[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF ANTIOCH COLLEGE AND THE UNIVERSITY OF ARIZONA]

CYCLIZATION OF 2-AMINOPYRIDINE DERIVATIVES. II. THE REACTION OF SUBSTITUTED 2-AMINOPYRIDINES WITH ETHYL MALONATE[1]

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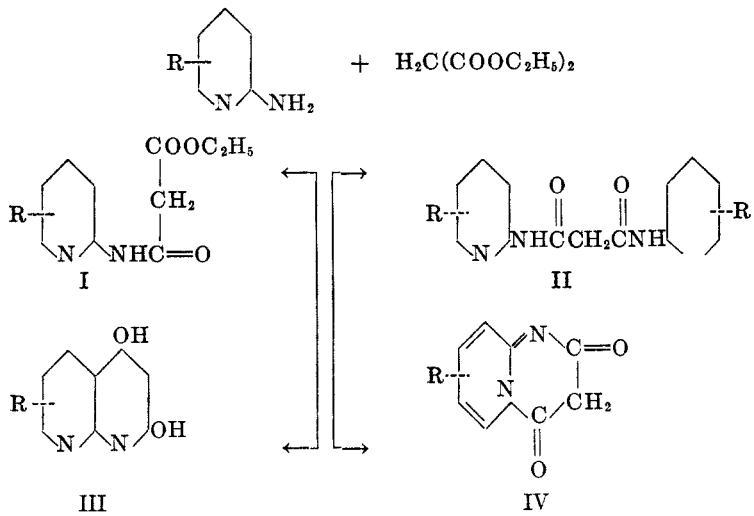
The reaction of ethyl malonate with 2-aminopyridines might proceed to give several non-cyclic or cyclic products as indicated below. Chichibabin (1) investigated the reaction of 2-aminopyridine with ethyl malonate, heating the mixture



under vacuum to 300° or higher. The only product isolated was 2H-pyrido-[1,2-a]pyrimidine-2,4-(3H)dione (IV, R = H) obtained in nearly quantitative yield. More recently the reaction of ethyl malonate with 5-chloro-, 5-bromo-, 5-nitro-, and 3,5-dichloro-2-aminopyridine was investigated by Kucherova, *et al.* (2). They reported that the monohaloaminopyridines gave only non-cyclic products, both Type I and Type II being obtained, and that the nitro- and dichloro-aminopyridine failed to react with the ester.

We were led to investigate this reaction in a search for a means of synthesis of certain 1,8-naphthyridine derivatives (Type III) and herein report the results of the reaction of a number of 2-aminopyridines with ethyl malonate. Both non-cyclic and cyclic products were obtained, the former appearing as by-products of the cyclizations. No attempt was made to prepare the non-cyclic products in

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high yield and the actual yields varied widely from one cyclization to another. Both Type III and Type IV cyclic products were obtained, although a given 2-aminopyridine led to either one or the other exclusively. The structures of these

TABLE I

NON-CYCLIC PRODUCTS

R	TYPE I			TYPE II		
	M.P., °C.	Analyses[a], N		M.P., °C.	Analyses[a], N	
		Calc'd	Found		Calc'd	Found
H	[b]			235 dec.	21.85	21.41
4-CH_3	[b]			167–168	19.73	19.78
5-CH_3	69–70	12.60	12.83	200 dec.	19.73	19.97
6-CH_3	72–73	12.60	12.85	145–146	19.73	19.76
5-I	[b]			230 dec.	11.07	10.88
6-NH_2	[c]			[c]		
6-NHAc	[c]			145–146	22.70	22.54
6-OC_2H_5	[b]			[b]		

[a] Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill. [b] No exhaustive attempt made to isolate. [c] Not found on exhaustive attempt to isolate.

TABLE II

CYCLIC PRODUCTS

R	TYPE	M.P., °C.	CYCLIZATION METHOD	YIELD, %	ANALYSES[a], N	
					Calc'd	Found
4-CH_3	IV	270 dec.	A	73	15.90	15.73
			B	50		
5-CH_3	IV	300 dec.[b]	A	78	15.90	15.86
6-CH_3	III	300 dec.[b]	B	5	15.90	15.74
			A	0		
			C	trace		
5-Cl	IV	310 dec.[b]	C	91	14.30	13.98
			A	trace		
			B	0		
5-Br	IV	310 dec.[b]	C	82	11.60	11.77
5-I	[c]					
6-NH_2	III	325 dec.[b]	B	100	23.70	24.01
6-NHAc	III	325 dec.[b]	B	85	19.15	18.98
6-OC_2H_5	III	325 dec.[b]	B	92	13.59	13.48

[a] Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill. [b] Decomposed slowly without melting when held at this temperature. [c] Starting materials decomposed in each method of cyclization.

products were established by the easy hydrolysis of Type IV and the stability to hydrolysis of Type III. Cyclizations were carried out in the absence of solvent (Method A), using diphenyl ether as a solvent (Method B), and employing a new sublimation-cyclization technique (Method C). Method C gave, on a semi-

micro scale, high yields of cyclic products with the haloaminopyridines (R=5-chloro or 5-bromo), contrary to Kucherova's report that these could not be cyclized. The results of these reactions are reported in Tables I and II.

