[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

Derivatives of Quinoline. I. Nupercaine Analogs. I

BY M. E. SMITH AND C. B. POLLARD

During the last few years, as a result of attempts to find new local anesthetics, a number of substituted 2-alkoxycinchoninamides have been prepared, of which nupercaine, N-diethyl-N'-(2-*n*-butoxycinchoninyl) ethylenediamine, is perhaps the best known. It has seemed advisable to extend this work to include certain piperazine and morpholine compounds.

In this investigation, 2-chlorocinchoninyl chloride was prepared by the method of Mulert,[1] except that purified commercial heptane (b. p. 93–97°) was used instead of ligroin to extract the product, and the hot heptane solution was filtered through a suction filter instead of being used in a Soxhlet extraction apparatus. 2-Chlorocinchoninyl chloride was treated with piperazine, N-phenylpiperazine, and morpholine to give N,N'-bis-(2-chlorocinchoninyl)-piperazine, N-phenyl-N'-(2-chlorocinchoninyl)-piperazine, and N-(2-chlorocinchoninyl)-morpholine, respectively. N-Phenyl-N'-(2-chlorocinchoninyl)-piperazine was treated with a number of sodium alcoholates to give several N-phenyl-N'-(2-alkoxycinchoninyl)-piperazines. The methoxy and ethoxy derivatives of N-(2-chlorocinchoninyl)-morpholine were prepared similarly.

The N-(2-ethoxycinchoninyl)-morpholine compound exhibited pronounced anesthetic action when tested on the tongue.

Pharmacological studies of these compounds are now being made under the direction of Dr. James C. Munch of John Wyeth and Brother. A report of these studies will appear at a later date.

(1) Mulert, *Ber.*, **39**, 1901–1908 (1906).

Experimental

N,N'-Bis-(2-Chlorocinchoninyl)-piperazine.—A hot benzene solution of 22.6 g. (0.1 mole) of 2-chlorocinchoninyl chloride was added with stirring to 19.4 g. (0.1 mole) of melted piperazine hexahydrate. A white precipitate settled out. After this product had been washed well with water, acetone, alcohol and ether, it weighed 19.8 g. This compound was not appreciably soluble in any of the common organic solvents.

N-Phenyl-N'-(2-chlorocinchoninyl)-piperazine.—A hot benzene solution of 22.6 g. (0.1 mole) of 2-chlorocinchoninyl chloride was added with stirring to a mixture of 16.2 g. (0.1 mole) of N-phenylpiperazine in an aqueous solution of 5.3 g. (0.05 mole) of sodium carbonate. The resulting mixture was stirred for fifteen minutes and then allowed to stand for several hours. The product was filtered and washed with several portions of warm water, followed by a very small amount of acetone. The yield was 33.3 g. The compound was recrystallized twice from acetone before the melting point was determined. This compound is fairly soluble in alcohol and benzene, but is insoluble in water.

N-(2-Chlorocinchoninyl)-morpholine.—A hot benzene solution of 11.3 g. (0.05 mole) of 2-chlorocinchoninyl chloride was added while stirring to a mixture of 4.3 g. (0.05 mole) of morpholine in an aqueous solution of 2.7 g. (0.025 mole) of sodium carbonate. The resulting mixture was stirred for half an hour and then allowed to stand for several hours. The product was then filtered and washed with several portions of water, followed by a very small amount of acetone. The yield was 13.5 g. The product was recrystallized twice from 95% ethanol before the final

TABLE I

		M. p., °C. (corr.)	Yield, %	Formula	Analyses % N Calcd.	Found
1	N,N'-bis-(2-Chlorocinchoninyl)-piperazine	Not under 300	85	$C_{24}H_{18}Cl_2N_4O_2$	12.05	11.86
2	N-Phenyl-N'-(2-chlorocinchoninyl)-piperazine	189.2–190.2	95	$C_{20}H_{18}ClN_3O$	11.95	11.84
3	N-Phenyl-N'-(2-methoxycinchoninyl)-piperazine	149.5–150.2	Quant.	$C_{21}H_{21}N_3O_2$	12.10	12.02
4	N-Phenyl-N'-(2-ethoxycinchoninyl)-piperazine	154.0–154.5	Quant.	$C_{22}H_{23}N_3O_2$	11.63	11.34
5	N-Phenyl-N'-(2-*n*-propoxycinchoninyl)-piperazine	102.8–103.3	52	$C_{23}H_{25}N_3O_2$	11.20	11.00
6	N-Phenyl-N'-(2-isopropoxycinchoninyl)-piperazine	116.2–117.2	66	$C_{23}H_{25}N_3O_2$	11.20	11.00
7	N-Phenyl-N'-(2-*n*-butoxycinchoninyl)-piperazine	77.2–78.2	54	$C_{24}H_{27}N_3O_2$	10.80	10.67
8	N-Phenyl-N'-(2-alloxycinchoninyl)-piperazine	129.5–130.5	50	$C_{23}H_{23}N_3O_2$	11.26	11.06
9	N-Phenyl-N'-(2-beta-methoxyethoxycinchoninyl)-piperazine	91.6–92.3	41	$C_{25}H_{25}N_3O_3$	10.74	10.51
10	N-Phenyl-N'-(2-(N-phenyl-piperazino-N'-beta-ethoxy)-cinchoninyl)-piperazine	134.7–135.2	90	$C_{32}H_{35}N_5O_2$	13.43	13.18
11	N-(2-Chlorocinchoninyl)-morpholine	173.6–174.4	Quant.	$C_{14}H_{13}ClN_2O_2$	10.13	9.97
12	N-(2-Methoxycinchoninyl)-morpholine	134.0–134.9	65	$C_{15}H_{16}N_2O_3$	10.29	10.10
13	N-(2-Ethoxycinchoninyl)-morpholine	69.0–69.8	56	$C_{16}H_{18}N_2O_3$	9.79	9.47

melting point was determined. This compound is fairly soluble in acetone and benzene, but is insoluble in water.

