and, therefore, it was converted to the hydrochloride by treating with one equivalent of *N* hydrochloric acid. Removal of solvent *in vacuo* left a crystalline solid which was purified by several crystallizations from absolute ethanol–ether; yield 0.2 g., m. p. 176–177° (cor.), softens at 170°. The substance formed colorless elongated prisms which are slightly hygroscopic.

*Anal.* Calcd. for $C_9H_{18}O_3NCl$: C, 48.32; H, 8.11; N, 6.26. Found: C, 48.25; H, 8.29; N, 6.25.

**Methiodide of VII.**—The mother liquor from the crystallization of 2-(1-hydroxyethyl)-1-pyrrolidineacetic acid hydrochloride (see above) was taken to dryness *in vacuo*. The residual oil (1.2 g.) was taken up in 40 cc. of distilled water and shaken with a slight excess of freshly precipitated silver carbonate for twenty-five minutes. After filtering off the silver chloride formed, the filtrate was extracted with several 30-cc. portions of ether. The combined ethereal extracts were dried over anhydrous potassium carbonate and the ether removed by distillation. The basic oil which remained (0.5 g.) was divided into two equal portions and used for the preparation of a methiodide and picrate. The methiodide was prepared by dissolving the first portion in 5 cc. of dry acetone and refluxing the solution with 1 cc. of methyl iodide for thirty minutes. On cooling crystallization occurred; yield 0.25 g. The substance was purified by several crystallizations from absolute ethanol–ether; long fine prisms, m. p. 242–243° (cor.).

*Anal.* Calcd. for $C_9H_{18}O_2NI$: C, 36.38; H, 5.42. Found: C, 36.53; H, 5.55.

*Rotation.* 0.1232 g. made up to 5 cc. with methanol at 29° gave $\alpha^{29}D$ −0.37; *l*, 1; $[\alpha]^{29}D$ −15.02.

**Picrate of VII.**—The second portion of the basic oil was dissolved in 5 cc. of absolute ethanol and a saturated solution of picric acid in ethanol added. The picrate that separated was purified by crystallization from 95% ethanol; yellow prisms, m. p. 169–170° (cor.).

*Anal.* Calcd. for $C_{14}H_{18}N_4O_9$: C, 43.75; H, 4.20; N, 14.58. Found: C, 44.06; H, 4.40; N, 14.77.

**Conversion of 2-(1-Hydroxyethyl)-1-pyrrolidineacetic Acid to the Lactone (VII).**—A mixture of 0.20 g. of the hydrochloride of 2-(1-hydroxyethyl)-1-pyrrolidineacetic acid and 8 cc. of acetic anhydride was heated on the steam cone for one and one-half hours. All of the hydrochloride was in solution after fifteen to twenty minutes heating. The acetic anhydride was removed *in vacuo* at 60° and the dark brown product which remained was taken up in 5 cc. of water. This solution was treated with freshly precipitated silver carbonate, filtered, and extracted with several portions of ether. After drying, the ethereal extract was concentrated to 6–8 cc. and 5 cc. of a saturated solution of picric acid in ethanol added. The yield of purified picrate was 0.07 g.; m. p. 169–170°, mixed melting point with the picrate described above produced no depression.

## Summary

1. The unsaturated base, isoheliotridene (IV), has been prepared from desoxyretronecine (II) in two steps.

2. Ozonolysis of the hydrochloride of isoheliotridene leads to the formation of 2-acetyl-1-pyrrolidineacetic acid (V). This substance was characterized by preparation of a 2,4-dinitrophenylhydrazone and by reduction to the carbinol (VI). The carbinol lost water readily to yield a lactone and formed a betaine upon treatment with diazomethane.

3. The isolation of this amino acid on ozonolysis definitely establishes the position of the double bond in isoheliotridene and retronecine as being between carbon atoms 1 and 2.

