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]

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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.

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(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).

TABLE I

4-ACETOACETAMIDO-4'-R-DIPHENYLMETHANES

R	M. p., °C.	Formula	% Nitrogen Calcd.	% Nitrogen Found	2,4-Dinitrophenylhydrazone[c] M. p., °C.	Formula	% Nitrogen Calcd.	% Nitrogen Found
Chloro[a,b]	109–111	$C_{17}H_{16}ClNO_2$	4.66	4.81	174–176	$C_{23}H_{20}ClN_5O_5$	14.54	14.46
Bromo[a,b]	123–126	$C_{17}H_{16}BrNO_2$	4.04	3.95	183–185	$C_{23}H_{20}BrN_5O_5$	13.31	12.99
Methoxy[a,b]	95– 98	$C_{18}H_{19}NO_3$	4.72	4.92	172–174	$C_{24}H_{23}N_5O_6$	14.67	14.63
Acetamido[b]	174–175	$C_{19}H_{20}N_2O_3$	8.64	8.32				

Solvent for recrystallization: [a] Benzene–ligroin (1:1); [b] 90–95% ethyl alcohol; [c] Diethyl cellosolve–water (2:1).

TABLE II

6-R-4-METHYLCARBOSTYRILS

R	M. p., °C.	Formula	% Nitrogen Calcd.	% Nitrogen Found
p-Chlorobenzyl[a]	238–240	$C_{17}H_{14}ClNO$	5.19	5.09
p-Bromobenzyl[a]	247–248	$C_{17}H_{14}BrNO$	4.46	4.48
p-Methoxybenzyl	188.5–190.5	$C_{18}H_{17}NO_2$	5.02	5.38
p-Acetamidobenzyl[b]	290–292	$C_{19}H_{18}N_2O_2$	9.15	8.90
p-Aminobenzyl[c]	241–243	$C_{17}H_{16}N_2O$	10.60	10.23

Solvent for recrystallization: [a] 95% ethyl alcohol–carbitol (2–5:1); [b] glacial acetic acid; [c] 95% ethyl alcohol.

and the corresponding substituted aniline. In the case of *p*-nitroaniline, it was necessary to use chloroform as a solvent to obtain a higher temperature. The yield of the recrystallized material was 85–93%. The crotonate from ethyl *p*-aminophenylacetate was a non-crystallizable oil which was converted to the 4-hydroxyquinaldine without purification.

TABLE III

METHYL β-(R-ANILINO)-CROTONATES

R	M. p., °C.	Formula	% Nitrogen Calcd.	% Nitrogen Found
4-(*p*-Chlorobenzyl)[a]	87–88	$C_{18}H_{18}ClNO_2$	4.44	4.51
4-(*p*-Bromobenzyl)[a]	101–102.5	$C_{18}H_{18}BrNO_2$	3.89	3.90
4-(*p*-Methoxybenzyl)[a]	71.5–73	$C_{19}H_{21}NO_3$	4.50	4.49
4-(*p*-Acetamidobenzyl)[b]	120–121	$C_{20}H_{22}N_2O_3$	8.30	8.46
2,5-Dimethoxy[c]	59–60	$C_{13}H_{17}NO_4$	5.58	5.73
p-Nitro[b]	164–165.5	$C_{11}H_{12}N_2O_4$	11.86	11.84
p-Carbethoxy[c]	71–73	$C_{14}H_{17}NO_4$	5.32	5.62

Solvent for recrystallization: [a] benzene–ligroin (1:20); [b] Benzene; [c] Ligroin (b. p. 70–80°).

Ethyl 4-Hydroxyquinaldine-6-acetate.—A mixture of 26.8 g. (0.15 mole) of ethyl *p*-aminophenylacetate, 20 g. (0.18 mole) of methyl acetoacetate and 1 drop of dilute hydrochloric acid in 50 ml. of methylene chloride was treated as in the case of methyl β-[4-(*p*-chlorobenzyl)-anilino]-crotonate but the intermediate crotonate could not be obtained as a solid. The yield of oil was 45 g. Thirty grams of the crude methyl β-(*p*-carbethoxymethyl-anilino)-crotonate was added to 180 g. of diphenyl ether at 245–250°. After the methyl alcohol distilled and the solution cooled, 100 ml. of low boiling ligroin was added, the solid removed by filtration, washed and dried. The yield of crude substance was 23.7 g. (96%), m. p. 179.5–182°. Recrystallized twice from an isopropyl alcohol–benzene (1:1) solution, 5 g. gave 3.2 g. of purified material, m. p. 182.5–184°.

The substituted 4-hydroxyquinaldines summarized in Table IV were prepared by ring closure of the corresponding β-arylaminocrotonates in boiling phenyl ether as described for the preparation of ethyl 4-hydroxyquinaldine-6-acetate, except in the case of 6-(*p*-aminobenzyl)-4-hydroxyquinaldine which was obtained from the *p*-acetamidobenzyl compound by acid hydrolysis followed by neutralization with dilute alkali.

TABLE IV

R-4-HYDROXYQUINALDINES

R	M. p., °C.	Formula	% Nitrogen Calcd.	% Nitrogen Found
6-(*p*-Chlorobenzyl)[a]	234–235	$C_{17}H_{14}ClNO$	5.19	4.84
6-(*p*-Bromobenzyl)[a]	252–253	$C_{17}H_{14}BrNO$	4.46	4.43
6-(*p*-Methoxybenzyl)[a]	218–219	$C_{18}H_{17}NO_2$	5.02	5.13
6-(*p*-Acetamidobenzyl)[a]	289–291	$C_{19}H_{18}N_2O_2$	9.16	9.15
6-(*p*-Aminobenzyl)[a]	225–227	$C_{17}H_{16}N_2O$	10.61	10.78
6-Carbethoxymethyl	182.5–184	$C_{14}H_{15}NO_3$	5.72	5.86
5,8-Dimethoxy[b]	210–211	$C_{12}H_{13}NO_3$	6.39	6.58
6-Nitro[c]	Above 330	$C_{10}H_8N_2O_3$	13.72	13.85
6-Carbethoxy[d]	255–256	$C_{13}H_{13}NO_3$	6.76	6.63

Solvent for recrystallization: [a] 95% ethyl alcohol; [b] Water; [c] Nitrobenzene; [d] *n*-Butyl alcohol.

Summary

The preparation of the 6-substituted *p*-chloro-, *p*-bromo-, *p*-amino- and *p*-methoxybenzyl-4-methylcarbostyrils as well as the corresponding 4-hydroxyquinaldine derivatives is described. The Knorr–Limpach method was used also in the synthesis of ethyl 4-hydroxyquinaldine-6-acetate, 5,8-dimethoxy-4-hydroxyquinaldine and 6-carbethoxy-4-hydroxyquinaldine.

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