## REFERENCES

(1) Seeling, R. P., "The Physics of Powder Metallurgy," McGraw Hill Book Co., Inc., New York N. Y., 1951, p. 344.

(2) Nelson, E., Busse, L. W., and Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 223(1955).

(3) Endersby, V. A., *Proc. Am. Soc. Test. Mater.*, **40**, 1154(1940).

(4) Bowden, F. P., and Tabor, D., "Symposium on the Properties of Metallic Surfaces," Institute of Metals, London England, 1952, p. 197.

(5) Higuchi, T., Elowe, L. N., and Busse, L. W., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 685(1954).

(6) Bertelson, A., and Gitter, A. J., "Measuring Surface Temperatures and Indicating Temperature Distribution," (8-R-64F). Presented before the American Ceramic Society, Refractories Division, Virginia Beach, Virginia, date unknown.

(7) Technical Brochure, H. V. Hardman Co., Inc., Belleville, N. J.

(8) Hodgman, C. D., Weast, R. C., and Shelby, S. M., "Handbook of Chemistry and Physics," 40th Edition, Chemical Rubber Publishing Co., Cleveland, Ohio, 1958, p. 2260.

(9) Glasstone, S., "Textbook of Physical Chemistry," 2nd ed., D. Van Nostrand Co., Inc., Princeton, N. J., 1946, p. 184.



*Keyphrases*

Compression—solids
Thermodynamic effects—compression
Tablets—heat of compression
Temperature indicating pigments—heat of compression
Heat of compression, measured—water temperature change
Pressure relation—thermal effects
Speed of compression—thermal effects


# Notes

## Synthesis of Several Dibasic Acid Esters of 3-Quinuclidinol as Potential Pharmacological Agents

By HILLEL LIEBERMAN and SAMUEL ELKIN

**Eight new dibasic acid esters of 3-quinuclidinol have been synthesized and isolated as their free bases using an alcoholysis reaction. A ninth compound, 3-quinuclidinyl hydrogen homophthalate, could not be isolated with sufficient purity to obtain an elemental analysis. However, this compound showed characteristic ester bands and gave a positive hydroxamic acid test. In a preliminary pharmacological evaluation in dogs, 3-quinuclidinyl hydrogen phthalate and 3-quinuclidinyl hydrogen 2,3-pyridinedicarboxylate gave a substantial increase in blood pressure and produced central stimulation as evidenced by a marked increase in respiration. Five compounds showed varying degrees of local anesthetic activity.**

SERIES OF ESTERS of 3-quinuclidinol have been prepared by Sternbach and Kaiser (1) and by Mikhlina and Rubtsov (2). All of these esters produced marked spasmolytic activity. Of great interest was the observation that many of these esters showed a much higher antiacetylcholine activity than the analogous esters derived from diethylaminoethanol and other generally used basic alcohols. One of the most active of the series was 3-diphenylacetoxyquinuclidine.

Many other therapeutically active quinuclidine derivatives have been synthesized and pharmacological activity has been found in both mono- and disubstituted products. Several 3-substituted derivatives of quinuclidine have been reported by Grob (3) to stimulate the central nervous system. A series of 2-aminomethyl quinuclidines has been prepared and tested by Rubtsov *et al.* (4). Some members of the series were found to have strong ganglionic blocking activity while one member, diethylaminoethylquinuclidine-2-carboxylate (5), was found to be a good hypotensive. Ganglionic blocking was also noticed with 2,3-disubstituted derivatives (6). Perrine (7) has synthesized a series of 4-phenyl substituted compounds for investigation as possible analgesics.

The research involved in this work devotes itself to the synthesis of a series of dibasic acid esters of 3-quinuclidinol and the preliminary pharmacological testing of these products. These compounds evoked one or more of the following pharmacological responses: local anesthetic activity, respiratory and vasomotor stimulation.

Eight new compounds were synthesized and are represented by the general formula, I. All products

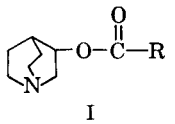
Received July 19, 1967, from Temple University School of Pharmacy, Philadelphia, PA 19140

Accepted for publication October 23, 1967.

Abstracted, in part, from a thesis presented by Hillel Lieberman in partial fulfillment of the requirements for the Master of Science degree.