URBANA, ILLINOIS RECEIVED JULY 2, 1943

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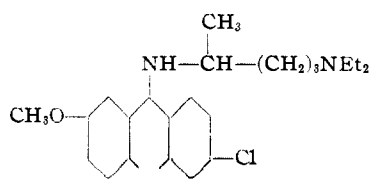
[CONTRIBUTION FROM THE PARKE, DAVIS & COMPANY RESEARCH LABORATORIES]

# N-Substituted 2-Methoxy-6-chloro-9-aminoacridines

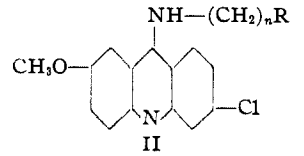
BY J. H. BURCKHALTER, ELDON M. JONES, W. F. HOLCOMB AND L. A. SWEET

Since the discovery of atabrine (I) by Mietzsch and Mauss,[1] a great number of acridine compounds have been synthesized by chemists throughout the world. The most promising of these from the standpoint of antimalarial activity have been derivatives of 9-aminoacridine, many of which follow a rather uniform pattern (II).

In this Laboratory, several compounds of Type II in which there are wide variations of the R group, as well as a few simple aromatic and heterocyclic derivatives of 9-aminoacridine, were




I




II

$n$ = 1, 2, 3, etc.
R = $NEt_2$, $NMe_2$

prepared. The variations include aliphatic, aro-

(1) Mietzsch and Mauss, *Angew. Chem.*, **47**, 633 (1934) [*C. A.*, **28**, 7360 (1934)].

TABLE I

INTERMEDIATES

| β-Substituent | Yield, % | B. p. °C. | Mm. | $n^{20}D$ | Formula | N Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| **A. Propionitriles** | | | | | | | |
| Di-*n*-propylamino | 90 | 104–105 | 10 | 1.4372 | $C_9H_{18}N_2$ | 18.16 | 18.42 |
| Di-isopropylamino | 12 | 100–102 | 13 | 1.4397 | $C_9H_{18}N_2$ | 18.16 | 18.09 |
| Di-*n*-butylamino[a] | 96 | 127–131 | 11 | 1.4403 | $C_{11}H_{22}N_2$ | 15.37 | 15.01 |
| Di-isobutylamino | 51 | 116–117 | 10 | 1.4378 | $C_{11}H_{22}N_2$ | 15.37 | 15.14 |
| *n*-Amylamino | 88 | 112–113 | 10 | 1.4400 | $C_8H_{16}N_2$ | 19.98 | 19.53 |
| Di-*n*-octylamino | 80 | 180–182 | 2 | 1.4513 | $C_{19}H_{38}N_2$ | 9.51 | 9.21 |
| Di-β′-ethylhexylamino | 65 | 163–164 | 2 | | $C_{18}H_{38}N_2$ | 9.51 | 9.26 |
| Ethyl-β′-hydroxyethylamino[b] | 72 | 133–134 | 7 | 1.4590 | $C_7H_{14}N_2O$ | | |
| *n*-Butyl-β′-hydroxyethylamino[c] | 61 | 147–148 | 7 | 1.4563 | $C_9H_{18}N_2O$ | | |

[a] U. S. Patent 1,992,615 gives b. p. 140–142° (22 mm.); 64% yield. [b] Analyzed as the picrate, m. p. 72–74°. Calcd. for $C_{12}H_{17}N_5O_8$: C, 42.52; H, 4.62. Found: C, 42.24; H, 4.55. [c] Analyzed as the picrate, m. p. 62–63°. Calcd. for $C_{15}H_{21}N_5O_3$: N, 17.54. Found: N, 17.45.

