The residue was poured into 20 ml. of cold, dry ethyl ether with vigorous stirring. The pink precipitate which formed, was collected on a filter, washed with 20 ml. cold, dry ethyl ether and dried in the absence of air at 25°; yield, 150 mg. The brominated histidine decomposed rapidly on exposure to air. It was soluble in water, ethanol and acetic acid, insoluble in ethyl ether. It was acid to methyl red and reacted with aqueous silver nitrate.

Anal. Calcd. for $C_6H_8O_2N_3Br \cdot 2HBr$: total Br, 60.57; Br as HBr, 5.05 ml. 0.1 *N* $AgNO_3$ per 100 mg. Found: total Br, 57.8; Br as HBr, 5.40 ml. 0.1 *N* $AgNO_3$ per 100 mg. These data are summarized in Table II.

Preparation of Bromozein Hydrobromide.—Ten grams of bromine in 500 ml. of glacial acetic acid was added slowly to a solution of 50 g. of zein in 450 ml. of 90% acetic acid. The reaction mixture was allowed to stand twenty-four hours at 25° in diffuse daylight and then poured slowly into 7 liters of dry ethyl ether with vigorous stirring. The white precipitate which formed, was collected on a filter, washed with 3 to 4 liters of dry ethyl ether and dried forty-eight hours at 50°; yield, 55.00 g. This solid was soluble in 90% acetic acid and 70% ethanol. It reacted with sodium hydroxide and silver nitrate in ethanol and liberated iodine from potassium iodide in acetic acid. An accelerated gelation test of bromozein hydrobromide in 70% ethanol showed only a slight tendency toward gel formation.

Anal. Moisture, 5.2; N, 12.90; amide N, 3.96; Br, 13.10; three samples, each of 500 mg., required 5.25 ml. 0.1 *N* NaOH, 5.25 ml. 0.1 *N* $AgNO_3$, and 1.50 ml. 0.1 *N* $Na_2S_2O_3$, respectively.

Preparation of Bromozein.—Zein was allowed to react with bromine as described in the preparation of bromozein hydrobromide. The reaction mixture was poured into 20 liters of 0.25% aqueous sodium chloride with vigorous stirring. The bromozein coagulated readily and the supernatant liquid was removed with a siphon. The product was resuspended in 20 liters of distilled water and allowed to settle. This washing process was repeated twice. The bromozein was collected on a filter and dried forty-eight hours at 50° and two hours at 105°; yield, 47.63 g. It was soluble in acetic acid and 70% ethanol but did not react with sodium hydroxide, silver nitrate, or potassium iodide. An accelerated gelation test of bromozein in 70% ethanol showed only a slight tendency toward gel formation.

Anal. N, 14.10; amide N, 4.06; Br, 5.34; C, 49.10.

The first supernatant liquid from the precipitation of bromozein was concentrated to 200 ml. and filtered. The addition of sodium hydroxide to this concentrate produced ammonia before and after digestion with sulfuric acid.

Conversion of Bromozein Hydrobromide into Bromozein.—An amount of 5 g. of bromozein hydrobromide was dissolved in 500 ml. of 0.05 *N* sodium hydroxide. The addition of 100 ml. of 2.5 *N* acetic acid to this solution resulted in the precipitation of a nearly white solid which was collected on a filter, dissolved in 10 ml. of glacial acetic acid, reprecipitated in dry ether, collected on a filter, washed free of acetic acid and dried forty-eight hours at 50° and two hours at 105°; yield, 4.3 g. It was soluble in acetic acid and 70% ethanol, but did not react with sodium hydroxide, silver nitrate, or potassium iodide.

Anal. N, 14.04; Br, 5.30; C, 49.02.

Control Experiment with Zein.—Five grams of zein was dissolved in 45 ml. of 90% acetic acid, allowed to stand twenty-four hours at 25° in diffuse daylight, and then poured into 2 liters of 0.25% aqueous sodium chloride with vigorous stirring. The zein was washed and dried as described in the preparation of bromozein: yield, 4.51 g.

Anal. N, 16.04.

The first supernatant liquid from the precipitation of zein was concentrated to 100 ml. and filtered. The addition of sodium hydroxide to this concentrate did not produce ammonia before or after digestion with sulfuric acid.

Acknowledgment.—This work was supported by the American Maize-Products Co., and the A. E. Staley Manufacturing Co. Acknowledgment is made of the counsel of Mr. W. L. Morgan.

