[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Antimalarials. IV.[1] The Synthesis of Certain Compounds Related to Quinacrine[2]

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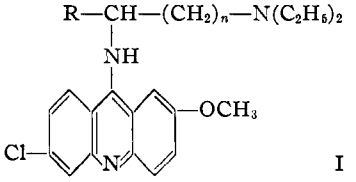
A number of quinacrine analogs (I, $n = 3$) have recently been prepared in this Laboratory.[1] The present paper describes the synthesis of another quinacrine analog, in which R = $CO_2C_2H_5$, and of several related compounds in which R = CH_3 and n = 1 and 7, and in which R = H and n = 2, 3, 4, 5 and 6. The last five compounds have been prepared previously by Magidson and Grigorowsky.[3] We have prepared them on a much larger scale, certain cases requiring modifications of their procedures. An unsuccessful attempt has been made to prepare the quinacrine analog in which R = CF_3 and n = 3, although certain of the intermediates were synthesized.



I

As usual,[1a] the appropriate diamines were synthesized and coupled with 2-methoxy-6,9-dichloroacridine in the presence of phenol to form I. These acridine compounds were isolated as dihydrochlorides, which were hydrated yellow powders (see Table I).

The diamines, R—CH(NH_2)—$(CH_2)_n$—N(C_2H_5)$_2$, were prepared in various ways. N^δ,N^δ-Diethylornithine ethyl ester (R = $CO_2C_2H_5$, n = 3) was synthesized by a modification of the method of Bouveault and Locquin[4] for the preparation of amino acids. The reactions may be illustrated by the transformation.

$$CH_3COCH(Na)CO_2C_2H_5 \xrightarrow{Cl(CH_2)_3N(C_2H_5)_2} CH_3COCH(CH_2)_3N(C_2H_5)_2 \xrightarrow{NOSO_4H} \underset{\displaystyle CO_2C_2H_5}{CH_3COCH(CH_2)_3N(C_2H_5)_2} \xrightarrow{[H]} (C_2H_5)_2N(CH_2)_3C(=NOH)CO_2C_2H_5 \longrightarrow (C_2H_5)_2N(CH_2)_3CH(NH_2)CO_2C_2H_5$$

Although the over-all yield is poor, the synthesis has the advantage of being comparatively short and of being well adapted for small-scale work.

1-Diethylamino-2-aminopropane (R = CH_3, n = 1) has been prepared in good yield by the reduction of diethylaminoacetone in the presence of ammonia. This method has been mentioned in a patent[5] but no details were given. The diethylaminoacetone was prepared from chloroacetone as described previously.[6]

$$CH_3COCH_2Cl \xrightarrow{(C_2H_5)_2NH} CH_3COCH_2N(C_2H_5)_2 \xrightarrow[[H]]{NH_3} CH_3CH(NH_2)CH_2N(C_2H_5)_2$$

Raney nickel reduction of the oxime of diethylaminoacetone gave only a poor yield of the diamine, in sharp contrast to the reduction of other oximes of this type.[1]

1-Diethylamino-8-aminononane (R = CH_3, n = 7) was prepared according to the following transformation.

$$CH_3COCH(Na)CO_2C_2H_5 \xrightarrow{Br(CH_2)_6N(C_2H_5)_2} \underset{\displaystyle CO_2C_2H_5}{CH_3COCH(CH_2)_6N(C_2H_5)_2} \xrightarrow{H_2SO_4} CH_3CO(CH_2)_7N(C_2H_5)_2 \xrightarrow{H_2NOH\cdot HCl} CH_3C(=NOH)(CH_2)_7N(C_2H_5)_2 \xrightarrow{[H]} CH_3CH(NH_2)(CH_2)_7N(C_2H_5)_2$$

The diamines, 2-diethylaminoethylamine, 3-diethylaminopropylamine, 4-diethylaminobutylamine and 5-diethylaminopentylamine (R = H and n = 2, 3, 4 and 5, respectively) were prepared by methods described in the literature (see Experimental). 6-Diethylaminohexylamine (R = H, n = 6) was prepared by a Gabriel synthesis and by a method described recently[7]; we prefer either of these methods to that of Magidson and Grigorowsky[3] for large-scale preparations.

