CHEMOTHERAPEUTIC STUDIES IN BACTERIOSTASIS

PART II. TERTIARY AMINES AND QUATERNARY AMMONIUM SALTS CONTAINING THE SKELETON OF *p*-TOLUIDINE

BY W. H. LINNELL AND S. V. VORA

From the Pharmaceutical Chemistry Research Laboratories of the School of Pharmacy, University of London

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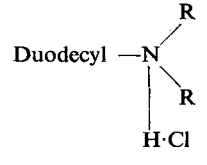
AMONG the chemical substances having antiseptic action, the surface active cations (such as long chain amino and quaternary salts) represent a well-defined class. The antibacterial action of these substances was reported by Hartmann and Kegi.[1] Domagk[2] first gave a detailed description of the bacteriological properties of some of the potent members of this group. Since then an ever-increasing number of cations with different types of substituents have been prepared and studied chemotherapeutically.

Stanley and his colleagues[3] who investigated a series of cyclohexyl-substituted amines of the formula I showed that the molecule of 16 to 18 carbon atoms possessed the highest antibacterial action.

$$C_6H_{11}\cdot(CH_2)_n\cdot N(Et)_2HCl \qquad I$$

Leffler and Volwiler[4] who investigated various duodecyl amines of the type II reported that the bacterial toxicity was greater when R was alkyl than when it was hydrogen.

Volko and Dubois[5] studied the effect of the side chain on the bactericidal power of several amines and quaternary salts, and made some important observations. (*a*) In a series of primary and tertiary amine hydrochlorides the activity reaches its maximum with the duodecyl chain; (*b*) In a series of higher aliphatic dimethylbenzylammonium chlorides the maximum potency is achieved with 12 to 14 carbon atoms; (*c*) in homologous series of alkyl dimethyl alkyl ammonium bromides, the antibacterial activity reached its peak at a chain length of 14 to 16 carbon atoms. It appears from these results that so long as the general molecular structure and the polar groups are unchanged, the length of the alkyl chain has a regular effect.



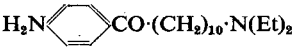
II

The mechanism by which amines and quaternary salts kill micro-organisms has not yet been clearly demonstrated but it bears no obvious relation to their effectiveness as emulsifiers, wetting agents or foaming agents, nor does it appear to be *entirely* connected with their ability as surface tension depressants. The bacterial action, like surface activity, reaches its peak and then declines. This probably means that as with phenols the initial action of these compounds depends on surface activity, when surface activity is present and is sufficient to pierce the plasma

membrane and render it permeable to the cation the difference in activity of the various cations may be a reflection of their efficiency as enzyme poisons.

In consideration of these facts, it appeared to be a matter of interest to introduce a skeleton of *p*-toluidine (*p*-aminobenzoyl and *p*-aminobenzyl group) into such compounds, possibly in the hydrocarbon chain. Such compounds, while retaining their surface active properties, might exhibit, at the same time, an increased enzyme activity associated with the metabolite group.

The synthesis of the following compounds was therefore undertaken.



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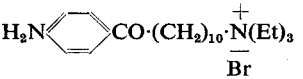

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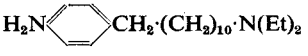

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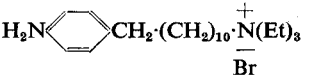

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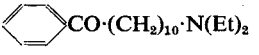

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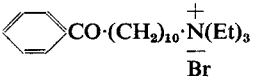
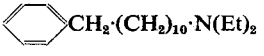
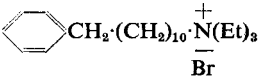


VIII



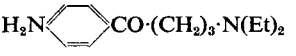
IX



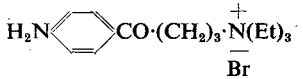
X

Unfortunately, the synthesis of the compounds III, IV, V and VI could not be accomplished because of certain difficulties which are mentioned in the experimental part. The synthesis of the last 4 has been accomplished.