Summary

1. A bromozein and its hydrobromide have been prepared.

2. Bromozein hydrobromide is acidic, reacts with silver nitrate and liberates iodine from potassium iodide. Sodium hydroxide converts it to bromozein.

3. Bromozein is neutral and does not react with silver nitrate or potassium iodide.

4. Bromozein and its hydrobromide have only a slight tendency toward gel formation.

COLUMBUS, OHIO RECEIVED NOVEMBER 8, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Preparation of Stable Ketimines from 2,2,6-Trimethylcyclohexanecarbonitrile

BY H. L. LOCHTE, JOE HORECZY,[1] P. L. PICKARD[2] AND A. D. BARTON[3]

In 1942 Horeczy isolated the very highly hindered 2,2,6-trimethylcyclohexanecarboxylic acid from California petroleum.[4] Shortly thereafter an attempt was made to synthesize the corresponding ketone by reaction of phenylmagnesium bromide with the nitrile of this acid. The usual Grignard synthesis yielded a very stable ketimine instead of the ketone.[5]

Since this ketimine is not hydrolyzed even on prolonged heating with acids or bases either in aqueous or alcoholic solution, and since it possesses other interesting properties, the corresponding methyl ketimine was prepared.[6] This ketimine is equally stable to hydrolysis, thus indicating that the abnormal stability is due mainly to the 2,2,6-

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(3) Du Pont Fellow 1947–1948.

(4) Shive, Horeczy, Wash and Lochte, THIS JOURNAL, **64**, 385 (1942).

(5) The observation that reaction of the nitrile with phenylmagnesium bromide produced a basic compound instead of a ketone was first made by William Shive in this Laboratory.

(6) P. L. Pickard, Ph.D. Dissertation, University of Texas, 1947.

trimethylcyclohexane group, rather than to the combination of the phenyl group and this group.[7]

It was thought that the corresponding aldimine (2,2,6-trimethylcyclohexanecarboxaldimine) might also be stable. Attempts to prepare this aldimine by partial hydrogenation of the nitrile have led only to complete reduction of the nitrile, the corresponding primary amine being the only product isolated.

It seemed possible that the unusual stability of these ketimines might be due to the fact that they possess an ene-amine structure. Accordingly, attempts were made to determine whether these compounds are primary or secondary amines. When treated with nitrous acid, no nitrogen is liberated, and each ketimine yields a neutral liquid compound which contains two atoms of nitrogen per molecule. Although attempts to purify these compounds were unsuccessful, they appear to be nitroso derivatives. Treatment of either ketimine with chloroform, ethanol and sodium hydroxide solution does not produce an isonitrile odor; each ketimine gives a monobenzenesulfonamide derivative which is insoluble in 10% (or more dilute) sodium hydroxide solution. However, since these ketimines are unusually unreactive, and since the hydrochloride of the phenyl ketimine is extremely insoluble in water, the results of the amine tests given above did not appear to be entirely conclusive. Therefore, attempts were made to prepare the corresponding primary amines by reduction of the ketimines.

On hydrogenation in the presence of Adams platinum catalyst, the phenyl ketimine takes up three moles of hydrogen but the reduction product gives the same amine reactions as the starting material. Apparently, only the benzene ring is hydrogenated. The methyl ketimine does not take up hydrogen in the presence of Adams catalyst. In alcoholic solution, neither compound is reduced by 3% sodium amalgam. When treated with sodium in liquid ammonia containing 5% methanol, each ketimine yields a reduction product which reacts as follows: when treated with nitrous acid each reduction product liberates the calculated volume of nitrogen; when treated with chloroform, ethanol and sodium hydroxide solution each gives a characteristic isonitrile odor; but each gives a monobenzenesulfonamide derivative insoluble in sodium hydroxide solution.

On hydrogenation with Adams catalyst or on reduction with sodium in liquid ammonia containing methanol, the nitrile (2,2,6-trimethylcyclohexanecarbonitrile) gives the same reduction product; this reduction product gives the same primary amine reactions as the reduction products of the ketimines.

Since these two ketimines react like secondary amines in the isonitrile and nitrous acid tests before they are reduced and since they yield reduction products which react like primary amines, it is probable that these compound do possess the ketimine structure which is abnormally stable due to steric hindrance.

(7) Quite recently, the preparation of a stable ketimine was reported by Schultz, Robb and Sprague, THIS JOURNAL, **69**, 2454 (1947).

