man Kodak Co. grade. The purity of all of the above substances was further tested by determining their current–voltage curves at high sensitivity. The absence of irregularities indicated the absence of more than very small traces of interfering electroreducible impurities.

Summary

The dropping mercury electrode has been applied to determinations of electroreducible substances in anhydrous acetic acid. It has been found that such substances with half wave reduction potentials lying between about −0.3 and −1.4 volts may be determined normally, while other substances give discontinuous curves or are interfered with by the hydrogen ion curve and cannot be determined polarographically. Dissolved oxygen exerts a marked influence on current–voltage curves in acetic acid.

LAFAYETTE, INDIANA RECEIVED NOVEMBER 17, 1941

[CONTRIBUTION FROM THE PARKE, DAVIS & COMPANY RESEARCH LABORATORIES AND THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Derivatives of 4-Amino-6-methoxyquinaldine*

BY WALTER F. HOLCOMB AND CLIFF S. HAMILTON

Magidson[1] has described several 6-methoxyquinolines substituted in the four position by dialkylaminoalkylamino groups which exhibited considerable antiplasmodial action whereas the corresponding quinaldines, particularly 4-γ-diethylaminopropylamino - 6 - methoxyquinaldine, were reported by Krichevskii[2] to be void of antimalarial activity. Since the chemical characterization of the above diethylaminopropyl derivative was not published, this product was prepared and when tested for its action in avian malaria was found to have a noticeable effect.[3] Kermack[4] has prepared 6-methoxy-4-piperazinoquinaldine and the corresponding piperidino derivative but the activity of these compounds has not yet been published. In view of the apparent discrepancy regarding the activity of basically substituted aliphatic quinaldines, and the lack of information on the heterocyclic substituted compounds of the above type, it was deemed advisable to prepare a representative series of these drugs for antimalarial studies.

γ-Diethylaminopropylamine has been prepared by Shriner[5] through the Gabriel phthalimide type of synthesis and γ-morpholinepropylamine has been prepared by Utermohlen[6] in a similar manner. Both of these compounds were readily obtained in about double the previous yields by hydrogenation of the corresponding nitriles using Raney nickel catalyst. β-Diethylaminopropionitrile[7] is available commercially and β-morpholinepropionitrile was obtained by the reaction of acrylonitrile[7] with morpholine at 50°. The preparation of higher homologs of the series by this method, such as γ-di-*n*-butylaminopropylamine[8] and γ-di-*n*-amylaminopropylamine, indicates that this reaction is quite general.

Condensation of γ-diethylaminopropylamine and γ-morpholinepropylamine with 4-chloro-6-methoxyquinaldine proceeded quite well at 175° yielding the corresponding substituted quinaldine, but with 4-amino-1-diethylaminopentane it was necessary to resort to a sealed tube reaction at 225°.

Attempts to condense 2-aminopyridine directly with 4-chloro-6-methoxyquinaldine gave unsatisfactory results, but 3-aminopyridine reacted readily to give rather poor yields of the expected β-pyridylaminoquinaldine.

Morpholine reacted very readily with the above chloroquinaldine at 140° giving good yields of the desired morpholine compound. 8-Aminoquinoline, 8-amino-6-methoxyquinoline, thionine, and 5-aminoindazole condensed easily with 4-chloro-6-methoxyquinaldine at about 170° and fair yields of these substituted derivatives were obtained.

Experimental

β-Di-*n*-amylaminopropionitrile.—A well mixed solution of 15.9 g. (0.3 mole) of acrylonitrile and 47.1 g. (0.3 mole)

* Presented before the Organic Division of the American Chemical Society, Memphis, April 20-24, 1942.

(1) Magidson and Rubtsov, *J. Gen. Chem.* (U. S. S. R.), **7**, 1896 (1937) [*C. A.*, **32**, 564 (1938)].

(2) Krichevskii, Shternberg and Halperin, *J. Microbiol., Epidemol., and Immunobiol.* (U. S. S. R.), **14**, 642 (1935) [*C. A.*, **30**, 4218 (1936)].

