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ANTIMALARIALS.[1] SOME NEW LONG-CHAIN ALIPHATIC DI-(AMINO ALCOHOLS)

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In view of the interest in long-chain diamines, diamidines, diguanidines, and di-(amino alcohols) (1, 2, 3, 4, 5) in connection with the malaria problem, the synthesis of some new compounds in the latter field was undertaken in 1942, but the investigation was soon discontinued in favor of more promising leads. Only a few compounds of the di-(amino alcohol) type had been made up to this time, notably the di-(diethylamino and piperidino alcohols) with twelve-carbon chains (5) and the di-(*tert.*-amino *tert.*-alcohol) made by the addition of methylmagnesium iodide to 1,14-dipiperidyltetradecanedione-2,13 (5).

The series here reported, made from sebacic acid, was chosen for study primarily because of the ready availability of the starting materials. The synthetic procedure was similar to that employed by Work (5). Sebacyl chloride (I) was converted in 87–91% yields through diazomethylation and hydrobromination into the di-(bromomethyl ketone) (III), and this upon condensation with the appropriate secondary amines gave the di-(aminomethyl ketones) (IV) which were reduced catalytically or by aluminum isopropoxide to the di-(amino alcohols) (V). Work (5), who had used the di-(chloromethyl ketone), had found the aluminum isopropoxide method to be impractical under his circumstances.

$$\underset{\text{I}}{ClCO(CH_2)_8COCl} \xrightarrow{CH_2N_2} \underset{\text{II}}{N_2CHCO(CH_2)_8COCHN_2} \xrightarrow{HBr}$$

$$\underset{\text{III}}{BrCH_2CO(CH_2)_8COCH_2Br} \xrightarrow{NHR_2}$$

$$\underset{\text{IV}}{R_2N{-}CH_2CO(CH_2)_8COCH_2{-}NR_2} \xrightarrow{Pt + H_2}$$

$$R_2N{-}CH_2\underset{OH}{CH}(CH_2)_8\underset{OH}{CH}CH_2{-}NR_2$$

V

The compounds prepared for screening tests are listed in the Table.

The condensations of the amines with the di-(bromomethyl ketone) proceeded rapidly but the yields of the di-(amino ketones) were small (25–40%); the compounds were often oils and except in the case of the tetrahydroisoquinolyl com-

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pound, tended to be unstable and to undergo decomposition on long standing; the hydrochlorides were stable.

The catalytic reductions of the di-(amino ketones) were slow and it was found to be important to use pure materials. In this connection it should be noted that Work (5) in his platinum catalyzed reduction of two unpurified di-(amino ketones), the di(diethylamino) and dipiperidyl compounds, found the reactions to be slow and incomplete.

The aluminum isopropoxide reduction method was used in several cases where the di-(amino ketones) were not pure enough to warrant a catalytic reduction.

TABLE I

DI-(AMINO ALCOHOLS)

	SN[3]	
VI	4672	$(C_2H_5)_2N\text{-}CH_2\text{-}CHOH\text{-}(CH_2)_8\text{-}CHOH\text{-}CH_2\text{-}N(C_2H_5)_2$
VII	4908	$(C_2H_5)_2N\text{-}CH_2C(CH_3)(OH)\text{-}(CH_2)_8\text{-}C(CH_3)(OH)CH_2\text{-}N(C_2H_5)_2$
VIII	4901	$(Butyl)_2N\text{-}CH_2\text{-}CHOH\text{-}(CH_2)_8\text{-}CHOH\text{-}CH_2\text{-}N(butyl)_2$
IX	6421	$C_6H_5CH_2N(CH_3)\text{-}CH_2CO\text{-}(CH_2)_8\text{-}COCH_2\text{-}N(CH_3)CH_2C_6H_5$
X	—	Morpholinyl-$CH_2CO\text{-}(CH_2)_8\text{-}COCH_2$-morpholinyl
XI	3933	Piperidyl-$CH_2CO\text{-}(CH_2)_8\text{-}COCH_2$-piperidyl
XII	3934	Piperidyl-$CH_2\text{-}CHOH\text{-}(CH_2)_8\text{-}CHOH\text{-}CH_2$-piperidyl
XIII	3643	Tetrahydroisoquinolyl-$CH_2CO\text{-}(CH_2)_8\text{-}COCH_2$-tetrahydroisoquinolyl
XIVA	5033	Tetrahydroisoquinolyl-$CH_2\text{-}CHOH\text{-}(CH_2)_8\text{-}CHOH\text{-}CH_2$-tetrahydroisoquinolyl
XIVB	6346	The stereoisomer of XIVA

Here the reductions also proceeded slowly as compared with the usually much more rapid reductions of the ordinary aryl amino ketones (6).