Experimental

2,2,6-Trimethylcyclohexanecarbonitrile.—This nitrile was prepared from the corresponding acid *via* the acid chloride and the amide as described previously.[4]

Phenyl 2,2,6-Trimethylcyclohexyl Ketimine.—Phenylmagnesium bromide was prepared by the addition of 20.4 g. of bromobenzene to 3.15 g. of magnesium in anhydrous ether; 18.6 g. of 2,2,6-trimethylcyclohexanecarbonitrile dissolved in anhydrous ether was added and the mixture was refluxed for twelve hours. When the reaction mixture was poured into cold, dilute sulfuric acid, 22 g. of a solid sulfate salt of a base separated; 9 g. of unreacted nitrile was recovered from the ether layer. When the sulfate salt was treated with dilute sodium hydroxide solution a liquid was obtained which on fractionation yielded 13.2 g. (90% based on nitrile not recovered) of a compound characterized by the following data: b. p. 310° (750 mm.); d^{20}_4 0.9842; $n^{20}D$ 1.5406; MR_D calcd. 72.87; found 73.18.

Anal. Calcd. for $C_{16}H_{23}N$ as a secondary amine: C, 83.83; H, 10.12; N, 6.05; primary amino N, none; mol. wt., 229. Found: C, 83.47; H, 10.21; N, 6.11; primary amino N (Van Slyke), none; mol. wt. (in acetone), 236.

The ketimine dissolved readily in concentrated hydrochloric acid; when the resulting solution was neutralized most of the ketimine separated in the form of a hydrochloride salt which was extremely insoluble in water. The ketimine was liberated very slowly from this salt even in the presence of a strongly alkaline solution.

One drop of the ketimine, 3 drops of chloroform and 5 drops of ethanol were mixed and shaken continuously with 5 ml. of 10% sodium hydroxide solution and heated intermittently on a steam cone for five minutes. Even after the mixture had been allowed to stand for some time, no isonitrile odor was detected.

The benzenesulfonamide derivative was prepared by heating the ketimine with a slight excess of benzenesulfonyl chloride in pyridine solution on a steam cone for two hours. The mixture was then poured into a large volume of water and the material which separated was recrystallized from 50% aqueous alcohol, yielding small colorless needles: m. p. 114.5–116°. All of the benzenesulfonamide derivatives described in this paper are insoluble in 10% or more dilute sodium hydroxide solution.

Anal. Calcd. for $C_{22}H_{27}NO_2S$: N, 3.79. Found: N, 3.76.

The nitroso derivative was prepared by adding an aqueous sodium nitrite solution to a solution of the ketimine in ethanol containing hydrochloric acid. The solution was evaporated and the residue was extracted with ether. The ether extract was washed with dilute aqueous acetic acid and then with water. After the solution was dried with Drierite (anhydrous calcium sulfate) the ether was evaporated and the viscous residue was dried *in vacuo* over calcium chloride. Analysis indicated 8.27% nitrogen, whereas the value calculated for the pure nitroso derivative, $C_{16}H_{22}N_2O$, is 10.64. Although attempts to prepare this nitroso derivative (as well as the nitroso derivative of the methyl ketimine) in pure form were unsuccessful, it is evident that the treatment with nitrous acid introduced a second nitrogen atom into the molecule, whereas the nitrogen atom already present should have been eliminated had the compound been an eneamine.

Methyl 2,2,6-Trimethylcyclohexyl Ketimine.—Methylmagnesium iodide was prepared by the addition of 23.1 g. of methyl iodide to 3.96 g. of magnesium in anhydrous ether; 7.38 g. of 2,2,6-trimethylcyclohexanecarbonitrile in 100 ml. of anhydrous toluene was added, the ether was distilled off and the mixture was heated on a steam cone

for twenty hours. The resulting solution was poured on a mixture of chipped ice and ammonium chloride and was then extracted with ether. The ether layer was extracted with hydrochloric acid and the acid layer was then made strongly basic with sodium hydroxide and extracted with ether. The ether extract was dried and evaporated, leaving a liquid residue which, when distilled, yielded 7.5 g. (94%) of a compound with the following characteristics: b. p. 79–80° (4 mm.); d^{20}_4 0.8957; $n^{20}D$ 1.4730; MR_D calcd. 53.15, found 52.72.

