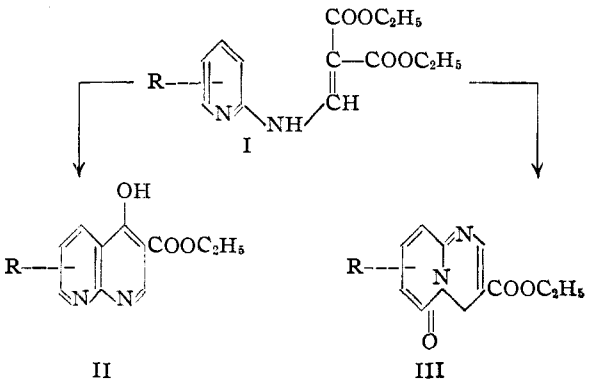
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF ANTIOCH COLLEGE]

Cyclization of 2-Aminopyridine Derivatives. I. Substituted Ethyl 2-Pyridylaminomethylenemalonates[1,2]

BY GERALD R. LAPPIN

The work of Seide[3] and of Mangini and Colonna[4] has shown that two modes of cyclization exist for N-2-pyridyl benzoylacetamides. The amide derived from 2-aminopyridine gave 4-phenyl-2H-pyrido[1,2-a]pyrimidine-2-one[3] while that derived from 2;6-diaminopyridine gave 2-hydroxy - 4 - phenyl - 7 - amino - 1,8 - naphthyridine.[4] Similar results have been observed in other such cyclization reactions; for example, it has been shown[5] that the reaction of ethyl ethoxymethylenemalonate with 2,6-diaminopyridine gave a 1,8-naphthyridine derivative but that no product was obtained when 2-aminopyridine was used. The great difference in behavior of 2-aminopyridine and 2,6-diaminopyridine has usually been attributed to activation of the 3-position by the electron releasing amine group. No investigation has ever been made as to the effect of other substituents in the pyridine nucleus on the course of such reactions. The work described herein was carried out to determine these effects.

The cyclization of ethyl 2-pyridylaminomethylenemalonates (I) might give either the previously reported 3-carbethoxy-4-hydroxy-1,8-naphthyridine derivative[5] (II) or a substituted 3-carbethoxy-2H-pyrido[1,2-a]pyrimidine-4-one (III). The two possible products should be readily distinguishable through basic hydrolysis. Type II products should yield the corresponding 3-carboxy-4-hydroxy-1,8-naphthyridine, while Type III would be expected to suffer rupture of the pyrimidine ring at the amide linkage to yield a non-cyclic derivative of the 2-aminopyridine or the 2-aminopyridine itself.



With the exception of 2-amino-6-hydroxypyridine, 2-amino-5-nitropyridine and ethyl 6-aminonicotinate, which failed to react under any conditions, all of the 2-aminopyridines investigated reacted readily with ethyl ethoxymethylenemalonate (EMME) at 110° to give nearly quantitative yields of ethyl 2-pyridylaminomethylenemalonates (I). The melting points of these products are recorded in Table I. Cyclization of I, except when R = hydrogen, 6-bromo or 4-chloro, proceeded readily in refluxing phenyl ether to give moderate to high yields of solid product.

Two different types of product were obtained, the type depending on the nature and position of R. One melted at relatively high temperatures without decomposition and was insoluble in all organic solvents except pyridine. These products were quite resistant to basic hydrolysis but gave on long heating with aqueous sodium hydroxide followed by acidification an acidic product shown by analysis and neutral equivalent to be derived by hydrolysis of the ester group of the cyclized product. These substances were, therefore, derivatives of 1,8-naphthyridine (II). The other type, shown to be derived from III by their rapid and complete hydrolysis to the corresponding 2-aminopyridine, melted with decomposition at relatively low temperatures and was soluble in most common organic solvents. Only one type of product could be isolated from the cyclization of a given ethyl 2-pyridylaminomethylenemalonate. The product type, yield, melting point and analytical data are given in Table I.

