in a reasonable length of time. These condensation products are also fairly hard, transparent masses, which on heating soften between 70–80° and form mobile liquids in the neighborhood of 90°.

Glyoxal Semiacetate 2,4-Dinitrophenylhydrazone.—To a lukewarm and clear solution of 2.34 g. of 2,4-dinitrophenylhydrazine in 72 ml. of concentrated acetic acid were added 1.8 g. of freshly prepared semiacetate. After standing for ten minutes at room temperature 150 ml. of distilled water were added in small portions, the hydrazone sucked off, washed with water and dried *in vacuo* over sodium hydroxide. Yield 2.75 g. (72%) of already analytically pure glyoxal semiacetate 2,4-dinitrophenylhydrazone: m. p. 143–144°.

Anal. Calcd. for $C_{12}H_{12}O_8N_4$ (340): N, 16.48; CH_3CO-, 25.3. Found: N, 16.33, 16.38; CH_3CO-, 25.3, 25.6, 25.3.

At room temperature the hydrazone is readily soluble in benzene, dioxane and chloroform, slightly soluble in methanol, ethanol and ether, and insoluble in petroleum ether and water.

Glyoxal Semiacetate Dimedone Compound.—To a solution of 6.3 g. of dimedone in 75 ml. of concentrated acetic acid was added 3.6 g. of freshly prepared glyoxal semiacetate and the mixture was set aside at room temperature. After twenty-four hours the solution was diluted with 400 ml. of distilled water, the dimedone compound sucked off, washed with water and dried *in vacuo* over sodium hydroxide. The crude product, which weighed 2.3 g. (24.2% yield) and melted at 168–169°, was dissolved in 25 ml. of acetone and reprecipitated by the addition of 75 ml. of water; yield 2.1 g. of fairly pure glyoxal semiacetate dimedone compound, m. p. 169.5–170°.

Anal. Calcd. for $C_{22}H_{30}O_8$ (422.2): C, 62.52; H, 7.10; CH_3CO-, 20.36. Found: C, 62.12; H, 7.20; CH_3CO-, 19.80, 19.75.

Glyoxal Tetraacetate from Glyoxal Semiacetate (III → I).—To a mixture of 0.58 g. of freshly prepared glyoxal semiacetate and 0.40 g. of acetic anhydride was added a small drop of concentrated sulfuric acid. The mixture became immediately very warm and crystals formed. After the reaction had subsided, the almost solid product was drowned in ice water, the crystals collected at the pump, washed with water and dried *in vacuo* over sodium hydroxide. The yield of fairly pure glyoxal tetraacetate (m. p. 96–100°) was 0.78 g. or 82.2%. It was obtained in analytically pure form by recrystallization from ethyl acetate, m. p. 103–104°. A mixed melting point with an authentic sample of glyoxal tetraacetate showed no depression.

Acknowledgment.—The authors wish to express their sincerest thanks to Dr. R. N. Jones, for his investigation of the ultraviolet absorption spectrum of the glyoxal semiacetate.

Summary

The pyrolysis of pure glyoxal tetraacetate in the temperature range of 245 to 265° (normal pressure) yields two main reaction products, namely, glyoxal semiacetate and acetic anhydride. The glyoxal derivative has been isolated in a yield of 55%.

An improved method for the preparation of glyoxal tetraacetate is described.

TORONTO, CANADA RECEIVED FEBRUARY 19, 1947

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, COLUMBIA UNIVERSITY AND THE UNIVERSITY OF NOTRE DAME]

Some Derivatives of 6-Methoxy-8-aminolepidine[1,2]

BY KENNETH N. CAMPBELL, ROBERT C. ELDERFIELD, WALTER J. GENSLER, ARMIGER H. SOMMERS, CHESTER B. KREMER, S. MORRIS KUPCHAN, JOHN F. TINKER, JANE A. DRESSNER, B. NOEL ROMANEK AND BARBARA K. CAMPBELL

In the latter part of the antimalarial program carried out under the Committee on Medical Research, it was found that 8-(6′-diethylaminohexylamino)-6-methoxylepidine (SN-14,011)[3] had an extremely high antimalarial activity in avian tests; the introduction of the 4-methyl group had increased the quinine equivalent by about tenfold when tested against lophurae malaria in the duck. In view of this remarkable effect of the 4-methyl group, it became desirable to synthesize other 8-aminolepidines for testing as antimalarials. Several such compounds have been prepared at Columbia University and the University of Notre Dame, and are reported jointly in this paper.