The authors thank Dr. David Mann, Temple University School of Pharmacy, for his guidance in the pharmacological studies.

were prepared as the free base. A ninth compound, 3-quinuclidinyl hydrogen homophthalate, could not be isolated in sufficient purity for elemental analysis; however, it did show characteristic ester bands and gave a positive hydroxamic acid test.



I

| Compound | R |
|---|---|
| 1 | —$CH_2CH_2COOH$ |
| 2 | HOOC— |
| 3 | —CH=CHCOOH |
| 4 | —$(CH_2)_3COOH$ |
| 5 | HOOC— |
| 6 | HOOC— |
| 7 | —$CH_2CH(C_{10}H_{21})COOH$ |
| 8 | —$CH_2CH(C_{16}H_{33})COOH$ |

All compounds were prepared by alcoholysis, an acylation reaction between an anhydride and an alcohol (8). All types of alcohols are acylated by anhydrides. Cyclic anhydrides of dibasic acids are cleaved by alcohols to the monoester of the corresponding dibasic acid (9). The method employed for the preparation of the aforementioned compounds was a modification of that used by Eliel and Burgstahler (10).

The dibasic cyclic anhydrides were dissolved in boiling dry benzene containing varied amounts of pyridine. 3-Quinuclidinol, dissolved in hot dry benzene, was added to a refluxing solution of the anhydride and the mixture was allowed to reflux for 12 hr. In the case of the phthalic acid ester and the 2,3-pyridinedicarboxylic acid ester, white precipitates appeared during the reflux. These were filtered and subsequently purified. In all other cases, a clear solution was obtained at the end of the reflux period from which the product precipitated upon cooling. All yields were greater than 70%.

One of the compounds, 3-quinuclidinyl hydrogen, homophthalate was very hygroscopic. Attempts were also made to prepare the hydrochloride and methiodide salts. The methiodide salt was prepared by adding excess methyl iodide dropwise to an isopropanol solution of the ester and precipitating the methiodide salt with anhydrous ether. The gummy residue which formed was extremely hygroscopic and could not be crystallized. The hydrochloride salt was prepared by bubbling dry HCl into an alcoholic solution of the ester and precipitating the hydrochloride salt with anhydrous ether. This gummy precipitate could not be crystallized; however, it gave a positive hydroxamic acid test and the IR spectrum showed a characteristic ester band at 5.8 mμ.

## EXPERIMENTAL

All melting points are uncorrected. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Clarke Microanalytical Laboratory, Urbana, Ill.

**Preparation of 3-Quinuclidinyl Hydrogen Succinate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 7.5 Gm. (0.075 mole) succinic anhydride and 100 ml. of dry benzene. This mixture was heated and 15 ml. of pyridine was added. Then 9.6 Gm. (0.075 mole) of 3-quinuclidinol[1] dissolved in 50 ml. of hot dry benzene was added all at once. Upon addition, the solution immediately turned greenish yellow. The mixture was refluxed for 12 hr. whereupon a clear, colorless solution resulted. The solution was distilled at atmospheric pressure to remove 100 ml. of benzene. The remaining solution was then allowed to stand at room temperature for 36 hr. at the end of which time a white precipitate had separated. The precipitate was filtered and recrystallized three times from isopropanol and ether to yield 14.1 Gm. (82.8%) of a white, crystalline product; m.p. 141–143°.

*Anal.*—Calcd. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.24; H, 7.92; N, 5.90.

**Preparation of 3-Quinuclidinyl Hydrogen Phthalate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 11.1 Gm. (0.075 mole) of phthalic anhydride and 75 ml. of dry benzene. This mixture was heated and 5 ml. of pyridine was added. Then 9.6 Gm. (0.075 mole) of 3-quinuclidinol dissolved in 50 ml. of hot dry benzene was added all at once. The mixture was refluxed for 5 hr. whereupon a white precipitate formed. The mixture was cooled to room temperature and filtered with suction. This precipitate was recrystallized three times from hot isopropanol to yield 18.0 Gm. (85.9%) of a white, crystalline product; m.p. 253–255°.

*Anal.*—Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.70; H, 6.41; N, 4.99.