When R = 6-bromo or 4-chloro only tars were obtained, presumably due to the active halogen taking part in some unwanted reaction. When R = hydrogen only tar could be obtained in refluxing phenyl ether but by heating 2-aminopyridine with EMME in the absence of solvent a small amount of crystalline product was obtained which hydrolyzed to give 2-aminopyridine and malonic acid. This reaction, together with analytical data, indicated that the product might have been the N-2-pyridylamide of 3-carboxy-2H-pyrido-[1,2-a]pyrimidine-4-one but no attempt was made to establish definitely its structure. The failure to obtain a product in phenyl ether was probably due to the decomposition of the Type III product presumably formed. Support was given to this hypothesis by the fact that all Type III products decomposed to give tars on longer heating in phenyl ether.

(1) The work described in this paper was carried out under a Frederick Gardner Cottrell Special Grant-in-Aid from the Research Corporation.

(2) Presented in part before the Division of Organic Chemistry of the American Chemical Society, Chicago, Ill., April 19, 1948.

(3) Seide, *Ber.*, **58**, 352 (1925).

(4) Mangini and Colonna, *Boll. sci. facoltà chim. ind. Bologna*, **85** (1941); *C. A.*, **36**, 5476 (1942).

(5) Adams, Bradsher, Breslow, Amore and Hauser, THIS JOURNAL, **68**, 1317 (1946).

TABLE I

R	M. p., I, °C.	Product type	Yield, %	M. p., °C.	Formula	N Analyses, % [b] Calcd.	Found
H	65–66	Tar[a]					
4-CH_3	72–73	III	68	171–172	$C_{12}H_{12}N_2O_3$	12.05	12.31
5-CH_3	112–113	III	74	135–136	$C_{12}H_{12}N_2O_3$	12.05	12.00
6-CH_3	113–114	II	90	278–280	$C_{12}H_{12}N_2O_3$	12.05	11.87
4-Cl	Oil	Tar					
5-Cl	115–116	III	80	132–133	$C_{11}H_9ClN_2O_3$	11.10	10.81
5-Br	117–118	III	75	134–135	$C_{11}H_9BrN_2O_3$	9.76	9.84
6-Br	114–115	Tar					
4-C_2H_5O[c]	Oil	III	48	168–169	$C_{13}H_{14}N_2O_4$	10.68	10.93
6-C_2H_5O	116–117	II	95	219–220	$C_{13}H_{14}N_2O_4$	10.68	10.51

[a] Heating 2-aminopyridine with EMME in absence of solvent gave a small yield of crystalline product. [b] Microanalyses by the Clark Microanalytical Laboratory. [c] The preparation of 2-amino-4-ethoxypyridine will be described in a subsequent communication.

It may be seen from Table I that the normal mode of ring closure of I involves the ring nitrogen and yields only derivatives of pyrido[1,2-a]pyrimidine (III). This is unaffected by all substituents studied except electron releasing groups in position 6 which completely prevented it, giving derivatives of 1,8-naphthyridine (II), exclusively. If only activation of the 3-position decided the direction of cyclization electron releasing substituents in position 4 should also have yielded Type II products. Their failure to do so might be attributed to steric hindrance by the 4-substituent or to a shift of the tautomeric equilibrium in I to favor the imine form. The latter is unlikely inasmuch as similar groups in positions 4 and 6 should have the same qualitative effect on this tautomerism. The former is also unlikely as the steric requirements for ring closure at position 3 would be expected to be nearly identical to those involved in the cyclization of ethyl anilinomethylenemalonates. Here the ortho effect of such substituents as the methyl group is not sufficient to prevent ring closure at the hindered position. The reaction with 3,4-dimethylaniline, for example, gave both 6,7-dimethyl and 5,6-dimethylquinoline derivatives.[6] It seems most probable, therefore, that the formation of 1,8-naphthyridines is due to prevention of ring closure at the 1-position by the ortho effect of the 6-substituent since the steric requirements of closure at a nitrogen atom might well differ considerably from those at a carbon atom. Activation of the 3-position is in all probability also required.[7]

Acknowledgments.—The author gratefully acknowledges the gift of a generous supply of phenyl ether and of 2,6-dibromopyridine by the Dow Chemical Company as well as that of 2-aminopyridine and 2,6-diaminopyridine by the Pyridium Corporation.

(6) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(7) It has recently been observed that in a reaction with higher activational requirements, the reaction of 2-aminopyridines with ethyl malonate, certain 6-substituents not only fail to give sufficient activation of the 3-position but also prevent cyclization at the ring nitrogen. These results will be described in a subsequent communication from this Laboratory.