The di-tetrahydroisoquinolyl compounds were of special interest because one of them (XIVB) showed slight but definite antimalarial activity against avian malaria. In the case of the di-(amino alcohol) one isomer (XIVA, of m.p. 120–121°) was isolated in a pure condition; however the other sample (XIVB of m.p. 102–103°; $Q^4 = 0.1$), while it is believed to be the nearly pure stereoisomer, might be a constant crystallizing mixture since it gives no mixture melting point depression with XIVA.

[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 are tabulated in the monograph (7).

[4] This is the A-1 screening test against *gallinaceum* in the chick, determined under the direction of Dr. G. Robert Coatney of the National Institute of Health.

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EXPERIMENTAL[5]

1,12-Dibromododecanedione-2,11 (III). A solution of 58 g. (0.243 mole) of sebacyl chloride in 75 ml. of absolute ether was added slowly under stirring to 60 g. (1.43 moles) of diazomethane in 2 l. of ether (5–10°) over three hours; the di-(diazomethyl ketone) (II) separated as a solid but was not isolated; a small sample melted at 84–86° [W. (5), 91°]. After standing overnight at room temperature 235 g. (1.22 mole) of 42% hydrobromic acid in 200 ml. of ether was added slowly under stirring (18°); the di-(bromomethyl ketone) appeared in the form of a light yellow solid. After standing 8–10 hours (the evolution of nitrogen had ceased) the mixture was cooled to 0° and the product was filtered; 75 g. (87%); m.p. 97–98°. After repeated crystallizations from ethanol it melted at 102–103°.

Anal. Calc'd for $C_{12}H_{20}Br_2O_2$: C, 40.47; H, 5.66.
Found: C, 40.62; H, 5.97.

1,12-Di-(diethylamino)dodecanediol-2,11 (VI). A suspension of 40 g. (0.112 mole) of the di-(bromomethyl ketone) in a mixture of 41 g. (0.56 mole) of diethylamine and 400 ml. of absolute ether was warmed to 30° to initiate reaction, and after standing for one hour the diethylamine hydrobromide was filtered (32 g.; 93%). Evaporation of the solvent and excess diethylamine under reduced pressure left a red oil which failed to yield a crystalline hydrochloride. Extraction with acid, liberation by potassium hydroxide, and isolation by extraction with ether, gave 25 g. (66%) of the base. This was dissolved in 300 ml. of 2.5 *N* aluminum isopropoxide. Reduction was complete after sixty-five hours of refluxing as indicated by a negative acetone test in the distillate. Upon evaporation of the solvent, treatment with 10 *N* potassium hydroxide, and extraction by ether, an oil was obtained which failed to give a crystalline hydrochloride. Fractionation at 2 mm. pressure gave a cut of 10 g. (26%) of b.p. 198–199°; n_D^{25} 1.4618; it also failed to give a crystalline dihydrochloride.

Anal. Calc'd for $C_{20}H_{44}N_2O_2$: N, 8.13. Found: N, 8.38.

The *dipicrate*, obtained by treatment with picric acid in ethanol (warmed to 50°) was recrystallized from ethanol; m.p. 118–121° [W. (5), 121°].

Anal. Calc'd for $C_{35}H_{50}N_8O_{16}$: N, 13.96. Found: N, 14.02.

1,12-Diethylamino-2,11-dimethyldodecanediol-2,11 (VII). To a solution of 125 ml. of 1.7 *N* ethereal methylmagnesium iodide was added dropwise at 18° with stirring a 275 ml. absolute ether solution of 30 g. of the crude di-(diethylamino ketone). The reaction was vigorous. After two hours at room temperature and 1.5 hours of refluxing, hydrolysis in ice and dilute hydrochloric acid, and basification with ammonium hydroxide, the product was isolated by evaporation of the ether solution and was fractionally distilled; the cut of b.p. 215–218° (2 mm.) was 9 g. (28%); n_D^{25} 1.4631.

Anal. Calc'd for $C_{22}H_{48}N_2O_2$: N, 7.52. Found: N, 7.85.