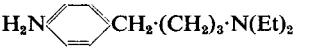
During the investigation of the different methods for the synthesis of the first 4 compounds using easily available intermediates such as β-diethylaminoethanol, the following compounds were prepared:—



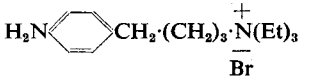
XI



XII

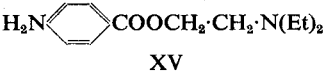


XIII



XIV

The therapeutic properties of these compounds are of interest since Woods[6] has reported that diethylaminoethyl-*p*-aminobenzoate (XV),

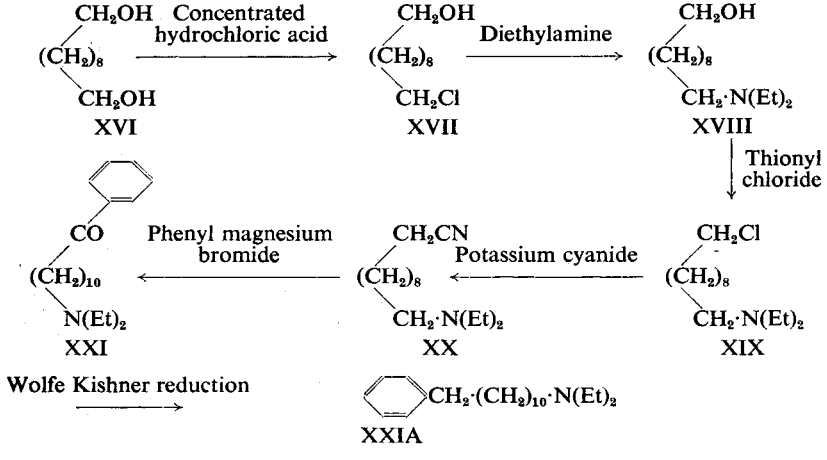


XV

a local anæsthetic, is as active as *p*-aminobenzoic acid in antagonising sulphonamide action. It appears likely that this molecule is hydrolysed to *p*-aminobenzoic acid in the body. The above substances which are similar in structure to this ester are incapable of hydrolysis and may, therefore, act as enzyme inhibitors.

The methods hitherto used for the synthesis of such compounds, consist of either reacting a diethylaminoalkyl cyanide with the appropriate Grignard reagent (phenyl magnesium bromide or *p*-aminophenyl lithium)[7] or condensing a long chain ω-halogeno-acid chloride with benzene or acetanilide by Friedel and Craft's reaction and reacting the resulting aroyl alkyl halide with diethylamine.[8]

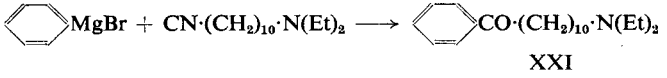
The application of the first method required the compound ω-diethylaminodecyl cyanide as an intermediate. This was prepared by chlorinating decamethylene glycol with hydrochloric acid, treating the chlorohydrin formed with diethylamine, chlorinating the resulting alcohol with thionyl chloride and replacing the chlorine atom by the cyano group with potassium cyanide. This method, although very lengthy, is comparatively easy to carry out.



The second step of this reaction series, viz., the synthesis of diethylamine decanol (XVIII) from the chlorohydrin, has been the subject of a patent.[9] It consists of refluxing chlorohydrin with large excess of diethylamine in anhydrous conditions for several hours. This procedure gave only about a 25 per cent. yield of compound XVIII. Increasing the quantity of diethylamine caused a drop in the refluxing temperature and a consequent drop in the yield. On the other hand, if an equimolecular quantity of diethylamine is used, the reaction can be carried out at a much higher temperature and the yield is quantitative.

The synthesis of the proposed ketones from the cyano compound XX by the Grignard reaction proved to be a difficult problem. Although compound XX reacted easily with phenyl magnesium bromide in ether to give 1-benzoyl-10-diethylaminodecane (XXI) in 50 per cent. yield it