Anal. Calcd. for $C_{11}H_{21}N$ as a secondary amine: N, 8:37; primary amine N, none. Found: N, 8.60; primary amino N, none.

When tested, this ketimine produced no isonitrile odor.

The benzenesulfonamide derivative was prepared by shaking a few drops of the ketimine with a slight excess of benzenesulfonyl chloride in 10% aqueous sodium hydroxide solution. Since the product did not crystallize, it was extracted with ether and the ether extract was washed with dilute acid, then with dilute alkali and finally with water; after the solution was dried, the ether was evaporated and the liquid residue was dried *in vacuo*.

Anal. Calcd. for $C_{17}H_{25}NO_2S$: N, 4.55. Found: N, 4.27.

The picrate of the ketimine was prepared in ethanol solution and recrystallized from aqueous ethanol: m. p. 143–144°.

Anal. Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.06. Found: N, 14.21.

The nitroso derivative was prepared by adding a solution of the ketimine hydrochloride to a solution of sodium nitrite. The red liquid which separated was extracted with ether and the ether solution was washed with dilute acid, then with dilute alkali and finally with water. After the solution was dried and treated with charcoal, the ether was evaporated and the yellow viscous residue was dried *in vacuo*. Analysis indicated 12.12% nitrogen; the value calculated for the pure nitroso derivative, $C_{11}H_{20}N_2O$, is 14.26.

Attempted Hydrolysis of the Ketimines.—Each ketimine was refluxed for eight to ten hours with aqueous hydrochloric acid solution (37%) and with aqueous (33%) and alcoholic (10%) potassium hydroxide solutions without showing any evidence of hydrolysis.

Each ketimine was refluxed for eight hours with 50% aqueous potassium hydroxide solution containing 10% ethanol; each mixture was then steam distilled and the distillate was tested for ammonia with Nessler reagent. In each case the distillate contained some unchanged ketimine but no trace of ammonia was detected.

A small sample of each ketimine was dissolved in concentrated sulfuric acid and heated on a steam cone for one hour. Each solution was then cooled and poured into a large volume of water. The resulting solutions were made strongly alkaline with 50% potassium hydroxide solution and then steam distilled. Each distillate contained some unreacted ketimine but showed no trace of ammonia present when tested with Nessler reagent. The nitrile (2,2,6-trimethylcyclohexanecarbonitrile) was converted quantitatively to the corresponding amide (2,2,6-trimethylcyclohexanecarboxamide) when heated with concentrated sulfuric acid on a steam cone for one hour, and poured into a large volume of water.

Reduction of Phenyl 2,2,6-Trimethylcyclohexyl Ketimine. (a) Hydrogenation with Adams Catalyst.—When 317.4 mg. (1.38 millimoles) of phenyl 2,2,6-trimethylcyclohexyl ketimine dissolved in 50 ml. of methanol containing 1 ml. of glacial acetic acid was shaken with 14 mg. of Adams platinum catalyst in an atmosphere of hydrogen at room temperature and pressure, 94.0 cc. (4.20 millimoles) of hydrogen were absorbed. The catalyst was filtered off and the filtrate was evaporated to one fifth of its original volume; 20 ml. of water was added, the mixture was made strongly alkaline with sodium hydroxide and then extracted with ether. One portion of the ether solution was evaporated and the liquid residue was used for the isonitrile test and to prepare the benzenesulfonamide derivative of the reduction product. The other portion of the ether solution was shaken with the calculated quantity of concentrated hydrochloric acid solution. The cyclohexyl 2,2,6-trimethylcyclohexyl ketimine hydrochloride, which separated as a white solid, was washed with ether and with water and was dried *in vacuo*. Analysis indicated no primary amino nitrogen present.

When tested, this catalytic reduction product produced no isonitrile odor.

The benzenesulfonamide derivative of the catalytic reduction product was prepared in pyridine solution. This derivative proved to be a liquid, and it was purified in the same manner as the benzenesulfonamide derivative of methyl 2,2,6-trimethylcyclohexyl ketimine.

Anal. Calcd. for $C_{22}H_{33}NO_2S$: N, 3.73. Found: N, 3.82.

The picrate of the catalytic reduction product was prepared in ethanol solution and recrystallized from aqueous ethanol: m. p. 168–170°.

Anal. Calcd. for $C_{22}H_{32}N_4O_7$: N, 12.06. Found: N, 12.15.

