# Synthesis of δ-Aminolaevulinic Acid Analogues as Potential Antimalarial Agents

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As part of a study of the synthesis of potential antimalarial agents, a number of analogues of δ-aminolaevulinic (5-amino-4-oxopentanoic) acid were prepared: (1) methyl 5-(morpholino-, piperidino-, or *N*-methylbenzylamino-)4-oxopentanoate, (2) 1-amino-4-(phenyl- or *p*-chlorophenyl)sulphonylbutan-2-one hydrochloride, (3) 1-(benzoyl- or nicotinoyl-)2-glycylhydrazine hydrobromide, (4) 1-glycyl-2-(*p*-tolyl- or *p*-chlorophenyl-)sulphonylhydrazine hydrobromide, (5) glycine phenacyl- or *p*-bromophenacyl-amide hydrobromide, (6) glycine 2-(phenyl- or *p*-tolyl-)sulphonylethylamide hydrobromide, and (7) 1-ethoxycarbonyl-2-glycylhydrazine hydrochloride.

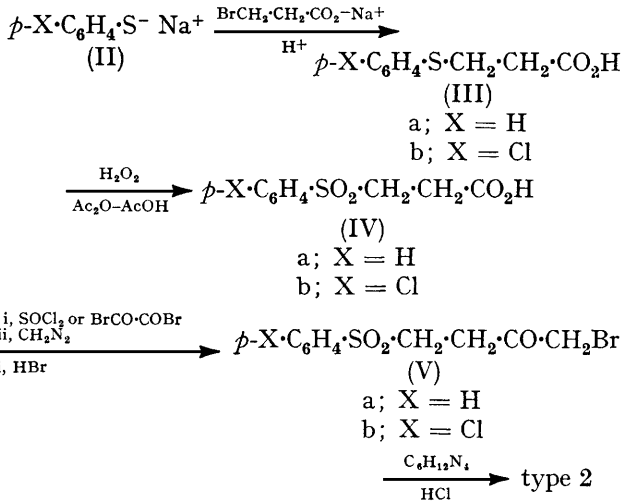
In view of the current need for effective agents against drug-resistant malarial parasites and of the significant role of δ-aminolaevulinic (5-amino-4-oxopentanoic) acid (I) in the metabolism of porphyrins,[1] a number of analogues of (I) have been synthesised.

$$NH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$
(I)

*Type* 1: $RCH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$ (R = morpholino, piperidino, or *N*-methylbenzylamino).—These compounds were synthesised by reaction of methyl δ-chlorolaevulinate [2] with secondary amines.

*Type* 2: $\overset{+}{N}H_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2R\ Cl^-$ (R = phenyl or *p*-chlorophenyl).—These compounds were synthesised as shown in Scheme 1.

The synthesis of compounds (IIIa) and (IIIb) was based on that described by Krollpfeiffer and Schultze.[3,4] Oxidation of these compounds with 30% hydrogen peroxide in acetic acid–acetic anhydride [5] gave compounds (IVa) and (IVb), the m.p. of the former agreed with that reported by Otto,[6] who prepared the compound from sodium benzenesulphinate and 3-iodopropionic acid. Compound (IVb) was identical with that prepared by Gresham *et al.*,[7] from propiolactone and *p*-chlorobenzenesulphinic acid (17%) or sodium *p*-chlorobenzenesulphinate (4%). In view of the relative inaccessibility of 3-iodopropionic acid and the poor yields of 3-*p*-chlorophenylsulphonylpropionic acid reported by




Scheme 1

previous investigators, the present method, which gave excellent yields of 3-arylsulphonylpropionic acids, constitutes a considerable improvement. Compound (IVa)

[1] D. Shemin, 'The Succinate-Glycine Cycle,' in Ciba Foundation Symposium on Porphyrin Biosynthesis and Metabolism, Little, Brown and Company, Boston, Massachusetts, 1955.
[2] A. Neuberger and J. J. Scott, *J. Chem. Soc.*, 1954, 1820.
[3] F. Krollpfeiffer and H. Schultze, *Ber.*, 1923, **56***B*, 1891.
[4] F. Krollpfeiffer, H. Schultze, H. Schlumbohm, and H. Sommermeyer, *Ber.*, 1925, **58**B, 1654.
[5] A. Pomerantz and R. Connor, *J. Amer. Chem. Soc.*, 1939, **61**, 3386.
[6] R. Otto, *Ber.*, 1888, **21**, 95.
[7] T. L. Gresham *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 1323.