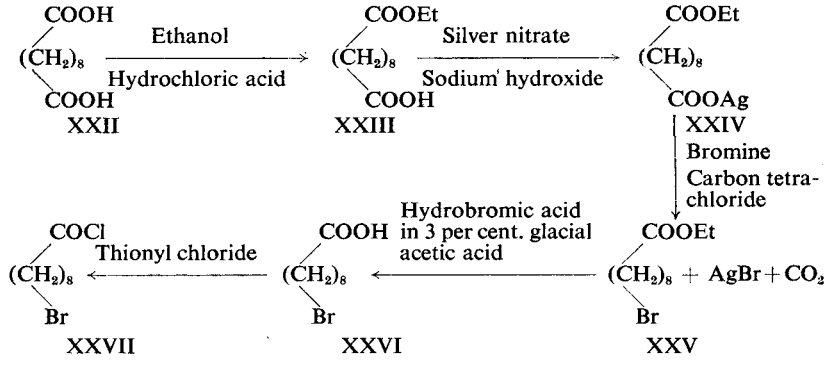
would not react with *p*-aminophenyl lithium in the same manner (even after refluxing for 12 hours).



XXI

At this stage resort was made to the second method—the Friedel and Craft reaction between ω-halogeno acid chloride and acetanilide.

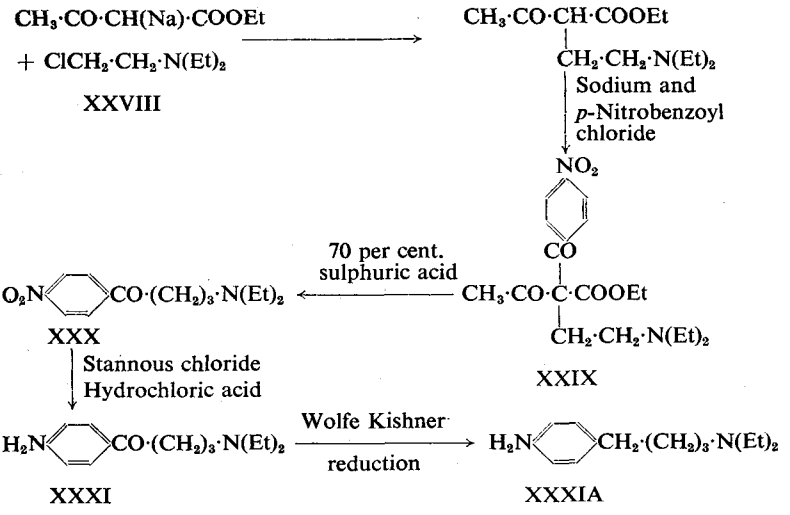
Sebacic acid provided a convenient starting point for this process. This acid was half esterified according to the process of Swan and Oehler[10]; the resulting acid ester XXIII was converted into its silver salt XXIV and brominated in carbon tetrachloride. The decarboxylation and bromination took place simultaneously and ethyl-ω-bromo octoate (XXV) was produced in excellent yields. This was hydrolysed with 3 per cent. hydrobromic acid in glacial acetic acid and the acid (XXVI) produced was converted to acid chloride (XXVII) with thionyl chloride.



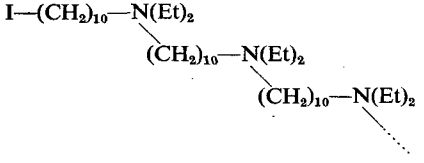
The condensation of XXVII with acetanilide was attempted in carbon disulphide using aluminium chloride catalyst according to the directions of Kunkell,[8] but unfortunately the activity of the long chain acid chloride proved to be insufficient to cause the acylation. The use of nitrobenzene as solvent also proved ineffective.

A third attack on the synthesis of the long chain amino ketones was developed using acetoacetic ester. Owing to the difficulty of obtaining the required diethylaminodecyl chloride, the method had to be explored with diethylaminoethyl chloride which was easily available by treating the corresponding alcohol with thionyl chloride. The reaction of this chloride (XXVIII) with sodioacetoacetic ester followed by replacement of the second hydrogen atom with *p*-nitrobenzoyl chloride gave the compound XXIX. This on treatment with 70 per cent. v/v sulphuric acid at 100° C. gave compound XXX, the decarboxylation and hydrolysis of the acetyl group taking place simultaneously.

