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ANTIMALARIALS.[1] ALIPHATIC AMINO KETONES AND ALCOHOLS

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The synthesis of a variety of aliphatic amino ketones and alcohols was initiated in 1942 in order to explore the field for possible antimalarial drugs, and to evaluate the effectiveness in this respect of the β-aminoethanol grouping, either in a completely aliphatic system or separated from an aryl group by at least one intervening methylene group. The work was soon discontinued however because the few compounds made proved to be without significant activity (1). These compounds are being reported for comparison with the α-aryl-β-aminoethanols listed in a preceding paper (2) and with the di-(amino alcohols) described in a following paper (3). The investigations in this field were anticipated in part in two papers by Work (4, 5).

The amino ketones were made from the aliphatic acids, lauric, stearic, cyclohexane carboxylic, and diphenylacetic, by way of the following steps: conversion to the acid chlorides, diazomethylation, hydrobromination to the bromo ketones, and condensation with the appropriate secondary amines. The amino ketones were reduced catalytically or by aluminum isopropoxide to the amino alcohols.

$$RCOOH \rightarrow RCOCl \rightarrow RCOCHN_2 \rightarrow RCOCH_2Br \rightarrow RCOCH_2NR_2 \rightarrow \underset{\displaystyle OH}{\overset{\displaystyle |}{RCHCH_2NR_2}}$$

The new compounds obtained and characterized are listed in the table.

The results of screening tests against *gallinaceum* in the chick showed most of these compounds to be without significant antimalarial activity; however, it is probable that this field has not had an adequate trial, because the number of compounds made is very small, and because in most cases the choice of substituents on nitrogen has probably not been the optimum, judging from the extensive subsequent results in the α-phenyl-β-dialkylaminoethanol series which are described in a preceding paper (2). It is hoped that some further representatives of this series may still be made.

EXPERIMENTAL[4]

1-Bromotridecanone-2. A solution of 60 g. (1.43 mole) of diazomethane in 2 l. of dry ether (0°) was treated with 104 g. (0.477 mole) of lauroyl chloride [b.p. 184–188° (100 mm.)] in 150 ml. of dry ether by dropwise addition over 3 hours under stirring, and was allowed to stand

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[4] All melting points are corrected.

overnight. A solution of 235 g. (1.22 moles) of 42% hydrobromic acid in 200 ml. of ether was added slowly with continuous stirring over 4 hours, with the temperature maintained at 18°. Upon standing at room temperature for 8 hours and cooling to 0°, the white bromomethyl ketone separated; 95 g.; m.p. 50–52°; second crop, 26 g.; m.p. 48.5–50°; total yield 92%. Repeated crystallization from ethanol brought the melting point to 53°.

Anal. Calc'd for $C_{12}H_{25}BrO$: C, 56.31; H, 9.00.

Found: C, 56.00; H, 8.84.

1-N-(Diethylamino)tridecanone-2 hydrochloride (I). Diethylamine hydrobromide precipitated immediately in 95% yield upon slow addition with stirring of 21 g. (0.274 mole) of diethylamine to a solution of 30 g. (0.11 mole) of 1-bromotridecanone-2 in 300 ml. of absolute ether. After washing out the excess diethylamine with water, the ether was evaporated and the residual oil was dissolved in dry acetone and neutralized (to Congo) with ethereal hydrogen chloride. The crystalline precipitate was recrystallized from acetone; 18 g.

TABLE I

AMINO KETONES AND ALCOHOLS

	SN[3]	FORMULA
I	1627	$CH_3(CH_2)_{10}$-CO-CH_2-N$(C_2H_5)_2$
II	2014	$CH_3(CH_2)_{10}$-CHOH-CH_2N$(C_2H_5)_2$
III	2596	$CH_3(CH_2)_{10}$-CO-CH_2-morpholinyl
IV	2595	$CH_3(CH_2)_{10}$-CHOH-CH_2-morpholinyl
V	8083	$CH_3(CH_2)_{16}$-CO-CH_2-piperidyl
VI	—	Cyclohexyl-CHOH-CH_2N(n-amyl)$_2$
VII	—	$(C_6H_5)_2$CH-CO-CH_2-N$(C_2H_5)_2$
VIII	3263	$(C_6H_5)_2$CH-CHOH-CH_2-N$(C_2H_5)_2$
IX	2743	$(C_6H_5)_2$CH-CO-CH_2-morpholinyl
X	3264	$(C_6H_5)_2$CH-CHOH-CH_2-morpholinyl

(54.5%); m.p. 73–73°. A mixture melting point with the hydrochloride of I showed a significant depression.

