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1. *Synthesis of Lipophilic Chemotherapeuticals. Part I.*

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Experiments are recorded on the synthesis of representatives of known (and new) chemotherapeutically active types, which contain fatty or steroid residues and are, therefore, expected to show lipophilic character. The types investigated are quinine, azo-dyes, arsanilic acid, azo-systems containing arsonic acid groups, and quinoline. Some synthetic experiments in the acridine and the cetylaniline series are also reported.

4-Cetylaminoazobenzene-4'-arsonic acid exhibits a surprisingly low toxicity.

The systematic synthesis of substances expected to have chemotherapeutical value is based on Ehrlich's postulate that they should have affinity for the tissue forming the cell-wall of the parasite but not for that of the host. There are still a few maladies in which chemotherapeutical investigations have had but little success, *e.g.*, tuberculosis, leprosy, and parasitic diseases of the *Theileria* type.

In seeking a new type of chemotherapeutical, intended to have affinity to the lipoids and not to the proteins, we were influenced by two considerations: (i) the cell-walls of tubercle and of leprosy bacilli are known to consist largely of lipoid material, so it was expected that they would exhibit a selective affinity for lipophilic substances; (ii) such substances should be effective in all those cases in which the infected tissue is lipoidal in character. We have therefore started experiments in two directions: (*a*) introduction of " fatty " radicals (long-chain alkyls and acyls, steroid residues) into substances known to contain chemotherapeutically active groups, and (*b*) synthesis of " fatty " substances containing chemically active groups not yet known to have any chemotherapeutical effect.

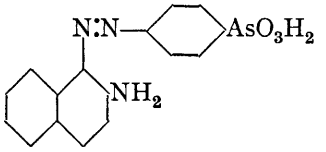
Certain representatives of the first group had previously been prepared for other purposes, especially dyes containing long-chain alkyl groups (*e.g.*, Seidel and Engelfried, *Ber.*, 1936, **69**, 2567; I.G. Farbenind. A.G., *Chem. Centr.*, 1937, I, 3551; du Pont de Nemours et Cie, *ibid.*, p. 4396; II, 4238), and 30 years ago Sulzberger (*ibid.*, 1907, II, 1668; 1908, I, 1011) emphasised the remarkable physical properties of " fatty azo-dyes."

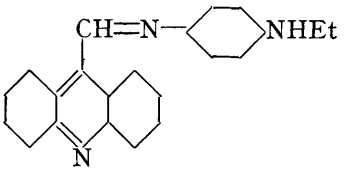
With regard to the second group, it is known that quaternary ammonium salts containing long-chain alkyl groups are powerful disinfectants; further, von Jancso and von Jancso (*ibid.*, 1935, I, 4666) reported the curative action of synthalin and synthalin B (deca- and dodeca-methylenediguanidine) on trypanosomiasis of mice, and ascribed the effect to an indirect influence of the synthalins on the trypanosomes *via* a change in the carbohydrate metabolism. This need not be correct, for we found some time ago that certain members of the above-mentioned group of quaternary ammonium salts have chemotherapeutical activity and, being neither dyes nor derivatives of arsenic, antimony, or bismuth, constitute a new type of drug. Moreover, the branched chains are now under investigation, for they are easily available by Weizmann, Bergmann, and Haskelberg's modification (*Chem. and Ind.*, 1937, **56**, 587; cf. Lourie and Yorke, *Ann. Trop. Med.*, 1937, **81**, 435) of Guerbet's method. Since King, Lourie, and Yorke (*Lancet*, 1937, **233**, 1360) have made an analogous observation on the effect of long-chain diamidines on trypanosomiasis, we report our synthetic experiments, although both these and the

physiological tests are in a preliminary stage. These experiments were inaugurated by Prof. S. Adler, of the Hebrew University, Jerusalem, and have been carried out in close collaboration with him and with his co-workers, to whom we express our thanks.

(1) *Quinine derivatives.* (i) Stearoylquinine was prepared by means of stearoyl chloride. (ii) Quinine reacted smoothly with cholesteryl chloroformate (the bromide failed to react). In both cases the *hydrochlorides* obtained were converted into the free bases, which lack the characteristic bitter taste of quinine.

(2) *Azo-dyes.* In view of the biological affinity of azo-dyes, benzeneazo-α- and -β-naphthylamine have been condensed with both stearoyl chloride and cholesteryl chloroformate, giving crystalline derivatives.

