reported melting point for the ethyl ester is 93°; for butyl 64°.[16]

Anal. Calcd. for $C_8H_{15}O_4N$: N, 7.41. Found: N, 7.24, 7.44.

The 42-g. pot residue was recrystallized three times from ether–petroleum ether mixture to yield 38 g. of fine white needles, m. p. 42–43°. Four grams of this solid was saponified in the manner previously described. The saponification distillate gave a positive ceric nitrate test and a negative iodoform test. Treatment of the alcoholic phase of the distillate with 3,5-dinitrobenzoyl chloride resulted in an ester, m. p. 63–64°. The reported melting point for butyl 3,5-dinitrobenzoate is 64°.[16]

Anal. Calcd. for $C_{10}H_{19}O_4N$: N, 6.45. Found: N, 6.34, 6.28.

(16) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 185.

Acknowledgment.—The authors wish to express their appreciation to the Hooker Electrochemical Company for the generous supply of allyl chloroformate.

Summary

The synthesis of a number of new alkyl azamalonate has been described and a redistribution reaction has been postulated for the formation of the symmetrical di-esters. These compounds are to be tested for their pharmacological activity.

Fungicidal data are presented.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED, HUNGARY]

A Synthesis of Adrenaline-like Compounds

BY GÁBOR FODOR AND ÖDÖN KOVÁCS

According to a recent review[1] on the subject, the best method of obtaining aryl methylaminoethanols, *e. g.*, synephrine, is the condensation of ω-chloro-*p*-benzoyloxyacetophenone with methylbenzylamine, followed by hydrolysis and subsequent hydrogenation.[2] Another useful method[3] consists of the condensation of hydroxy derivatives of benzaldehyde bisulfite with a salt of nitromethane, followed by the reductive condensation of the nitro ethanol with formaldehyde[3] to the corresponding aryl aminoethanol.

An excellent synthesis of ephedrine is described by Manske and Johnson[4] from phenyl methyl methyl diketone with methylamine. In this process the authors applied, for the first time, ketonic aldehydes and diketones as starting materials[5]; no similar reactions have been reported previously in the literature.

However, the use of methoxy and hydroxy derivatives, even in the case of diketones, offered some difficulties. It was thought, therefore, to be of interest to work out a synthesis of hydroxy aryl ethanolamines, starting from hydroxy arylglyoxals, similar to that of phenyl-methylaminopropanol.[4]

4-Hydroxyphenylglyoxal[6] (II) has been obtained from phenol through 4-hydroxyphenyltrichloromethyl-carbinol.[7] We have synthesized it in another manner: first, 4-hydroxyacetophenone (I) was prepared according to Meerwein.[8] This was then oxidized with selenium dioxide, without protecting the phenolic group, to 4-hydroxyphenylglyoxal; this latter was isolated as a crystalline hydrate and further identified by its well defined quinoxaline derivative (V). Several attempts were made for the condensation of this ketonic aldehyde with methylamine, with subsequent or simultaneous reduction of the azomethine formed (III). However, when this amorphous compound or an equimolecular mixture of the glyoxal and of methylamine was reduced catalytically, a sudden initial reaction occurred, but the hydrogen consumption stopped with an absorption of only 0.5 to 0.8 mole of hydrogen against the calculated 2 moles. The expected 1-(4-hydroxyphenyl)-2-methylamine ethanol (IV) could not be obtained from the reaction mixture. We supposed that our failure to obtain the desired compound was due to the fact that the 4-hydroxyphenylglyoxal reacted with methylamine in much the same manner as phenylglyoxal, which gives heterocyclic condensation products with hydroxylamine,[9] ammonia[10] and methylamine.[11] In order to prevent these undesired reactions, we carried out experiments in which the azomethine was reduced instantaneously after its formation: the alcoholic solution of 4-hydroxy-phenylglyoxal was added under vigorous mechanical stirring drop by drop to a suspension of palladium on charcoal in an alcoholic solution of methylamine in a hydrogen atmosphere. Two moles of hydrogen were consumed for each mole of 4-hydroxy phenylglyoxal hydrate and a colorless solution resulted giving 1-(4′-hydroxyphenyl)-2-methylaminoethanol with good yield and high degree of purity. It seems, there-

(1) Priestley and Moness, *J. Org. Chem.*, **5**, 355 (1940).

(2) Stolz and Hallensleben, *Chem. Zentr.*, **102**, II, 1056 (1931), German Patent 526,087.

