[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

8-Aminoquinolines with Allylamine Substituents[1]

BY CHARLES D. HURD AND REX J. SIMS

The synthesis of two plasmochin analogs is described in this paper, namely, 8-(6-allylaminohexylamino)-6-methoxyquinoline and 8-(6-diallylaminohexylamino)-6-methoxyquinoline, the important points of difference being the allylamino and diallylamino groups at the end of the side chain on position 8. Selection of the hexyl chain, rather than 1-methylpentyl, was merely because of greater availability of necessary intermediates.

In general, routine procedures were followed. 1,6-Dibromohexane was converted into 1-bromo-6-methoxyhexane by reaction with sodium methoxide. Reaction with allylamine or diallylamine yielded N-allyl-6-methoxyhexylamine or N,N-diallyl-6-methoxyhexylamine, respectively. These methoxy amines were cleaved at the ether functions by hydrobromic acid. The salts thus obtained, (N-(6-bromohexyl)-allylammonium bromide and N-(6-bromohexyl)-diallylammonium bromide), were converted to the desired quinoline derivatives by reaction with 6-methoxy-8-aminoquinoline following the general procedure of Rohrmann and Shonle.[2]

8-(6-Allylaminohexylamino)-6-methoxyquinoline was obtained as a yellowish oil, collected as distillate from a molecular still. It was purified further by conversion to its crystalline oxalic salt. This oxalate formed readily, but it is interesting to note that attempts to prepare a crystalline chloroplatinate were not successful.

8-(6-Diallylaminohexylamino)-6-methoxyquinoline also was obtained as a viscous oil, soluble in organic solvents and dilute acids. These two bases were submitted for pharmacological testing by Survey of Antimalarial Drugs as SN-15126 (monoallyl) and SN-15128 (diallyl).

Experimental

N-Allyl-6-methoxyhexylamine.—A mixture of 78 g. of 1-bromo-6-methoxyhexane and 50.4 g. of allylamine was refluxed eight hours, then poured into dilute hydrochloric acid. After ether extraction to remove unreacted bromide, alkali was added, and the amine was taken up in ether and dried over solid potassium hydroxide. Distillation yielded 50 g. (73%) at 90–98° (8 mm.) and the second, which was analyzed, at 106–110° (15 mm.).

Anal. (by M. Ledyard) Calcd. for $C_{10}H_{21}NO$: N, 8.14. Found: N, 7.95.

N,N-Diallyl-6-methoxyhexylamine.—After seventeen hours refluxing of 19.5 g. of 1-bromo-6-methoxyhexane and 21.4 g. of diallylamine, the mixture was processed as for the monoallyl analog. Fourteen grams (66% yield) was collected at 122–130° (16 mm.); redistilled, the main fraction boiled at 125–125.5° (16 mm.). For analysis, redistillation gave a middle fraction at 112–114° (11 mm.).

Anal. (by M. Ledyard) Calcd. for $C_{13}H_{25}NO$: N, 6.63. Found: N, 6.52.

N-(6-Bromohexyl)-allylammonium Bromide.—Twenty grams of N-allyl-6-methoxyhexylamine was refluxed four hours with 137 g. of 40% hydrobromic acid, then evaporated to dryness at 100°. The light brown crystals weighed 31 g. (88%). They were used without purification in the next step.

8-(6-Allylaminohexylamino)-6-methoxyquinoline.—This compound is new, but the general procedure of Rohrmann and Shonle[2] was followed.

The 31 g. of bromide salt (above) was refluxed two days with 16.4 g. of 6-methoxy-8-aminoquinoline and 60 ml. of absolute ethanol, during which a solid separated. The mixture was poured into 300 ml. of water, made alkaline with sodium hydroxide, cooled, the free base ether extracted, dried ($MgSO_4$), filtered, freed of solvent (100°, 20 mm.), and distilled in a molecular still. Three arbitrary fractions were taken, based largely on viscosity difference. The temperature of the air-bath surrounding the flask was noted. Pressure was kept at 10^{-5} to 10^{-6} mm.

