considerable decomposition, there was obtained a viscous distillate, b. p. 260 (1 mm.), which partially solidified. Crystallization from methanol gave 4 g. of tribenzoylbenzene, m. p. 120–121°. A mixture of this with tribenzoylbenzene prepared from the sodium salt of α-formylacetophenone according to the method of Claisen[11] melted at 120.5–122°. *Anal.* Calcd. for $C_{27}H_{18}O_3$: C, 83.05; H, 4.65. Found: C, 83.36; H, 5.00.

The trioxime melted at 210–211°.

1-Methoxy-2,4-dibenzoyl-1,3-pentadiene.—To a stirred suspension of 45 g. of the orange solid in 100 ml. of methanol, maintained at 10°, there was added 72 g. (0.5 mole) of methyl iodide. The mixture was allowed to gradually warm to room temperature and stand overnight. It was diluted with 500 ml. of ether and the benzyltrimethylammonium iodide allowed to settle. The liquid phase was separated by decantation, the quaternary ammonium iodide transferred to a filter with the aid of ether and washed with additional ether. After drying at 60° there was obtained 34 g. of the quaternary ammonium iodide. *Anal.* Calcd. for $C_{10}H_{16}NI$: N, 5.05. Found: N, 4.72.

The liquid phase and ether washings were combined and distilled under reduced pressure. After removing ether, there was obtained a yellow semisolid material which was crystallized from methanol, m. p. 103–106°; yield 6 g. After successive recrystallizations from petroleum ether–methanol it weighed 3.5 g., m. p. 108–109°, and corresponded in composition to 1-methoxy-2,4-dibenzoyl-1,3-pentadiene.

Anal. Calcd. for $C_{20}H_{18}O_3$: molecular weight, 306.4; C, 78.39; H, 5.91; $-OCH_3$, 10.13; Br No. (as cg. Br/g. sample) 52.1. Found: molecular weight (ebulliometric in acetone) 298; C, 78.49; H, 5.96; $-OCH_3$, 9.39; Br No. (as cg. Br/g. sample) 49.5.

(11) Claisen, *Ann.*, **281**, 307 (1894).

Summary

1. Phenylacetylene condenses with methyl benzoate in the presence of benzyltrimethylammonium methoxide to give β-methoxychalcone (II) and 1,3-diphenyl-3,3-dimethoxy-1-propanone (III).

2. Acetylene and methyl benzoate in the presence of this base yields a benzyltrimethylammonium complex of the reaction products from which tribenzoylbenzene is obtained.

3. A mechanism is postulated for the formation of these products.

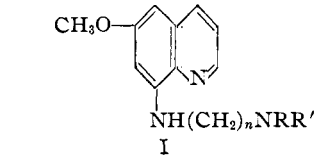
PHILADELPHIA, PA. RECEIVED JANUARY 11, 1949

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

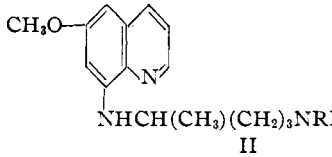
Some N¹-(6-Methoxy-8-quinolylaminoalkyl)-guanidines[1]

BY NATHAN L. DRAKE AND JOHN A. GARMAN[2]

Pentaquine (I, R = isopropyl, R′ = H, n = 5) and isopentaquine (II, R = isopropyl, R′ = H) are two 8-aminoquinoline drugs which combine curative action against vivax malaria with sufficiently low toxicity to permit their use without extreme precautions. Pamaquine (II, R = R′ = ethyl), is considerably more toxic than pentaquine or isopentaquine, and SN-12,904 (I, R = R′ = ethyl, n = 5) has a much higher toxicity than



I



II

Pentaquine. It may be concluded from this and other similar evidence that the character of the side chain in an 8-aminoquinoline is one of the units of structure whose modification may result in a decided change in toxicity.

It was, therefore, considered pertinent to investigate a series of drugs in which the terminal amino group of Pentaquine was replaced by an N¹-guanidine moiety. To this end a group of compounds of formula I, in which R is H, R′ is —NHC(=NH)NH₂, and n is 2, 3, 4 or 5 was prepared.

These new compounds are notable for their low toxicity and for the fact that the neuronal toxicity characteristic of Plasmocid[3] is absent from those homologs in which n is 2 or 3. Indeed, the toxic symptoms of these compounds[4] are referable to effects on the gastrointestinal tract and resemble those of Paludrine rather than Pamaquine.