N-Phenyl-N'-(2-alkoxycinchoninyl)-piperazines.—A hot solution of 8.8 g. (0.025 mole) of N-phenyl-N'-(2-chlorocinchoninyl)-piperazine in 140 ml. of benzene was added to a solution of 1.0 g. of sodium dissolved in 25 ml. of the appropriate alcohol, and the resulting mixture was refluxed four to fifty hours, after which it was filtered free from sodium chloride. In the cases of the methyl, ethyl, propyl and allyl compounds, the filtrate was evaporated to dryness, washed with water and recrystallized from 95% ethanol. In the cases of the others, the filtrate was washed with water and then evaporated to an oil, which was then dissolved in ethanol. Crystals eventually appeared from these alcoholic solutions, although with difficulty in some cases. All of the compounds were crystallized again from ethanol before their melting points were determined. These compounds are fairly soluble in acetone and benzene, but are insoluble in water.

N-(2-Alkoxycinchoninyl)-morpholines.—A hot solution of 5.5 g. (0.02 mole) of N-(2-chlorocinchoninyl)-morpholine in 50 ml. of benzene was added to a solution of 1.0 g. of sodium dissolved in 50 ml. of the appropriate alcohol. This mixture was refluxed for four hours, filtered and then evaporated to a solid. This was washed with water and then dissolved in ethanol. The crystals which later appeared were again crystallized before the melting points were determined.

A summary of the new nupercaine analogs is shown in Table I.

Summary

1. Thirteen new quinoline compounds analogous to nupercaine have been prepared and characterized.

2. At least one of these compounds has anesthetic properties.

3. Pharmacological studies of these compounds are now under way under the direction of Dr. James C. Munch of John Wyeth and Brother.

4. Work on these series of compounds is being continued in this Laboratory.

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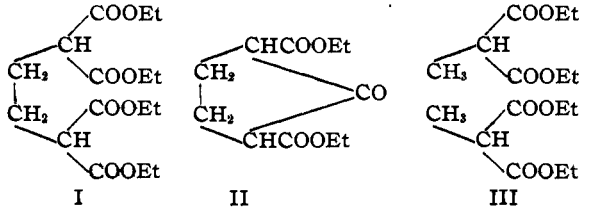
The Reaction of Certain Monosubstituted Malonic Esters and Methylene Dimalonic Esters with Sodium Ethoxide

BY J. R. ROLAND AND S. M. MCELVAIN

The fact that ethylene dimalonic ester (I) undergoes intramolecular condensation to give a dicarbethoxycyclopentanone[1] (II), led to the expectation that two molecules of methylmalonic ester (III), on account of their similarity to I in structure, should condense intermolecularly. As a matter of fact, such an intermolecular condensation of monosubstituted malonic esters had been predicted by Dieckmann[2] on the basis of his interpretation of the mechanism of the acetoacetic ester condensation. Later, however, Dieckmann and Kron[3] mentioned briefly in a footnote the failure of methylmalonic ester to undergo this condensation.



I II III

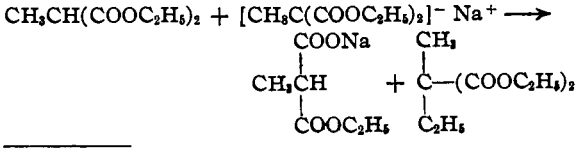
(1) Meincke, Cox and McElvain, THIS JOURNAL, **57**, 1133 (1935). *Cf.* also the condensation of the homologous trimethylene dimalonic ester [Guha and Seshadriengar, *Current Sci.*, **3**, 20 (1934)].

(2) Dieckmann, *Ber.*, **33**, 2678 (1900).

(3) Dieckmann and Kron, *ibid.*, **41**, 1260 (footnote 1) (1908).

In view of this reported failure to realize an intermolecular condensation of III, it seemed worth while to ascertain what products, if any, result from the reaction of sodium ethoxide and methylmalonic ester. Of course the first product formed from these reactants is the sodium enolate of methylmalonic ester and an equivalent of alcohol. When the latter is removed by distillation the reactants remaining are this enolate and the excess methylmalonic ester. Such enolates are, therefore, the real condensing agents when such an ester as I is condensed.

When the sodium enolate of methylmalonic ester was heated at 140–160° with an excess of the ester, the reaction products isolated were monoethylmethylmalonate, methylethylmalonic ester and α-methylbutyric ester. The first two of these products are the result of the alkylation of the enolate by methylmalonic ester,[4] thus



(4) *Cf.* Walter and McElvain, THIS JOURNAL, **57**, 1891 (1935).