TABLE 1

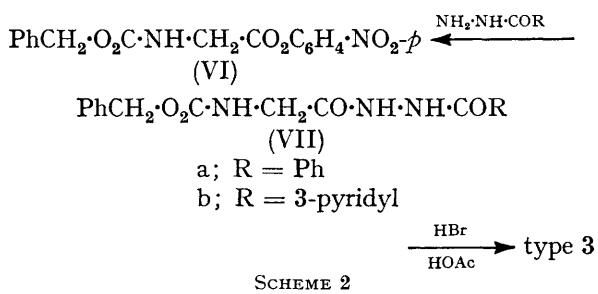
δ-Aminolaevulinic acid analogues X·$CH_2$·CO·Y·Z

| Compound | X | Y | Z | Yield (%) | M.p. | Recryst. solvent |
|---|---|---|---|---|---|---|
| 1 | $C_5H_{10}N$ | $CH_2$·$CH_2$ | $CO_2Me$ | 61 | *a* | *b* |
| 2 | $C_4H_8ON$ | $CH_2$·$CH_2$ | $CO_2Me$ | 60 | *c* | *d* |
| 3 | $MeNCH_2Ph$ | $CH_2$·$CH_2$ | $CO_2Me$ | 70 | *e* | *f* |
| 4 | Br | $CH_2$·$CH_2$ | $SO_2Ph$ | 15 | 98—100° | $CHCl_3$–pet *g* |
| 5 | Br *h* | $CH_2$·$CH_2$ | $SO_2$·$C_6H_4$Cl-*p* | 25 | 134—136 | EtOH |
| 6 | $Cl^-$ $^+NH_3$ | $CH_2$·$CH_2$ | $SO_2Ph$ | 77 | 121—123 | BuOH |
| 7 | $Cl^-$ $^+NH_3$ | $CH_2$·$CH_2$ | $SO_2$·$C_6H_4$Cl-*p* | 93 | 190—192 | BuOH |
| 8 | $PhCH_2$·$O_2C$·NH | NH·NH | Bz | 78 | 161—163 | EtOH |
| 9 | $PhCH_2$·$O_2C$·NH | NH·NH | 3-CO·$C_5H_4N$ | 86 | 158—160 | EtOH |
| 10 | $Br^-$ $^+NH_3$ | NH·NH | Bz | 100 | 261·5—264 (decomp.) | EtOH–$H_2O$ |
| 11 | $Br^-$ $^+NH_3$ | NH·NH | 3-CO·$C_5H_4N$ | 100 | 281—283° (decomp.) | MeOH |
| 12 | $PhCH_2$·$O_2C$·NH | NH·NH | $SO_2$·$C_6H_4$Me-*p* | 62 | 180—182 | MeOH |
| 13 | $PhCH_2$·$O_2C$·NH | NH·NH | $SO_2$·$C_6H_4$Cl-*p* | 78 | 212—214·5 | $H_2O$–DMF *i* |
| 14 | $Br^-$ $^+NH_3$ | NH·NH | $SO_2$·$C_6H_4$Me-*p* | 100 | 234—236 | EtOH–$Et_2O$ |
| 15 | $Br^-$ $^+NH_3$ | NH·NH | $SO_2$·$C_6H_4$Cl-*p* | 78 | 239—240 | MeOH–$Et_2O$ |
| 16 | $PhCH_2$·$O_2C$·NH | NH·$CH_2$ | CO·$C_6H_4$Br-*p* | 100 | 177—179 | EtOAc–$CHCl_3$ |
| 17 | $PhCH_2$·$O_2C$·NH | NH·$CH_2$ | Bz | 50 | 116—118 | EtOH |
| 18 | $Br^-$ $^+NH_3$ | NH·$CH_2$ | CO·$C_6H_4$Br-*p* | 100 | 216—218 (decomp.) | MeOH–EtOH |
| 19 | $Br^-$ $^+NH_3$ | NH·$CH_2$ | Bz | 100 | 193—195 (decomp.) | MeOH |
| 20 | $PhCH_2$·$O_2C$·NH | NH·$CH_2$·$CH_2$ | $SO_2Ph$ | 77 | 84—86 | EtOH |
| 21 | $PhCH_2$·$O_2C$·NH | NH·$CH_2$·$CH_2$ | $SO_2$·$C_6H_4$Me-*p* | 88 | 106—109 | EtOH |
| 22 | $Br^-$ $^+NH_3$ | NH·$CH_2$·$CH_2$ | $SO_2$·Ph | 100 | 196—197 | BuOH |
| 23 | $Br^-$ $^+NH_3$ | NH·$CH_2$·$CH_2$ | $SO_2$·$C_6H_4$Me-*p* | 100 | 212—214 | BuOH |