After considerable exploratory work, the reaction of S-methylisothiourea sulfate with the appropriate 8-(amino-alkylamino)-6-methoxyquinoline in aqueous propanol was chosen for the preparation of the desired compounds. Purification was effected by precipitation of a carbonate of the drug from a butanol–ether solution by addition of solid carbon dioxide. Carbonates so prepared showed evidence of decomposition on prolonged storage, and inasmuch as their recrystallization proved impossible, they were converted to hydrochlorides by titration with dilute alcoholic hydrogen chloride. The monohydrochlorides of these bases are nearly colorless; the dihydrochlorides are highly colored. These

(1) Taken in part from a thesis submitted to the Graduate School of the University of Maryland by John A. Garman in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) du Pont Predoctoral Fellow, 1946-1947.

(3) "Survey of Antimalarial Drugs 1941–1945," F. Y. Wiselogle, editor, J. W. Edwards, Ann Arbor, Michigan, 1946: (a) Vol. I, p. 114; (b) Vol. I, p. 458.

(4) Personal communication from L. H. Schmidt, Christ Hospital, Cincinnati.

facts can be utilized conveniently in converting the carbonates to hydrochlorides.

The hydrochlorides prepared showed a pronounced tendency to form hydrates from which the last traces of water were very difficult to remove. The dinitrates, however, showed no evidence of hydration and crystallized well from aqueous alcohol. The addition of a concentrated aqueous solution of ammonium nitrate to an aqueous solution of one of the dihydrochlorides caused crystallization of the corresponding dinitrate. Two treatments with ammonium nitrate solution usually sufficed to yield a salt which was free from chloride ion.

Preparation of the several 8-(aminoalkylamino)-6-methoxyquinolines reported followed procedures previously described.[5] It was found that isolation of a crystalline salt following the hydrazinolysis of an 8-(phthalimidoalkylamino)-6-methoxyquinoline was more advantageous than the isolation and distillation of the base itself. Those bases (formula I) in which n is 4 or 5 and R and R′ are hydrogen showed evidence of rather extensive decomposition during distillation.

The method of preparing bromoalkylphthalimides described in the experimental part represents a considerable improvement over previously described methods.[5,6]

Some salts, not previously reported, of two of the 8-(aminoalkylamino)-6-methoxyquinolines employed as intermediates are described.

Experimental

N¹-(2-(6-Methoxy-8-quinolylamino)-ethyl)-guanidine Dinitrate.—A mixture of 15.25 g. (0.07 mole) of 8-(2-aminoethylamino)-6-methoxyquinoline, dissolved in 50 ml. of 1-propanol and 10 ml. of water, and 10.45 g. (0.075 mole) of S-methylisothiourea sulfate was heated under reflux for eighteen hours. The resultant solution was concentrated slightly and then diluted with acetone whereupon the product separated as a plastic mass which, after treatment with several small portions of acetone and then with one of alcohol, finally crystallized. More of the product was thrown out of the ethanol by cautious addition of acetone, and the resultant solid was removed by filtration and dried. The crude dry substance weighed 19 g. A 17-g. portion of this material was suspended in water, treated with an excess of concentrated sodium hydroxide solution, and the liberated organic base was extracted by means of one 60-ml. portion of 1-butanol. The butanol solution was washed with several small portions of water, filtered, and diluted with ether to a volume of about 600 ml. Small pieces of Dry Ice were then added to the ether solution until no more solid separated. The precipitated carbonate, after removal by filtration, washing with ether and drying, weighed 10 g.

A 1-g. portion of the carbonate was dissolved in about 50 ml. of alcohol and titrated with dilute alcoholic hydrogen chloride. The first equivalent of acid caused almost no change in the color of the solution, but a sharp color change occurred when the second equivalent of acid began to be added. On the basis of the above titration, the amount of acid required to form the dihydrochloride of the remainder of the carbonate was calculated, and added to a solution of the carbonate in alcohol. The resulting solution was warmed and diluted with acetone until it was turbid; dihydrochloride (10 g.) separated from the cooled solution.

Conversion of the hydrochloride to the nitrate was accomplished by dissolving the former in 15 ml. of water, heating the solution to boiling, and adding 20 ml. of 30% aqueous ammonium nitrate solution; dinitrate separated from the cooled solution. This product was again dissolved in water and treated with ammonium nitrate solution; the resulting nitrate showed no test for chloride ion when treated in dilute nitric acid with aqueous silver nitrate.

To further purify the salt it was dissolved in 25 ml. of water and diluted with 500 ml. of absolute alcohol. This solution was concentrated to about 200 ml. and cooled. The crystals were removed by filtration and recrystallized three times from the same solvent. The purified product (7 g., 29%) sintered at 191° and melted at 193–193.5°. *Anal.* Calcd. for $C_{13}H_{17}ON_5 \cdot 2HNO_3$: C, 40.51; H, 4.96. Found: C, 40.84, 40.55; H, 5.16, 5.45.