Anal. Calc'd for $C_{17}H_{35}NO\cdot HCl$: C, 66.74; H, 11.86; N, 4.58.

Found: C, 66.08; H, 11.90; N, 4.15. (The compound was very hygroscopic).

1-N-(Diethylamino)tridecanol-2 hydrochloride (II). Catalytic reduction of 15 g. of the hydrochloride of I in 300 ml. of 95% ethanol with 0.25 g. of platinum oxide proceeded in 6 hours and stopped with absorption of one molecule of hydrogen. Evaporation, addition of water and addition of sodium carbonate precipitated the oily base which was converted into the hydrochloride from dry acetone by ethereal hydrogen chloride; it was recrystallized from acetone; 12 g. (80%); m.p. 76–78°.

Anal. Calc'd for $C_{17}H_{37}NO\cdot HCl$: C, 66.30; H, 12.44; N, 4.55.

Found: C, 66.52; H, 12.20; N, 4.31.

1-N-Morpholinotridecanone-2 hydrochloride (III), made like I, was recrystallized from benzene; yield 39%; m.p. 126–127°.

Anal. Calc'd for $C_{17}H_{33}NO_2\cdot HCl$: N, 4.38. Found: N, 4.31.

1-N-Morpholinotridecanol-2 hydrochloride (IV) was obtained by hydrogenation of the amino ketone hydrochloride in the same way as II except that the bulk of the alcohol was evaporated under reduced pressure until the hydrochloride began to precipitate; addition of

[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 the Survey Numbers have been assigned have been tabulated in the monograph (1).

absolute ether gave 14 g. of the salt (82.5%); m.p. 145–147°. Two crystallizations from butanone brought the melting point to 149–150°.

Anal. Calc'd for $C_{17}H_{35}NO_2 \cdot HCl$: C, 63.42; H, 11.27.
Found: C, 63.35; H, 11.19.

1-Bromononadecanone-2. Ninety-two grams of stearic acid was converted into the acid chloride by treatment with 60 g. of thionyl chloride and evaporation of the excess reagent under reduced pressure. The crude product (97 g.) was dissolved in 100 ml. of absolute ether and added under stirring to 50 g. of diazomethane in 1500 ml. of absolute ether over 3.5 hrs. at 5°, and the mixture was allowed to stand overnight at room temperature. A solution of 150 g. of 42% hydrobromic acid in 100 ml. of ether was added slowly under stirring; after standing 3 hrs. the volume of solvent was reduced to 300 ml. by distilling, and the bromo ketone separated on cooling to 0°; 100 g. (86.5%); m.p. 69–72°. A second crop of 10 g. was obtained (m.p. 63–66°). Two crystallizations from acetone and two from isopropanol brought the melting point to 70–72°.

Anal. Calc'd for $C_{19}H_{37}BrO$: C, 63.17; H, 10.36.
Found: C, 63.32; H, 10.67.

1-(N-Piperidyl)nonadecanone-2 hydrochloride (V). The reaction between 20 g. (0.055 mole) of crude bromo ketone and 14.1 g. (0.166 mole) of piperidine in 300 ml. of absolute ether proceeded rapidly, and after 0.5 hr. at room temperature, 9 g. of piperidine hydrobromide had separated (98%). Evaporation of the solvent and washing gave a crude solid of m.p. 39–45° which was converted into the hydrochloride in absolute ether; this was crystallized from a 1:9 methanol-acetone mixture; 7.5 g. (57%); m.p. 111–113°.

Anal. Calc'd for $C_{24}H_{47}NO \cdot HCl$: C, 71.68; H, 12.03.
Found: C, 71.55; H, 12.25.