*a* $n_D^{25}$ 1·4650. *b* B.p. 110—114°/0·75 mm. *c* $n_D^{25}$ 1·4522. *d* B.p. 132—134°/0·25 mm. *e* Semisolid. *f* B.p. 120—122°/0·05 mm. *g* Light petroleum (b.p. 30—60°). *h* Oxalyl chloride used in place of thionyl chloride. *i* Dimethylformamide.

was converted into its acid bromide by stirring at room temperature with an excess of thionyl bromide. The product was not purified but treated directly with diazomethane and hydrogen bromide to give compound (Va) (15% overall). Use of oxalyl bromide in place of thionyl bromide resulted in a 25% overall conversion of (IVb) into (Vb). Bromomethyl ketones have been converted into aminomethyl ketones by use of hexamethylenetetrammine and subsequent acid hydrolysis;[8,9] this method was used to convert compound (V) to compounds of type 2.

*Type* 3: $^+NH_3$·$CH_2$·CO·NH·NH·COR $Br^-$ (R = phenyl or 3-pyridyl).—These compounds were synthesised as shown in Scheme 2. Whereas benzyloxycarbonylglycine




SCHEME 2

*p*-nitrophenyl ester[10] (VI) reacted readily with aromatic acid hydrazides, reaction with aromatic sulphonic acid hydrazides was sluggish and gave considerable amounts of benzyloxycarbonylglycine amide.

*Type* 4: $^+NH_3$·$CH_2$·CO·NH·NH·$SO_2$R $Br^-$ (R = *p*-tolyl or *p*-chlorophenyl).—Compounds of this type were prepared by tosylation of benzyloxycarbonylglycine hydrazide and subsequent debenzyloxycarbonylation.

*Type* 5: $^+NH_3$·$CH_2$·CO·NH·$CH_2$·COR $Br^-$ (R = phenyl or *p*-bromophenyl) *and type* 6:

$^+NH_3$·$CH_2$·CO·NH·$CH_2$·$CH_2$·$SO_2$R $Br^-$ (R = phenyl or *p*-tolyl).—Use of phenacylamine hydrobromide and *p*-bromophenacylamine hydrobromide (prepared from *p*-bromophenacyl bromide and hexamethylenetetrammine)

TABLE 2

Analyses

| Compound | Formula | Required (%) C | H | N | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|
| 1 | $C_{11}H_{19}NO_3$ | 61·9 | 8·9 | 6·6 | 61·9 | 8·8 | 6·5 |
| 2 | $C_{10}H_{17}NO_4$ | 55·8 | 8·0 | 6·5 | 55·5 | 7·7 | 6·3 |
| 3 | $C_{14}H_{19}NO_3$ | 67·5 | 7·7 | 5·6 | 67·7 | 7·8 | 5·7 |
| 4 | $C_{10}H_{11}BrO_3S$ *a* | 41·3 | 3·8 | | 41·4 | 3·7 | |
| 5 | $C_{10}H_{10}BrClO_3S$ | 36·9 | 3·1 | | 37·0 | 2·9 | |
| 6 | $C_{10}H_{14}ClNO_3S$ *b* | 45·5 | 5·4 | 5·3 | 45·7 | 5·4 | 5·3 |
| 7 | $C_{10}H_{13}Cl_2NO_3S$ *c* | 40·2 | 4·4 | 4·7 | 40·1 | 4·8 | 4·6 |
| 8 | $C_{17}H_{17}N_3O_4$ | 62·4 | 5·2 | 12·8 | 62·3 | 4·9 | 13·0 |
| 9 | $C_{16}H_{16}N_4O_4,\frac{1}{2}H_2O$ | 56·8 | 5·1 | 16·6 | 56·6 | 5·1 | 16·6 |
| 10 | $C_9H_{12}BrN_3O_2$ | 39·4 | 4·4 | 15·3 | 39·1 | 4·5 | 15·2 |
| 11 | $C_8H_{12}Br_2N_4O_2$ | 27·0 | 3·4 | 15·7 | 27·0 | 3·1 | 15·8 |
| 12 | $C_{17}H_{19}N_3O_5S$ | 54·1 | 5·1 | 11·1 | 53·9 | 5·2 | 11·3 |
| 13 | $C_{16}H_{16}ClN_3O_5S$ *d* | 48·3 | 4·1 | 10·6 | 48·3 | 3·9 | 10·9 |
| 14 | $C_9H_{14}BrN_3O_3S$ | 33·3 | 4·4 | 13·0 | 33·5 | 4·2 | 12·7 |
| 15 | $C_8H_{11}BrClN_3O_3S$ | 27·9 | 3·2 | 12·2 | 27·8 | 3·3 | 12·3 |
| 16 | $C_{18}H_{17}BrN_2O_4$ | 53·3 | 4·2 | 6·9 | 53·6 | 4·2 | 6·9 |
| 17 | $C_{18}H_{18}N_2O_4$ | 66·2 | 5·6 | 8·6 | 66·5 | 5·8 | 8·8 |
| 18 | $C_{10}H_{12}Br_2N_2O_2$ | 34·1 | 3·4 | 8·0 | 34·4 | 3·4 | 8·0 |
| 19 | $C_{10}H_{13}BrN_2O_2$ | 44·0 | 4·8 | 10·3 | 44·1 | 4·8 | 10·1 |
| 20 | $C_{18}H_{20}N_2O_5S$ | 57·4 | 5·4 | 7·4 | 57·6 | 5·3 | 7·2 |
| 21 | $C_{19}H_{22}N_2O_5S$ | 58·5 | 5·7 | 7·2 | 58·5 | 5·8 | 7·1 |
| 22 | $C_{10}H_{15}BrN_2O_3S$ | 37·2 | 4·7 | 8·7 | 37·3 | 4·6 | 8·4 |
| 23 | $C_{11}H_{17}BrN_2O_3S$ | 39·2 | 5·1 | 8·3 | 39·3 | 5·0 | 8·3 |