(I.) 



(II.)

(3) *Arsenicals.* Arsanilic acid was treated with palmitoyl chloride, stearoyl chloride, and cholesteryl chloroformate; the crystalline derivatives did not melt but decomposed at high temperatures. 4-Arsonobenzeneazo-β-naphthylamine (I) has been condensed with palmitoyl chloride and with cholesteryl chloroformate; and analogous systems containing the azo-group, arsenic, and long-chain alkyls have been synthesised from diazotised arsanilic acid by coupling with cetylaniline, *N*-(2-ethylhexyl)aniline, and *N*-(2-ethylhexyl)-β-naphthylamine (Weizmann, Bergmann, and Haskelberg, *loc. cit.*). Among these substances, 4-cetylaminoazobenzene-4′-arsonic acid is noteworthy, for doses as large as 1·6 g. per kg. proved non-toxic to mice. The influence of chain-length on the toxicity in this series is being investigated.

(4) *Quinoline derivatives.* In view of the fundamental importance of "plasmoquin" (8-amino-6-methoxyquinoline) for the synthesis of antimalarials (cf. Robinson *et al.*, J., 1934, 1264, 1267, 1322, 1520, 1524, and earlier work; Magidson *et al.*, *Arch. Pharm.*, 1933, **271**, 359; 1934, **272**, 74; 1935, **273**, 320), its N-*palmitoyl* derivative was prepared, as well as its reaction product with cholesteryl chloroformate.

(5) *Acridine derivatives.* 5-Methylacridine (Blum, *Ber.*, 1929, **62**, 881) could easily be condensed with *p*-nitroso-*N*-ethylaniline to yield (II), but the imino-hydrogen atom in this did not react as expected with cholesteryl chloroformate or stearoyl chloride, the former giving, as one *product*, white crystals, $C_{30}H_{45}N_3$, and the latter an amorphous olive-coloured substance. It is therefore proposed to start with the fairly readily accessible 5-acridylaldehyde (Kaufmann and Valette, *Ber.*, 1912, **45**, 1740), or with 5-methylacridine methiodide, for quaternary salts of heterocyclic bases are much more reactive than the bases themselves (see Scheuing and Winterhalder, *Annalen*, 1929, **473**, 126), and this methiodide reacts smoothly with *m*-nitrobenzaldehyde, affording 5-(m-*nitrostyryl*)*acridine methiodide.*

(6) Some fruitless attempts are described to prepare *p*-nitroso-*N*-cetyl-, -*N*-cholesteryl-, and -*N*-methyl-*N*-cetylaniline. In the first two cases, rearrangement experiments with the *N*-nitroso-compounds resulted merely in removal of the nitroso-group (cf. Hickinbottom, J., 1933, 946).

From *N*-methylaniline and cholesteryl chloroformate cholesterylaniline was formed.

The fact that the hydrochlorides of cetyl-aniline and -methylaniline are easily soluble in light petroleum (cf. *idem*, J., 1937, 1119) shows the influence of the long-chain alkyls on the physical properties of these substances.

Experimental.

(1) *Quinine Derivatives.*—(i) When quinine (0·02 mol.) and cholesteryl chloroformate (0·02 mol.) (Wieland, Pascual Vila, and Honold, *Z. physiol. Chem.*, 1923, **130**, 335) in toluene (30 c.c.) were heated for 1 hour on the water-bath, a *hydrochloride* separated. After recrystallisation from methanol, it had m. p. 246—247° (decomp.); it was easily soluble in chloroform, but

insoluble in ether, water, and light petroleum (Found: N, 3·5. $C_{48}H_{68}O_4N_2$,HCl requires N, 3·6%); $\alpha_D^{19°}$ + 0·09°; $[\alpha]_D^{19°}$ + 8·4° (l = 1; c = 1·07 in chloroform). The free *base* was prepared by treating a hot benzene solution of the hydrochloride with concentrated ammonia solution, and evaporating the benzene. The viscous residue was dissolved in hot acetone and crystallised, on cooling and scratching, in needles, m. p. 150° (Found: N, 4·0. $C_{48}H_{68}O_4N_2$ requires N, 3·8%); $[\alpha]_D^{19°}$ − 2·0° (l = 1; c = 1·28 in chloroform).