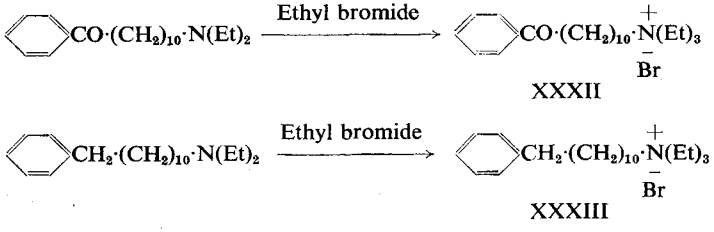
Application of the above method to the synthesis of long chain ketones proved to be unsuccessful. Diethylaminodecyl chloride, unlike compound XXVIII, failed to react with acetoacetic ester even after 48 hours; the activity of the terminal chlorine atom of the former compound appeared



to be insufficient. Replacement of chlorine by iodine was attempted by refluxing the compound with sodium iodide in acetone, but this gave rise to polymerisation probably on the lines shown below.



The reduction of the ketones (XXI and XXXI) to the corresponding alkyl derivatives (XXIA and XXXIA) was achieved in good yields by using the Haung-Minlon modification[11] of the Wolfe Kishner process. The compounds were isolated from the reaction mixture by dilution with water and extraction with ether.



The quaternary ammonium salts of all the 4 tertiary amines (XXI, XXIA, XXXI and XXXIA) were prepared by treating them with ethyl bromide. The compounds XXI and XXIA were easily quaternised by refluxing with ethyl bromide for 2 hours on a water-bath. Evaporation of excess of ethyl bromide followed by crystallisation from absolute ethanol gave colourless very hygroscopic crystals of XXXII and XXXIII.

The quaternisation of the amines XXXI and XXXIA presented some

difficulty. As they contain an aromatic primary amino group which is easily attacked by the alkyl halide, the above simple procedure could not be used, and an alternative method had to be developed. Successful results were obtained by the following procedure. The amines were acetylated in benzene solution with a similar solution of acetic anhydride, the acetyl derivatives were quaternised with ethyl bromide and the acetyl group was removed by heating with hydrobromic acid. Both compounds XII and XIV crystallised from boiling anhydrous methanol in pale yellow crystals changing to brown on standing. These were moderately readily soluble in hot methanol, practically insoluble in absolute ethanol and were extremely hygroscopic.

Bacteriological tests are presented at the end of the paper.

Experimental

Decamethylene glycol (*XVI*). This was obtained by the reduction of ethyl sebacate with sodium and ethanol, according to the method of Menske.[12] Yield 82 per cent., m.pt. 71° C.

Decamethylene chlorohydrin (*XVII*). This was synthesised by refluxing the glycol with concentrated hydrochloric acid sp. gr. (1·18) for 4 hours according to the directions of Alberti and Smiecinszewski.[13] Yield 60 per cent.; b.pt. 164° to 166° C./24 mm.

1-*Hydroxy*-10-*diethylaminodecane* (*XVIII*). Compound XVII 30 g. and diethylamine (11 g.) were refluxed on an oil bath for 24 hours. Crystals gradually separated. The mixture was made strongly alkaline with dilute sodium hydroxide solution and extracted with ether. The ether and excess diethylamine were removed on a water-bath, the higher boiling residue was mixed with ether and extracted with 2N hydrochloric acid. The acid phase, on being made alkaline, liberated the base which was extracted with ether dried over anhydrous magnesium sulphate and distilled. Pale yellow oil; b.pt. 178 to 183° C./16 mm.; $n_D^{18°C.}$, 1·4581. Yield 90 per cent.

1-*Chloro*-10-*diethylaminodecane* (*XIX*). This was prepared according to a method described in a patent.[9] A colourless oil, b.pt. 173° to 175° C./20 mm. Yield 6 g.

1-*Cyano*-10-*diethylaminodecane* (*XX*). In a 50-ml. flask equipped with a mercury-sealed stirrer, a reflux condenser and a dropping funnel, was placed a solution of potassium cyanide, 95 per cent. (2·3 g.) in water (5 ml.). The flask was heated on a sand bath and, while refluxing, a solution of XIX (8·5 g.) in ethanol (15 ml.) was added drop by drop with stirring. The mixture was kept refluxing and stirring for 12 hours, cooled, saturated with sodium carbonate and extracted with ether. The ether phase was dried over anhydrous sodium sulphate. The ether was removed and the residual oil subjected to fractional distillation.