Initial isolation of the crude product as carbonate appears to be necessary to the success of the preparation. It has been found, however, that preparation of the nitrate *via* the hydrochloride is not necessary. Direct titration of the carbonate with dilute nitric acid serves to almost double the yield.

N¹-(3-(6-Methoxy-8-quinolylamino)-propyl)-guanidine Dinitrate.—An 18% yield of this salt was obtained by the method described above. The substance sinters at 219° and melts at 221.5–223°. *Anal.* Calcd. for $C_{14}H_{19}ON_5 \cdot 2HNO_3$; C, 42.10; H, 5.30. Found: C, 42.07, 42.37; H, 5.40, 5.42.

N¹-(4-(6-Methoxy-8-quinolylamino)-butyl)-guanidine Dinitrate.—A 35% yield of this dinitrate was obtained. The product sinters at 173° and melts at 173.5–174.5°. *Anal.* Calcd. for $C_{15}H_{21}ON_5 \cdot 2HNO_3$: C, 43.57; H, 5.60. Found: C, 43.49, 43.87; H, 5.56, 5.80.

N¹-5-(6-Methoxy-8-quinolylamino)-amyl)-guanidine Dinitrate.—The yield obtained in the preparation of this compound amounted to 23% of that theoretically possible; the salt sinters at 180° and melts at 182–183°. *Anal.* Calcd. for $C_{16}H_{23}ON_5 \cdot 2HNO_3$: C, 44.96; H, 5.90. Found: C, 44.97, 45.16; H, 6.06, 6.00.

8-(2-Aminoethylamino)-6-methoxyquinoline Monohydrochloride.—This monohydrochloride was prepared from the corresponding dihydrochloride by dissolving the latter in a small amount of water, adding saturated sodium acetate solution until the yellow color was discharged, and then warming the solution and adding sodium chloride. This operation was repeated twice, and the product so obtained was crystallized from absolute alcohol and ether to a constant melting range. The substance sinters at 206° and melts at 207–212°. *Anal.* Calcd. for $C_{12}H_{15}ON_3 \cdot HCl$: Cl, 13.98. Found: Cl, 14.03, 14.08.

8-(2-Aminoethylamino)-6-methoxyquinoline Monopicrate.—This picrate, prepared in the usual manner by adding an alcoholic solution of picric acid to an alcoholic solution of the base, crystallized in reddish-purple needles; after recrystallization to constant melting point, the compound sintered at 205° and melted at 206–207°. *Anal.* Calcd. for $C_{18}H_{18}O_8N_6$: C, 48.43; H, 4.06. Found: C, 48.31, 48.35; H, 3.93, 3.96.

8-(4-Aminobutylamino)-6-methoxyquinoline Dipicrate.—Prepared as above, this picrate crystallized in the form of orange-yellow needles; it sintered at 180° and melted at 181–182.5°. *Anal.* Calcd. for $C_{26}H_{25}O_{15}N_9$: C, 44.38; H, 3.58. Found: C, 44.37, 44.15; H, 3.60, 3.60.

N-(2-Bromoethyl)-phthalimide.—Potassium phthalimide (92.6 g., 0.5 mole) was added in four equal portions over a 4-hr. period to a boiling solution of 187.9 g. (1.0 mole) of ethylene dibromide in 500 ml. of acetone. The resulting mixture was boiled under reflux for twenty-four hours, cooled to room temperature, and filtered to remove potassium bromide. After the bulk of the acetone had been removed by distillation, the residue was distilled under diminished pressure. The fraction which distilled at 124–126° (0.1 mm.) was recrystallized from its own

(5) Baldwin, *J. Chem. Soc.*, 2959 (1929); Beer, *J. Gen. Chem. (U. S. S. R.)*, **9**, 2158 (1939); *C. A.*, **34**, 4148 (1940); Von, Kissinger and Carmack, THIS JOURNAL, **68**, 1563 (1946); Mosher, *ibid.*, **68**, 1565 (1946); Quin and Robinson, *J. Chem. Soc.*, 555 (1943).

(6) Salzberg and Supniewski, "Organic Syntheses," Coll. Vol. I, 2nd Edition, p. 119; Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

volume of ethanol. This once-recrystallized substance melted at 75–80° and weighed 114 g. (90%). A second recrystallization from ethanol (recovery almost quantitative) yielded a product which, after drying at 56° for twelve hours under diminished pressure, had a melting point of 79–81°.