*a* Found: Br, 27·3. Required: Br, 27·4%. *b* Found: Cl, 13·2. Required: Cl, 13·4%. *c* Found: Cl, 23·8. Required: Cl, 23·8%. *d* Found: Cl, 9·0. Required: Cl, 8·9%.

[8] K. Miescher and H. Kaegi, *Helv. Chim. Acta*, 1941, **24**, 1471.
[9] L. L. Bambas, H. D. Troutman, and L. M. Long, *J. Amer. Chem. Soc.*, 1950, **72**, 4445.
[10] M. Bodanszky and V. du Vigneaud, *J. Amer. Chem. Soc.*, 1959, **81**, 5688.
[11] S. Gabriel and J. Colman, *Ber.*, 1911, **14**, 3628.
[12] S. Gabriel, *Ber.*, 1907, **40**, 2648.

in place of the acid hydrazides in Scheme 2 gave compounds of type 5. Compounds of type 6 were prepared by use of the appropriate 2-aminoethyl aryl sulphone hydrochlorides [11] in Scheme 2.

*Type* 7: $\overset{+}{N}H_3 \cdot CH_2 \cdot CO \cdot NH \cdot NH \cdot CO_2Et\ Cl^-$. This compound was prepared from the reaction of phthalimidoacetyl chloride [12] and ethyl hydrazinoformate. The 1-ethoxycarbonyl-2-phthalimidoacetylhydrazine obtained (86%) was converted into the final product (81%) by hydrazinolysis.

The physical properties and analytical data for all the compounds described are summarised in the Tables.

## EXPERIMENTAL

*Methyl 5-Morpholinolaevulinate* (*5-Morpholino-4-oxopentanoate*).—Methyl 5-chlorolaevulinate [2] (8·3 g., 0·05 mole) dissolved in ether (50 ml.) was added dropwise with stirring to a solution of morpholine (8·7 g., 0·1 mole) in ether (50 ml.). The mixture was set aside for 2 days and the precipitated morpholine hydrochloride was filtered off. Concentration of the filtrate and distillation of the oily residue gave 7·0 g. of *product*.

3-p-*Chlorophenylsulphonylpropionic Acid* (IVb).—3-(*p*-Chlorophenylthio)propionic acid [4] (93·0 g., 0·43 mole) was dissolved in glacial acetic acid–acetic anhydride (1 : 1; 440 ml.). The stirred solution was cooled to 0° and 30% hydrogen peroxide (116 ml.) was added dropwise. The mixture in the ice bath was gradually warmed to room temperature and then set aside at room temperature for 5 days. It was then added to ice–water (1·5 l.) and the precipitated *solid* (91·5 g.) was collected.