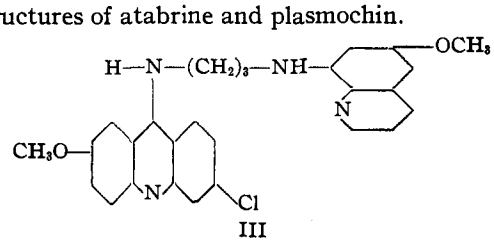
B. Propylamines

| γ-Substituent | Yield, % | B. p. °C. | Mm. | Dipicrate M. p., °C. | Formula | Analyses, % Calcd. C | H | Found C | H |
|---|---|---|---|---|---|---|---|---|---|
| Di-*n*-propylamino | 81 | 91–93 | 15 | 180–181 | $C_{21}H_{28}N_8O_{14}$ | 40.91 | 4.58 | 40.95 | 4.53 |
| Di-isopropylamino | 61 | 98–99 | 15 | 211–213 d. | $C_{21}H_{28}N_8O_{14}$ | 40.91 | 4.58 | 40.96 | 4.64 |
| Di-*n*-butylamino | 70 | 121–123 | 16 | 182–184 | $C_{23}H_{32}N_8O_{14}$ | 42.86 | 5.00 | 42.66 | 5.07 |
| Di-isobutylamino | 62 | 104–108 | 10 | 190–192 d. | $C_{23}H_{32}N_8O_{14}$ | 42.86 | 5.00 | 42.84 | 4.80 |
| *n*-Amylamino | 61 | 102–103 | 15 | 173–174 | $C_{20}H_{26}N_8O_{14}$ | 39.87 | 4.35 | 39.63 | 4.25 |
| Ethyl-β′-hydroxyethylamino[a] | 60 | 130–131 | 15 | | | | | | |
| *n*-Butyl-β′-hydroxyethylamino[a] | 55 | 147–148 | 15 | | | | | | |

[a] Amine condensed directly with 2-methoxy-6,9-dichloroacridine.

matic, and heterocyclic amino groups and also several simple substituents, such as hydroxyl, chloro and carboxyl.

It is well known that most acridine antimalarials display a characteristic schizonticidal action, whereas quinolines usually show greater activity against the gametocidal form of the plasmodium. It was of interest, therefore, to prepare 2-methoxy-6-chloro-9-[γ-(6′-methoxy-8′-quinolylamino)-propylamino]-acridine (III) and similar derivatives which combine the essential structures of atabrine and plasmochin.




III

Several dialkylaminoalkylaminoacridines were prepared by addition of appropriate secondary amines to acrylonitrile,[2] reduction of the nitriles to the corresponding amines,[2] and condensation of these amines with 2-methoxy-6,9-dichloroacridine. Reaction between the dioctylamines and acrylonitrile did not occur at 50°, but condensation was easily effected in a pressure vessel at 100°. The yields of nitrile obtained varied directly with the time of heating, a maximum being reached at about a hundred hours.

Some heterocyclic substituted aliphatic amines were prepared according to the method of Baldwin[3] and Robinson,[4] and a few aromatic-aliphatic amines were also obtained by a modified Gabriel synthesis. Samples of γ-(β′-diethylaminoethoxy)-propylamine, γ-(2′-amino-4′-pyrimidylamino)-propylamine, and ω-(2′-amino-4′-pyrimidylamino)-hexylamine were supplied by Dean F. C. Whitmore and Dr. H. S. Mosher of the Pennsylvania State College, State College, Pa. Details of their preparation will appear in THIS JOURNAL.

The intermediate N-substituted β-aminopropionitriles and corresponding propylamines are listed in Table I, while the 2-methoxy-6-chloro-9-aminoacridines appear in Table II.

A number of the dialkylaminoalkylaminoacridines listed in Table II were prepared by Procedure I, which is essentially that described by Mietzsch and Mauss[5] and involves the condensa-

(2) Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

(3) Baldwin, *J. Chem. Soc.*, 2959 (1929).

(4) Robinson and Tomlinson, *ibid.*, 1524 (1934).

(5) I. G. Farbenindustrie, German Patent 553,072 (1930) [*C. A.* **26**, 4683 (1932)].

TABLE II

2-METHOXY-6-CHLORO-9-AMINOACRIDINES

Compounds 1, 2, 3, 4, 5, 7, 12 and 17 were prepared by Procedure I; compounds 6, 8, 21, 22 and 23 by Procedure II; and compounds 9, 13, 14, 15, 16, 18, 19, 20, 24 and 25 by Procedure III.

