

Search for Potential Filaricides. I

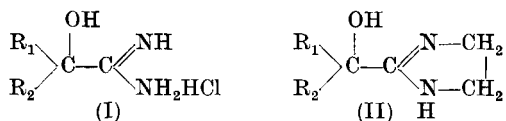
Synthesis of Dialkyl Amidines and Dialkyl Imidazolines

By A. B. SEN and K. SHANKER

Abstract

A number of new substituted amidines (I) and imidazolines (II) have been synthesised as potential filaricides.

Compounds having amidinium skeleton in which a positively charged quarternary nitrogen atom is linked to another tertiary nitrogen atom by a conjugated chain of carbon atoms have been found to be effective against Filariasis¹). Both the nitrogen atoms should be incorporated in the heterocyclic ring as in the filaricidal cyanine dyes. Based on this hypothesis substituted acetamidines (I) and imidazolines (II) having essentially the same arrangement of nitrogen atoms as in the amidinium compounds were synthesised by the condensation of dialkyl imidates with ethylenediamine.



Dialkyl cyanohydrins were at first prepared by the action of sodium cyanide and hydrochloric acid on diethyl, dimethyl, ethyl methyl, and methyl isobutyl ketones at 0 °C. The dialkyl cyanohydrins thus obtained were then treated with ethanolic HCl to yield the imidates.

The imidates were then condensed with ethylene diamine in absolute alcohol giving the required imidazolines.

The dialkyl acetamidines were prepared by treating the imidates with alcoholic ammonia.

The phenyl carbamido and carbethoxy grouping which have been found to enhance filaricidal activity were also introduced in the imidazolines by condensing them with phenyl isocyanate and with ethyl chloroformate respectively.

¹) E. BUEDING, *Anal. N. Y. Acad. Sc.* **50**, 115 (1948).

Experimental

Substituted dialkylcyanohydrins: These were prepared in the usual way by the action of sodium cyanide and HCl (36%) in appropriate ketones. Acetone cyanohydrin²⁾ (b. p. 85/10 mm), diethyl ketone cyanohydrin³⁾ (b. p. 105–108/12 mm) methyl isobutyl ketone cyanohydrin⁴⁾ (b. p. 100/10 mm, ethyl methyl ketone cyanohydrin⁵⁾ (b. p. 85/10 mm) were thus synthesised.

Dialkyliminoethers: Alkyl cyanohydrin (0.45 M) was dried in vacuum and dry HCl gas was passed in a solution of cyanohydrin (0.45 M) in absolute alcohol (0.3 M) till the weight increased by 10 gm. It was then left in the cold for four days when crystals of the iminoether separated out. These were filtered, washed with dry ether and dried in a vacuum desiccator. M. P., yield and analysis etc. of these are given in Table 1.

Dialkylimidazoline: To a cooled solution of ethylenediamine (0.1 M) in absolute ethyl alcohol (100 cc) was added slowly with stirring (1/2 hr) the iminoether HCl. The reaction mixture was stirred for another hour at 0°C, and then heated on a water bath, till no more ammonia was evolved. It was then acidified with alcoholic HCl to Congo red and filtered hot. The filtrate was concentrated in vacuum and cooled, when the crystals of the imidazoline HCl separated out. It was recrystallized from acetone. The free base was obtained as follows:

Sodium (1.5 g) was dissolved in absolute alcohol (50 cc) and the imidazoline HCl (0.1 M) was then added to it. The sodium chloride which separated out was filtered, and the filtrate concentrated in vacuum. The residual oil was left overnight in the cold where upon a solid was obtained which was recrystallised from acetone or petroleum ether.

M. Ps, yield and analysis etc. are given in Table 2.

Dialkylacetamidines: The appropriate imidate HCl (0.1 M, powdered) was added gradually to an excess of alcoholic ammonia (50 ml. of 9% ammonia solution) with stirring. It was stirred for another three hours and then filtered. The filtrate was then concentrated in vacuum and the ammonium chloride which separated out, was filtered and the filtrate cooled, where upon the amidine HCl separated out. This was filtered and recrystallised from petroleum ether. (B. P. 40–60). Melting point, yield, analysis are given in Table 1.

Dialkylphenylcarbamido, imidazoline. To a solution of imidazoline (0.0014 M) in toluene (20 ml) was added phenyl isocyanate (0.0016 M) and the mixture refluxed in an oil bath at 130°C for twelve hours. Excess of toluene and phenyl isocyanate were removed under reduced pressure. The residue was recrystallized from acetone-petroleum ether or absolute alcohol-petroleum ether (40–60). Melting point, yield, analysis are given in Table 1.