1-*Cyano*-10-*diethylaminodecane* (*XX*) distilled at 125° to 130° C./6 mm. as a colourless liquid with a slightly fishy odour. $n_D^{17°C.}$, 1·4518. Yield 5·1 g. Found: C, 74·8; H, 12·8; N, 12·02; $C_{15}H_{30}N_2$ requires C, 75·63; H, 12·6; N, 11·75 per cent.

1-*Benzoyl*-10-*diethylaminodecane* (*XXI*). In a 100 ml. round-bottomed

flask equipped with a mercury-sealed stirrer, a reflux condenser protected by a calcium chloride tube and a dropping funnel (also protected by a calcium chloride tube) were placed clean, dry magnesium turnings (0·3 g.) ether (5 ml.) and a crystal of iodine. In the funnel was placed a solution of bromobenzene (1·9 g.) in ether (5 ml.). The addition of 1 ml. of this solution and gentle heating started a prompt reaction; with stirring the remainder of the solution of bromobenzene was added at a rate which maintained vigorous refluxing. The mixture was stirred and refluxed for 30 minutes and then a solution of compound XX (3 g.) in ether (60 ml.) was added drop by drop over a period of 30 minutes. Stirring and refluxing were continued for a further 6 hours. The cooled mixture was then decomposed by the slow addition of aqueous ammonium chloride (10 ml.). The ether was removed on a water-bath. After heating for 1 hour to insure hydrolysis of ketimines the product was extracted with ether, dried over anhydrous sodium sulphate and fractionally distilled. The first fraction, boiling at 162° to 175° C./6 mm., was discarded. 1-Benzoyl-10-diethylaminodecane came over at 214° to 216° C./6 mm. as a pale yellow oil; $n_D^{20°C}$, 1·4954. Yield 1·8 g. (50 per cent.). *Picrate*, pale yellow needles from ethanol, m.pt. 58° to 59° C. Found: C, 59·21; H, 6·87; N, 9·95; $C_{27}H_{38}N_4O_8$ requires C, 59·33; H, 6·96; N, 10·25 per cent.

1-*Benzyl*-10-*diethylaminodecane* (*XXIA*). The ketone XXI was added to ethylene glycol (35 ml.) containing hydrazine hydrate 85 per cent. (3 ml.) and sodium hydroxide (2·5 g.). The mixture was refluxed over a free flame for 1 hour. The condenser was then removed and the thermometer fixed so that the bulb was placed in the liquid, the refluxing was continued thus until the thermometer recorded 195° C. approx., when the condenser was replaced, and the refluxing continued for 3 more hours. After cooling, the contents of the flask were diluted with water (100 ml.) and extracted with ether; the ether extract was dried over anhydrous sodium sulphate and distilled. 1-Benzyl-10-diethylaminodecane distilled at 160° C./0·2 mm. as a colourless oil, soluble in all the usual organic solvents and in dilute mineral acids. Yield 2·2 g. Found: C, 83·36; H, 12·04; N, 4·30; $C_{21}H_{37}N_1$ requires C, 83·44; H, 11·92; N, 4·63 per cent.

Attempted Synthesis of *p*-Aminobenzoyl-alkyl-diethylamine by Friedel and Crafts's Reaction

Ethyl hydrogen sebacate (*XXIII*). This was prepared from sebacic acid according to the method described in "Organic Synthesis."[10] B.pt. 183° to 187° C./6 mm., m.pt. 34° to 36° C. Yield 68 per cent.

Silver salt of ethyl hydrogen sebacate. Ethyl hydrogen sebacate (130 g.) was dissolved in N potassium hydroxide, and silver nitrate (92 g.) was added. The solution on heating formed a white bulky precipitate of the silver salt which was filtered, washed free from silver nitrate and dried at 60° to 70° C., powdered and dried again. Yield 152 g.