| | 9-Substituent | M. p., °C. | Yield, % | Formula | N Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|
| 1 | γ-Di-*n*-propylaminopropylamino[a] | 228–229 d. | 45 | $C_{23}H_{30}ClN_3O\cdot 2HCl$ | 8.89 | 8.99 |
| 2 | γ-Di-isopropylaminopropylamino[a] | 227–230 d. | 62 | $C_{23}H_{30}ClN_3O\cdot 2HCl$ | 8.89 | 8.73 |
| 3 | γ-Di-*n*-butylaminopropylamino[a] | 200–201 | 50 | $C_{25}H_{34}ClN_3O\cdot 2HCl$ | 8.39 | 8.22 |
| 4 | γ-Di-isobutylaminopropylamino[a] | 219–221 d. | 73 | $C_{25}H_{34}ClN_3O\cdot 2HCl$ | 8.39 | 8.29 |
| 5 | γ-*n*-Amylaminopropylamino[b] | 90–91 | 65 | $C_{22}H_{28}ClN_3O$ | 10.89 | 10.84 |
| 6 | γ-Di-*n*-amylaminopropylamino[a] | 165–166 | 63 | $C_{27}H_{43}ClN_3O\cdot 2HCl$ | 7.94 | 7.92 |
| 7 | γ-Ethyl-β′-hydroxyethylaminopropylamino[a] | 246-247 d. | 65 | $C_{21}H_{27}ClN_3O_2\cdot 2HCl$ | 9.19 | 9.19 |
| 8 | γ-*n*-Butyl-β′-hydroxyethylaminopropylamino[a] | 180–182 | 53 | $C_{23}H_{30}ClN_3O_2\cdot 2HCl$ | 8.60 | 8.52 |
| 9 | β-Hydroxyethylamino[c] | 201–202 | 55 | $C_{15}H_{15}ClN_2O_2$ | 9.26 | 9.29 |
| 10 | β-Chloroethylamino[d] | 265 d. | 64 | $C_{16}H_{14}Cl_2N_2O\cdot HCl$ | 7.83 | 7.91 |
| 11 | Carboxymethylamino | 248 d. | 58 | $C_{16}H_{13}ClN_2O_3$ | 8.84 | 8.57 |
| 12 | γ-(4′-Diethylaminophenylamino)-propylamino | 185 d. | 79 | $C_{27}H_{31}ClN_4O\cdot 2HCl$ | 10.46 | 10.26 |
| 13 | Phenylamino | 199–201 | 65 | $C_{20}H_{15}ClN_2O$ | 8.37 | 8.27 |
| 14 | 4′-Dimethylaminophenylamino | 187–188 | 66 | $C_{22}H_{20}ClN_3O$ | C, 69.93 | C, 69.86 |
| | | | | | H, 5.34 | H, 5.46 |
| 15 | 4′-Diethylaminophenylamino | 127–129 d. | 48 | $C_{24}H_{24}ClN_3O$ | 10.35 | 10.26 |
| 16 | 4′-Methoxyphenylamino | 177–179 | 79 | $C_{21}H_{17}ClN_2O_2$ | 7.68 | 7.53 |
| 17 | γ-(β′-Diethylaminoethoxy)-propylamino[a] | 221–222 d. | 40 | $C_{23}H_{30}ClN_3O_2\cdot 2HCl$ | 8.60 | 8.40 |
| 18 | 3′-Pyridylamino[e] | 202–203 d. | 57 | $C_{19}H_{14}ClN_3O\cdot H_2O$ | C, 64.50 | C, 64.38 |
| | | | | | H, 4.56 | H, 4.55 |
| 19 | γ-(2′-Amino-4′-pyrimidylamino)-propylamino | 221–222 | 75 | $C_{21}H_{21}ClN_6O$ | C, 61.68 | C, 61.39 |
| | | | | | H, 5.18 | H, 5.36 |
| 20 | ω-(2′-Amino-4′-pyrimidylamino)-hexylamino | 217–220 d. | 80 | $C_{24}H_{27}ClN_6O$ | C, 63.92 | C, 63.96 |
| | | | | | H, 6.04 | H, 5.86 |
| 21 | γ-(6′-Methoxy-8′-quinolylamino)-propylamino[a] | 241–242 d. | 76 | $C_{27}H_{25}ClN_4O_2\cdot 2HCl$ | C, 59.41 | C, 59.23 |
| | | | | | H, 4.98 | H, 5.03 |
| 22 | ω-(6′-Methoxy-8′-quinolylamino)-butylamino[a] | 231–233 | 48 | $C_{28}H_{27}ClN_4O_2\cdot 2HCl$ | C, 60.06 | C, 60.03 |
| | | | | | H, 5.22 | H, 5.03 |
| | | | | | N, 10.00 | N, 9.73 |
| 23 | ω-(6′-Methoxy-8′-quinolylamino)-amylamino[a] | 135–138 d. | 55 | $C_{29}H_{29}ClN_4O_2\cdot HCl$ | 10.42 | 10.23 |
| 24 | γ-(2′-Methoxy-6′-chloro-9′-acridylamino)-propylamino[a] | 189–190 d. | 72 | $C_{31}H_{26}Cl_2N_4O_2$ | 10.05 | 9.79 |
| 25 | γ-(2′-Methoxy-6′-chloro-9′-acridylamino)-β,β-dimethylpropylamino[a] | 112–113 | 60 | $C_{33}H_{30}Cl_2N_4O_2$ | 9.57 | 9.46 |