(ii) *Stearoylquinine hydrochloride* was obtained by heating equivalent weights of quinine and stearoyl chloride for 6 hours in benzene solution at 100°. It was soluble in water, alcohol, chloroform, insoluble in acetone, ethyl acetate, and ether, and was purified by precipitation of its alcoholic solution with ether; m. p. 227—228° (decomp.) (Found: N, 4·6. $C_{38}H_{58}O_3N_2$,HCl requires N, 4·5%). The free base, prepared with ammonia in aqueous solution, formed a gelatinous product from boiling ligroin.

(2) 1-*Benzeneazo*-2-*stearoylaminonaphthalene*.—Stearoyl chloride (0·05 mol.) and benzeneazo-β-naphthylamine (0·05 mol.) were heated in ethereal solution with potassium carbonate (0·05 mol.) for 12 hours. The filtered solution was evaporated, and the residue recrystallised from a small amount of alcohol. The *substance*, which was easily soluble in all organic solvents, formed orange-red needles, m. p. 88° (Found: C, 79·3; H, 9·1; N, 8·4. $C_{34}H_{47}ON_3$ requires C, 79·5; H, 9·2; N, 8·2%).

Benzeneazo-β-*naphthylamine and Cholesteryl Chloroformate*.—The reagents (0·05 mol. each) and potassium carbonate (0·05 mol.) were heated in benzene solution for 6 hours. Isolation as above gave needles, m. p. 196°, from benzene, soluble in chloroform and hydrocarbons, insoluble in water, sparingly soluble in alcohol and acetone (Found: N, 6·3. $C_{44}H_{57}O_2N_3$ requires N, 6·4%).

4-*Benzeneazo*-1-*stearoylaminonaphthalene*.—Prepared from benzeneazo-α-naphthylamine (see isomer, above), this formed reddish needles, m. p. 140·5°, from light petroleum or alcohol (Found: N, 8·6. $C_{34}H_{47}ON_3$ requires N, 8·2%).

Benzeneazo-α-*naphthylamine and Cholesteryl Chloroformate*.—This product was prepared as for the β-isomer, but in ethereal solution with 8 hours' heating; it separated from methyl ethyl ketone in brown-red crystals, m. p. 193° (Found: N, 6·5. $C_{44}H_{57}O_2N_3$ requires N, 6·4%).

p-(Cholesterylcarbamido)phenylarsonic acid was prepared from sodium arsanilate and cholesteryl chloroformate (see Lieb *et al.*, *Annalen*, 1935, **509**, 222; 1936, **512**, 89) (Found: N, 2·6. Calc. for $C_{34}H_{52}O_5NAs$: N, 2·2%).

(3) *Arsenicals*.—N-*Palmitoylarsanilic acid*. Atoxyl (6·9 g.), stearoyl chloride (8·7 g.), and benzene (60 c.c.) were shaken together at 60° for 24 hours. The mass was centrifuged, the solid phase washed with benzene and with water, and recrystallised from alcohol, giving needles, insoluble in water, soluble in olive oil (Found: N, 3·3. $C_{22}H_{38}O_4NAs$ requires N, 3·1%). N-*Stearoylarsanilic acid* was similarly prepared and recrystallised. Owing to the presence of arsenic, the analysis for carbon was unsatisfactory (Found: C, 57·7; H, 8·8. $C_{24}H_{42}O_4NAs$ requires C, 59·6; H, 8·7%).

4-*Arsonobenzeneazo*-β-*naphthylamine and palmitoyl chloride*. The azo-compound was prepared according to Ehrlich and Bertheim (*Ber.*, 1907, **40**, 3286) and isolated as hydrochloride (Found: N, 9·9. Calc. for $C_{16}H_{14}O_3N_3As$,HCl: N, 10·3%). Its sodium salt (4 g.) and palmitoyl chloride (2·7 g.) were mixed in benzene (50 c.c.). Reaction took place immediately and was completed by 2 hours' heating. The benzene was evaporated, the residue dissolved in alcohol, sodium chloride filtered off, and the solution evaporated. Purified by dissolution in sodium hydroxide solution and precipitation with dilute hydrochloric acid, the *substance* formed a crystalline powder, decomp. 294° (shrinking at 270°) (Found: N, 7·6. $C_{32}H_{44}O_4N_3As$ requires N, 7·0%).