1,12-Di-(di-n-butylamino)dodecanediol-2,11 (VIII). A mixture of 20 g. of the di-(bromomethyl ketone), 32 g. of dibutylamine, and dry ether was refluxed for two hours and the resulting secondary amine hydrobromide was filtered. The ether solution was washed with 10% sodium carbonate and dried over sodium sulfate. Evaporation gave 20 g. of oil which was reduced by 150 ml. of 3 *N* aluminum isopropoxide (refluxing until the evolution of acetone ceased). Evaporation of the isopropanol and hydrolysis with potassium hydroxide gave an oil which was fractionally distilled, giving a cut of 12 g. (60%) of b.p. 235–240° (1 mm.); n_D^{20} 1.4657.

Anal. Calc'd for $C_{28}H_{60}N_2O_2$: C, 73.62; H, 13.24.
Found: C, 73.32; H, 13.56.

[5] All melting points are corrected.

The *dipicrate* formed from ethanol; sinters at 129°.

Anal. Calc'd for $C_{28}H_{60}N_2O_2 \cdot 2C_6H_3N_3O_7$: N, 12.25. Found: N, 12.38.

1,12-Di-(benzylmethylamino)dodecanedione-2,11 dihydrochloride (IX). A suspension of 50 g. (0.14 mole) of the di-(bromomethyl ketone) in 300 ml. of absolute ether was treated with 86 g. (0.71 mole) of benzylmethylamine; the reaction was initiated by warming to 30°, and after one hour the benzylmethylamine hydrobromide was filtered (54 g., 95%). The remaining basic constituents were extracted by 1 *N* hydrochloric acid and liberated; the excess benzylmethylamine was evaporated at 95° (4 mm.) and the residual oil was converted to a crystalline hydrochloride from acetone with ethereal hydrogen chloride; it was recrystallized from an isopropanol-ethyl acetate mixture, with added ethereal hydrogen chloride; three crystallizations from isopropanol (including one Darco treatment) gave 15.5 g. (35%); m.p. 157–158°.

Anal. Calc'd for $C_{28}H_{40}N_2O_2 \cdot 2HCl$: C, 65.99; H, 8.31; N, 5.50.
Found: C, 65.78; H, 7.98; N, 5.46.

1,12-Di-(N-morpholinyl)dodecanedione-2,11 (X) was made like XI. The base crystallized upon concentrating the ether solution of the crude product (m.p. 62–63°). It was converted into the dihydrochloride from ethanol by addition of ethereal hydrogen chloride; three crystallizations from isopropanol gave 11 g. (25%) of m.p. 189–190°.

Anal. Calc'd for $C_{20}H_{36}N_2O_4 \cdot 2HCl$; N, 6.35. Found: N, 6.15.

The *base* crystallized from ethanol as blade-shaped scales; m.p. 72–73°.

Anal. Calc'd for $C_{20}H_{36}N_2O_4$: C, 65.18; H, 9.85.
Found: C, 65.05; H, 9.83.

1,12-Di(N-piperidyl)dodecanedione-2,11 (XI). Thirty grams of piperidine was added slowly with stirring to 25 g. of the di-(bromomethyl ketone) suspended in 350 ml. of absolute ether. The reaction proceeded slowly, and after one hour and cooling to 0°, the precipitated piperidine hydrobromide was filtered (96%). After repeated washing with water and evaporation of the solvent under reduced pressure, a residue of m.p. 39–40° was obtained. In a separate experiment the product at this point was recrystallized from ethanol and handled as the free base (yield 54%). The melting point reported by Work (5) was 43°. The crude base was converted into the hydrochloride in acetone by ethereal hydrogen chloride. Three crystallizations from isopropanol by addition of ether gave 11.5 g. of pure product (37.5%); m.p. 177–178°.

Anal. Calc'd for $C_{22}H_{40}N_2O_2 \cdot 2HCl$: N, 6.40. Found: N, 6.26.

The *dipicrate* formed from ethanol from which it was recrystallized six times; m.p. 127–128°.

Anal. Calc'd for $C_{22}H_{40}N_2O_2 \cdot 2C_6H_3N_3O_7$: C, 49.63; H, 5.63; N, 13.62.
Found: C, 49.72; H, 5.84; N, 13.34.

The *dihydrobromide* was recrystallized five times from isopropanol; m.p. 189–190°.

Anal. Calc'd for $C_{22}H_{40}N_2O_2 \cdot 2HBr$: N, 5.32. Found: N, 5.37.

The *base* crystallized from dilute ethanol as thin rhombic plates; m.p. 39.5–40°.

Anal. Calc'd for $C_{22}H_{40}N_2O_2$: C, 72.47; H, 11.06; N, 7.69.
Found: C, 72.24; H, 11.11; N, 7.40.

