Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.28; H, 10.93.

The 2,4-dinitrophenylhydrazone prepared in the usual manner from the product obtained by acid hydrolysis of 2-ethoxytetrahydropyrane melted at 109° and gave no depression in a mixed melting point determination with the 2,4-dinitrophenylhydrazone prepared from 5-hydroxypentanal.[5]

2,4-Pentadienal (VII).—To a solution of 40 ml. of 85% phosphoric acid in 200 ml. of water was added with stirring 40 g. of 2-ethoxy-Δ^3-dihydropyrane. Within a few minutes the solution became homogeneous. This solution was added dropwise to a solution of 50 ml. of 85% phosphoric acid in 200 ml. of water which was already undergoing steam distillation. Steam distillation was continued until the distillate no longer had the characteristic odor of pentadienal. The steam distillate was itself steam distilled to concentrate the aldehyde. After the addition of potassium chloride, the pentadienal was extracted with ether and dried over sodium sulfate. After removal of the ether under reduced pressure, the aldehyde was distilled; yield 14 g. (55%), b. p. 36–37° (20 mm.), $n^{25}D$ 1.5163.

Anal. Calcd. for C_5H_6O: C, 73.14; H, 7.37. Found: C, 72.99; H, 7.85.

Pentadienal Semicarbazone.—The semicarbazone of 2,4-pentadienal prepared in the usual manner was a white crystalline compound which was recrystallized from water. This substance decomposed progressively on heating to 260°.

Anal. Calcd. for $C_6H_9ON_3$: C, 51.77; H, 6.52. Found: C, 51.67, 51.65, 52.08; H, 6.21, 6.49, 6.67.

2,4-Pentadienal-2,4-dinitrophenylhydrazone.—2,4-Pentadienal was converted in the usual way almost quantitatively into a red 2,4-dinitrophenylhydrazone. The product was recrystallized from ethyl alcohol, m. p. 176–177°.

Anal. Calcd. for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84. Found: C, 50.11, 50.38; H, 3.81, 3.88.

(5) Woods and Sanders, THIS JOURNAL, **68**, 2111 (1946).

Summary

1. 2,3-Dibromotetrahydropyrane reacts with methyl and ethyl alcohol to form the corresponding 2-alkoxy-3-bromo-tetrahydropyrane.

2. 2-Alkoxy-Δ^3-dihydropyranes are formed by the reaction of 2-alkoxy-3-bromotetrahydropyrane with alcoholic potassium hydroxide or sodium alcoholate.

3. The preparation of 2,4-pentadienal is described. The semicarbazone and 2,4-dinitrophenylhydrazone of this compound are characterized.

COLLEGE PARK, MD. RECEIVED JUNE 11, 1946

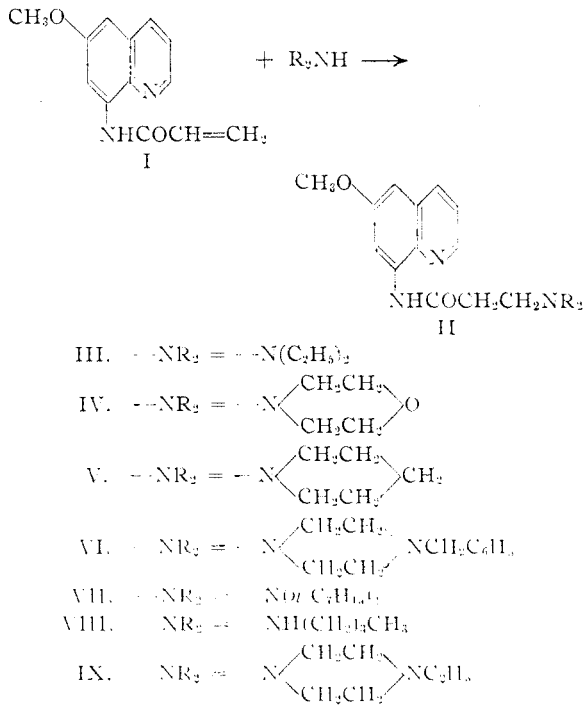
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Some 6-Methoxy-8-(β-aminopropionylamino)-quinolines

BY H. R. SNYDER AND HERBERT E. FREIER[1]

In the search for an antimalarial drug which might possess the desirable properties of plasmochin but have a lower toxicity, a number of amides of the type represented by formula II have been prepared.[2] The principal difference between the compounds prepared and plasmochin lies in the fact that in the former the aromatic amino group is joined to an acyl group rather than to an alkyl group; there are differences also in the details of structure of the side chains and in the distance between the two acyclic nitrogen atoms.

The new compounds were prepared by the addition of the appropriate amines to 6-methoxy-8-acrylaminoquinoline (I). The acrylamide (I) was obtained in 57% yield by the reaction of the aminoquinoline with acrylyl chloride (prepared from sodium acrylate and phosphorus oxychloride according to the procedure of Kohler[3]). The reaction of I with diethylamine was carried out in an excess of the aliphatic amine; the reactions of I with other amines were carried out in benzene solutions. It is possible that the reagents



and products are sufficiently basic to act as catalysts in these reactions; no other catalyst was employed.

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(2) The present work was substantially complete at the time of the announcement of other similar amides by Brice and Bowman in a paper presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society on April 10, 1946.