Experimental[8]

Ethyl 2-Pyridylaminomethylenemalonates (I).—An equimolecular mixture of the 2-aminopyridine and ethyl ethoxymethylenemalonate (EMME) was heated at 110° for thirty minutes and the residue recrystallized from ethanol to give I in nearly quantitative yield. Longer heating or higher temperatures gave a greatly decreased yield of highly colored product.

Cyclization of I.—The recrystallized I was added to fifteen parts by weight of refluxing phenyl ether and vigorous refluxing was continued for ten minutes. The solution was cooled as rapidly as possible and diluted with five volumes of hexane. The precipitate was collected in the usual manner and recrystallized from ethanol, pyridine or a mixture of these. The type of product obtained, the yield, melting point and analytical data are summarized in Table I.

These conditions give good results for runs up to about 0.1 mole. Larger runs invariably give much lower yields. Use of impure I also decreases the yield and gives a product which is difficult to purify.

Hydrolysis of Cyclized Products.—The product, 1.0 g., was refluxed with 15 ml. of 10% aqueous sodium hydroxide solution until solution was complete (in the case of R = 6-C_2H_5O solution was not complete after two weeks of refluxing so the solution was filtered hot before further examination). After cooling, the basic solution was extracted with three 10-ml. portions of ether. The ether solution was dried over Drierite and evaporated to dryness *in vacuo*. With Type II products no residue remained but with Type III products a nearly quantitative yield of the original 2-aminopyridine was obtained. This was identified by mixture melting point with an authentic sample. The basic filtrate was then acidified and the precipitate, if any, collected. With Type III products the solution evolved carbon dioxide and gave no precipitate. With Type II products at nearly quantitative yield of the 1,8 naphthyridine carboxylic acid were obtained. In this way were obtained 3-carboxy-4-hydroxy-7-methyl-1,8-naphthyridine, m. p. 278–280° with decomposition, (*Anal.* Calcd. for $C_{10}H_8N_2O_3$: N, 13.73; neut. eq. 204. Found: N, 13.90; neut. eq. 204), and 3-carboxy-4-hydroxy-7-ethoxy-1,8-naphthyridine, m. p. 225–230° with decomposition (*Anal.* Calcd. for $C_{11}H_{10}N_2O_4$: N, 11.96; neut. eq., 234. Found: N, 12.12; neut. eq., 230).

Reaction of 2-Aminopyridine with EMME in Absence of Solvent.—A mixture of 5.0 g. (0.053 mole) of 2-aminopyridine and 15.0 g. (0.070 mole) of EMME was heated in an open flask at 150° for one hour, at 200° for thirty minutes, and at 260° for fifteen minutes. The mixture was cooled and diluted with 25 ml. of ethanol. The precipitate was collected and recrystallized from pyridine

(8) All melting points herein reported were determined on a Fisher–John melting point block and are uncorrected.

to give 1.2 g. of pale yellow crystals, m. p. 273–274°. Hydrolysis of this substance in the previously described manner gave 2-aminopyridine and a copious evolution of carbon dioxide on acidification of the basic solution.

Anal. Calcd. for $C_{14}H_{10}N_4O_2$: N, 22.0. Found: N, 21.5.

Summary

The normal course of cyclization of ethyl 2-pyridylaminomethylenemalonates has been found to involve the ring nitrogen to give derivatives of pyrido[1,2-a]pyrimidine. Substituents in positions 4 and 5 did not affect this mode but electron releasing substituents in position 6 completely prevented it resulting in the formation of derivatives of 1,8-naphthyridine.

The preparation of two new derivatives of 1,8-naphthyridine and of five new derivatives of pyrido[1,2-a]pyrimidine are described.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Substituted Quinolines[1,2]

BY C. E. KASLOW AND R. D. STAYNER[3]

The present paper deals with the synthesis of several substituted quinolines of the lepidine and quinaldine series. The substituted 2-hydroxylepidines were prepared by ring closure from the corresponding substituted acetoacetanilides while the substituted 4-hydroxyquinaldines were obtained by ring closure of the corresponding β-arylaminocrotonates. The exploratory work on the syntheses was done to determine the general usefulness of these ring closure methods for the preparation of certain substituted quinolines not readily available by methods employing drastic conditions used quite generally in the Skraup and Doebner–Miller reactions.