TABLE I

Fraction	Color	Air bath, temp., °C.	G.
1	Light yellow	110–150	10.6
2	Light yellow	170–200	8.3
3	Dark red	200–220	7.6

Each of these fractions was analytically low in nitrogen by about 1%, but purification was readily achieved by conversion to the oxalate.

Oxalate.—Into a mixture of 6.64 g. of the third fraction in 50 ml. of alcohol was added 1.91 g. of oxalic acid in 50 ml. of water. These represent equimolar parts. Eight grams of bright yellow crystalline precipitate separated. It was recrystallized (decolorizing charcoal) thrice from alcohol, using 40 ml. each time. Three grams of light tan crystals was obtained, which melted with decomposition at 172.5–173.5°.

Anal. (by M. Ledyard) Calcd. for $C_{21}H_{29}N_3O_5$: N, 10.41. Found: N, 10.14.

N-(6-Bromohexyl)-diallylammonium Bromide.—Refluxing for six hours a mixture of 20 g. of N,N-diallyl-6-methoxyhexylamine and 190 g. of 40% hydrobromic acid gave rise to a solution which, on evaporation, yielded 31.5 g. (97.3%) of residue, a red oil. The latter was used as such in the next step.

8-(6-Diallylaminohexylamino)-6-methoxyquinoline.—The 31.5 g. of red oil was heated for forty-eight hours at reflux temperature with 15.5 g. of 6-methoxy-8-aminoquinoline in 60 ml. of dry ethanol. As with the monoallylamino analog a solid separated during this period. Details concerning the separation and purification were the same as for the monoallylamino run. Four distillations at 10^{-4} mm. yielded these fractions, which were orange, viscous oils, soluble in organic solvents and dilute acids.

TABLE II

Fraction	Air bath, temp., °C.	G.
1	Below 100	2.4
2	100–150	10.7
3	160–200	7.5

Anal. of fraction 3 (by W. Brandt). Calcd. for $C_{22}H_{31}N_3O$: N, 11.90. Found: N, 11.08, 11.16.

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Northwestern University.

(2) Rohrmann and Shonle, THIS JOURNAL, 66, 1642 (1944).

Summary

The syntheses of 8-(6-allylaminohexylamino)-6-methoxyquinoline and 8-(6-diallylaminohexylamino)-6-methoxyquinoline are reported.

N-Allyl-6-methoxyhexylamine, N,N-diallyl-6-methoxyhexylamine, N-(6-bromohexyl)-allylammonium bromide, and N-6-(bromohexyl)-diallylammonium bromide were prepared as intermediates in this work.

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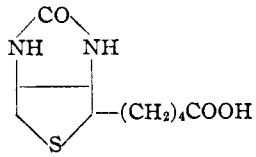
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Tetrahydrothiophene ("Thiophane") Derivatives

BY R. B. WOODWARD AND R. H. EASTMAN

The elucidation of the structure of biotin (I)[1] has stimulated interest during the past several years in the development of methods useful in the synthesis of tetrahydrothiophene ("thiophane") derivatives. The application of the Dieckmann reaction to compounds of the general structure (II) has received particular attention



I

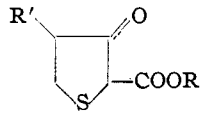
ROOCCHR′CH$_2$SCHR″COOR

II

IIa (R′ = R″ = H; R = CH$_3$)

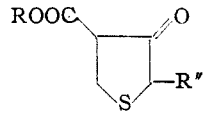
and in a specific case[2] (II, R = CH$_3$ *or* C$_2$H$_5$, R′ = —NHCOC$_6$H$_5$, R″ = H) constituted an important step in the brilliant series of reactions which culminated in the total synthesis of natural biotin[2,3] in this country, while another example[4] (II, R = C$_2$H$_5$, R′ = H, R″ = —(CH$_2$)$_4$OCH$_3$) played an equally important role in the total synthesis of *dl*-biotin abroad.[5]

In those cases in which R′ *or* R″ is not a hydrogen atom, cyclization can take place in one direction only, with the formation of (III)[2,6] or (IV),[4,7,8] respectively. On the other hand, *a priori* the cyclization of the unsubstituted ester (II, R′ = R″ = H) can take place in two ways, with the formation of the cyclic β-keto esters (V) and (VI). Karrer and Schmid,[9] Buchman and Cohen,[10]