(3) Kamlet, *ibid.*, **110**, II, 3451 (1939).

(4) Manske and Johnson, THIS JOURNAL, **51**, 580 (1929).

(5) Manske, *ibid.*, **51**, 1907 (1929).

(6) Boehringer, *Chem. Zentr.*, **101**, II, 2442 (1930), German Patent 496,646.

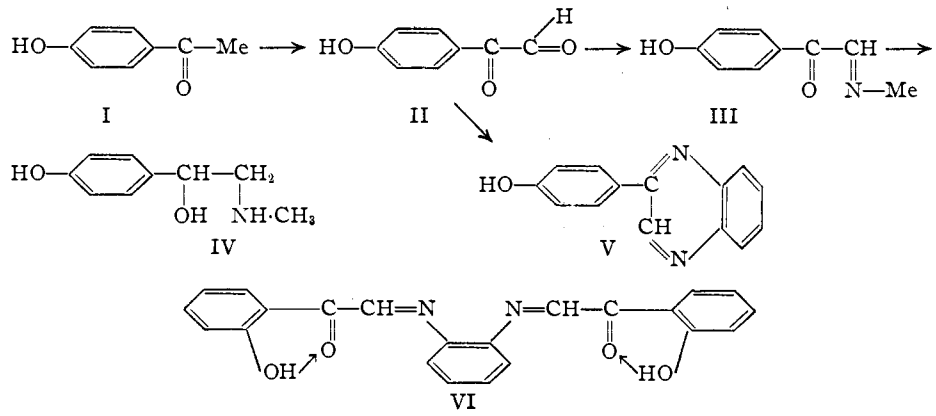
(7) Pauly and Schanz, *Ber.*, **56**, 981 (1923); *cf.* Austrian Patent 141,159.

(8) Meerwein, *Ber.*, **66**, 411 (1933).

(9) Angelico and Cusmano, *Gazz. chim. ital.*, **66**, 791 (1936).

(10) Müller and Pechmann, *Ber.*, **22**, 2559 (1889); *cf.* Pinner, *ibid.*, **35**, 1134 (1902).

(11) Gastaldi, *Gazz. chim. ital.*, **51**, 233 (1921).



fore, that the methylamine did not react with the ketonic group of the arylglyoxal (II).

Phenylglyoxal reacts with aminoguanidine in alkaline medium similarly as an aldehyde, whereas in acid medium a selective condensation of the ketonic group occurs.[12]

2-Hydroxyacetophenone[13] (Type I) was converted in a similar manner into the 2-hydroxy phenylglyoxal (Type II), characterized by its crystalline condensation product (VI) with *o*-phenylenediamine. Two moles of this *o*-hydroxy ketonic aldehyde reacted only with their aldehyde groups with one mole of diamine, as the ketonic group could be chelated by the *o*-standing hydroxy group, a hydrogen bridge being formed. Hydrogenation of 2-hydroxyphenylglyoxal by the method described above led to *o*-synephrine[14] (Type IV). 3-Hydroxyphenylglyoxal was obtained in the same way from 3-hydroxyacetophenone[15] and converted into the crystalline quinoxaline derivative.

4-Methoxyacetophenone[16] gave on oxidation with selenium dioxide the crystalline 4-methoxyphenylglyoxal hydrate (Type II). On reducing the latter together with methylamine, the expected amino alcohol could not be obtained; however, 1-(4′-methoxyphenyl)-ethanediol-1,2 was isolated with a good yield. Phenylglyoxal was converted similarly into 1-phenyl-ethanediol-1,2. In these cases the hydrogenation reaction of the ketonic aldehydes has a greater velocity than their condensation reaction with methylamine.

In order to employ the method for the synthesis of adrenaline derivatives, *e. g.*, N-isopropyl-noradrenaline,[17] it was necessary to prepare 3,4-dihydroxyphenylglyoxal as an intermediate. This was obtained by the oxidation of 3,4-diacetoxyacetophenone[18] to the corresponding 3,4-diacetoxyphenylglyoxal and subsequent hydrolysis with boiling water. It could not be obtained by the direct oxidation of 3,4-dihydroxyacetophenone with selenium dioxide as the *o*-hydroxy groups are oxidized prior to the methyl group.