(b) Reduction with Sodium Amalgam.—A sample of phenyl 2,2,6-trimethylcyclohexyl ketimine in 95% ethanol was stirred for twelve hours with 3% sodium amalgam. The ketimine was recovered unchanged and there was no evidence to indicate that any of the ketimine had been reduced.

(c) Reduction with Sodium and Methanol in Liquid Ammonia.—Reduction by means of sodium in liquid ammonia containing methanol was carried out under the conditions described by Watt, Knowles and Morgan.[8] To 100 ml. of liquid ammonia containing 5 ml. of anhydrous methanol was added 1.0 ml. of phenyl 2,2,6-trimethylcyclohexyl ketimine. Over a period of an hour, approximately 1.5 g. of sodium was added in small pieces and the mixture was stirred continuously. The gummy ketimine slowly disappeared and a copious white precipitate accumulated. The ammonia was allowed to evaporate, water was added and the mixture was extracted with ether. The reduction product and its hydrochloride were obtained in the same manner as the catalytic reduction product of phenyl 2,2,6-trimethylcyclohexyl ketimine.

Anal. Calcd. for α-phenyl-2,2,6-trimethylcyclohexanemethylamine hydrochloride, $C_{16}H_{26}NCl$: primary amino N, 5.23. Found: primary amino N, 5.40, 5.14.

When tested, this reduction product gave a characteristic isonitrile odor.

The benzenesulfonamide derivative was prepared in pyridine solution. The crude product was recrystallized three times from 95% ethanol, yielding small colorless needles: m. p. 193–195°. This sulfonamide, like the others, was insoluble in dilute sodium hydroxide solution.

Anal. Calcd. for $C_{22}H_{29}NO_2S$: N, 3.77. Found: N, 3.94.

On hydrogenation in the presence of Adams catalyst, 60.0 mg. (0.224 millimole) of the reduction product (hydrochloride) absorbed 15.7 cc. (0.70 millimole) of hydrogen, apparently indicating that the benzene ring was not attacked when the phenyl ketimine was treated with sodium in liquid ammonia containing methanol.

Reduction of Methyl 2,2,6-Trimethylcyclohexyl Ketimine. (a) Hydrogenation with Adams Catalyst.—When a small quantity of methyl 2,2,6-trimethylcyclohexyl ketimine dissolved in methanol containing acetic acid was shaken with Adams catalyst in an atmosphere of hydrogen at room temperature and pressure, no hydrogen was absorbed.

(b) Reduction with Sodium Amalgam.—A small quantity of methyl 2,2,6-trimethylcyclohexyl ketimine was treated with 3% sodium amalgam in the manner described above. The ketimine was recovered unchanged and there was no evidence to indicate that any of the ketimine had been reduced.

(8) Watt, Knowles and Morgan, THIS JOURNAL, **69**, 1657 (1947).

(c) **Reduction with Sodium and Methanol in Liquid Ammonia.**—Methyl 2,2,6-trimethylcyclohexyl ketimine in liquid ammonia containing methanol was treated with sodium and the reduction product was isolated according to the procedure described above. The ether solution containing the reduction product was washed repeatedly with water, dried with Drierite and evaporated. The liquid residue was dried *in vacuo* over calcium chloride.

Anal. Calcd. for α-methyl-2,2,6-trimethylcyclohexanemethylamine, $C_{11}H_{23}N$: primary amino N, 8.27. Found: primary amino N, 8.31, 7.99.

When tested, this reduction product gave a characteristic isonitrile odor.

The benzenesulfonamide derivative of the reduction product was prepared in 10% sodium hydroxide solution. The solid material which separated was recrystallized twice from 50% aqueous ethanol to yield colorless needles: m. p. 121–122°.

Anal. Calcd. for $C_{17}H_{27}NO_2S$: N, 4.53. Found: N, 4.68.

Reduction of 2,2,6-Trimethylcyclohexanecarbonitrile. (a) Hydrogenation with Adams Catalyst.—2,2,6-Trimethylcyclohexanecarbonitrile was hydrogenated with Adams catalyst and the reduction product and its hydrochloride salt were isolated according to the procedure described above; 156.5 mg. (1.03 millimoles) of the nitrile absorbed 47.4 cc. (2.12 millimoles) of hydrogen.

Anal. Calcd. for 2,2,6-trimethylcyclohexanemethylamine hydrochloride, $C_{10}H_{22}NCl$: primary amino N, 7.31. Found: primary amino N, 7.42, 7.32.