(3) Kohler, *Am. Chem. J.*, **42**, 380 (1909).

TABLE

1,4-ADDITION OF AMINES TO 6-METHOXY-8-ACRYLAMINOQUINOLINE (I)

Subst. I, g.	Amine, g.	Benzene, ml.	Time, hr.	Compound isolated	Recrystn. solvent	M. p., °C.	Yield, %	Analyses, % Carbon Found	Carbon Calcd.	Hydrogen Found	Hydrogen Calcd.
6	Diethylamine 10.5	0	1.5	III[a]	Abs. EtOH	198–202[a]	61[a]	54.50[a]	54.55[a]	6.98[a]	6.73[a]
12	Morpholine 4.5	90	2.5	IV	Methanol	126–128	69	64.71	64.74	6.83	6.71
10	Piperidine 3.8	100	2	V	Pet. ether (b. p. 85–110°)	105–107	80	69.19	68.98	7.27	7.40
12	N-Benzylpiperazine[b] 9.2	250	0.5	VI	Ethanol	132–134	85	71.35	71.26	7.11	6.98
2	Di-*n*-heptylamine 1.9	15	1.5	VII[d]	Methanol	126–127[d]	..	52.22[d]	52.05[d]	5.52[d]	5.49[d]
0.5	*n*-Butylamine 0.16	10	10	VIII[c]	Ethanol	157–159[c]	..	52.26[c]	52.07[c]	5.06[c]	4.94[c]
1.5	1-Ethyl-4-aminopiperidine 0.85	20	1	IX[d]	Nitromethane	237–239[d]	..	46.94[d]	47.11[d]	4.38[d]	4.22[d]

[a] Dihydrochloride. [b] Prepared by procedure of Baltzly, Buck, Lorz and Schön, THIS JOURNAL, **66**, 263 (1944). [c] Monopicrate. [d] Dipicrate.

Four of the new amides (III, IV, V and VI) were submitted for testing against *P. lophurae* in ducks; all were found inactive.[4]

Experimental

6-Methoxy-8-acrylaminoquinoline (I).—To a cold suspension of 35 g. of freshly distilled 6-methoxy-8-aminoquinoline in 300 ml. of 10% sodium hydroxide was added a solution of 19 g. of acrylyl chloride[3] in 75 ml. of dry chloroform. After the mixture had been shaken vigorously for a few minutes the solid dissolved. The mixture was shaken for an additional thirty minutes and then the chloroform solution was separated, washed with water, dried over potassium carbonate, and filtered. The chloroform was removed by distillation and after the residue had been cooled in an ice-bath a pink solid formed. The product, after one recrystallization from 50 ml. of 95% ethyl alcohol, weighed 25 g. (57%) and had a melting point of 111–113°. After further purification by recrystallization from ethyl alcohol the compound melted at 114–115°.

Anal. Calcd. for $C_{13}H_{12}O_2N_2$: C, 68.40; H, 5.30. Found: C, 68.58; H, 5.48.

Dihydrochloride of 6-Methoxy-8-(3-diethylaminopropionylamino)-quinoline (III).—A mixture of 6 g. of I and 10.5 g. of diethylamine was heated under reflux for one and one-half hours. The brown solution was treated with Darco, filtered and the excess diethylamine was removed by distillation. The residual brown oil weighed 7.5 g.

This material was dissolved in 140 ml. of absolute ethyl alcohol. A slow stream of dry hydrogen chloride gas was passed through the solution until an orange semi-solid mass formed (about twenty-five minutes). The mixture was cooled in an ice-bath and then filtered. The yellow crystals collected by filtration were dissolved in 75 ml. of absolute ethyl alcohol. The solution was treated with Darco, filtered and cooled in an ice-bath. The yellow solid which precipitated was recrystallized twice from 60-ml. portions of absolute ethyl alcohol. The pure dihydrochloride melting at 198–202° weighed 6 g. (61% over-all yield).

Anal. Calcd. for $C_{17}H_{25}O_2N_3Cl_2$: C, 54.55; H, 6.73. Found: C, 54.50; H, 6.98.

The monopicrate of III after recrystallization from methyl alcohol melted at 146–148°.

Anal. Calcd. for $C_{23}H_{28}O_9N_6$: C, 52.07; H, 4.94. Found: C, 52.34; H, 5.07.

6-Methoxy-8-(3-morpholinopropionylamino)-quinoline (IV).—A mixture of 12 g. of I, 4.5 g. of morpholine and 90 ml. of benzene was heated under reflux for two and one-half hours; after the mixture had been heated for a few minutes a solution resulted. The benzene was removed by distillation and the residual oil solidified after it had been cooled in an ice-bath. To this residue was added 90 ml. of petroleum ether (b. p. 30–60°) and the solid was collected on a Buchner funnel. This material after two recrystallizations from 75 ml. of methyl alcohol weighed 11.2 g. (69%). The white crystalline product melted at 126–128°.

Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71. Found: C, 64.71; H, 6.83.

The other compounds prepared by this procedure are shown in the table.

Summary

6-Methoxy-8-acrylaminoquinoline undergoes 1,4-addition of primary and secondary amines to form 6-methoxy-8-β-aminopropionylaminoquinolines. The products of this type which have been tested have little or no antimalarial activity.

(4) The tests were carried out by the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.

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