Attempts to prepare the diamine, 1,1,1-trifluoro-2-amino-5-diethylaminopentane (R = CF_3, n = 3) by the reduction of the corresponding oxime by several methods failed. With Raney nickel, reduction seemed to occur but the desired diamine could not be isolated and, because of the urgency of other problems, the experiment was not repeated. However, the reactions employed in the synthesis of the oxime are of interest. The ketone, from which the oxime was obtained in good yield, was synthesized in 16–20% yield (a)

(1) For previous papers of this series see (a) Breslow, Yost, Walker and Hauser, THIS JOURNAL, **66**, 1921 (1944); (b) Breslow, Walker, Yost and Hauser, *ibid.*, **67**, 1472 (1945); (c) Bloom, Breslow and Hauser, *ibid.*, **67**, 2206 (1945).

(2) 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 Duke University.

(2a) Present address: Hercules Experiment Station, Wilmington, Delaware.

(3) Magidson and Grigorowsky, *Ber.*, **69B**, 396 (1936).

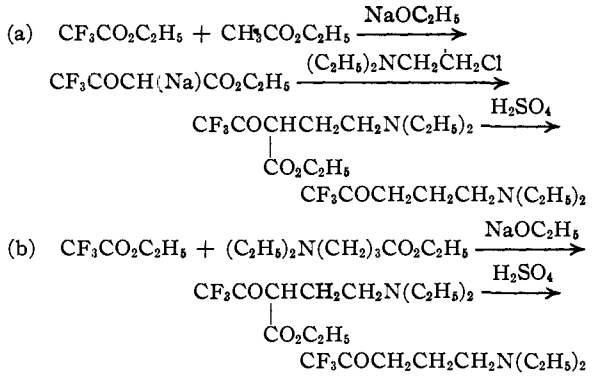
(4) Bouveault and Locquin, *Bull. soc. chim.*, [3] **31**, 1055 (1904).

(5) Eisleb and Ehrhart, I. G. Farbenindustrie, German Patent 551,436; *Chem. Zentr.*, **103**, II, 740 (1932).

(6) Stoermer and Dzimski, *Ber.*, **28**, 2226 (1895).

(7) Breslow and Hauser, THIS JOURNAL, **67**, 686 (1945).

by the alkylation[8] of ethyl trifluoroacetoacetate with β-diethylaminoethyl chloride and subsequent cleavage, and (b) by the condensation of ethyl trifluoroacetate with ethyl γ-diethylaminobutyrate and cleavage, thus



Experimental[9]

Preparation of $(C_2H_5)_2N—(CH_2)_n—NH_2$.—2-Diethylaminoethylamine was prepared by sodium in alcohol reduction of diethylaminoacetonitrile.[10] 4-Diethylaminobutylamine was prepared by catalytic reduction of γ-diethylaminobutyronitrile.[11] 3-Diethylaminopropylamine and 5-diethylaminopentylamine were prepared according to Magidson and Grigorowsky.[3]

6-Diethylaminohexylamine was prepared by a Gabriel synthesis. Hexamethylene glycol[12] was converted into hexamethylene bromide by treatment with hydrogen bromide.[13] This was coupled with potassium phthalimide in the usual manner,[14] a 90% yield of crude 6-bromohexylphthalimide being obtained. The crude compound (223 g., 0.72 mole) was treated with a four-molar excess of diethylamine, the reaction mixture being refluxed for twenty-four hours. The excess diethylamine was distilled and the residue was refluxed with 500 ml. of concentrated hydrochloric acid for six hours. The solution was concentrated to about one-half its original volume and cooled. The precipitated phthalic acid was filtered off, washed with water and the combined filtrates were neutralized with solid potassium carbonate. Solid potassium hydroxide was added until two layers formed, the diamine was extracted with benzene and the benzene solution was dried over potassium hydroxide. The benzene was distilled and the residue distilled through a short Vigreux column; the fraction boiling at 200–240° was collected and redistilled *in vacuo*, b. p. 103–107° at 10 mm., 61 g. (49%) of 6-diethylaminohexylamine being obtained.

