacological and malarialogical tests enabled us to direct chemical efforts into the more promising channels, and consequently to avoid a good deal of superfluous work, seen in the light of therapeutic success.

The first paper of this series deals with amino alcohols derived from 1,2,3,4-tetrahydrophenanthrene. The starting point for this series was 9-acetyltetrahydrophenanthrene, which was prepared for the first time and elucidated in its structure by Bachmann and Struve (13). From this compound the alkamines were prepared in the customary manner *via* the bromo ketones and amino ketones.[4] Various difficulties were met with, particularly in the purification of amino ketones, further in their reduction, and in the purification of the final carbinolamines. In the catalytic reduction (PtO_2) of the *dl-trans*-decahydroquinolino ketone (IV), both of the possible diastereomeric amino alcohols (V) were obtained in an approximate ratio of 5:1.



IV



V

We also employed in this reaction *d-trans*-decahydroquinoline, but were able to detect in the reduction mixture of the amino ketone only one of the expected isomers.

The tolerated doses (chicks) of the drugs, varying roughly from 0.1–1.0 mg. per g. tend to increase from the dimethylamino derivative to the didecylamino derivative (Dr. Nathan B. Eddy, 14), while the effectiveness against *Plasmodium gallinaceum* tends to increase from the dimethylamino compound to the diheptylamino compound (Dr. G. Robert Coatney and Dr. W. Clark Cooper, 15). None of the drugs showed any activity towards sporozoite-induced *gallinaceum* malaria (15). SN 1796 (also recorded as NIH 204) and SN 5241 (also recorded as NIH 700) were investigated clinically. In spite of their high antimalarial activity in man, which equals approximately that of quinine, these two drugs have not been considered as practical competitors of quinine or Atabrine.[6] Some of the tetrahydrophenanthrene alkamines are very effective as inhibitors of plasma cholinesterase. This effectiveness is dependent upon the size of the dialkylamino group, passing through the maximum with the dipropylamino derivative (Dr. Charles I. Wright, 16).

[6] The clinical studies with these two drugs will be published by the several groups to whom these compounds were assigned by the Board for Coordination of Malaria Studies.

ACKNOWLEDGMENTS

We wish to thank Dr. R. C. Elderfield for a large supply of dihexylamine, and Mr. Edward A. Garlock, Jr., for carrying out the microanalyses.

TABLE I[5]

ANTIMALARIAL ACTIVITY OF AMINO ALCOHOLS

SN	$C_{14}H_{13}$-9-	Q
1792	$CHOHCH_2N(CH_3)_2$	1/8
1793	$CHOHCH_2N(C_2H_5)_2$	1/2
1794	$CHOHCH_2N(C_3H_7)_2$	1/4
5868*	$CHOHCH_2N(i\text{-}C_3H_7)_2$	—
1798	$CHOHCH_2N(allyl)_2$	—
1795	$CHOHCH_2N(C_4H_9)_2$	1/8
5869*	$CHOHCH_2N(i\text{-}C_4H_9)_2$	—
1796 (NIH 204)	$CHOHCH_2N(C_5H_{11})_2$	1/4
6687*	$CH(OCOCH_3)CH_2N(C_5H_{11})_2$	—
8845	$CHClCH_2N(C_5H_{11})_2$	1/4
2673	$COCH_2N(C_5H_{11})_2$	—
3956	$CHOHCH_2N(i\text{-}C_5H_{11})_2$	1/4
5478	$CHOHCH_2N(C_6H_{13})_2$	1/4
5479*	$CHOHCH_2N(i\text{-}C_6H_{13})_2$	1/4
3957*	$CHOHCH_2N(C_7H_{15})_2$	1/2
3516	$CHOHCH_2N(C_8H_{17})_2$	1/2
5241* (NIH 700)	$CHOHCH_2N(C_9H_{19})_2$	1/4
5866*	$CHOHCH_2N(C_{10}H_{21})_2$	—
1799	$CHOHCH_2$piperidino	1/16
1803	$CHOHCH_2$morpholino	—
5990	$COCH_2$morpholino	—
2718	$COCH_2$tetrahydroquinolino	—
1800; 9930	$CHOHCH_2$*dl-trans*-decahydroquinolino	1/8
1800	$CHOHCH_2$*d-trans*-decahydroquinolino	1/8
1802	$CHOHCH_2$tetrahydro-*i*-quinolino	—

* See footnote 5.