In general, the synthesis followed the one described earlier[4] but certain modifications were made which improved the yields. In particular, it was found that 6-methoxy-8-nitrolepidine could be reduced to the amino compound more readily by iron and acetic acid than by catalytic hydrogenation. Reduction by stannous chloride in hydrochloric acid led to a product contaminated by a chloro compound (presumably the 5-chloro derivative); this is in agreement with the results obtained by others[5] in the reduction of 8-nitroquinolines by stannous chloride.

Experimental[6]

4-Methyl-6-methoxy-8-nitroquinoline.—The reaction was carried out as described previously[4] using either 1,3,3-trimethoxybutane or methyl vinyl ketone (du Pont 80–85% azeotrope), but the reaction mixture was worked

(1) This work was carried out on contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Notre Dame and Coumbia University.

(2) A part of this material was presented before the Medicinal Chemistry Division of the American Chemical Society, Chicago, September, 1946.

(3) The Survey Number of a drug identifies it in the files of the Antimalarial Survey Office; the antimalarial activities of these drugs are tabulated in a monograph, "Antimalarial Drugs, 1941–1945," Edwards Brothers, Ann Arbor, Michigan, 1946.

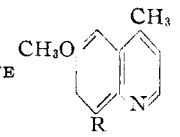
(4) Campbell, Sommers, Kerwin and Campbell, THIS JOURNAL, **68**, 1556 (1946).

(5) Dikshoorn, *Rec. trav. chim.*, **48**, 147 (1929); Elderfield, *et al.*, THIS JOURNAL, **68**, 1589 (1946).

(6) The microanalyses were carried out by Miss Lois May, Columbia University, and by Mr. Charles Beazley, Microtech. Laboratory, Skokie, Illinois.

TABLE I

DERIVATIVES OF 6-METHOXY-8-AMINOLEPIDINE



Drug numbers[f] SN	R	Method	Yield, %	B. p. base, °C.	P (mm.)	M. p. of di-HCl, °C., dec.	Analysis of di-HCl[a] Calcd. C	Calcd. H	Found C	Found H	Homogeneity, %	Antimalarial activity x quinine	Test[g]
15312	$NH(CH_2)_2N(C_2H_5)_2$	B	32	170–173	0.1	217–220	56.7	7.6	56.5	7.5	95 ± 3	50	G-4
15311	$NH(CH_2)_3NHCH(CH_3)_2$	B	30	179–183	.3	205–207[c]	56.7	7.6	57.0	7.9	97 ± 2	200	G-4[h]
15342	$NH(CH_2)_3N(C_2H_5)_2$	A	30	182–183	.1	228–230	57.7	7.8	57.8	7.8	94 ± 2	80	G-5
15313	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	B	12	195–200	.6	192–195	59.7	8.3	59.6	8.1	91 ± 3	200	G-5
15310	$NHCH(CH_3)(CH_2)_3NHCH_2CH_2CH_3$	B	18	185–190	.4	197–200	58.8	8.1	58.8	8.0	95 ± 3	750	G-4
15306	$NHCH(CH_3)(CH_2)_3NHCH(CH_3)_2$	B	22	185–190	.4	125–130	58.8	8.1	58.9	8.0	97 ± 2	800	G-4
15302	$NH(CH_2)_3NHCH(CH_3)_2$	B	44	198–202	.4	200–203	58.8	8.1	58.9	8.0	95 ± 2	256	D-1
15307	$NHCH(CH_3)(CH_2)_4N(C_2H_5)_2$	B	32	200–205	.5	139–142	60.6	8.5	60.6	8.6	95 ± 3	64	D-1
15308	$NHCH(CH_3)(CH_2)_4NHCH(CH_3)_2$	B	26	190–195	.5	[b]	59.7	8.3	59.5	8.2	98 ± 2	400	G-4[i]
15340	$NH(CH_2)_6NHC_2H_5$	A	30	185–190	.2	198–200	57.4	8.1[c]	57.4	7.9	....	200	G-5
15341	$NH(CH_2)_6NHCH(CH_3)_2$	A	25	195–200	.5	145–147	56.8	8.4[d]	57.1	7.9	....	150	G-5
15343	$NH(CH_2)_6NHCH(CH_3)CH_2CH_3$	A	30	195–200	.3	160–162	59.3	8.5[c]	59.0	8.7	95 ± 2	150	G-5