**Preparation of 3-Quinuclidinyl Hydrogen Maleate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 7.5 Gm. (0.075 mole) of maleic anhydride and 75 ml. of dry benzene. This mixture was kept at room temperature and 9.6 Gm. (0.075 mole) of 3-quinuclidinol dissolved in 50 ml. of hot dry benzene was added all at once. Upon addition, the solution immediately assumed a yellow color which turned brown within 10 min. After the solution turned brown, 50 ml. of pyridine was added all at once and a brown gelatinous mass was deposited on the bottom of the flask. The mixture was refluxed for 4 hr. at the end of which time, a brown gelatinous mass remained at the bottom of the flask. The solution was distilled at atmospheric pressure to remove 75 ml. of benzene. The remaining solution was then allowed to stand at room temperature for 36 hr. and filtered with suction. The precipitate was washed with ether and then dissolved in hot isopropanol The solution was cooled and the product reprecipitated with anhydrous ether. This pre-

[1] Supplied by U. S. Army Chemical Center, Edgewood, Maryland. Can be prepared by the method of Aaron, H. S., Elkin, S., Owens, O. O., Rosenstock, P. D., Leonard, S., and Miller, J. I., *J. Org. Chem.*, 30, 1331(1965).

cipitate was recrystallized three times from hot isopropanol and ether to yield 12.5 Gm. (73.9%) of product; m.p. 160–164°.

*Anal.*—Calcd. for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.65; H, 6.50; N, 5.95.

**Preparation of 3-Quinuclidinyl Hydrogen Glutarate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 8.6 Gm. (0.075 mole) of glutaric anhydride and 100 ml. of dry benzene. This mixture was heated and 25 ml. of pyridine was added. Then 9.6 Gm. (0.075 mole) of 3-quinuclidinol dissolved in 50 ml. of hot dry benzene was added all at once. The mixture was refluxed for 15 hr. whereupon a clear, colorless solution resulted. The solution was distilled at atmospheric pressure to remove 100 ml. of benzene. After allowing the solution to cool to room temperature, anhydrous ether was added until cloudiness developed. The mixture was then permitted to stand at room temperature for 30 hr. at the end of which time a white precipitate separated. The mixture was filtered and the residue washed with ether and dried at 50° for 30 min. The white crystalline powder was then dissolved in hot isopropanol and the solution allowed to come to room temperature. Anhydrous ether was added until a white precipitate formed. This precipitate was recrystallized three times from hot isopropanol and ether to yield 14.6 Gm. (80.7%) of a white crystalline product; m.p. 91–94°.

*Anal.*—Calcd. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.29; H, 7.95; N, 5.63.

**Preparation of 3-Quinuclidinyl Hydrogen 1,2-Cyclohexane Dicarboxylate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 11.6 Gm. (0.075 mole) of 1,2-cyclohexanedicarboxylic anhydride and 125 ml. of dry benzene. The mixture was heated and 20 ml. of pyridine was added. Then 9.6 Gm. (0.075 mole) of 3-quinuclidinol dissolved in 50 ml. of hot dry benzene was added all at once. The mixture was refluxed for 15 hr. whereupon a clear, colorless solution resulted. The solution was distilled at atmospheric pressure to remove 125 ml. of benzene. The remaining solution was then allowed to stand at room temperature for 36 hr. at the end of which time a white precipitate had separated. The mixture was filtered and the gummy white residue was washed with anhydrous ether. The residue was dissolved in hot isopropanol and, after cooling, anhydrous ether was added until a white precipitate formed. This precipitate was recrystallized three times from isopropanol and ether to yield 18.1 Gm. (87.7%) of a white, crystalline product; m.p. 205–206°.

*Anal.*—Calcd. for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.88; H, 8.30; N, 4.87.

**Preparation of 3-Quinuclidinyl Hydrogen 2,3-Pyridinedicarboxylate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 11.18 Gm. (0.075 mole) of 2,3-pyridinedicarboxylic anhydride and 150 ml. of dry benzene. The mixture was heated and 10 ml. of pyridine was added. Then, 9.6 Gm. (0.075 mole) of 3-quinuclidinol dissolved in 50 ml. of hot dry benzene was added all at once. The mixture was refluxed for 6 hr. whereupon a white precipitate formed. The mixture was cooled to room temperature and filtered with suction. This precipitate was recrystallized three times from isopropanol and ether to yield 19.6 Gm. (94.7%) of a white crystalline product; m.p. 218°.