1-Diethylamino-2-aminopropane.—To 126 g. (1.37 moles) of chloroacetone[15] was added slowly 200 g. (2.73 moles) of diethylamine dissolved in 150 ml. of ether. The reaction mixture was cooled intermittently to prevent too violent a reaction. After the reaction had subsided the reaction mixture was refluxed for five hours, cooled and the diethylamine hydrochloride was filtered off. The precipitate was washed with ether, the ether was distilled from the combined filtrates and the residue was distilled through a 15-cm. Vigreux column; 127 g. (72%) of diethylaminoacetone, b. p. 55–58° at 16 mm.,[16] was obtained.

Diethylaminoacetone (21.0 g., 0.16 mole) was dissolved in 50 g. of 17% methanolic ammonia, Raney nickel was added and the mixture was reduced at 70° in a high-pressure bomb. The catalyst was filtered off, the methanol was distilled and the residue was fractionated; 13.2 g. (62%) of 1-diethylamino-2-aminopropane, b. p. 150–153°, was obtained. The diamine picrate was prepared, m. p. 180–182°.

Anal.[17] Calcd. for $C_{13}H_{21}O_7N_5$: N, 19.5. Found: N, 19.0.

1-Diethylamino-8-aminononane.—To 100 g. (0.32 mole) of 1-bromo-6-diethylaminohexane hydrobromide[18,19] were added 200 ml. of benzene and 25 g. of crushed ice. Cold sodium hydroxide (17 g. in 36 ml. of water) was added with stirring, the temperature being maintained below 5°. The reaction mixture was stirred until all the solid had dissolved, the benzene layer was separated and dried over Drierite in the cold. The benzene solution of 1-bromo-6-diethylaminohexane was then used to alkylate sodioacetoacetic ester in the manner described previously,[1a] the β-keto ester being decarboxylated with dilute sulfuric acid in the usual manner. A 43% yield of 1-diethylamino-8-ketononane, b. p. 130–137° at 10 mm., was obtained.

Anal. Calcd. for $C_{13}H_{27}ON$: neut. equiv., 213. Found: neut. equiv., 207.

The oxime of the ketone was prepared in 79% yield as described previously,[1a] b. p. 153–156° at 2.5 mm.

Anal. Calcd. for $C_{13}H_{28}ON_2$: neut. equiv., 228. Found: neut. equiv., 227.

The oxime was reduced to 1-diethylamino-8-aminononane in the presence of Raney nickel[1a] in 79% yield, b. p. 136–141° at 10 mm. The diamine formed a monopicrolonate, m. p. 165.5–166.5°.

Anal.[20] Calcd. for $C_{23}H_{38}O_5N_6$: N, 17.6. Found: N, 17.3.

N^{δ},N^{δ}-Diethylornithine Ethyl Ester.—Ethyl α-acetyl-δ-diethylaminovalerate, b. p. 132–135° at 5 mm., was prepared in 51% yield by alkylating sodioacetoacetic ester with γ-diethylaminopropyl chloride[1b] in dioxane, using the same procedure as was used in alkylating β-keto esters with β-diethylaminoethyl chloride.[1a]

In a three-necked flask equipped with a stirrer and thermometer and cooled in a Dry Ice–ether-bath was placed 50 g. of concentrated sulfuric acid. Ethyl α-acetyl-δ-diethylaminovalerate (50 g., 0.21 mole) was added with stirring, the temperature being maintained at −15 to −10°. Then a cooled mixture of 29.2 g. of nitrosyl sulfuric acid[21] in 30 ml. of concentrated sulfuric acid was added very slowly with vigorous stirring, the temperature being kept below 0°. The reaction mixture was then poured onto 100 g. of ice in a beaker surrounded by an ice–

(8) Drs. William T. Miller and George M. Weiman of Cornell University have previously found that the alkylation of ethyl trifluoroacetoacetate with ordinary alkyl halides similarly gives only low yields (private communication).

(9) We wish to acknowledge the assistance of Melvin S. Bloom and Martin J. Weiss in preparing some of the intermediates described in this paper.

(10) Bloom, Breslow and Hauser, THIS JOURNAL, **67**, 539 (1945).

(11) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, *ibid.*, **66**, 725 (1944).

(12) We are indebted to H. S. Holt, Experimental Station, E. I. Du Pont de Nemours and Co., Wilmington, Delaware, for a sample of hexamethylene glycol.