[a] Forms a stable hydrate; analytical data are for the anhydrous compound. [b] Recrystallized from ethanol. [c] German Patent 553,072 [*C. A.*, **26**, 4684 (1932)] gives m. p. 191–192°. [d] Mentioned in German Patent 553,072 but not described. [e] Loses water at 150° C.

tion of 2-methoxy-6,9-dichloroacridine with the appropriate amine followed by purification of the free base by treatment with dilute acetic acid. A few heterocyclic aminoalkylaminoacridines, found to be insoluble in dilute acetic acid, were made by Procedure II, and several miscellaneous derivatives were precipitated directly, according to Procedure III, as yellow crystalline bases from phenolic solutions by the addition of dilute sodium hydroxide. The 2-methoxy-6-chloro-9-(β-chloroethylamino)-acridine was easily derived from the corresponding β-hydroxyethylaminoacridine, while 2-methoxy-6-chloro-9-carboxymethylaminoacridine was obtained from the condensation of glycine and 2-methoxy-6,9-dichloroacridine.

Nearly all the compounds described in Table II have been tested for their antimalarial action against *P. cathemerium* in canaries by Professor A. L. Tatum of the University of Wisconsin. Details of the results of testing will be reported by Professor Tatum.

## Experimental

**β-Di-(β′-ethylhexyl)-aminopropionitrile.**—A well mixed solution of 15.9 g. (0.30 mole) of acrylonitrile and 48.2 g. (0.20 mole) of di-(β-ethylhexyl)-amine was placed in a small pressure bottle and heated in a steam-bath for one hundred hours. The product was distilled twice from a modified Claisen flask and the fraction boiling at 163–164° (2 mm.) collected; yield 38 g. (65%).

**β-Di-*n*-octylaminopropionitrile.**—This nitrile was prepared in exactly the same manner as β-di-(β′-ethylhexyl)-aminopropionitrile.

**γ-(4-Diethylaminophenylamino)-propylphthalimide.**—A mixture of 21.4 g. (0.13 mole) of *p*-aminodiethylaniline and 35 g. (0.13 mole) of γ-bromopropylphthalimide was heated in an oil-bath at 120–130° for six hours. The hard black residue was taken up in hot alcohol, filtered, and the filtrate concentrated to dryness. The oily residue was treated with 10% ammonia and, after washing several times with water, the residue became solid. The product was taken up in acetone and treated with Darco; the solvent was removed and the phthalimide recrystallized from 85% ethanol; m. p. 106–107°.

*Anal.* Calcd. for $C_{21}H_{25}N_3O_2$: N, 11.96. Found: N, 11.91.

**4-(γ-Aminopropylamino)-diethylaniline.**—A solution of 8 g. (0.02 mole) of γ-(4-diethylaminophenylamino)-propylphthalimide in 25 cc. of ethanol was refluxed for one hour with 1.5 cc. (0.025 mole) of 85% hydrazine hydrate. The solvent was removed from the solid reaction product and the residue warmed in the steam-bath for twenty minutes with an excess of 10% hydrochloric acid. The mixture was cooled, filtered, and the filtrate neutralized with ammonia. The amine was extracted with chloroform and, after drying over potassium carbonate, the solvent was removed. The crude oil weighed 4.5 g. and was used without further purification for condensation with 2-methoxy-6,9-dichloroacridine.

**Procedure I (Compounds 1, 2, 3, 4, 5, 7, 12 and 17).**—A mixture of 13.9 g. (0.05 mole) of 2-methoxy-6,9-dichloroacridine and 60 g. of phenol was heated in the steam-bath until solution was effected. To the hot phenolic solution was added 0.05 mole of the desired amine over a period of fifteen minutes. The reaction mixture was then heated with occasional shaking for three hours. The cooled solution was poured into an excess of cold 2 *N* sodium hydroxide and the product extracted with ether. Purification was effected by treating the ether solution with dilute acetic acid, and then the product was precipitated from the ether layer by the addition of alcoholic hydrogen chloride.