*Anal.*—Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 59.86; H, 6.09; N, 10.10.

**Preparation of 3-Quinuclidinyl Hydrogen n-Decylsuccinate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 18.0 Gm. (0.075 mole) of *n*-decylsuccinic anhydride and 100 ml. of dry benzene. The mixture was heated and 25 ml. of pyridine was added. Then, 9.6 Gm. (0.075 mole) of 3-quinuclidinol, dissolved in 50 ml. of hot dry benzene, was added all at once. The mixture immediately developed an amber color. The mixture was refluxed for 18 hr. whereupon a clear, colorless solution resulted. The solution was distilled at atmospheric pressure until only a viscous oil remained. Upon cooling, the oil solidified to a white, waxy material. This was dissolved in a minimum amount of hot isopropanol and after cooling, anhydrous ether was added until a white precipitate formed. This precipitate was recrystallized three times from isopropanol and ether to yield 24.8 Gm. (89.8%) of a white, crystalline product; m.p. 100–103°.

*Anal.*—Calcd. for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 67.94; H, 10.18; N, 3.77.

**Preparation of 3-Quinuclidinyl Hydrogen n-Hexadecylsuccinate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 24.3 Gm. (0.075 mole) of *n*-hexadecylsuccinic anhydride and 125 ml. of dry benzene. The mixture was heated and 25 ml. of pyridine was added. Then 9.6 Gm. (0.075 mole) 3-quinuclidinol, dissolved in 50 ml. of hot dry benzene, was added all at once. The mixture immediately developed an amber color. The mixture was refluxed for 18 hr. whereupon a clear, colorless solution resulted. The solution was distilled at atmospheric pressure leaving a viscous oil. Upon cooling, the oil solidified to a white, waxy material. This was dissolved in the minimum amount of hot isopropanol and, after cooling, anhydrous ether was added until a white precipitate formed. This precipitate was recrystallized three times from isopropanol and ether to yield 30.7 Gm. (89.5%) of a white, crystalline product; m.p. 82–85°.

*Anal.*—Calcd. for $C_{27}H_{49}NO_4$: C, 71.79; H, 10.94; N, 3.10. Found: C, 71.05; H, 11.20; N, 3.27.

**Attempted Preparation of 3-Quinuclidinyl Hydrogen Homophthalate**—Into a 3-necked flask equipped with a stirrer, dropping funnel, and condenser were added 12.2 Gm. (0.075 mole) of homophthalic anhydride and 12.5 ml. of dry benzene. The mixture was heated and 15 ml. of pyridine was added. Then 9.6 Gm. (0.075 mole) of 3-quinuclidinol, dissolved in 50 ml. of hot, dry benzene, was added all at once. A dark brown gelatinous mass formed immediately. The mixture was refluxed for 8 hr. at the end of which time a clear amber solution resulted.

All attempts to extract the product from this solution yielded a brown, gelatinous, hygroscopic mass. Repeated trials to produce a crystalline compound (by purification and salt formation) failed.

The IR spectrum of this compound showed the characteristic ester bands and the compound gave a positive hydroxamic acid test.

## PHARMACOLOGY

All compounds were tested as aqueous solutions of the ester free base. Although each of the compounds synthesized has not, as yet, been investigated, information is available for a preliminary report. The conclusions drawn from the results should be accepted as tentative and preliminary to more thorough investigation.[2]

**Local Anesthetic Activity: Procedure**—Four rabbits were placed in rabbit boxes and the hair around the eyes was carefully clipped. The winking reflex was tested by gently touching the cornea with a glass rod. The lower lid of the rabbit's conjuctival sac was held to form a cup, and then four drops of a 1% solution of either procaine or one of the drugs tested were instilled. After instillation of the drug, the solution was allowed to remain in contact with the surface of the eyeball for 2 min. by gently pressing the lids together. Anesthesia was tested for, after 2 min., by touching the glass rod to the cornea. This testing was done at regular intervals in order to note the time required for the winking reflex to return to normal. After recovery from the effects of the drugs, a second trial was made (following the above procedure) in order to compare the duration of anesthesia with that attained in the first trial.

**Results**—Procaine was utilized for comparative anesthetic effects. Of the seven esters tested, five produced anesthesia in both trials for varying lengths of time. The two esters that gave negative results failed to produce anesthesia in either trial. All results are tabulated in Table I.