4-*Arsonobenzeneazo*-β-*naphthylamine and cholesteryl chloroformate*. The sodium salt of the azo-compound (4 g.) and cholesteryl chloroformate (4·5 g.) in xylene (50 c.c.) were boiled for 4 hours. The solution was evaporated, the residue triturated with alcohol, dissolved in sodium hydroxide solution, and precipitated with dilute hydrochloric acid. The crystals were again dissolved in alcohol containing hydrochloric acid, and precipitated with water; m. p. 290° (decomp.) (Found: N, 5·6. $C_{44}H_{58}O_5N_3As$ requires N, 5·3%).

4-*Cetylaminoazobenzene*-4′-*arsonic acid*. Arsanilic acid (4·3 g.) was dissolved in water (50 c.c.) containing concentrated sulphuric acid (1·65 c.c.) and diazotised at 0° with sodium nitrite (1·4 g. in 7 c.c. of water). To this solution, *N*-cetylaniline (6·4 g.) in glacial acetic acid was added. After 12 hours, the red *acid* was collected and twice recrystallised from alcohol; m. p. 283° (decomp.) (Found: N, 8·2. $C_{28}H_{44}O_3N_3As$ requires N, 7·7%).

1-4′-*Arsonobenzeneazo*-2-*octylaminonaphthalene*. A solution of diazotised arsanilic acid

(21·7 g.) was diluted with glacial acetic acid (100 c.c.), and octyl-β-naphthylamine (25·5 g.) in glacial acetic acid (150 c.c.) added. After 12 hours, the *acid* was completely salted out by concentrated sodium acetate solution, collected, and recrystallised from glacial acetic acid or alcohol; m. p. 206° (decomp.) (Found: N, 9·2. $C_{24}H_{30}O_3N_3As$ requires N, 8·8%).

4-*Octylaminoazobenzene-4'-arsonic acid.* The reaction and purification were carried out exactly as for the cetyl compound; the *acid* was a dark red crystalline powder; m. p. 155° (decomp.) (Found: N, 9·8. $C_{20}H_{26}O_3N_3As$ requires N, 9·7%).

(4) *Quinoline Derivatives.*—6-*Methoxy-8-cholesterylcarbamidoquinoline.* 8-Amino-6-methoxyquinoline (5·1 g.) and cholesteryl chloroformate (13·2 g.) in toluene (100 c.c.) were boiled for 6 hours in presence of potassium carbonate (2 g.). The solution was filtered, and evaporated in a vacuum, and the residue triturated with acetone (20 c.c.). The needles were twice recrystallised from ethyl acetate; m. p. 129°; yield, 11·2 g. (Found: C, 77·9, 77·6; H, 9·5, 9·6. $C_{38}H_{54}O_3N_2$ requires C, 77·8; H, 9·2%). The hydrochloride, prepared with alcoholic hydrochloric acid, formed yellow needles, which, after recrystallisation from amyl alcohol, had m. p. 165°.

8-*Palmitamido-6-methoxyquinoline.* 8-Amino-6-methoxyquinoline (3·4 g.), palmitoyl chloride (5·4 g.), and potassium carbonate (2·8 g.) were boiled with ether (50 c.c.) for 5 hours. The ether was evaporated, and the yellow residue treated with dilute potassium hydroxide solution, filtered off, washed with water, and recrystallised from light petroleum, then from alcohol, giving colourless leaflets (7 g.), m. p. 74—75° (Found: C, 75·5, 75·1; H, 9·5, 9·6; N, 7·1; OMe, 7·6. $C_{26}H_{40}O_2N_2$ requires C, 75·7; H, 9·7; N, 6·8; OMe, 7·55%).

(5) *Acridine Derivatives.*—5-*Acridylaldehyde-p-ethylaminoanil* (II). Equivalent weights of 5-methylacridine and *p*-nitroso-*N*-ethylaniline (Fischer, *Ber.*, 1886, **19**, 2993; *Annalen*, 1895, **286**, 156) were heated for 2 hours at 100° and for 1 hour at 130°. By trituration with alcohol the mass was converted into brown-red crystals, which, recrystallised from pyridine–benzene, had m. p. 210° (Found: N, 12·9. $C_{22}H_{19}N_3$ requires N, 12·9%). The anil (5 g.), heated with stearoyl chloride (6 g.) at 100°, gave an olive-coloured, amorphous product, insoluble in water and light petroleum, soluble in all the other usual organic solvents.