Condensation of imidazoline with ethylchloroformate. To a mixture of imidazoline (0.019 M), anhydrous sodium carbonate (0.3 M) and absolute alcohol (150 ml) was added dropwise with stirring under reflux a solution of ethyl chloroformate (0.038 M) in 20 ml of absolute alcohol. The solution was further stirred for five hours, the reaction mixture was then cooled and filtered to remove the inorganic salts. The filtrate was concentrated in vacuum. The residue was taken up in (30 ml. of 5%) sodium hydroxide solution and the solution repeatedly extracted with ether. The ether extract dried over anhydrous sodium carbonate. Solvent removed and the residue distilled in vacuum.

Boiling point, yield, analysis etc. are given in Table 1.

²⁾ COX and STORMANT, *Org. Synthesis*, Vol. II.

³⁾ COLONGE and JOLY, *J. Ann. Chim.* (ii), 183 (1943).

⁴⁾ STEWART, *J. Bull. Soc.* 1932, 62.

⁵⁾ JACOBSON, *J. Amer. chem. Soc.* 68, 2628 (1946).

Table 1

R ₁	R ₂	M. P. or B. P.	Yield %	Nitrogen	
				Found	Calc.
$\begin{array}{c} \text{OH} \\ \\ \text{R}_1 \diagdown \text{C} - \text{C} \begin{array}{l} \diagup \text{OC}_2\text{H}_5 \\ \diagdown \text{=NH} \cdot \text{HCl} \end{array} \\ \\ \text{R}_2 \end{array}$					
CH ₃	CH ₃	100°	60	8.12	8.38
CH ₃	C ₂ H ₅	98°	45	7.24	7.73
C ₂ H ₅	C ₂ H ₅	78°	45	6.98	7.17
CH ₃	C ₄ H ₉	55°	60	6.52	6.90
$\begin{array}{c} \text{OH} \\ \\ \text{R}_1 \diagdown \text{C} - \text{C} \begin{array}{l} \diagup \text{N-CH}_2 \\ \diagdown \text{N-CH}_2 \\ \text{H} \end{array} \\ \\ \text{R}_2 \end{array}$					
CH ₃	CH ₃	140°	50	21.24	21.86
C ₂ H ₅	C ₂ H ₅	150°	45	17.62	17.94
CH ₃	C ₂ H ₅	170°	55	19.25	19.72
CH ₃	C ₄ H ₉	85°	60	16.10	16.47
$\begin{array}{c} \text{OH} \\ \\ \text{R}_1 \diagdown \text{C} - \text{C} \begin{array}{l} \diagup \text{N-CH}_2 \\ \diagdown \text{N-CH}_2 \\ \text{CoNH} \cdot \text{Ph} \end{array} \\ \\ \text{R}_2 \end{array}$					
CH ₃	CH ₃	205°	50	16.71	17.00
C ₂ H ₅	C ₂ H ₅	210°	30	15.00	15.27
CH ₃	C ₂ H ₅	250°	50	15.98	16.09
CH ₃	C ₄ H ₉	160°	60	14.22	14.53
$\begin{array}{c} \text{OH} \\ \\ \text{R}_1 \diagdown \text{C} - \text{C} \begin{array}{l} \diagup \text{=NH} \\ \diagdown \text{=NH}_2\text{HCl} \end{array} \\ \\ \text{R}_2 \end{array}$					
CH ₃	CH ₃	280°	60	20.10	20.28
C ₂ H ₅	C ₂ H ₅	170°	50	16.44	16.96
$\begin{array}{c} \text{OH} \\ \\ \text{R}_1 \diagdown \text{C} - \text{C} \begin{array}{l} \diagup \text{N-CH}_2 \\ \diagdown \text{N-CH}_2 \\ \text{CoOC}_2\text{H}_5 \end{array} \\ \\ \text{R}_2 \end{array}$					
CH ₃	CH ₃	140°/8	45	13.75	14.30
C ₂ H ₅	C ₂ H ₅	110°/10	50	12.00	12.28
CH ₃	C ₂ H ₅	135°/10	40	13.00	13.08
CH ₃	C ₄ H ₉	120°/8	55	11.10	11.57

Lucknow (India), Chemistry Department, Lucknow University.

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