**Vasomotor and Respiratory Activity**—Compounds tested were 3-quinuclidinyl hydrogen glutarate and 3-quinuclidinyl hydrogen 2,3-pyridinedicarboxylate. A male dog was anesthetized with an i.p. injection of sodium pentobarbital. The dose given was 30 mg./Kg. of body weight. The animal was strapped to a bench and the hair was shaved from the neck region. A thin, longitudinal strip of skin in the middle of the neck was cut with a scissors to expose the longitudinal muscles and these were separated along the midline with a blunt forceps. The left carotid artery located in the carotid sheath beside and slightly below the trachea was exposed. A ligature was tied around the artery peripherally and a loose ligature was placed around the artery centrally. A bulldog clamp was placed on the most central portion (beyond the loose ligature) of the artery. During this procedure the entire exposed area was flooded with 10% sodium citrate solution. Then, a fluid-filled system for recording blood pressure was prepared. The system included a Bourdon blood pressure transducer attached to a sodium citrate filled glass cannula. This cannula, which was inserted into the artery, lead to the transducer which detected pressure changes and sent impulses to the recorder. A fluid filled system which included a U-shaped glass tube filled with mercury was used to standardize the blood pressure at intervals to be used as reference points. This was done by squeezing a rubber bulb to change the height of the mercury. After standardization, this manometer-type apparatus was disconnected.

[2] Procedures employed in the pharmacological evaluation were taken from: Mann, D. E., "A Laboratory Manual of Pharmacology," 3rd ed., Temple University, School of Pharmacy, Philadelphia, Pa., 1962–1964.

TABLE I—LOCAL ANESTHETIC ACTIVITY[a]

| Compound Tested | Duration of Anesthesia, min. |
|---|---|
| **Trial I** | |
| Procaine | 42 |
| 1 | ... |
| 2 | 20 |
| 3 | 12 |
| 4 | 10 |
| 5 | ... |
| 7 | 6 |
| 8 | 14 |
| **Trial II** | |
| Procaine | 28 |
| 1 | ... |
| 2 | 15 |
| 3 | 10 |
| 4 | 10 |
| 5 | ... |
| 7 | 12 |
| 8 | 15 |

[a] The duration of anesthesia does not include the 2 min. when the lids were compressed. All drugs were administered in a dose of 4 drops of 1% aqueous solution.

A V-shaped opening was cut halfway through the artery close to the peripheral ligature to allow for adequate insertion space. The artery was placed over the tip of the cannula and the loose ligature was tied securely around the arterial flap on the tip of the cannula. The bulldog clamp was removed and the area was checked for leakage of blood. The stopcock was opened and the pressure was recorded on the physiograph. Respiration was recorded by means of an impedance pneumograph which was attached to the skin on the chest of the animal.

The thigh area of the dog was shaved and the femoral vein exposed. It was cleared of extraneous matter and two ligatures were slipped around the vein. The vein was cut open and a needle was inserted. Each compound to be tested was injected through the exposed femoral vein. All exposed areas on the dog were kept saturated with the citrate solution.

There was a substantial increase in blood pressure produced upon the administration of 10 mg. of each of the compounds tested. Both compounds produced a marked increase in respiration.

## REFERENCES

(1) Sternbach, L. H., and Kaiser, S., *J. Am. Chem. Soc.*, **74**, 2219(1952).
(2) Mikhlina, E. E., and Rubtsov, M. V., *Zhur. Obshchei. Khim.*, **30**, 163(1960); through *Chem. Abstr.*, **54**, 22632(1960).
(3) Grob, C. A., U. S. pat. 2,917,515, (Dec. 15, 1959.)
(4) Nikitskaya, E. S., Usovskaya, V., and Rubtsov, M. V., *Zhur. Obshchei. Khim.*, **28**, 161(1958); through *Chem. Abstr.*, **52**, 12863*e*(1958).
(5) Rubtsov, M. V., Nikitskaya, E. S., and Usovskaya, V., *ibid.*, **26**, 130(1956); through *Chem. Abstr.*, **50**, 139041 (1956).
(6) Rubtsov, M. V., Mikhlina, E. E., and Yakhontov, L. N., *Russian Chem. Rev.*, **29**, 44(1960).
(7) Perrine, T. D., *J. Org. Chem.*, **22**, 1484(1957).
(8) Fieser, L. F., and Fieser, M., "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 392.
(9) Wagner, R. B., and Zook, H. D., "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1953, p. 482.
(10) Eliel, E. L., and Burgstahler, A. W., *J. Am. Chem. Soc.*, **71**, 2251(1949).
(11) Bellamy, L. J., "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1954, p. 152.
(12) *Ibid.*, pp. 161–163.
(13) *Ibid.*, p. 153.