[a] For analysis the salts were usually dried at 78° *in vacuo* over anhydrous calcium sulfate. [b] Melted partially at 110°, resolidified and then melted at 201–203°. [c] Calculated for the hemi-hydrate. [d] Calculated for the monohydrate. [e] M. p. of free base 70–72°. [f] These survey numbers were assigned by the National Institute of Health after completion of the Survey Monograph and do not appear in the Monograph. [g] The tests are the standardized ones used by the Survey of Antimalarial Drugs.[3] [h] SN-15311 gave Q 100 in test G-5. [i] SN-15308 gave Q 200 in test G-5.

up differently. The mixture from a one-mole run was poured into one liter of water, filtered and the filtrate was diluted successively to three and six liters, filtering after each dilution. The precipitates (mostly tars) were discarded. The final filtrate was made basic with ammonium hydroxide and the reddish precipitate was collected and dried; the yield of crude product melting at 158–160° was about 168 g. This material was dissolved in 2 to 2.5 liters of 10% hydrochloric acid and the solution was heated on the steam-bath for fifteen minutes with Norit, and then filtered. The cooled solution was neutralized with ammonium hydroxide, and the dried precipitate was recrystallized from 2 to 2.5 liters of ethyl acetate, using Norit. The mother-liquors from the first crop were concentrated to 500 ml. to give a second crop. The total yield of material melting at 169–171° or higher was 130 g. (55–60%).

4-Methyl-6-methoxy-8-aminoquinoline.—In large-scale runs the catalytic hydrogenation of the nitro compound[4] did not always proceed satisfactorily, as poisoning of the catalyst occurred. Better results were obtained with iron and acetic acid, as follows: A 3-liter, 3-necked flask, fitted with an efficient reflux condenser and a Hershberg stirrer, was charged with 218 g. (1 mole) of 4-methyl-6-methoxy-8-nitroquinoline, 220 g. of degreased 40-mesh iron filings (Eastman Kodak Co. material works very well), 800 ml. of water, 25 ml. of glacial acetic acid and 25 ml. of dibutyl ether. The mixture was heated on a steam-bath for 15–18 hours, cooled and filtered. The residue was boiled with three 600-ml. portions of dioxane, and the combined dioxane filtrates were evaporated to dryness. The solid residue was distilled from a flask with a wide side-arm, to yield 169–179 g. of product (90–95%) boiling at 150–154° 0.3 mm., m. p. 87–89°.

Reduction of the nitrolepidine with stannous chloride and hydrochloric acid gave a product which contained chlorine, and which showed 11–24% inhomogeneity by the Craig technique.[7] In all probability, chlorination occurred in the 5-position, since reduction of other 8-nitroquinolines with stannous chloride leads to 5-chloro derivatives.[5]

Preparation of Side-chains.—2-Diethylaminoethyl chloride and 5-*i*-propylaminopentyl chloride were obtained from Sharples Chemicals, Inc., and were recrystallized before use. 3-*i*-Propylaminopropyl chloride, 5-diethylamino-2-bromopentane, 5-*n*-propylamino-2-bromopentane and 5-*i*-propylamino-2-bromopentane were prepared by the methods of Elderfield and co-workers.[8] 6-Diethylamino- and 6-*i*-propylamino-2-bromohexane were also prepared according to Elderfield and co-workers.[9] 6-Ethylamino-, 6-*i*-propylamino-, and 6-*s*-butylamino-1-bromohexanes were prepared as described by Campbell and co-workers.[4]