When 3,4-dihydroxy phenylglyoxal was reduced catalytically together with isopropylamine, N-isopropylamino-nor-adrenaline[17] was obtained, as sulfate. We synthesized the same compound also from 3,4-dibenzyloxy phenylglyoxal, prepared from 3,4-dibenzyloxyacetophenone[19] with selenium dioxide, by reductive condensation with isopropylamine with a simultaneous hydrogenolysis of the benzyl ether linkage.

It is surprising that under our experimental conditions reductive condensation occurs smoothly only in the presence of free phenolic hydroxyl.

This 3-step synthesis of synephrine is far simpler than those discussed by Priestley and Moness,[1] or by Kamlet.[3] The new synthesis of N-isopropyl-nor-adrenaline, from catechol, via diacetoxyacetophenone and dihydroxyphenylglyoxal is also useful, as only these two intermediates must be isolated. The method is consequently of general value for the preparation of hydroxyaryl ethanolamines.[20]

Experimental

Phenylglyoxal hydrate[21] was converted in a concentrated aqueous solution into 2-phenylquinoxaline,[22] m. p. 78°.

4-Hydroxyphenylglyoxal Hydrate.—Twenty-two and two-tenths grams (0.2 mole) of selenium dioxide was dissolved in 120 ml. of dioxane and 4 ml. of water at 60°, then 27.2 g. (0.2 mole) of 4-hydroxyacetophenone[8] was added and the reaction mixture boiled for four hours in a steam-bath. The separated selenium was filtered off, the yellow solution was evaporated in vacuum at 40°. The residue was treated with 150 ml. of water on the steam-bath for three hours under stirring, the resulting solution decolorized with charcoal, filtered and concentrated to a small volume. The yellowish colored hydrate crystallized. Yield was 31.4 g. (87%). Recrystallized from the fourth amount of water, 27 g. of greenish white prisms was obtained, m. p. 111°.[6] Oxidation in alcoholic solution gave a similar

(12) Ekeley, Carlson and Ronzio, *Rec. trav. chim.*, **59**, 496 (1940).
(13) Friedländer and Neudörfer, *Ber.*, **30**, 1080 (1897).
(14) Legerlotz, German Patent 522,790.
(15) Rupe and Majewski, *Ber.*, **33**, 3407 (1900).
(16) Kästner, "Neuere Methoden d. präparativen organischen Chemie," Verlag Chemie, 1941, p. 413.
(17) Boehringer, Schwitzer Patent 214,499.
(18) Voswinckel, *Ber.*, **42**, 4653 (1911).
(19) Dützmann and Krauss. *Chem. Zentr.*, **96**, II, 612 (1925).
(20) Servita, Ltd., Fodor and Kovács, Hungarian Patent Appl. no. S-20,468.
(21) Organic Syntheses, Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 509.
(22) Fischer and Schindler, *Ber.*, **39**, 2243 (1906).

(85%) yield; whereas in aqueous solution only 42% 4-hydroxyphenylglyoxal could be obtained.

2-(4'-Hydroxyphenyl)-quinoxaline was recrystallized from methanol as white plates, m. p. 204°.

Anal. Calcd. for $C_{14}H_{10}ON_2$: C, 75.66; H, 4.54. Found: C, 75.85; H, 4.68.

4-Methoxyphenylglyoxal Hydrate.—A mixture of 50 ml. of dioxane, 2 ml. of water, 11.1 g. (0.1 mole) of selenium dioxide and 15 g. (0.1 mole) of 4-methoxyacetophenone[16] was refluxed for forty-eight hours. After removal of selenium and of the solvent, the oily residue was treated with 500 ml. of water at 100° for four hours with stirring, the solution was clarified with charcoal, the hydrate crystallized on cooling. A second crop of crystals was obtained by concentrating the solution: yield was 15 g. (82%), m. p. 84°.

2-(4'-Methoxyphenyl)-quinoxaline.—Long colorless needles, from ethanol, m. p. 102°.

Anal. Calcd. for $C_{15}H_{12}ON_2$: C, 75.76; H, 5.12. Found: C, 75.99; H, 4.88.

3-Hydroxyphenylglyoxal.—A mixture of 10 g. of selenium dioxide (0.09 mole), 60 ml. of dioxane, 2 ml. of water and 13.6 g. (0.1 mole) of 3-hydroxyacetophenone[15] was refluxed for twenty hours, then worked up as described above. The hydrate, 14.3 g., could not be crystallized. It was identified by its crystalline quinoxaline derivative.