1-*Carbethoxy*-8-*bromo-octane* (*XXV*). The silver salt 130 g. was suspended in anhydrous carbon tetrachloride (260 g.) and bromine (62 g.)

was added drop by drop with occasional stirring and cooling over a period of 30 minutes. The mixture was then heated on a water-bath for 15 minutes, cooled and filtered; the filtrate was shaken with anhydrous potassium carbonate to remove any unchanged acid, the solvent distilled off and the residual oil distilled under reduced pressure. 1-Carbethoxy-8-bromoctane was obtained as a colourless oil b.pt. 180° C./30 mm. $n_D^{20°C.}$, 1·4610. Yield 65 per cent. (with reference to the silver salt).

8-Bromo-octane-1-carboxylic acid (*XXVI*). The ester XXV was dissolved in a solution of hydrobromic acid 3 per cent. in glacial acetic acid 120 ml. and water 10 ml. and refluxed on a free flame for 10 hours. The acetic acid was removed under slight vacuum. The residual acid solidified on cooling. It was purified by dissolving in dilute sodium hydroxide, extracting the impurities with ether and acidifying the aqueous solution with hydrochloric acid. The acid separated as an oil and on cooling solidified to crystals of m.pt. 25° to 30° C. Recrystallisation from aqueous methanol raised the m.pt. to 36° C. Yield 11 g. (45 per cent.).

Evaporation of the ether phase gave 7 g. of the unchanged ester.

8-Bromo-octane-1-carboxylic acid chloride (*XXVII*). The acid (XXVI) (9 g.) and thionyl chloride (13·2 g.) were refluxed together for 2 hours. The excess of thionyl chloride was removed under reduced pressure, using a water-pump, and the residue distilled *in vacuo* using an oil pump. 8-Bromo-octane-1-carboxylic acid chloride came over as a colourless oil b.pt. 153° to 155° C./12 mm. Yield 87 per cent.

This substance gave a test for ionisable chlorine, and on boiling with aqueous sodium hydroxide and acidification gave the corresponding acid, thus proving its constitution.

The attempted condensation of compound XXVII with acetanilide in the presence of anhydrous aluminium chloride failed to give the desired ketone. The reaction mixture on distillation gave back all the acetanilide and some 8-bromo-octane-1-carboxylic acid.

Attempts to Synthesise *p*-Aminobenzoyl-alkyl-diethylamine Using Acetoacetic Ester

3-Carbethoxy-1-diethylaminopentan-4-one. This was prepared from ω-diethylaminoethyl chloride according to the directions of Breslow, Yost *et al.*[14] The product was purified by vacuum distillation. 3-Carbethoxy-1-diethylaminopentan-4-one was obtained as a colourless oil, b.pt. 144° to 148° C./12 mm. Yield 82 per cent.

1-(4′-Nitrobenzoyl)-3-diethylaminopropane (*XXX*). Sodium (4·8 g.) was finely divided in toluene, washed with dry benzene and suspended in dry benzene (260 ml.) in a flask provided with a mercury-sealed stirrer, a reflux condenser and a dropping funnel and 3-carbethoxy-1-diethylaminopentan-4-one (50 g.) was added at room temperature. The mixture was heated on a steam bath with stirring until all the sodium had dissolved (3 hours). The solution was cooled to about 40° C. and a solution of *p*-nitrobenzoyl chloride (37 g.) in benzene (140 ml.) was added drop by drop with stirring. The reaction mixture was heated on a steam bath with stirring for 2 hours; kept at room temperature overnight and refluxed for

2 more hours next day. The separated solid, which consisted of *p*-nitrobenzoic anhydride and sodium chloride, was filtered off, and the benzene removed under slight vacuum. The residue was diluted with anhydrous ether and some more *p*-nitrobenzoic anhydride which separated, was again filtered off. The ether solution was shaken twice with aqueous sodium carbonate, dried over anhydrous sodium sulphate and evaporated to remove the ether.