α-Cyclohexyl-β-di-n-amylaminoethanol (VI). Cyclohexane carboxylic acid (100 g.) was converted in the usual way by thionyl chloride into the acid chloride which distilled at 184–188° under 755 mm.; yield 103 g. (91%). Sixty-eight grams of this in 150 ml. of absolute ether was added slowly with stirring over 4 hrs. to 68 g. of diazomethane in 2 l. of absolute ether (0 to −5°); after standing overnight, 190 g. of 42% hydrobromic acid in 200 ml. of ether was added over 3 hrs. at 180° under vigorous stirring. The ether solution was washed with water to remove hydrogen bromide and was evaporated. Half of the residual crude oily bromomethyl ketone was added to an ether solution of 85 g. of diamylamine; the reaction proceeded rapidly and after 1.5 hrs. a 96% yield of diamylamine hydrobromide had separated. The crude amino ketone (oil) was treated with 400 ml. of 1.9 *N* aluminum isopropoxide (refluxing for 4 hrs.) and the product was isolated in the usual way as an oil. It was fractionated and the cut of b.p. 161–170° (2 mm.); n_D^{25} 1.4631–1.4632, was analyzed.

Anal. Calc'd for $C_{18}H_{37}NO$: C, 76.26, H, 13.16.
Found: C, 76.44; H, 12.98.

1-N-Diethylamino-3,3-diphenylpropanone-2 hydrochloride (VII). Diphenylacetyl chloride (5) [113 g. (0.49 mole)] in 400 ml. of absolute ether was added under stirring over 2 hrs. to 60 g. (1.43 mole) of diazomethane in 2 l. of absolute ether (cooled in ice-salt), and the mixture after standing overnight at room temperature was cooled in ice and treated dropwise over 4 hrs. under stirring with 200 g. (1.04 moles) of 42% hydrobromic acid in 100 ml. of ether. Upon concentrating and cooling, the bromomethyl ketone crystallized and was recrystallized from ligroin; 100 g. (78%); m.p. 48–52°. Three crystallizations from isopropanol brought the melting point to 69–70°. This material gave good results in the next steps but analytical results for carbon ran consistently over 1% high.

Treatment of the bromomethyl ketone in absolute ether with diethylamine in the usual way gave an oil which crystallized as the hydrochloride from acetone upon the addition of ethereal hydrogen chloride; yield 45%; m.p. 184–187° decomp. Two crystallizations from isopropanol and one from a 1:4 methanol-acetone mixture gave a product melting at 187–188°.

Anal. Calc'd for $C_{19}H_{23}NO \cdot HCl$: N, 4.41. Found: N, 4.39.

1-N-Diethylamino-3,3-diphenylpropanol-2 hydrochloride (VIII). Reduction of 14.3 g. of the amino ketone in 300 ml. of 95% ethanol using 0.33 g. of platinum oxide went to completion rapidly and stopped afrer absorption of one molecule of hydrogen. The oil obtained was dissolved in isopropanol and crystallized as the hydrochloride upon adding ethereal hydrogen chloride till acid to Congo; 9 g. (62.5%); m.p. 158–159°. Repeated recrystallizations from isopropanol brought the melting point to 161–162°.

Anal. Calc'd for $C_{19}H_{25}NO \cdot HCl$: C, 71.34; H, 8.19.
Found: C, 71.52; H, 8.54.

3,3-Diphenyl-1-(N-morpholinyl)propiophenone-2 hydrochloride (IX) was prepared like VII; yield 52%; m.p. 215–218° decomp. One crystallization from 3:7 methanol-acetone and one from 1:9 methanol-isopropanol mixture raised the melting point to 224–225° decomp.

Anal. Calc'd for $C_{19}H_{21}NO_2 \cdot HCl$: N, 4.22. Found: N, 3.85.

3,3-Diphenyl-1-(N-morpholinyl)propanol-2 hydrochloride (X) was prepared like VIII in 88% yield and recrystallized from ethanol; m.p. 185–186°.

Anal. Calc'd for $C_{19}H_{23}NO_2 \cdot HCl$: C, 68.35; H, 7.25.
Found: C, 68.63; H, 7.38.

SUMMARY

Five new aliphatic α-amino ketones and five β-aminoethanols have been synthesized for antimalarial testing. These were made from lauric, stearic, cyclohexane carboxylic and diphenylacetic acids through diazomethylation of the acid chlorides, hydrobromination and condensation with the appropriate secondary amines. The amino alcohols were made from the amino ketones by catalytic or aluminum isopropoxide reductions.

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