IIII

V (R′ = H)



IV

VI (R″ = H)

Avison, Bergel, Cohen, and Haworth,[8] and the present authors[11] have studied the cyclization in this simplest case. The Swiss workers effected internal condensation of (II, R = C$_2$H$_5$, R′ = R″ = H) by means of sodium amide in absolute ether, or sodium ethoxide in toluene, in each case at 40–50°. They considered the product to be mainly 4-carbethoxy-3-ketotetrahydrothiophene (VI, R = C$_2$H$_5$), since on methylation, hydrolysis, and decarboxylation, there was obtained 4-methyl-3-ketotetrahydrothiophene, different from the isomeric 2-methyl-3-ketotetrahydrothiophene synthesized by an unambiguous route. On the other hand, the isolation from the cyclized ester of two phenylhydrazones, m.p. 142 and 167°, of which the lower-melting isomer predominated, led to the conclusion that the material was a mixture.[7a] Buchman and Cohen cyclized the di-ester (II, R = C$_2$H$_5$, R′ = R″ = H) by means of sodium metal in benzene suspension. The product was described as giving a phenylhydrazone, m.p. 100°, and a semicarbazone, m.p. 176°, and was assigned the structure (VI) on the basis of analogies drawn from work on the Dieckmann condensation of nitrogen-containing esters. Avison, Bergel, Cohen and Haworth, likewise using powdered sodium in benzene, brought forward evidence in support of the view that the major product of the cyclization of esters (II, R′ = R″ = H) was always the 2-carbalkoxy derivative (V).

In this communication it is shown that the direction of cyclization may be controlled by the choice of reaction conditions. After some preliminary experiments with the ethyl ester (II, R = C$_2$H$_5$, R′ = R″ = H), we confined our studies to the methyl ester (IIa), which was obtained smoothly in excellent yield by the piperidine-catalyzed addition of methyl thioglycolate to methyl acrylate.[12] When the ester (IIa) was cyclized by

(1) du Vigneaud, *Science*, **96**, 455 (1942); Hofmann, Kilmer, Melville, du Vigneaud and Darby, *J. Biol. Chem.*, **145**, 503 (1942); du Vigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy and Harris, *ibid.*, **146**, 475 (1942); Melville, Moyer, Hofmann and du Vigneaud, *ibid.*, **146**, 487 (1942); Hofmann, *Advances in Enzymol.*, **3**, 289 (1943).

(2) Harris, Easton, Heyl, Wilson and Folkers, THIS JOURNAL, **66**, 1757 (1944).

(3) Harris, Wolf, Mozingo and Folkers, *Science*, **97**, 447 (1943); Harris, Wolf, Mozingo, Anderson, Arth, Easton, Heyl, Wilson and Folkers, THIS JOURNAL, **66**, 1756 (1944); Harris, Wolf, Mozingo, Arth, Anderson, Easton and Folkers, *ibid.*, **67**, 2096 (1945); Wolf, Mozingo, Harris, Anderson and Folkers, *ibid.*, **67**, 2100 (1945).

(4) Schmid, *Helv. chim. acta*, **27**, 127 (1944).

(5) Grüssner, Bourquin and Schnider, *ibid.*, **28**, 517 (1945).

(6) Karrer and Schmid, *ibid.*, **27**, 1280 (1944).

(7) (a) Karrer and Schmid, *ibid.*, **27**, 124 (1944); Karrer and Kehrer, *ibid.*, **27**, 142 (1944); Karrer, Keller and Usteri, *ibid.*, **27**, 237 (1944); (b) Cheney and Piening, THIS JOURNAL, **66**, 1040 (1944).

(8) Avison, Bergel, Cohen and Haworth, *Nature*, **154**, 459 (1944).

(9) Karrer and Schmid, *Helv. Chim. Acta*, **27**, 116 (1944).

(10) Buchman and Cohen, THIS JOURNAL, **66**, 247 (1944).

(11) Our results formed the subject of a preliminary communication, THIS JOURNAL, **66**, 849 (1944).

(12) Buchman and Cohen (ref. 10) independently devised a similar method for the preparation of the corresponding ethyl ester.