The analogous reaction of the anil (3·3 g.) with cholesteryl chloroformate (4·5 g.) in toluene (20 c.c.) gave in 12 hours at 100° a crystalline mass, which was extracted with alcohol. The residue was amorphous; the extract, on cooling, deposited microscopic crystals, which were recrystallised from glacial acetic acid and were then chlorine-free; m. p. 232° (Found: C, 80·9, 80·6; H, 10·1, 10·5; N, 9·3; *M*, in camphor, 500. $C_{30}H_{45}N_3$ requires C, 80·5; H, 10·0; N, 9·4%; *M*, 447).

5-*Methylacridine methiodide.* Reaction between acridine (32·1 g.) and methylmagnesium iodide (2·43 g. of magnesium, 6·5 c.c. of methyl iodide) afforded a blue solution, which after treatment with ice and dilute hydrochloric acid deposited 5 : 10-dimethyl-5 : 10-dihydroacridine; this was recrystallised from alcohol (yield, 9 g.), then dissolved in alcohol, treated with iodine (11 g.), and the red-brown precipitate washed with sodium bisulphite solution, water, and methyl alcohol.

5-(m-*Nitrostyryl*)*acridine methiodide.* The foregoing methiodide (3·4 g.) and *m*-nitrobenzaldehyde (1·5 g.) were mixed with alcohol (10 c.c.); on addition of piperidine (1 c.c.), a green homogeneous liquid mass was obtained, which turned brown. On standing, the product separated as a viscous oil. It was triturated with acetone, filtered off, and recrystallised from glacial acetic acid, forming dark orange-red prisms (black in thick layers), m. p. 232° (decomp.) (Found: N, 5·7. $C_{22}H_{17}N_2I$ requires N, 6·4%).

(6) Cholesteryl chloroformate (4·5 g.) and *N*-methylaniline (3 g.) were boiled together for 3 hours, and poured into dilute hydrochloric acid; the cholesterylaniline which separated was crystallised from butyl alcohol, forming silky leaflets, m. p. 189°.

N-*Nitroso*-N-*cholesterylaniline.* Cholesterylaniline (12 g.) was mixed with concentrated hydrochloric acid (5 c.c.) and water (100 c.c.) at 5°, and sodium nitrite (2 g.) in water (10 c.c.) added dropwise. The mass was extracted with ether, the ether evaporated, and the residue recrystallised from alcohol–ether; needles, m. p. 147·5° (Found: C, 80·2; H, 10·4; N, 5·9. $C_{33}H_{50}ON_2$ requires C, 80·8; H, 10·2; N, 5·7%). When treated in ethereal solution with concentrated alcoholic hydrochloric acid, this afforded cholesterylaniline hydrochloride.

Cetylaniline was prepared by heating together for 6 hours 1 mol. of cetyl bromide and 3 mols. of aniline, and pouring the mass into cold water; m. p. 42° from methanol (cf. Dridau, *Annalen*, 1852, **83**, 20; Hickinbottom, J., 1927, 1120). The *hydrochloride* crystallised from alcohol, acetone, or light petroleum in shining leaflets, m. p. 102°, insoluble in water (Found: N, 4·0. Calc. for $C_{22}H_{39}N,HCl$: N, 4·0%).

N-*Nitrosocetylaniline.* To a well-cooled mixture of cetyl aniline (16 g.), concentrated hydrochloric acid (25 c.c.), and water (100 c.c.), amyl nitrite (10 g.) in ether (150 c.c.) was added dropwise. The mass was stirred until all the organic material dissolved, the solution was washed with water, dried, and evaporated in a vacuum, and the residue recrystallised from alcohol, giving needles, m. p. 53° (Hickinbottom, *loc. cit.*, gives 40—41°) (Found : C, 76·0; H, 11·5. Calc. for $C_{22}H_{38}ON_2$: C, 75·9; H, 11·0%).

N-*Methyl*-N-*cetylaniline hydrochloride.* Cetyl bromide (15 g.) and *N*-methylaniline (15 g.) were boiled for 3 hours, and the mass poured into dilute hydrochloric acid; the *hydrochloride* which separated was collected and recrystallised from acetone, then from light petroleum; leaflets, m. p. 104°; yield, 12 g. (Found : N, 4·0. $C_{23}H_{41}N,HCl$ requires N, 3·8%).

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