(13) McEwen, "Organic Syntheses," Vol. 20, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 24.

(14) Salzberg and Supniewski, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 119.

(15) Buchman and Sargent, THIS JOURNAL, **67**, 400 (1945).

(16) Stoermer and Dzimski[6] give the boiling point as 64° at 16 mm.

(17) Analysis by Arlington Laboratories, Fairfax, Virginia.

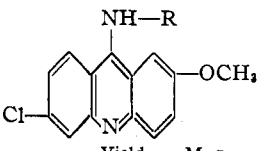
(18) Magidson, Madajewa and Rubzow, *Arch. Pharm.*, **273**, 324 (1935).

(19) The hydrobromide was prepared by the action of diethylamine on 1-bromo-6-methoxyhexane followed by cleavage of the ether with 48% hydrogen bromide according to a procedure supplied to us by Dr. Nathan L. Drake, Department of Chemistry, University of Maryland, College Park, Maryland. We are also indebted to Dr. Drake for a sample of 1-bromo-6-methoxyhexane.

(20) Analysis by Dr. T. S. Ma, Department of Chemistry, University of Chicago, Chicago, Illinois.

(21) Biltz and Biltz, "Laboratory Methods of Inorganic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1928, p. 206.

TABLE I



	R =		Yield, %	M. p., °C.	Formula[a]	Cl⁻ Analyses,[b] % Calcd.	Found
1)	$(C_2H_5)_2N—(CH_2)_2—$	(SN 5228)	85	257–259	$C_{20}H_{24}ON_3Cl\cdot 2HCl\cdot H_2O$	15.80	15.80
2)	$(C_2H_5)_2N—(CH_2)_3—$	(SN 2033)	86	254–255	$C_{21}H_{26}ON_3Cl\cdot 2HCl\cdot H_2O$	15.32	15.42
3)	$(C_2H_5)_2N—(CH_2)_4—$	(SN 5341)	92	259–261	$C_{22}H_{28}ON_3Cl\cdot 2HCl\cdot 2H_2O$	14.33	14.51
4)	$(C_2H_5)_2N—(CH_2)_5—$	(SN 8020)	90	266–267	$C_{23}H_{30}ON_3Cl\cdot 2HCl$	15.00	15.16
5)	$(C_2H_5)_2N—(CH_2)_6—$	(SN 3870)	90	253–254	$C_{24}H_{32}ON_3Cl\cdot 2HCl\cdot H_2O$	14.05	14.10
6)	$(C_2H_5)_2N—CH_2CHCH_2$	(SN 12,867)	85	160–162	$C_{21}H_{26}ON_3Cl\cdot 2HCl\cdot 2H_2O$	14.75	14.76
7)	$(C_2H_5)_2N—(CH_2)_7—CHCH_3$	(SN 12,868)	85	136–138	$C_{27}H_{38}ON_3Cl\cdot 2HCl\cdot H_2O$	12.96	12.91
8)	$(C_2H_5)_2N—(CH_2)_3—CHCO_2C_2H_5$	(SN 7547)	13	98–100	$C_{28}H_{42}O_3N_3Cl\cdot 2HCl\cdot 2H_2O$	12.51	12.66

[a] Magidson and Grigorowsky (ref. 3) give the following: (1) anhydrous, m. p. 258–259°; (2) trihydrate, m. p. 249–250°; (3) dihydrate, m. p. 246–248°; (4) monohydrate, m. p. 266–268°; (5) anhydrous, m. p. 232–235°. [b] Macro-analyses by the Misses Mary K. Scholl and Passie Saperstein.

salt-bath. The solution was neutralized with sodium bicarbonate and the liberated oxime was extracted with ether. The ethereal solution was dried over sodium sulfate followed by Drierite and was distilled *in vacuo* after removing the solvent, yielding 11.6 g. (26%) of oxime, b. p. 169–171° at 4 mm. The oxime was reduced with Raney nickel[18a] in 58% yield, the substituted ornithine ester obtained boiling at 120–123° at 6 mm. It formed a dipicrolonate, m. p. 184.5–185.5°.

Anal.[20] Calcd. for $C_{31}H_{40}O_{12}N_{10}$: N, 18.8. Found: N, 18.4.