EXPERIMENTAL

All melting points are uncorrected.

9-ω-Bromoacetyl-1,2,3,4-tetrahydrophenanthrene (13). To a suspension of 20 g. of

[5] In Table I are listed the compounds which were submitted for biological investigations. In the first column are given the identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council. The third column shows the approximate "Quinine equivalents" expressing the effectiveness of the drugs towards *Plasmodium gallinaceum*, compared with that of quinine. A dash indicates that the equivalent is less than $\frac{1}{16}$.

All compounds listed in the Table were administered as hydrochlorides, except SN 2718 which was administered as base.

The compounds marked with an asterisk were prepared, within a cooperative program, by Dr. Robert C. Elderfield at Columbia University. SN 8845 was prepared by Dr. Nelson K. Richtmyer of the National Institute of Health. The chemistry of these compounds will be described by the named authors in forthcoming issues of the Journal of Organic Chemistry.

9-acetyl-1,2,3,4-tetrahydrophenanthrene (13, 17)[7] in 100 cc. of dry ether cooled in an ice-salt bath was added dropwise with stirring 14.4 g. (4.8 cc.) of bromine over a period of thirty to forty-five minutes. While allowing the reaction mixture to warm to room temperature, air was blown over the surface to remove some hydrogen bromide. After cooling again to 0°, the pale yellow bromo ketone was filtered off and washed with a little cold ether. It weighed 18.5 g. and melted at 88–89°. By concentration of the filtrate 3.5 g. of an equally pure product was obtained, making the total yield 81%. This material was pure enough for the next step. A small sample recrystallized from methanol-ether melted at 91–92°, as reported by Bachmann and Struve (13).

In only one experiment out of an approximate total of twenty, a lower-melting, more soluble modification of the bromo ketone separated. It consisted of needles and melted at 70–72°. Upon dissolving it in warm ether, the higher-melting form separated immediately.

Amino alcohols. 9-ω-Bromoacetyl-1,2,3,4-tetrahydrophenanthrene (one molecular equivalent) was suspended in four to five times its weight of ether and the secondary amine (two molecular equivalents) was added. The reactants were shaken together for two to fifteen hours depending upon the reactivity of the amine. In some cases, especially when large runs were made, it was necessary to cool during the initial stage of the reaction. After cooling in the ice-box, the precipitated secondary amine hydrobromide was filtered off, or washed out with water. From this point one of the four following procedures was used.

Procedure I (for compounds 2, 4, 6, 8, 15, 18, 24). The ether solution of the amino ketone was dried over sodium sulfate and made just acid to Congo red paper with alcoholic hydrogen chloride. The precipitated hydrochloride was recrystallized from the appropriate solvent combination (see Table). Unless Norit was used in this recrystallization the subsequent catalytic reduction proceeded sluggishly or not at all. The amino ketone hydrochloride was dissolved in methanol (or 95% ethanol) and the solution shaken under hydrogen with 0.025–0.05 g. of platinum oxide catalyst per gram of hydrochloride. The reductions required from eighteen to seventy-two hours and hydrogen absorption rarely came to a standstill but slowed to a constant rate after about one molecular equivalent had been absorbed. The catalyst was filtered off, the solvent evaporated under diminished pressure and the residual amino alcohol hydrochlorides were triturated with acetone or acetone-ether and purified by recrystallization. The yields (based on bromo ketone) were 40–70%.