The viscous residue (3-carbethoxy-1-diethylamino-3-(4′-nitrobenzoyl)-pentan-4-one) was warmed on a steam bath for 20 minutes with 70 per cent. v/v sulphuric acid (280 ml.), stirring by hand in a vessel large enough to allow frothing. Some more *p*-nitrobenzoic acid separated; this was filtered off quickly through sintered glass; the filtrate was cooled and neutralised cautiously with solid sodium carbonate. The liberated base was extracted with ether, dried over anhydrous sodium sulphate; the ether was removed and the residue fractionally distilled under vacuum. The 1(4′-nitrobenzoyl)-3-diethylaminopropane distilled at 180° to 190° C./0·1 mm. as a dark red oil, soluble in ether, in benzene, in ethanol and in dilute mineral acids, insoluble in light petroleum. Yield 25 g. (43 per cent.).

The following derivatives were prepared:—*Picrate*, long yellow needles from acetic acid m.pt. 169° C. Found: C, 48·8; H, 4·8; N, 14·17; $C_{20}H_{23}N_5O_{10}$ requires C, 48·67; H, 4·6; N, 14·2. 2 : 4-*Dinitrophenyl hydrazone*; saffron coloured plates from nitrobenzene, m.pt. 231° to 232° C. *Semicarbazone*, small greenish cubes from hot water, m.pt. 198° C. *Ethiodide*; hygroscopic white prisms from absolute ethanol changing to light brown on standing.

1-(4′-*Aminobenzoyl*)-3-*diethylaminopropane* (*XXXI*). The nitro derivative (XXX) (5 g.) was dissolved in concentrated hydrochloric acid (100 ml.) and stannous chloride (20 g.) was added slowly with stirring. After the addition, the mixture was heated on a water-bath for 1 hour, cooled, made strongly alkaline with sodium hydroxide and extracted with ether. The ether extract after drying over anhydrous sodium sulphate on evaporation gave a residue which solidified on cooling. It was recrystallised from light petroleum (b.pt. 100° to 120° C.) in long pale yellow needles, m.pt. 68° C. Yield 3·1 g. (68 per cent.). Found: C, 51·78, H, 5·42; N, 14·6; $C_{14}H_{22}N_2O$ requires C, 51·83; H, 5·4; N, 15·4 per cent. 2 : 4 *Dinitrophenylhydrazone*, orange coloured plates from ethanol m.pt. 165° to 167° C. (frothing).

1-(4′-*Aminobenzyl*)-3-*diethylaminopropane* (*XXXIA*). The ketone (XXXI) (3 g.) was reduced to 1(4′-aminobenzyl)-3-diethylaminopropane (XXXII) by the Wolfe Kishner process in exactly the same way as described for compound XXIA. It distilled at 140° to 142° C./6 mm. as a colourless oil, soluble in benzene, ether and chloroform, but insoluble in light petroleum. Yield 2·3 g. *Chloroplatinate complex* from dilute hydrochloric acid solution as yellow silky needles; m.pt. 215° C. (decomp.). Found: C, 27·2; H, 4·19; N, 4·61; Pt, 31·0; $C_{14}H_{24}N_2PtCl_6$ requires C, 26·8; H, 4·13; N, 4·44; Pt, 31·6 per cent.

1-*Benzoyl decyltriethyl ammonium bromide* (*XXXII*). The tertiary

amine (XXI) 1 g. was mixed with ethyl bromide (4 ml.) in a dry test-tube provided with a calcium chloride tube and heated on an oil bath at 100° C. for half an hour. The solution on cooling solidified to a crystalline mass which on recrystallisation from absolute ethanol gave colourless cubes (0·8 g.) insoluble in benzene and light petroleum, but soluble in water. Found: C, 65·1; H, 9·16; N, 3·23. $C_{23}H_{40}N_1OBr$ requires C, 64·7; H, 9·39; N, 3·28 per cent. Eq. wt. 435; required 426.

1-*Benzyldecyltriethylammonium bromide* (*XXXIII*). The amine XXIA was treated with ethyl bromide in exactly the same way as described above. Colourless cubes from absolute methanol, changing to brown. Very hygroscopic. Eq. wt. 421; required, 412.