1,1,1-Trifluoro-5-diethylaminopentanone-2 (Method A).—The sodium salt of ethyl trifluoroacetoacetate was prepared according to Swarts,[22] using 88.6 g. (0.63 mole) of ethyl trifluoroacetate,[23] 65 ml. of ethyl acetate, 14.4 g. (0.63 mole) of sodium and 36.6 ml. of absolute ethanol. The sodium salt was dried *in vacuo* and dissolved in 350 ml. of dry benzene. β-Diethylaminoethyl chloride (106 g., 0.78 mole) was added rapidly and the solution was heated and stirred at 50–60° for three hours. The reaction mixture was allowed to stand overnight at room temperature and was then refluxed for three hours. The sodium chloride was removed by centrifuging and the benzene was distilled under reduced pressure. The residue was heated on a steam-bath overnight with 800 ml. of 10% sulfuric acid. The ketone was salted out with potassium carbonate, extracted with ether, dried over potassium carbonate and distilled; 23 g. (17%) was collected at 78–88° at 30 mm.

1,1,1-Trifluoro-5-diethylaminopentanone-2 (Method B).—Sodium ethoxide, prepared from 5.8 g. (0.25 mole) of sodium and 14.8 ml. (0.25 mole) of absolute ethanol, was suspended in 85 ml. of dry ether. Ethyl trifluoroacetate (36 g., 0.25 mole) was added, a clear solution resulting, followed by 50 g. (0.27 mole) of ethyl γ-diethylaminobutyrate.[18c] The reaction mixture was intermittently refluxed and allowed to stand at room temperature for six days. The ether was distilled and the β-keto ester was cleaved with dilute sulfuric acid as described above, the ketone (11.4 g., 21%) being collected at 75–85° at 30 mm.

The ketone was converted into the corresponding oxime as previously described,[18a] a 60% yield of pure product being obtained, m. p. 76.5–77.0°.

Anal.[24] Calcd. for $C_9H_{17}ON_2F_3$: C, 47.8; H, 7.57; N, 12.4. Found: C, 47.9; H, 7.55; N, 12.5.

Quinacrine Analogs (Table I).—The diamines were coupled with 2-methoxy-6,9-dichloroacridine dissolved in phenol as described previously.[18a] The small-scale runs (compounds 6–8) were purified and converted into hydrochlorides in the usual manner, but the procedure in large-scale runs (compounds 1–5) had to be modified, as illustrated here by the preparation of 2-methoxy-6-chloro-9(3′-diethylaminopropylamino)-acridine (compound 3).

2-Methoxy-6,9-dichloroacridine[25] (97.5 g., 0.35 mole) and 440 g. of phenol were stirred and heated on a steam-bath until solution was complete. 3-Diethylaminopropylamine (52.0 g., 0.40 mole) was added to the hot solution with stirring over a period of thirty minutes. Heating was continued for an additional two hours, the reaction mixture was cooled and was poured into one liter of acetone. Ethanolic hydrogen chloride was added until the solution was acid to congo red paper, the mixture was chilled and the precipitated hydrochloride was filtered off. The precipitate was washed thoroughly with acetone followed by ether to remove most of the phenol and was then recrystallized. Compounds 1, 2 and 3 were recrystallized from hot, not boiling, water; compound 4 was recrystallized from 50% ethanol–water and compound 5 from ethanol–isopropyl ether. The precipitates were washed with acetone and ether and air-dried.

Summary

1. Eight compounds related to quinacrine have been synthesized in order to test their antimalarial activity.

2. 1,1,1-Trifluoro-5-diethylaminopentanone-2 and the corresponding oxime were prepared.

DURHAM, NORTH CAROLINA

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(22) Swarts, *Bull. classe sci., Acad. roy. Belg.*, [5] **12**, 692 (1926).

(23) Henne, Alderson and Newman, THIS JOURNAL, **67**, 918 (1945). We are indebted to the General Chemical Co. for a supply of antimony trifluoride needed in this preparation.

(24) We are indebted to Dr. Charles C. Price, Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois, for this analysis.

(25) We wish to thank the Abbott Laboratories, North Chicago, Illinois, for a supply of this compound.