Procedure II (for compounds 20, 21, 22, and 23). The ether solution of the *dl-trans*-decahydroquinolino (18)[8] ketone from which secondary amine hydrobromide had been filtered was concentrated somewhat, whence the crystalline base separated quantitatively. It was recrystallized from methanol, and hydrogenated in methanol solution (1.0 g. of base and 0.05 g. of platinum oxide in 50 cc. of methanol). At the end of fifteen to twenty hours, 1.2 molecular equivalents of hydrogen had been taken up, and absorption had slowed to the minimal constant rate. After removal of the catalyst, the solvent was evaporated under diminished pressure leaving a residue which crystallized on trituration with methanol. Upon standing in the ice-box overnight, 0.5 g. of solid separated. It was recrystallized from methanol to constant melting point (isomer A: see Table). Its hydrochloride was prepared by adding alcoholic hydrogen chloride to an acetone suspension of the amino alcohol base.

The original methanolic mother liquor was evaporated to dryness, and the oily residue was dissolved in the minimal amount of methanol and allowed to stand overnight. This yielded 0.1 g. of a diastereoisomer (B). Its hydrochloride was prepared as described above.

Procedure III (for compounds 2, 10, 11, 12). The dry ether solution of the amino ketone was treated with just enough dry gaseous hydrogen chloride to precipitate unchanged secondary amine as hydrochloride, which was filtered off. The amino ketone hydrochloride

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[7] We found the procedure by Bachmann and Struve (13) more advantageous for large scale preparation of this ketone, since in the subsequent bromination the 7-isomer is easily removed from the main product.

[8] The *trans*-decahydroquinoline was prepared according to Adkins and Cramer (18).

TABLE II

1,2,3,4-TETRAHYDROPHENANTHRENE DERIVATIVES

$C_{14}H_{13}$-9-	APPEARANCE	SOLVENT	M.P. °C.	FORMULA	% CARBON		% HYDROGEN		% CHLORINE	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
1. $COCH_2N(CH_3)_2 \cdot HCl$[a]	White diamond plates	Ethanol-acetone-ether	211–213*	$C_{18}H_{22}ClNO \cdot \frac{1}{2}H_2O$	69.09	68.68	7.41	7.20		
2. $CHOHCH_2N(CH_3)_2 \cdot HCl$	White prisms	Ethanol-acetone-ether	208–210	$C_{18}H_{24}ClNO$	70.69	70.37	7.91	7.91		
3. $COCH_2N(C_2H_5)_2 \cdot HCl$	Pale yellow needles	Ethanol-acetone-ether	190.5–192	$C_{20}H_{26}ClNO$	72.39	72.59	7.90	7.85		
4. $CHOHCH_2N(C_2H_5)_2 \cdot HCl$	White platelets	Acetone	161.5–163	$C_{20}H_{28}ClNO$	71.92	71.33	8.45	8.62	10.62	10.92
5. $COCH_2N(C_3H_7)_2 \cdot HCl$[b]	White needles	Acetone-ether	136–136.5	$C_{22}H_{30}ClNO \cdot H_2O$	69.91	69.69	8.54	8.11		
6. $CHOHCH_2N(C_3H_7)_2 \cdot HCl$	Broad white needles	Acetone-ether	171–173	$C_{22}H_{32}ClNO$	73.00	72.24	8.91	8.65		
7. $COCH_2N(C_4H_9)_2 \cdot HCl$[b]	White needles	Acetone-ether	91–98	$C_{24}H_{34}ClNO \cdot H_2O$	70.98	70.25	8.94	9.03	8.74	8.69
8. $CHOHCH_2N(C_4H_9)_2 \cdot HCl$	White prisms	Acetone-ether	136–137	$C_{24}H_{36}ClNO$	73.91	73.79	9.30	9.21		
9. $COCH_2N(C_5H_{11})_2 \cdot HCl$[b]	White rods	Ethyl acetate	147–150.5	$C_{26}H_{38}ClNO \cdot H_2O$	71.96	72.52	9.29	9.24		
10. $CHOHCH_2N(C_5H_{11})_2 \cdot HCl$	White prisms	Acetone-ether	134–135	$C_{26}H_{40}ClNO$	74.71	74.65	9.65	9.96	8.49	8.36
11. $CHOHCH_2N(C_6H_{13})_2 \cdot HCl$	White plates	Acetone-ether	136.5–137.5	$C_{28}H_{44}ClNO$	75.39	75.09	9.94	10.11		
12. $CHOHCH_2N(C_8H_{17})_2 \cdot HCl$	White rhombic plates	Ethyl acetate	110.5–112.5	$C_{32}H_{52}ClNO$	76.52	76.13	10.44	10.45		
13. $CHOHCH_2N(allyl)_2 \cdot HCl$	White square plates	Ethyl acetate	127–129	$C_{22}H_{28}ClNO$	73.82	73.45	7.88	8.19		
14. $COCH_2$-piperidino·HCl	White needles	Ethanol-ether	234*	$C_{21}H_{26}ClNO$	73.34	72.96	7.62	7.63		
15. $CHOHCH_2$-piperidino·HCl	White square plates	Ethanol-ether	235–235.5*	$C_{21}H_{28}ClNO$	72.91	72.67	8.16	8.12		
16. $COCH_2$-1,2,3,4-tetrahydroquinolino[c]	Yellow needles	Acetone	149.5–150.5	$C_{25}H_{25}NO$	84.47	84.10	7.09	7.35		
17. $COCH_2$-1,2,3,4-tetrahydroisoquinolino·HCl[d]	White needles	95% Ethanol	230–232*	$C_{25}H_{26}ClNO \cdot 2H_2O$					8.29	8.37
18. $CHOHCH_2$-1,2,3,4-tetrahydroisoquinolino·HCl	White plates	Ethanol-ether	221–223.5*	$C_{25}H_{28}ClNO$	76.22	76.05	7.16	7.32		