2-(3'-Hydroxyphenyl)-quinoxaline.—Yellow needles from ethanol, m. p. 169°.

Anal. Calcd. for $C_{14}H_{10}ON_2$: C, 75.66; H, 4.54. Found, C, 75.64; H, 4.65.

2-Hydroxyphenylglyoxal.—Thirteen and six-tenths grams (0.1 mole) of 2-hydroxyacetophenone[13] was oxidized in the same manner as described before. The oily glyoxal derivative, 12.1 g., could not be crystallized for identification; it was condensed with *o*-phenylenediamine.

1,2-*bis*-(2'-Hydroxyphenyl-glyoxalylidene)-phenylenediamine.—One and forty-three hundredths grams of the oily product was dissolved in 5 ml. of water, a hot solution of 1 g. *o*-phenylenediamine was added and the separated yellowish crystals filtered off. Recrystallization from ethanol produced delicate needles, 1.72 g., m. p. 295°.

Anal. Calcd. for $C_{22}H_{16}O_4N_2$: C, 70.79; H, 4.33; N, 7.54. Found: C, 70.69; H, 4.19; N, 7.20.

3,4-Dibenzyloxyphenylglyoxal.—From 10 g. (0.09 mole) of selenium dioxide in 150 ml. of ethanol (96%) and 33.2 g. (0.1 mole) of 3,4-dibenzyloxyacetophenone[19] 28.3 g. of recrystallized dibenzyloxyphenylglyoxal was obtained, m. p. 98–100°, white needles from ethanol.

2-(3',4'-Dibenzyloxyphenyl)-quinoxaline.—2-(3',4'-Dibenzyoxyphenyl)-quinoxaline was prepared in methanolic solution, since the glyoxal is insoluble in water; wadding-like needles from methanol, m. p. 118°.

Anal. Calcd. for $C_{28}H_{22}O_2N_2$: C, 80.36; H, 5.29. Found: C, 80.07; H, 5.30.

3,4-Dihydroxyphenylglyoxal.—A mixture of 11.1 g. (0.1 mole) of selenium dioxide and 26 g. (0.11 mole) of 3,4-diacetoxyacetophenone,[18] 65 ml. of dioxane and 2 ml. of water was refluxed for thirty hours. Selenium and the solvent were removed in the usual manner and the brownish oily residue hydrolyzed by treatment with 120 ml. of water and heating in a nitrogen atmosphere for six to ten hours in a steam-bath. The endpoint of the reaction is indicated by the formation in a sample taken from the solution of a crystalline precipitate with *o*-phenylenediamine. The decolorized solution yielded in the usual manner 18.1 g. of a solid foam.

2-(3',4'-Dihydroxyphenyl)-quinoxaline, yellow colored needles from diluted ethanol (50%), m. p. 254–256°.

Anal. Calcd. for $C_{14}H_{10}O_2N_2$: C, 70.58; H, 4.23. Found: C, 70.41; H, 4.42.

***dl*-1-(4'-Hydroxyphenyl)-2-methylaminoethanol.**—All reductions were carried out in a three-necked, round-bottomed flask, equipped with a ground glass mechanical stirrer (1000 to 1200 r. p. m.), a dropping funnel and a gas introducing tube.

One and six-tenths grams of Pd-charcoal (containing 12% PdO) in 100 ml. of ethanol was saturated with hydrogen, then 1.12 g. (0.03 mole or 20% excess) of methylamine in 60 ml. of ethanol was introduced. A solution of 5.31 g. (0.03 mole) 4-hydroxyphenylglyoxal hydrate in 80 ml. of alcohol was added slowly through the dropping funnel (10–12 drops per minute), followed by 40 ml. of alcohol. The mixture absorbed 1420 normal ml. of hydrogen in 110 minutes (calcd. 1344 ml. for 2 moles). The pale yellow colored solution was filtered from the catalyst and both the solvent and the excess methylamine were removed under reduced pressure at 50°. When the solution had been concentrated to one third of its volume, the product began to crystallize. The residue was cooled, filtered and washed with 5 ml. of ice-cold ethanol; yield was 4.05 g. (81%) of synephrine, m. p. 180°; after recrystallization from alcohol, the m. p. rose to 184°.[2]

Anal. Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84. Found: C, 64.61; H, 7.69. Similar yields were obtained by using an Adams catalyst, or a Raney-nickel catalyst instead of palladium-charcoal.