The same method has been used to prepare the corresponding 4-bromobutyl- and 5-bromoamylphthalimides. Yields obtained were above 70% of those calculated.

Discussion

The toxicity[4] of these compounds in rhesus monkeys is considerably less than that of Pamaquine. N^1-(5-(6-Methoxy-8-quinolylamino)-amyl)-guanidine nitrate was the only one of the group which was supplied in sufficient quantity for extensive study. This drug is about one-sixteenth (or slightly less) as toxic as Pamaquine and is interesting in that its toxic symptoms resemble those of Paludrine rather than those of Pamaquine or Plasmocid. Toxic symptoms included marked salivation, generalized weakness, and marked loss in weight. There was no effect on the numbers of formed elements in the peripheral blood, and no evidence of methemoglobin formation.[4]

The remaining three substances showed not the slightest evidence of toxicity at the dosage levels used (up to and including 48 mg./kg. daily dose) and are certainly less than one-eighth as toxic as Pamaquine. Lack of material prevented a more complete evaluation of toxicity. It is noteworthy that neuronal toxicity[3a] was *not* observed in either of those substances in which it might have been expected, *viz.*, the quinolylaminoethyl- and propylguanidines.

The last three compounds are inactive in the A-1 test against *Pl. gallinaceum* in the chick[3b] at the maximum tolerated dose.[7]

Tested against *Pl. cynomolgi* in the rhesus monkey, the quinolylaminoamylguanidine derivative did not prevent relapse, and would, therefore, not be expected to be a curative drug in man when administered with quinine in cases of vivax malaria. When administered to man at a dosage level of 240 mg./day for fourteen days both with and without 1.65 g./day of quinine for the same period, DR 15,526, the drug mentioned directly above, did not prevent relapse in cases of sporozoite-induced Chesson vivax malaria.[8]

Summary

1. Four N^1-quinolylaminoalkylguanidines have been described.

2. An improved method of preparing bromoalkylphthalimides has been described.

3. Several new salts of certain 8-(aminoalkylamino)-6-methoxyquinolines have been described.

4. The toxicity of the guanidines described and their effectiveness as antimalarials have been discussed.

(7) We are indebted to the Division of Tropical Diseases of the U. S. Public Health Service, National Institute of Health, for this information.

(8) These data are taken from N. I. H. Malaria Report No. 83 dated Sept. 1, 1948, and represent work done at Stateville Penitentiary by the staff of the Malarial Research Unit, Department of Medicine, University of Chicago, under the direction of Alf S. Alving and Lowell T. Coggeshall.

COLLEGE PARK, MARYLAND RECEIVED JANUARY 24, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Preparation and Properties of Aliphatic Esters of Erythrol

BY WILLET F. WHITMORE AND IRVING J. KREMS[1,2]

The recent appearance of butadiene monoxide in commercial quantities[3] has made available a practical source of the diesters of vinylethylene glycol, erythrol. However, since only the diacetate[4] had been reported, it proved of interest to prepare most of the lower and some of the higher aliphatic diesters and study certain of their properties.

The diacetate, dipropionate and dibutyrate were obtained in 61–76% yield by the action of

$$CH_2{=}CH\underset{\diagdown\,O\,\diagup}{CH}CH_2 + (RCO)_2O \xrightarrow{Fe_2Cl_6} CH_2{=}CHCH(OCOR)CH_2OCOR$$

(1) Abstracted from a dissertation by Irving J. Krems submitted to the Graduate Faculty of the Polytechnic Institute of Brooklyn, June 1947, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Colgate-Palmolive-Peet Co., Jersey City, N. J.

(3) Columbia Chemical Division, Pittsburgh Plate Glass Co.

(4) Henninger, *Ann. chim. phys.*, [6] **7**, 214 (1886).

the appropriate acid anhydride on butadiene monoxide in the presence of anhydrous iron(III) chloride catalyst.

Since the higher anhydrides were not readily available a more convenient general synthetic procedure was sought. The simplest appeared to be the reaction of 1 mole of oxide with at least two of the acid in the presence of a catalyst such as anhydrous iron(III) chloride to effect conversion first to the hydroxy ester, which could then be esterified to the desired diester by the excess acid present. This was tried for the preparation of the dicaprylate, but the only fair yield (40%) led to further revision. Thus, in the case of the dipalmitate only 1 mole of the acid was treated with 1 mole of the oxide to primarily form the hydroxy ester. This was then treated with an equivalent quantity of palmitoyl chloride in pyridine to effect conversion to the diester. The poor yield (22%) of pure product may be attributed to the consumption of oxide by side proc-