1-*Bromo*-4-p-*chlorophenylsulphonylbutan*-2-*one* (Vb).—Oxalyl bromide (50·0 g., 0·22 mole) was added dropwise with stirring to 3-*p*-chlorophenylsulphonylpropionic acid (25·0 g., 0·1 mole) suspended in dry benzene (400 ml.). The solution was heated under reflux for 2·5 hr., then stirred overnight at room temperature; the mixture was then concentrated *in vacuo*. Dry benzene (200 ml.) was added and the mixture was concentrated again. This process was repeated. The solid obtained was dissolved in chloroform (200 ml.) and added dropwise at −10° to 500 ml. of an ethereal solution (500 ml.) of diazomethane prepared from finely powdered *N*-methyl-*N*-nitrosourea (31·0 g.). The mixture was set aside for 2 days. Anhydrous hydrogen bromide was then bubbled through for 5 hr. at −5 to −10°. The solvents were removed *in vacuo* and the solidified residue yielded pure *product* (8·0 g.) after recrystallisation.

1-*Amino*-4-p-*chlorophenylsulphonylbutan*-2-*one Hydrochloride*.—A solution of 1-chloro-4-*p*-chlorophenylsulphonylbutan-2-one (6·5 g., 0·02 mole) and hexamethylenetetrammine (2·8 g., 0·02 mole) in chloroform (100 ml.) was stirred for 24 hr. as the adduct precipitated from solution. The solid was collected and heated under reflux for 30 min. in a solution of ethanol (90 ml.) and 9N-hydrochloric acid (7·5 ml.). A tan *solid* (5·5 g.) was deposited by the cooled solution.

1-*Benzyloxycarbonylglycyl*-2-*nicotinoylhydrazine* (VIIb).—A solution of benzyloxycarbonylglycine *p*-nitrophenyl ester [10] (16·5 g., 0·05 mole) and nicotinic acid hydrazide (6·9 g., 0·05 mole) in dimethylformamide (100 ml.) was warmed on a steam-bath for 3 hr. The solution was poured into ice–water (500 ml.) and the precipitated solid, after recrystallisation, afforded the *product* (14·0 g.).

1-*Glycyl*-2-*nicotinoylhydrazine Dihydrobromide*.—1-Benzyloxycarbonylglycyl-2-nicotinoylhydrazine (5·0 g., 0·015 mole) was added to glacial acetic acid (60 ml.) saturated with hydrogen bromide. The suspension was stirred at room temperature for 1 hr. After the addition of ether (250 ml.), a *solid* (5·5 g.) was collected.

1-*Benzyloxycarbonylglycyl*-2-p-*chlorophenylsulphonylhydrazine*.—Benzyloxycarbonylglycine hydrazide (12·5 g., 0·056 mole) was dissolved in pyridine (150 ml.), cooled to 5° in an ice-bath with stirring, and *p*-chlorobenzenesulphonyl chloride (11·8 g., 0·056 mole) was added in small portions. The bath was removed and the solution was stirred for 4 hr. The pyridine was removed *in vacuo* and the solid residue (17·5 g.) was collected after trituration with water.

*Benzyloxycarbonylglycine p-Bromophenacylamide*.—A solution of benzyloxycarbonylglycine *p*-nitrophenylester [10] (6·6 g., 0·02 mole) and *p*-bromophenacylamine hydrobromide (6·0 g., 0·02 mole) in dimethylformamide (90 ml.) was stirred at room temperature and sodium hydrogen carbonate (1·7 g., 0·02 mole) in water (20 ml.) was added dropwise. The mixture was stirred for 20 hr. at room temperature, then added to ice–water (300 ml.) to give the *product* (8·0 g.).

-*Ethoxycarbonyl*-2-*phthalimidoacetylhydrazine*.— Ethyl hydrazinoformate (10·4 g., 0·1 mole) and triethylamine (13·8 ml., 0·1 mole) were dissolved in dry acetonitrile (100 ml.), stirred, and cooled to 5°; phthalimidoacetyl chloride [12] (22·4 g., 0·1 mole) was added in portions. The temperature rose to 35°. After 30 min. the ice-bath was removed and stirring was continued for 30 min. The mixture was then heated under reflux for 30 min. During this time the precipitated solid dissolved. The acetonitrile was then removed *in vacuo*, water (100 ml.) was added to the residue and the *solid* (25·0 g.) was collected.

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