As in the previously reported cyclization of ethyl 2-pyridylaminomethylenemalonates (3) the normal mode of ring closure involved the ring nitrogen of the imino form of the aminopyridine leading to the formation of a 2H-pyrido[1,2-a]-pyrimidine-2,4(3H)-dione (IV). Only when a strongly activating group was present in the 6-position of the pyridine ring did cyclization involve the 3-carbon atom to yield a 2,4-dihydroxy-1,8-naphthyridine (III). However, one significant difference appears between the results of the reaction with ethyl malonate herein reported and the earlier reported reaction of the methylenemalonate derivatives. In the latter reaction a good yield of a 1,8-naphthryidine was obtained when R = 6-methyl; in the reaction herein reported the yield of naphthyridine in this case was very low although no other cyclic product was obtained. We believe that this substantiates to some degree the earlier hypothesis (3), that for 1,8-naphthyridine formation by cyclization of a 2-aminopyridine derivative both activation of the 3-position and steric hindrance of the ring nitrogen by a 6-substituent are required. In the case of R = 6-methyl it seems probable that sufficient activation for the reaction with ethyl malonate is not supplied, although the activation is sufficient for the reaction with ethyl ethoxymethylenemalonate. In both cases the normal mode of cyclization at the ring nitrogen is completely prevented by steric hindrance.

EXPERIMENTAL

CYCLIZATION METHODS

Method A. Absence of a solvent. This procedure is a modification of the one used by Chichibabin (1). Equimolar quantities of the 2-aminopyridine and ethyl malonate were placed in a distilling flask connected to a water aspirator. The flask was heated in an oil-bath until the interior temperature reached 150° and was then evacuated to about 20 mm. pressure. Heating was continued until the interior temperature reached 210–220°. The solid reaction product was worked up as described below.

Method B. Use of a high-boiling solvent.[5] Equimolar quantities of the 2-aminopyridine and ethyl malonate were dissolved in about three times their weight of diphenyl ether. The solution was warmed slowly until the vigorous initial evolution of ethanol had ceased and was then heated under reflux at the boiling point for thirty minutes. After cooling the cyclic product was precipitated by the addition of three volumes of a crude heptane fraction at 15–20°. The product was purified by recrystallization from pyridine or a pyridine-ethanol mixture.

Method C. Sublimation of a non-cyclic product. The starting material, either of Type I or II, was placed on a microscope cover glass heated on the Fisher-Jones melting-point block. Over this was placed a beaker of ice-water with the bottom no more than 0.5 mm. from the surface of the cover glass. The block was held at 250–260° until all of the material had sublimed, usually several hours being required. The product was purified by resublimation. Because only about 0.1 g. could be handled this way an attempt was made to use a semi-micro sublimation apparatus (4) which allowed samples of 1.0 g. However, the yield was ex-

[5] A preliminary investigation of this method was made by Peter Dresel in connection with a Senior Research Project, Antioch College, 1947.

tremely low, about as much being obtained from 1.0 g. by this method as from 0.1 g. by the first method. This procedure worked well only if R = 5-chloro or 5-bromo although a trace of cyclic product was obtained when R = 6-methyl. With the other non-cyclic amides no sublimate was obtained and only tar resulted.

Separation of cyclic and non-cyclic products. If Method A was used for the cyclization the non-cyclic products could be extracted from the solid reaction product with boiling ether in which the cyclic products were insoluble. The mixture of I and II thus obtained could be separated by fractional crystallization from an ether-heptane solvent pair, II being considerably less soluble than I.

If Method B was used the filtrate from the separation of the cyclic products was diluted with an additional ten volumes of heptane and kept at 10° for several days. The mixture of I and II which crystallized was separated as above.

Structure proof of cyclic products. Approximately 0.5 g. of the cyclic product was dissolved in 5 ml. of 6 *N* hydrochloric acid. The solution was refluxed for fifteen hours, cooled, and neutralized with ice-cold 12 *N* aqueous sodium hydroxide solution. If the cyclic product was Type III it precipitated unchanged at this point and could be recovered quantitatively. If no precipitate was formed the solution was saturated with potassium carbonate and extracted with ether. Evaporation of the ether gave a 50–70% yield of the original 2-aminopyridine derivative from which the Type IV product was made. This was identified by mixture melting point with an authentic sample of the starting material.

SUMMARY

The reaction of several substituted 2-aminopyridines with ethyl malonate has been reported. It has been shown that two cyclic products may be obtained from this reaction, 1,8-naphthyridine derivatives being obtained as well as the previously reported pyridopyrimidine derivatives. The type of product obtained from a given 2-aminopyridine depends only on the substituents present in the pyridine ring.

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