**Keyphrases**

3-Quinuclidinol dibasic acid esters—synthesis
Alcohol-anhydride acylation reaction
Anesthetic activity, local—3-quinuclidinol esters
Vasomotor activity—3-quinuclidinol esters
Respiratory activity—3-quinuclidinol esters

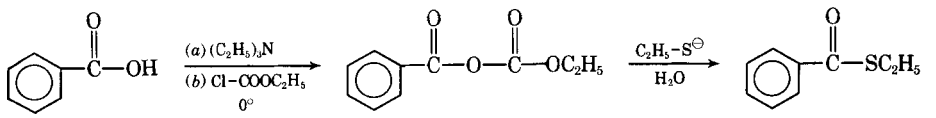
# α-Alkyloximino Acid Thiol Esters: New Class of Compounds Showing Antimalarial Activity

By DOMINICK A. COVIELLO and NORMAN L. HINES

**New derivatives of α-alkyloximino acids, the thiol esters, were prepared by modification of an application of mixed carboxylic-carbonic anhydrides. In general, the compounds show modest antimalarial activity, though one prolongs the lives of infected mice for more than 3 days longer than controls.**

IT IS THE PURPOSE of this communication to report the antimalarial activity of α-alkyloximinocarboxylic acid thiol esters prepared by a modification of a reported method (1). The method utilizes mixed carboxylic-carbonic anhydrides (acyl alkyl carbonates) which are decomposed by a mercaptan in the presence of triethylamine. The authors have found that aqueous solutions of mercaptides are equally efficient in the anhydride decomposition. The modification was inspired by a report that carboxamides are produced by reacting the acyl alkyl carbonates with aqueous ammonia (2) indicating that anhydrous conditions are not essential for success in the anhydride reaction.

In a model reaction, ethyl thiolbenzoate was prepared as follows:




It was found that a better elemental analysis for the product could be obtained in the case of the title compounds through the modified procedure.

The compounds prepared are shown in Table I.

**Biological Testing**—Groups of five mice were infected with *Plasmodium berghii*. Three days after challenge test compounds were administered subcutaneously The data are reported in Table II.

## EXPERIMENTAL

**α-Ethyloximinopropionic Acid**—This was obtained in 50% yield according to the procedure described by Ferris (3). It melted at 68–69°. Reported: 68–70°.

**α-Benzyloximinopropionic Acid**—The product was obtained by hypochlorite oxidation of the previously reported α-benzyloximinobutanone (3). The product melting at 84–85° was obtained in 52% yield. Reported melting point 84–85° (3).

**α-Methyloximinobutyric Acid**—Oxidation of α-methyloximino-2-pentanone in the manner described above gave a 13% yield of acid melting at 75–77°. Its confirmation was by elemental analysis of the thiol ester derivative (see Table I).

**α-Ethyloximinobutyric Acid**—The acid was prepared according to the procedure of Waters and Hartung (4). The yield was 48% and the melting point 58–59° was in agreement with the reported value.

**α-Benzyloximinobutyric Acid**—The product was obtained in 55% yield and had a melting point of 89–94° which was in agreement with the reported value (5).

**α-Ethyloximinocaproic Acid**—This was prepared in 82% yield according to the method of Waters and Hartung (5) and its boiling point of 76–80°/0.05

Received August 8, 1966, from the College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612

Accepted for publication October 13, 1967.

This investigation was supported by the University of Illinois Research Board and grant RH-00293-01 (MCHB) and RH-00293-02 (MCHB), National Center for Radiological Health, U. S. Public Health Service, Bethesda, Md.

Antimalarial testing and test data have been made available through the courtesy of Dr. David Jacobus, Walter Reed Army Institute of Research, Washington, D. C.

The technical assistance of J. C. Ziebell, W. L. Jacobson, and L. Sternson is also acknowledged.