Attachment of Side-chains.—Two general procedures were used. Procedure A is essentially that of Rohrmann and Shonle[10] and procedure B is essentially that of Elderfield and co-workers.[11]

In either case, the crude reaction mixture was poured into an excess of 10% hydrochloric acid and the unreacted 6-methoxy-8-aminolepidine was removed (as the hydrochloride) by filtration of the cold mixture. The filtrate was made strongly basic with sodium hydroxide, and exhaustively extracted with ether, chloroform or benzene. The dried extracts were evaporated, and the residue was distilled under reduced pressure. With the higher molecular weight side chains, the drug could be separated from any unreacted nucleus by fractionation. In the case of the ethyl and propyl side chains, it was found advisable to dissolve the crude, once-distilled product in benzene and extract it twice with a phosphate buffer at *p*H 4.98. The aqueous phosphate extracts were then made basic and the drug was recovered by extraction with benzene.

The purified drug (0.1 mole) was dissolved in 75 ml. of *n*-propanol and titrated with two equivalents of hydrogen chloride dissolved in *n*-propanol.[4] Anhydrous ether was added to turbidity and the mixture was cooled in an ice-bath. The dihydrochloride separated as a voluminous yellow precipitate and if necessary was recrystallized from acetone–*n*-propanol–ether mixture.

The essential data on the drugs together with their antimalarial activities are summarized in Table I.[12] The anti-

(7) Craig, *J. Biol. Chem.*, **161**, 321 (1945). We wish to thank Miss Jean Galbreath, Columbia University, for carrying out these determinations.

(8) Elderfield, *et al.*, THIS JOURNAL, **68**, 1579 (1946).

(9) Elderfield, *et al.*, unpublished results.

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

(11) Elderfield, *et al.*, *ibid.*, **68**, 1516 (1946).

(12) We are indebted to Dr. E. K. Marshall, Jr., of Johns Hopkins University Medical School and Dr. Arthur P. Richardson of the Squibb Institute for Medical Research for conducting screening tests on these compounds and for permission to incorporate their results in this paper.

malarial activities are against *P. lophurae* in the duck. Homogeneities were determined by the counter-current distribution method of Craig.[7] In the case of 6-methoxy-8-(2′-diethylaminoethylamino)-lepidine, this method showed that the dihydrochloride contained about 10% of a more basic impurity. To remove this, 22 g. of the salt was dissolved in 50 ml. of water, and phosphate buffer (*p*H 7.2) was added until no further turbidity was apparent. This mixture was then extracted with two 150-ml. portions of ether, and the extract was dried and distilled. The distillate solidified on cooling, and then melted at 71–72°.

Anal. Calcd. for $C_{17}H_{25}N_3O$: C, 71.1; H, 8.8. Found: C, 71.4; H, 8.7.

Summary

1. Improvements in the synthesis of 4-methyl-6-methoxy-8-aminoquinoline are recorded.

2. Several new derivatives of 4-methyl-6-methoxy-8-aminoquinoline have been synthesized for testing as antimalarials.

NEW YORK 27, N. Y.
NOTRE DAME, INDIANA RECEIVED FEBRUARY 10, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF DEPAUW UNIVERSITY]

1-Methyl-4-carbostyrilcarboxaldehyde and Certain Condensation Products

BY D. J. COOK AND MARTHA STAMPER

Recently the preparation of 1,4-dimethylcarbostyril (I) (see Chart I) and its subsequent condensation with ethyl oxalate in the presence of potassium ethoxide was reported.[1]

Although attempts to condense chloral and aromatic aldehydes with the 4-methyl group of 1,4-dimethylcarbostyril were unsuccessful, it has been found that this group can be oxidized to the aldehyde (II) with selenium dioxide. This oxidation, when carried out in the usual solvents such as ethyl alcohol or xylene, was found to be very slow and the yield quite low, but when the selenium dioxide was added to the fused 1,4-dimethylcarbostyril, the oxidation proceeded rapidly and in yields of 60–70%.