The hydrochlorides of these aliphatic substituted acridines crystallize readily from either methanol–acetone, ethanol–acetone, or methanol–ether mixtures.

**Procedure II (Compounds 6, 8, 21, 22 and 23).**—A mixture of 13.9 g. (0.05 mole) of 2-methoxy-6,9-dichloroacridine and 60 g. of phenol was heated in the steam-bath for fifteen minutes, after which 3.5 g. (0.025 mole) of potassium carbonate was added to the hot solution. After heating for another fifteen minutes, 0.05 mole of the desired amine was added. The mixture was heated with occasional stirring for four hours. The hot phenolic solution was poured cautiously into 500 cc. of ether and the phenol removed by washing with 2 *N* sodium hydroxide solution. The ethereal extract was washed well with water, dried over potassium carbonate, and filtered. The hydrochloride was precipitated by the addition of alcoholic hydrogen chloride.

These hydrochlorides crystallize readily from either methanol, ethanol, ethanol-acetone, or ethanol-ether mixtures.

**Procedure III (Compounds 9, 13, 14, 15, 16, 18, 19, 20, 24 and 25).**—A mixture of 13.9 g. (0.05 mole) of 2-methoxy-6,9-dichloroacridine and 60 g. of phenol was heated in the steam-bath until solution was effected, whereupon 0.05 mole of the appropriate amine was added and heating continued for three hours. (For compounds 24 and 25, only 0.025 mole of the diamine was used.) The cooled mixture was poured into an excess of 2 *N* sodium hydroxide solution and a colored solid usually precipitated at once. The product was recrystallized from either ethanol, dilute ethanol or cellosolve.

**2-Methoxy-6-chloro-9-(β-chloroethylamino)-acridine.**—The addition of 10 cc. of thionyl chloride to 2 g. of 2-methoxy-6-chloro-9-(β-hydroxyethylamino)-acridine resulted in an immediate reaction. The mixture was heated in the steam-bath for thirty minutes, cooled, and poured into ice-water. After all the thionyl chloride had decomposed, the yellow solid was filtered and washed well with water and then with ethanol. The product was treated with a 10% solution of sodium hydroxide and the acridine base extracted with chloroform. The chloroform layer was washed with water and dried over potassium carbonate. The solvent was evaporated to 20 cc. and diluted with 30 cc. of ethanol. Addition of an excess of alcoholic hydrogen chloride gave a yellow crystalline hydrochloride, which showed no elevation in melting point after recrystallization from alcohol.

**2-Methoxy-6-chloro-9-carboxymethylaminoacridine.**—A mixture of 13.9 g. (0.05 mole) of 2-methoxy-6,9-dichloroacridine and 60 g. of phenol was heated in the steam-bath until solution was effected, after which 4.5 g. (0.06 mole) of glycine was added and heating continued for five hours. Dilution with ether precipitated a yellow solid, which was washed well with ether and warm ethanol. The product was purified by twice precipitating it from an alkaline solution with hydrochloric acid and once with acetic acid. Finally, the compound was recrystallized from aqueous acetic acid.

The authors wish to express their appreciation to Dr. J. F. Olin, Sharples Solvents Corporation, Wyandotte, Mich., for samples of ethyl-β-hydroxyethylamine, butyl-β-hydroxyethylamine, di-*n*-propylamine, di-isopropylamine, di-*n*-butylamine, di-isobutylamine, di-*n*-amylamine, and di-*n*-octylamine. All micro analytical determinations were made by Arthur W. Spang, Margaret McCarthy, and Clara Johnston of Parke, Davis & Company.

## Summary

A number of intermediate N-substituted β-aminopropionitriles and corresponding propylamines have been prepared and their properties tabulated.

Twenty-five N-substituted 2-methoxy-6-chloro-9-aminoacridines have been described. These compounds include dialkylaminoalkylaminoacridines, aromatic and heterocyclic aminoalkylaminoacridines and miscellaneous N-substituted aminoacridines.

DETROIT, MICH. RECEIVED JULY 15, 1943