1,12-Di-(N-piperidyl)dodecane-2,11-diol (XII) (5). Reduction of 10 g. of the free di-(amino ketone) (m.p. 36–38°) in ethanol using platinum oxide proceeded slowly and stopped with absorption of one mole. Evaporation of the solvent under reduced pressure gave an oil which solidified on cooling in ice. It was recrystallized from acetone (m.p. *ca.* 60°) and converted into the hydrochloride from acetone with alcoholic hydrogen chloride and addition of ether; yield 3.3 g. (27.5%); m.p. 234–236°; recrystallized from isopropanol; m.p. 246.5–247.5°.

Anal. Calc'd for $C_{22}H_{44}N_2O_2 \cdot 2HCl$: N, 6.48. Found: N, 6.50.

The base was first recrystallized from an ethanol-water mixture (flat rhombohedral plates); repeated recrystallizations from dilute ethanol or acetone brought the melting point to 80–80.5° [W. 78° (5)].

Anal. Calc'd for $C_{22}H_{44}N_2O_2$: C, 71.68; H, 7.81.
Found: C, 71.89; H, 11.84.

The *dipicrate* melted at 151–152° (W. 152°).

Anal. Calc'd for $C_{34}H_{56}N_8O_{16}$: C, 49.39; H. 6.10; N, 13.55.
Found: C, 49.58; H, 6.55; N, 13.28.

1,12-Di(N-1,2,3,4-tetrahydroisoquinolyl)dodecanedione-2,11 (XIII). Forty-five grams (0.338 mole) of tetrahydroisoquinoline was added under stirring and external cooling to 25 g. (0.7 mole) of the di-(bromomethyl ketone) in 300 ml. of absolute ether (two hours); the tetrahydroisoquinoline hydrobromide was filtered off [30 g. (100%)]. Concentration of the ether solution gave 16 g. of crystals (m.p. 68–72°). Two recrystallizations from methanol and one from ligroin-ethyl acetate mixture gave 12 g. (37%) of m.p. 77–78°. It crystallized also from isopropanol-water mixtures.

Anal. Calc'd for $C_{30}H_{40}N_2O_2$: N, 6.08. Found: N, 6.39.

1,12-Di-(N-1,2,3,4-tetrahydroisoquinolyl)dodecanediol-2,11-A and -B (XIV A and B). Reduction of 8.83 g. of XIII (partially dissolved) in 300 ml. of methanol using 0.876 g. of platinum oxide at 26° and atmospheric pressure proceeded very slowly; one equivalent of hydrogen was absorbed over sixty-three hours (from time to time additional catalyst was added), and the reaction came to a stop. Upon filtering and cooling to 0°, 6.5 g. of crystals (m.p. 105–112°) separated. One crystallization from methanol, two from ligroin-ethyl acetate mixture, and a fourth from isopropanol brought the melting point to 120–121°. This product is designated as XIV A.

Anal. Calc'd for $C_{30}H_{44}N_2O_2$: C, 77.53; H, 9.55; N, 6.03.
Found: C, 77.32; H, 9.27; N, 5.75.

Four grams of material recovered from the solvents used in the above crystallizations was recrystallized once from methanol, twice from isopropanol, and twice from ligroin-ethyl acetate mixture; the product on the last few crystallizations melted at 102–103°. The sample (1.5 g.) was treated with refluxing isopropanol-aluminum isopropoxide solution (four hours) and recovered with the same melting point (102–103°).

Anal. Calc'd for $C_{30}H_{44}N_2O_2$: C, 77.53; H, 9.55; N, 6.03.
Found: C, 77.48; H, 9.79; N, 6.25.

Reduction in ethyl acetate required seven days, but did not go at all in 1 *N* hydrochloric acid.

SUMMARY

Eight dodecane di-(*tert.*-amino alcohols) were made for antimalarial tests. The syntheses started from sebacyl chloride and involved diazomethylation, hydrobromination of the di-(diazomethyl ketone) and condensation of the resulting di-(bromomethyl ketone) with the following secondary amines: diethylamine, dibutylamine, benzylmethylamine, morpholine, piperidine and tetrahydroisoquinoline. Four of the di-(*tert.*-amino ketones) were isolated; these, and also two which were not isolated, were reduced to the di-(*tert.*-amino alcohols) catalytically or by aluminum isopropoxide. Diastereoisomers were isolated in one case. One di-(*tert.*-amino *tert.*-alcohol) was made by addition of methylmagnesium iodide to a di-(*tert.*-amino ketone).

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