1-(2'-Hydroxyphenyl)-2-methylaminoethanol.—Five and a half grams of the crude 2-hydroxyphenylglyoxal was condensed in the same manner as above with 1.39 g. of methylamine in the presence of 1.2 g. of the catalyst in 280 ml. of ethanol; 1080 ml. of hydrogen (calcd. for 2 moles 1344 ml.) was absorbed in 230 minutes. Evaporation in a vacuum furnished a crop (2.8 g.) of white crystals of the amino alcohol; recrystallized from ethanol (87%), m. p. 211°.

Anal. Calcd. for $C_9H_{13}O_2N \cdot H_2O$: C, 58.35; H, 6.42; N, 7.56. Found: C, 58.17; H, 6.11; N, 7.31.

1-(3',4'-Dihydroxyphenyl)-2-isopropylaminoethanol (N-Isopropylnoradrenaline). A. From 3,4-Dihydroxyphenylglyoxal Hydrate.—To a suspension of 1.6 g. of Pd-charcoal in 160 ml. of ethanol containing 1.92 g. (0.033 mole) of isopropylamine, 5 g. (0.03 mole) of the amorphous 3,4-dihydroxyphenylglyoxal in 120 ml. of ethanol was added drop by drop (5–8 drops per minute) at 50° in a hydrogen atmosphere under mechanical stirring. During 370 minutes 980 ml. (standard) of hydrogen was taken up (calcd. 1090 ml.). The solution was neutralized with 2 *N* sulfuric acid (calcd. for isopropylamine) and evaporated to a small volume. The sulfate of N-isopropyl-nor-adrenaline crystallized in white prisms, yield 3.75 g. (47%), m. p. 180°. It may be recrystallized from alcohol (90%). This compound was assayed by Prof. B. Issekutz, Jr., on guinea pigs for bronchospasmolytic activity and found as effective as aleudrine.[17]

Anal. Calcd. for $C_{11}H_{17}O_3N \cdot 0.5H_2SO_4$: N, 5.3. Found: N, 5.1.

B. **From 3,4-Dibenzyloxyphenylglyoxal.**—Ten grams (0.03 mole) of 3,4-dibenzyloxyphenylglyoxal, 2 g. (0.034 mole) of isopropylamine in 280 ml. of alcohol in the presence of 1.6 g. Pd-charcoal absorbed at 50° 2580 N ml. of hydrogen (calcd. for 4 moles 2690 N ml.) in 330 minutes. Yield was 4.9 g. (61%) of the same amino alcohol sulfate.

1-Phenylethanediol-1,2.—A solution of 4.56 g. (0.03 mole) of phenylglyoxal hydrate was added in ninety minutes to a suspension of 0.8 g. of Pd-charcoal in 160 ml. of ethanol, containing 1.4 g. (0.045 mole) of methylamine by the above-described method. During 120 minutes 1370 N ml. of hydrogen was absorbed (calcd. for 2 moles 1344 ml.). The solution was evaporated, the residue recrystallized from 10 ml. of benzene, furnishing 2.95 g. (71%) of white needles, m. p. 67°.[23] It does not contain nitrogen.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.51; H, 7.22. Found: C, 69.49; H, 7.21.

1-(4'-Methoxyphenyl)-ethanediol-1,2.—Starting with 5.46 g. of 4-methoxyphenylglyoxal hydrate, hydrogenation occurs under the same conditions as described for phenylglyoxal. The addition of the glyoxal required 110 minutes, the uptake of hydrogen stopped after 190 minutes and was 1350 N ml. (instead of 1344 ml. calcd.).

(23) Zincke, *Ann.*, **216**, 293 (1883).

Recrystallization produced 4.45 g. (68%) of 4-methoxyphenylethanediol, m. p. 82°. It is free of nitrogen.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.32; H, 7.17. Found: C. 64.50; H, 7.17.

Acknowledgment.—The authors are indebted to Mrs. Bruckner-Hatz and to Miss Kovács Oskolás for the microanalyses and to Prof. B. Issekutz, Jr., for the pharmacological assay of some compounds.