When tested, this reduction product produced an isonitrile odor.

The benzenesulfonamide derivative of the reduction product was prepared in sodium hydroxide solution. The product was recrystallized twice from 50% ethanol, to give colorless needles: m. p. 111–112°.

Anal. Calcd. for $C_{16}H_{25}NO_2S$: N, 4.77. Found: N, 4.74.

Attempts were made to achieve partial hydrogenation of the nitrile by carrying out the hydrogenation in a small volume of methanol containing an excess of concentrated hydrochloric acid. In all cases, the only compounds isolated were the unreacted nitrile and the fully hydrogenated primary amine described above.

(b) **Reduction with Sodium and Methanol in Liquid Ammonia.**—2,2,6 - Trimethylcyclohexanecarbonitrile in liquid ammonia containing methanol was treated with sodium in the manner described above. The benzenesulfonamide derivative of the reduction product was prepared in 10% sodium hydroxide solution: m. p. and mixed m. p. with the benzenesulfonamide derivative of the catalytic reduction product of 2,2,6-trimethylcyclohexanecarbonitrile, 111–112°, indicating that the two methods give the same reduction product, 2,2,6-trimethylcyclohexanemethylamine.

Summary

1. Phenyl 2,2,6-trimethylcyclohexyl ketimine and methyl 2,2,6-trimethylcyclohexyl ketimine have been prepared by treating 2,2,6-trimethylcyclohexanecarbonitrile with phenylmagnesium bromide and methylmagnesium iodide, respectively. These ketimines are not hydrolyzed even on prolonged heating in the presence of concentrated acid or alkali.

2. It appears that these compound possess the ketimine structure because, before reduction, they react like secondary amines to the isonitrile and nitrous acid tests and they yield reduction products which react like primary amines.

3. It is concluded that the abnormal stability of these compounds is due to steric hindrance.

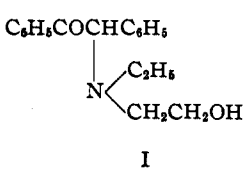
AUSTIN, TEXAS RECEIVED NOVEMBER 17, 1947

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

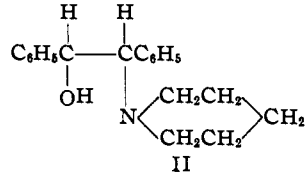
Secondary and Tertiary Amino Ketones and Alcohols Derived from Desoxybenzoin and 1,2-Diphenylethanol.[1] Ring-Chain Tautomerism of the α-(β-Hydroxyethylamino) Ketones[2]

BY ROBERT E. LUTZ, JAMES A. FREEK[3a] AND ROBERT S. MURPHEY[3b]

This investigation was initiated in the fall of 1942 in connection with the search for new types of antimalarials.[2a] The compounds obtained,[4] however, showed no significant activity against avian malaria. At the instigation of Dr. J. L. Hartwell they were then tested at the National Cancer Institute for activity against mammalian tumors, because of their relationship to the nuclear - substituted 1,2 - diphenylethylamines,[5] $ArCH_2CH(NH_2)Ar$, which had already been under investigation as tumor-necrotizing agents. Two of the new compounds when tested in mice gave evidence,[6] at high dosage, of damage to sarcoma 37; these two compounds were α-[N-ethyl-N-(β-hydroxyethyl)-amino]-desoxybenzoin [supposed at the time to have the open-chain structure (I)],



I



II

(1) Agents Causing Necrosis in Tumors. I. This is the first of a series of papers dealing with the search for compounds which may have significance in the hemical treatment of tumors.

(2) (a) The smaller part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia; (b) the larger part of this work was carried out under a Grant-in-Aid from the National Cancer Institute.

(3) (a) Present location, Department of Pharmacology, University of Virginia Medical School, Charlottesville, Va.; (b) at present holder of a National Cancer Institute Junior Research Fellowship.

(4) These compounds, fourteen in number, which were tested against avian malaria, are listed in the Tables I and II, and are designated by SN numbers which locate them in the "Survey of Antimalarial Drugs, 1941–1945" (by F. Y. Wiselogle, published by J. W. Edwards, 1946).

(5) Hartwell and Kornberg, THIS JOURNAL, 67, 1606 (1945).

(6) Unpublished work of Shear, Downing, MacCardle, Hartwell, *et al.*, at the National Cancer Institute.