19. $COCH_2$-*dl-trans*-decahydroquinolino	Light yellow needles	Methanol	95–97	$C_{25}H_{31}NO$	83.07	82.70	8.64	8.65
20. $CHOHCH_2$-*dl-trans*-decahydroquinolino (A)	White prisms	Ethanol	158.5–160	$C_{25}H_{33}NO$	82.60	82.38	9.15	9.17
21. A·HCl	Short white needles	Ethanol-ether	229.5–230	$C_{25}H_{34}ClNO$	75.05	74.60	8.57	8.30
22. $CHOHCH_2$-*dl-trans*-decahydroquinolino (B)	White hexagons	Methanol	139.5–141	$C_{25}H_{33}NO$	82.60	82.03	9.15	9.35
23. B·HCl	Long white needles	Ethanol-ether	206–209	$C_{25}H_{34}ClNO$	75.05	74.98	8.57	8.82
24. $CHOHCH_2$-*d-trans*-decahydroquinolino·HCl[e]	White needles	Ethanol-ether	216–218	$C_{25}H_{34}ClNO \cdot H_2O$	71.84	72.21	8.68	8.57
25. $COCH_2$-Morpholino·HCl[f]	White needles	Ethanol-ether	225–228.5	$C_{20}H_{24}ClNO_2 \cdot C_2H_5OH$	67.40	67.87	7.74	7.53
26. $CHOHCH_2$-Morpholino·HCl	White prisms	95% Ethanol	230*	$C_{20}H_{26}ClNO_2$	69.04	68.83	7.53	7.74

[a] Lost no water *in vacuo* at 77°. Decomposed at 110°. If m.p. is taken rapidly, it melts partially at 165°.

[b] Loss of water of crystallization was accompanied by decomposition. Thus, an accurate water determination could not be made.

[c] Reaction time was 48 hours for the preparation of this amino ketone. It absorbed 3 to 4 moles of hydrogen when reduced catalytically and no homogeneous crystalline products were isolable. Reduction with aluminum isopropoxide also failed to give the desired amino alcohol.

[d] The water determination was made by heating at 105–110° to constant weight. The m.p. after this was 239–241°. Calc'd for $2H_2O$, 8.42%. Found: 9.13%.