It was determined in the first experiments that methyl acetoacetate generally gave better yields in the condensation with the primary aromatic amines than did ethyl acetoacetate. It was also found that ring closure of the methyl β-arylaminocrotonates gave a better yield of the hydroxyquinaldine than did the ethyl ester and in general much better yields were obtained by ring closure in boiling phenyl ether than in hot mineral oil. For instance, the ring closure of methyl β-[4-(*p*-acetamidobenzyl)-anilino]-crotonate in mineral oil gave only an 11% yield of very impure 6-(*p*-acetamidobenzyl)-4-hydroxyquinaldine.

Attempted ring closure of 4-acetoacetamido-4′-methoxydiphenylmethane in sulfuric acid either did not occur or gave a 110% yield of a sulfur-containing compound which was soluble in sodium carbonate solution. The product is presumably a sulfonic acid which resulted from sulfonation of the *p*-methoxybenzyl group either before or after ring closure. This behavior has been observed also in the case of *p*-benzylacetoacetanilide.[4] The structures of these sulfonic acids have not yet been proven.

(1) A portion of this work was presented before the Division of Organic Chemistry, American Chemical Society, Chicago, Illinois, September 12, 1946.

(2) A portion of this was abstracted from a thesis submitted to the faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

(3) Present address: California Research Corporation, Richmond, California.

(4) D. J. Hart, unpublished results.

Experimental

4-Acetoacetamido-4′-chlorodiphenylmethane.—A stirred solution of 43.5 g. (0.2 mole) of 4-amino-4′-chlorodiphenylmethane[5] in 150 ml. of warm benzene was treated with 18 g. (0.22 mole) of diketene, the solution was refluxed for twenty minutes, diluted with an equal volume of ligroin, cooled in ice–water, then solid removed by filtration and washed with a cold benzene–ligroin mixture. After drying at 60°, the yield of the crude substance was 54.2 g. (89.5%); m. p. 102–106°. After recrystallization from a benzene–ligroin mixture (1:1) and from ethyl alcohol, the substance melted at 109–111°.

The corresponding 4′-bromo, 4′-methoxy and 4′-acetamido compounds were prepared in an analogous manner. The data are summarized in Table I.

6-(*p*-Methoxybenzyl)-4-methylcarbostyril.—To a solution of 4.5 g. of phosphoric anhydride in 50 ml. of 85% phosphoric acid was added 7.9 g. (0.027 mole) of 4-acetoacetamido-4′-methoxydiphenylmethane, then the mixture heated at 125° for two hours. After pouring the reaction mixture onto ice, the solid was removed by filtration, washed and dried. The yield of crude substance was 4.5 g. (61%); m. p. 175–183°. Recrystallized from ethyl alcohol–cellosolve (6:1); m. p. 188.5–190.5°.

The corresponding chloro, bromo and acetamido compounds were prepared by ring closure in sulfuric acid at 60–65° according to the directions of Kaslow and Sommer.[6] The 6-(*p*-aminobenzyl)-4-methylcarbostyril was obtained by hydrolysis of the 6-(*p*-acetamidobenzyl)-4-methylcarbostyril in boiling 15% hydrochloric acid. A hydrochloride (m. p. 314–320°) was obtained and this was converted to the white crystalline amino compound by boiling with 2% ammonia solution. The data on these substituted carbostyrils are summarized in Table II.

Methyl β-[4-(*p*-Chlorobenzyl)-anilino]-crotonate.—A solution of 10 g. (0.046 mole) of 4-amino-4′-chlorodiphenylmethane, 6 g. (0.052 mole) of methyl acetoacetate and one drop of 5% hydrochloric acid in 100 ml. of methylene chloride was refluxed under a water-cooled condenser attached to a water separator for immiscible liquids heavier than water until no more water was collected. After removal of most of the solvent, the reaction mixture was diluted with 30 ml. of ligroin, cooled and the solid removed by filtration. The yield was 12.6 g. (97%); m. p. 85–88°. The substance was recrystallized from a benzene–ligroin solution (1:20) as colorless platelets, m. p. 87–88°.

The substituted β-anilinocrotonates listed in Table III were prepared analogously from methyl acetoacetate

(5) Kaslow and Stayner, THIS JOURNAL, 68, 2600 (1946).

(6) Kaslow and Sommer, *ibid.*, 68, 646 (1945).