(3) A. L. Tatum, University of Wisconsin, private communication.

(4) Kermack and Smith, *J. Chem. Soc.*, 1356 (1930).

(5) Shriner and Hickey, THIS JOURNAL, **61**, 888 (1939).

(6) Utermohlen and Hamilton, *ibid.*, **63**, 156 (1941).

(7) Röhm and Haas Company, Philadelphia, Pa.

(8) U. S. Patent 1,992,615; *C. A.*, **29**, 2548 (1935).

TABLE I

MICRO ANALYSES BY ARTHUR W. SPANG AND FRANCES COPE HUMMEL OF PARKE, DAVIS AND COMPANY. CRYSTAL EXAMINATION BY ARTHUR W. SPANG

Name	Crystal form	M. p., °C.	Formula	N Analyses, % Calcd.	Found
4-γ-Diethylaminopropylamino-6-methoxyquinaldine	White prisms, parallel extinction	126–127	$C_{18}H_{27}ON_3 \cdot 2HCl \cdot 2H_2O$[a]	10.25	10.30
6-Methoxy-4-γ-morpholinepropylaminoquinaldine	White tetragonal rods	165–166	$C_{18}H_{25}O_2N_3 \cdot 3H_2O$[b]	11.38	11.43
4-[δ-Diethylamino-α-methylbutylamino]-6-methoxyquinaldine	White tetragonal rods	222–223	$C_{20}H_{31}ON_3 \cdot 2HCl \cdot 2H_2O$[c]	9.59	9.48
6-Methoxy-4-β-pyridylaminoquinaldine	White monoclinic prisms	199–200	$C_{16}H_{15}ON_3$	15.85	15.61
6-Methoxy-4-N-morpholinequinaldine	White monoclinic tablets	124–125	$C_{15}H_{18}O_2N_2$	10.85	10.78
6-Methoxy-4-[8′-quinolylamino]quinaldine	Bright yellow orthorhombic prisms	184–185	$C_{20}H_{17}ON_3$	13.33	13.56
6-Methoxy-4-[6′-methoxy-8′-quinolylamino]-quinaldine	Pale yellow monoclinic prisms	200–201	$C_{21}H_{19}O_2N_3$	12.18	12.38
3,7-Di-(6′-methoxy-2′-methyl-4′-quinolyl)-thionine	Deep blue amorphous powder	208–210	$C_{34}H_{27}O_2N_5S$	12.29	12.05
4-[5′-Indazoleamino]-6-methoxyquinaldine	Pale yellow microscopic crystals	303–305	$C_{18}H_{16}ON_4$	C, 71.07 H, 5.26	C, 70.88 H, 5.08

[a] Calcd.: H_2O, 8.78. Found: H_2O, 8.6. [b] Calcd.: H_2O, 14.63. Found: H_2O, 14.4. [c] Calcd.: H_2O, 8.23. Found: H_2O, 8.0.

of di-*n*-amylamine[9] was warmed to 50°, then allowed to stand overnight at room temperature. The product was distilled twice from a modified Claisen flask and the fraction boiling at 136° (6 mm.) collected; yield, 57 g. or 90%; $n^{20}D$ 1.4446.

Anal. Calcd. for $C_{18}H_{26}N_2$: C, 74.23; H, 12.46. Found: C, 74.20; H, 12.43.

γ-Di-*n*-amylaminopropylamine.—A solution of 21.0 g. (0.1 mole) of β-di-*n*-amylaminopropionitrile in 50 ml. of absolute ethanol was placed in the reduction container with 1.0 g. of Raney nickel catalyst. The reaction mixture was heated to 70° to start, the initial pressure of hydrogen was set at 60 lb. (4 atm.), and the mixture was agitated for five hours before the theoretical amount of hydrogen had been taken up. After filtering off the catalyst and removing the solvent the product was distilled from a modified Claisen flask. The fraction boiling at 129° (6 mm.) was collected; yield 10 g., or 47%. The dipicrate crystallized from absolute ethanol in long slender rods; m. p. 192–193°.