Summary

A new synthesis of hydroxyaryl N-alkylamino ethanols is described. Hydroxyaryl methyl ketones, respectively, their esters or ethers were oxidized by means of selenium dioxide with very good yields to the corresponding aryl glyoxals. Some hydroxyaryl, respectively, benzyloxyaryl glyoxals were reduced together with methyl amine, respectively, isopropylamine to the adrenalinelike aryl ethanolamines. Synephrine and N-isopropyl-nor-adrenaline were prepared with good yields. Phenylglyoxal and 4-methoxy phenylglyoxal gave under the same conditions only the corresponding glycols as in these cases condensation before reduction of the glyoxals did not take place.

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Alkaloids of *Dichroa febrifuga*. I. Isolation and Degradative Studies[1]

BY J. B. KOEPFLI, J. F. MEAD[2] AND JOHN A. BROCKMAN, JR.

A part of the war-born government sponsored research on malaria[3] was directed to a search for new antimalarials from plant sources. In papers by Liu[4] there is incidental mention of an antimalarial drug indigenous to Yunnan, and samples of this drug (SN 6355),[5] supplied by Liu, when tested in this country were found to be quite active against avian malaria. The samples were labeled "Chunine Leaf Powder" and further identified only as "from Saxifragaceae." The significance of the Saxifragaceae as a source of new antimalarials was further indicated when the Chinese drug Ch'ang Shan (SN 10767), reputed to be the roots of the Saxifrage, *Dichroa febrifuga*, Lour., also proved active in avian malaria. The availability of an adequate supply of Ch'ang Shan plant material led to this investigation the results of which have been briefly communicated by us.[6]

In 1943 when we began our work, the available information on Ch'ang Shan was meager and often contradictory.[7] Furthermore, we were particularly concerned as to the botanical identity of our plant material since the Ch'ang Shan supplied us had been obtained from Chinese herb stores either in this country or abroad. Comparison of some of our root material with herbarium specimens and information[8,9] later available indicate that the type of Ch'ang Shan used in this investigation is derived from the roots of *D. febrifuga*. Supporting evidence of a chemical nature was obtained when we were able to isolate from *D. febrifuga* (SN 6521), botanically identified at the time of collection in India, the same alkaloids isolated from our supply of Ch'ang Shan.

Since *D. febrifuga* has long been used in the treatment of "intermittent fevers" in southeastern Asia it is surprising that except for one reference to a possible glucoside, "dichroin(?),"[10] no chemical examination of the plant has been reported until lately. References to investigations which have appeared recently will be cited below.

Isolation and Characterization[11]

Isolation from Ethanol Extracts.—From crude basic fractions of *D. febrifuga* we have isolated two alkaloids for which we have proposed[6] the names febrifugine (DR 15381)[12] and isofebrifugine (SN 14821). Reports that this plant does not contain alkaloids[13,14] are probably explained by the fact that the alkaloidal content of the root material is small, 0.05 to 0.1%, and by the fact that Meyer's reagent which is commonly used as a test for alkaloids is remarkably insensitive for these bases.

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(2) Present address: University of California at Los Angeles.

(3) "A Survey of Antimalarial Drugs, 1941–1945," ed. by F. Y. Wiselogle, J. W. Edwards, Ann Arbor, Michigan, 1946.

(4) S. K. Liu, Y. Chang, T. Ch'un and S. Tan, *Chinese Medical Jour.*, **59**, 575–577 (1941); and S. K. Liu, *National Medical Jour. of China*, **27**, 327 (1941).

(5) The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs, ref. 3.

(6) J. B. Koepfli, J. F. Mead and J. A. Brockman, Jr., THIS JOURNAL, **69**, 1837 (1947).

(7) K. Kimura, *China Journal*, **23**, 109 (1935).

(8) C. S. Jang, *Chinese Medical Jour.*, April–June, 1944.

(9) C. Crevost and A. Petelot, "Catalogue des Produits de l'Indochine," Vol. V, Part 1, Produits Medicinaux, p. 164 (1928); and K. Heyne, "De Nuttige Planten van Nederlandsch Indië," 2nd ed., Vol. I, p. 687; Buitenzorg (1927).

(10) C. Hartwich, Neue Arzneidrog, 1897, p. 125; C. Wehmer, "Die Pflanzenstoffe," Vol. I, 2nd ed., G. Fisher, Jena, 1929, p. 428.

(11) All melting points are corrected.

(12) The designation "DR" identifies a drug in the Antimalarial Drug Repository of the National Institute of Health, Bethesda, Maryland.

(13) I. M. Tonkin and T. S. Work, *Nature*, **156**, 630 (1945).

(14) D. Hooper, *Nature*, **157**, 106 (1946).