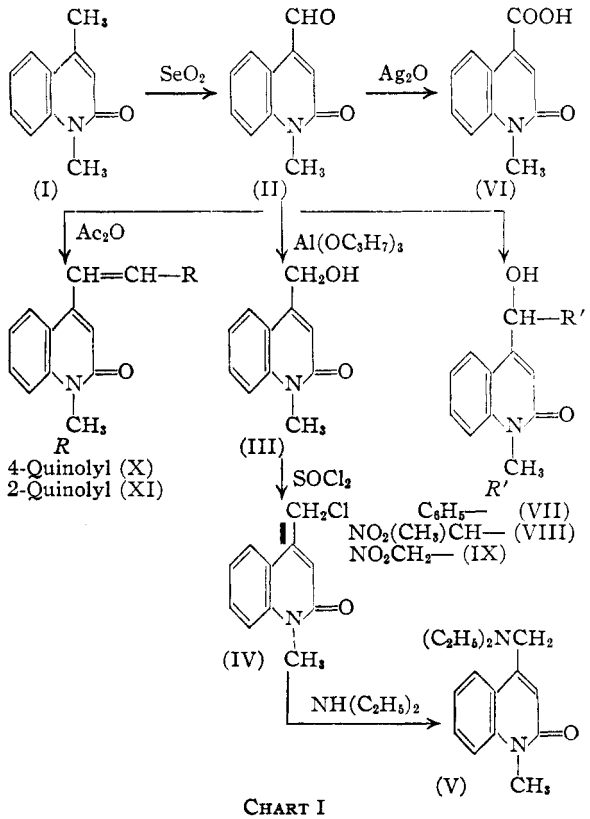


CHART I

The aldehyde was reduced to the alcohol (III) with aluminum *i*-propoxide and by treatment with thionyl chloride the alcohol was converted to 1-methyl-4-chloromethylcarbostyril (IV). This chloride was condensed with diethylamine to form the 1-methyl-4-diethylaminomethylcarbostyril (V). The aldehyde was oxidized with silver oxide to the 1-methyl-4-carbostyrilcarboxylic acid (VI).

By use of the proper Grignard reagent the aldehyde was converted to 1-methyl-4-carbostyrilphenylmethanol (VII). Various condensations were carried out with nitroethane, nitromethane, lepidine and quinaldine to give α-(1-methyl-4-carbostyril)-β-nitropropanol (VIII), α-(1-methyl-4-carbostyril)-β-nitroethanol (IX), 1-(1-methyl-4-carbostyril)-2-(4-quinolyl)-ethylene (X) and 1-(1-methyl-4-carbostyril)-2-(2-quinolyl)-ethylene (XI).

Of these compounds one was tested for antimalarial value. Compound V was found to have a Q value of 0.16 when tested against *p. lophurae* in ducklings. Thanks are due the Eli Lilly Research Laboratories for carrying out this test.

This study offers a method of preparing 1-methyl-carbostyrils with substituents in the 4-position.

Experimental[2]

Selenium Dioxide.—The selenium dioxide was prepared according to the directions outlined by Waitkins and Clark.[3] The selenium dioxide was purified immediately by sublimation and stored in a glass-stoppered bottle. The use of this material over a period of several months showed no change in its oxidizing capacity.

1,4-Dimethylcarbostyril (I).—The starting material was prepared as described by Kaslow and Cook.[1]

1-Methyl-4-carbostyrilcarboxaldehyde (II).—In a 500-ml., three-necked, round-bottomed flask equipped with an air condenser and mechanical stirrer was placed 19 g. (0.11 mole) of I. The flask was heated in an oil-bath to 150°. To the fused material 14 g. (0.126 mole) of sele-

(1) Kaslow and Cook, THIS JOURNAL, 67, 1969 (1945).

(2) All melting points were taken on a Fisher–Johns melting block.

(3) Waitkins and Clark, *Chem. Rev.*, 36, 235 (1945).