Anal. Calcd. for $C_{25}H_{36}O_{14}N_8$: C, 44.65; H, 5.39. Found: C, 44.71; H, 5.28.

γ-Diethylaminopropylamine and γ-Morpholinepropylamine.—These amines were prepared in a manner analogous to γ-di-*n*-amylaminopropylamine.

4-γ-Diethylaminopropylamino-6-methoxyquinaldine.—4-Chloro-6-methoxyqiunaldine (2.07 g.) (0.01 mole) was mixed well with 2.6 g. (0.02 mole) of γ-diethylaminopropylamine and heated in an oil-bath at 175° for eight hours. The gummy reaction mixture was cooled, diluted with 50 ml. of 5% sodium hydroxide, and washed several times with water by decantation. The residual oil was taken up in ether, dried over potassium carbonate, filtered, and the filtrate treated with absolute alcoholic hydrogen chloride. The somewhat sticky hydrochloride was recrystallized several times from ethanol and ethyl acetate; yield, 2.5 g. (61%). This product crystallized as the dihydrochloride dihydrate and the anhydrous form proved to be very hygroscopic.

6-Methoxy-4-γ-morpholinepropylaminoquinaldine.—This compound was prepared similarly to the above diethylamine derivative except that it was isolated as the free base. It crystallized readily from 50% ethanol and water as the trihydrate; yield, 70%. The anhydrous material was somewhat hygroscopic.

4-[δ-Diethylamino-α-methylbutylamino]-6-methoxyquinaldine.—A mixture of 4.15 g. (0.02 mole) of 4-chloro-6-methoxyquinaldine and 4.7 g. (0.03 mole) of δ-diethylamino-α-methylbutylamine was placed in a Carius tube and heated at 225° for ten hours. The product was extracted with dilute hydrochloric acid and neutralized with sodium hydroxide. The base was taken up in ether, dried over potassium carbonate, and the filtrate distilled from a small modified Claisen flask. The fraction boiling at 150–152° (0.5 mm.) was collected and converted to the dihydrochloride dihydrate in ethanol solution. The product was crystallized from an ethanol–ether mixture and again from ethanol and ethyl acetate; yield, 1.5 g. (34%).

6-Methoxy-4-β-pyridylaminoquinaldine.—A solution of 9.4 g. (0.1 mole) of 3-aminopyridine and 10.35 g. (0.05 mole) of 4-chloro-6-methoxyquinaldine in 25 ml. of cellosolve was refluxed for ten hours in an oil-bath. The cellosolve solution was diluted to 500 ml. with water then saturated with potassium carbonate. On standing pale amber crystals separated which were taken up in dilute hydrochloric acid and filtered. The filtrate was treated with a large excess of 10 *N* sodium hydroxide and the product thus obtained crystallized several times from a small volume of acetone and water; yield, 3.4 g. (26%).

6-Methoxy-4-N-morpholinequinaldine.—Two grams (0.01 mole) of 4-chloro-6-methoxyquinaldine was mixed with 2.6 g. (0.03 mole) of morpholine and heated in an oil-

(9) Supplied through the courtesy of Dr. J. F. Olin, the Sharples Solvents Corp., Wyandotte, Mich.

bath at 140° for eight hours. The product was isolated as the free base by crystallization from 50% ethanol and water; yield, 2.0 g. (80%).

Other Heterocyclic Substituted Aminoquinaldines.—4-Chloro-6-methoxyquinaldine (0.02 mole) was mixed well with 0.022 mole of the desired heterocyclic amine, *i. e.*, 8-aminoquinoline, 8-amino-6-methoxyquinoline, thionine (0.011 mole), and 5-aminoindazole. The reaction mixture in each case was heated in an oil-bath at 160–175° for three hours. The products were isolated and purified by washing the residues with 5% sodium hydroxide then numerous crystallizations from 90% ethanol; yields, approximately 60 to 70%.

Summary

A relatively simple and economical process for the preparation of basically substituted propylamines has been reported.