[e] Water determined by heating at 130° *in vacuo* (11 hrs.); m.p. 222–225°. Calc'd for H_2O, 4.31%. Found: 4.59%. *d-trans*-Decahydroquinoline was prepared essentially by the method of Mascarelli and Nigrisoli (20), and Mascarelli (21). Our m.p. for the *d*-bromocamphorsulfonate was 249–251°; reported, 239–240°. Our m.p. for the dextro base was the same as reported, but our rotation was $(\alpha)_D^{20}$ 8.28° (*c* 4.53, 95% EtOH); reported, $(\alpha)_D^{25}$ 4.86° (*c* 4.00). At present we cannot explain this discrepancy but intend to repeat the work in the near future.

[f] The analysis fits for one mole of alcohol of crystallization.

* Melts with decomposition.

was then precipitated as an oil by addition of gaseous hydrogen chloride in a very slight excess. On cooling and scratching, the hydrochloride crystallized and was collected. It was reconverted to the base with dilute aqueous ammonia. The base, after drying in ether, was dissolved in absolute ethanol (1.0 g. in 10 cc.) and the solution was shaken under hydrogen with platinum oxide catalyst (0.04 g. per gram of amino ketone). One molecular equivalent of hydrogen was absorbed in 25 to 35 hours, the reduction stopping at this point. After removal of catalyst and evaporation of solvent at reduced pressure, the residual oil was dissolved in ether and dry gaseous hydrogen chloride added in slight excess. The white amino alcohol hydrochloride precipitated in crystalline form on cooling. The yields were 60–70%.

9-(2-Dioctylamino-1-oxoethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride crystallized from ethyl acetate-ether in two forms. The less soluble one appeared as well-formed greenish prisms (m.p. 65–75°). It lost color slowly in the dry state and possibly contained a second mole of hydrogen chloride. The second form separated from the filtrate as hexagonal colorless plates (m.p. 81–83°). The latter could be converted to the prisms by recrystallizing in the presence of a little hydrogen chloride. Attempts to hydrogenate the compound melting at 65–75° resulted mainly in reductive fission, only a small amount of the expected amino alcohol hydrochloride being isolated. The second form (81–83°), on the other hand, absorbed hydrogen smoothly to give a 70% yield of the desired product. Either form when converted to the base could be reduced to the amino alcohol in 70% yield.

It may be generally stated, at this point, that the dialkylamino ketones, with the exception of dimethyl and diethyl, exhibited a green coloration in the presence of a large excess of alcoholic hydrogen chloride. This is believed to be due to the formation of a dihydrochloride of the amino ketone, the second molecule of hydrogen chloride being much less firmly held than that forming the normal hydrochloride.

Procedure IV (for compounds 10 and 13). In this procedure the amino ketones were reduced at the suggestion of Dr. E. M. Fry of this laboratory by the Meerwein-Ponndorf-Verley method, as modified by Lund (19), [see also "Organic Reactions" (22)]. The dried ether solution of the amino ketone was freed of solvent and reduced with 3 molecular equivalents of aluminum isopropoxide as a 3 *N* solution in isopropanol. Reaction time was one to two hours. The isopropanol was distilled under a water-pump vacuum, and the dark red oil remaining was partitioned between ether and an excess of 10% sodium hydroxide. The ether layer was washed twice with water and dried over sodium sulfate and the solvent evaporated. The residual amino alcohol was evaporatively distilled at 180–190° (0.1–0.5 mm.). The almost colorless distillate was dissolved in dry ether and made just acid to Congo red paper with dry gaseous hydrogen chloride, whereupon the white crystalline hydrochloride precipitated. The average yield, based on bromo ketone was 60%.

It is now believed that the compounds described in procedure I could be more advantageously prepared by either procedure III or IV, especially by the latter. Time did not permit us to substantiate this by experiment.

SUMMARY

A series of amino alcohols carrying the side chain —$CHOHCH_2NR_2$ in position 9 of 1,2,3,4-tetrahydrophenanthrene has been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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