4-Chloro-6-methoxyquinaldine has been condensed with a few basically substituted aliphatic amines and several heterocyclic amines to give the corresponding 4-substituted quinaldines.

DETROIT, MICH.
LINCOLN, NEBR. RECEIVED MARCH 16, 1942

[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, UNITED STATES DEPARTMENT OF AGRICULTURE]

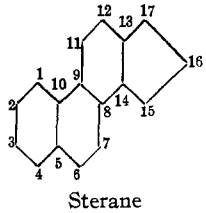
The Synthesis of Condensed Ring Compounds. VIII. Further Applications of the Dienyne Double Addition Reaction[1]

BY LEWIS W. BUTZ AND LLOYD M. JOSHEL[2]

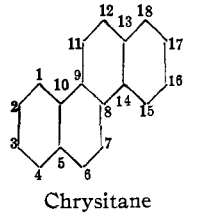
Although it has not yet been found possible to realize the previously mentioned aim of adding ethylene to dienynes,[3] the dienyne double addition reaction has been extended by the observation that methyl and ethyl fumarates can serve as dienophiles in this process. As was expected, the 6,7,11,12-tetracarbomethoxy-8(14),9-chrysitadiene (I)[4] formed by the reaction of dicyclohexenylacetylene and methyl fumarate proved to be a stereoisomer of the tetramethyl ester (IV)[5] prepared from the maleic anhydride adduct III.[6] By analogy with the Diels–Alder synthesis, it is to be expected that maleic anhydride will yield products with *cis*-anhydride groups and that alkyl fumarates will yield *trans*-1,2-diesters. The configurations of carbon 6 relative to carbon 7 and of carbon 11 relative to carbon 12 in these compounds may accordingly be considered as determined by the method of preparation. The other stereochemical relations illustrated have not been demonstrated but are suggestions partly based on the assumption that the rules developed for the Diels–Alder reaction[7] may be applicable to the dienyne double addition reaction. We have not indicated any configurations at the various angular centers since these are entirely uncertain at the present time. The diene esters I, II, and IV all exhibit characteristic absorption spectra[8] with molecular extinction coefficients of 24,000–24,500 at 2560–2570 Å.[9]

In addition to their different melting points, the contrast between I and IV is sharply illustrated by their respective behaviors toward hydrogen. IV, like the tetracarbomethoxysteradiene possessing the same configuration,[8] readily absorbs one and only one mole of hydrogen in the presence of Adams catalyst with the formation in high yield of a compound of probable structure V. Under the same conditions, I absorbs no hydrogen whatsoever.

In view of the invariable presence of the 3-hydroxyl or 3-keto group in naturally occurring steroids, it is of interest that 4-methoxycyclo-



Sterane



Chrysitane

(1) This work was supported by an appropriation from Bankhead–Jones funds (Bankhead–Jones Act of June 29, 1935) and is part of an investigation being carried out under the Physiology of Reproduction Project, a coöperative project of the Bureau of Animal Industry and the Bureau of Dairy Industry. Not subject to copyright. Paper VII, *J. Org. Chem.*, **7**, in press (1942).

(2) Present address: Chemicals Branch, War Production Board, Washington, D. C.

(3) Joshel and Butz, THIS JOURNAL, **63**, 3350 (1941).

(4) For convenience in referring to alicyclic structures of this type, perhydrochrysene will be designated by the systematic name *chrysitane* (suggested by *quinol* and *quinitol*) and derivatives will then be named by employing the system of numbering universally adopted for the closely related steroids.

(5) This compound was prepared by Mr. Julian Feldman.

(6) Joshel, Butz and Feldman, THIS JOURNAL, **63**, 3348 (1941).

(7) Alder and Stein, *Angew. Chem.*, **50**, 510 (1937); Alder and Windemuth, *Ber.*, **71**, 1939 (1938).

(8) Butz and Joshel, THIS JOURNAL, **63**, 3344 (1941).

(9) The absorption spectra were determined by Dr. Russell E. Davis and Mr. Harry Bastron of this Bureau.