1-(4′-*Aminobenzoyl*)-*propyltriethylammonium bromide.* 1(4′-Aminobenzoyl)-3-diethylaminopropane (1 g.) in benzene solution was refluxed with a similar solution of acetic anhydride (1 g.) for 2 hours and the residue left after the removal of the solvent was treated with sodium hydroxide solution. Chloroform then extracted a solid, which, after the evaporation of the chloroform, was boiled with ethyl bromide. The precipitated salt of 1-(4′-acetylaminobenzoyl)-propyltriethylammonium bromide was filtered off, washed with hot benzene, dried by suction, dissolved in aqueous hydrobromic acid and evaporated to dryness on a water-bath. The semi-solid residues on trituration with absolute ethanol gave 1-(4′-aminobenzoyl) propyltriethylammonium bromide which crystallised from boiling anhydrous methanol to give colourless prisms (0·7 g.). It was moderately soluble in hot methanol, practically insoluble in ethanol and very hygroscopic. Found: C, 55·8; H, 7·67; N, 8·5; $C_{16}H_{27}N_2BrO$ requires C, 56·0; H, 7·87; N, 8·18. Eq. wt. 340; required, 343.

1-(4′-*Aminobenzyl*)-*propyltriethylammonium bromide.* This was prepared from 1-(4′-aminobenzyl)-3-diethylaminopropane (1 g.) in exactly the same way as described above. Colourless crystals from absolute methanol changing to brown on standing. Yield 0·64 g. Found: C, 57·7; H, 9·3; N, 8·6; $C_{16}H_{29}N_2Br$ requires C, 58·2; H, 8·8; N, 8·43 per cent. Eq. wt. 325; required, 329.

Bacteriological Tests

Bacteriological tests were performed in a nutrient broth medium using *Staphylococcus aureus* and *Pseudomonas pyocyanea* as test organisms. The tests were also performed simultaneously using a nutrient broth containing the sodium salt of *p*-aminobenzoic acid at a concentration of 1 in 1,000. The addition of 1 : 1,000 of sodium salt of *p*-amino-benzoic acid did not alter the results, which are shown in Table I.

Conclusions

In general it can be said that the introduction of a metabolite structure into the molecule of the antibacterial agents chosen does not improve their chemotherapeutic properties. Both the amino and the ketone groupings appear to be distherapeutic. The fact that the activity of these compounds is not affected by the presence of *p*-aminobenzoic acid probably indicates that the mode of action of these substances is different

from that of the sulphonamide type compounds. Indeed, these results seem to militate against the popular concept that the resemblance of sulphonamides to *p*-aminobenzoic acid is the basis of their activity.

In the long chain aliphatic series the activity of compounds VI and VIII is very significant. In general the reduction of the ketone to the corresponding alkyl derivative and quaternisation of the tertiary amines increase the activity considerably. The total inactivity of all the compounds against Gram-negative organisms is in accordance with the general behaviour of the cationic detergents.

In the 8-hydroxyquinoline series the small activity shown by compounds I, II and IV may be due to the oxine portion rather than the metabolite structure. The higher antibacterial activity of compound III than of compound IV fits in well with the general theory of chelation, discussed by Albert, who has suggested that the presence of an electron-attracting structure such as benzoyl group in the ring containing the –OH group in the *ortho* or *para* position, should cause an increased ionisation of the –OH group resulting in the formation of more stable metal complexes.

TABLE I

Compound	*Staph. aureus* ("Oxford strain")		*Ps. pyocyanea* ("C.N. 200")	
	Inhibition	Growth	Inhibition	Growth
(1) 5(4′-Aminobenzoyl)-8-hydroxyquinoline ..	1 : 4000	1 : 8000	1 : 2000	1 : 4000
(2) 5(4′-Aminobenzyl)-8-hydroxyquinoline.. ..	1 : 34000	1 : 64000	No inhibition	
(3) 5(Benzoyl)-8-hydroxyquinoline	1 : 1024000	1 : 2048000	1 : 2000	1 : 4000
(4) 5(Benzyl)-8-hydroxyquinoline	1 : 34000	1 : 64000	No inhibition	
(5) 1-Benzoyl-10-diethylaminodecane HBr ..	1 : 64000	1 : 128000	1 : 1000	1 : 2000
(6) 1-Benzyl-10-diethylaminodecane HBr	1 : 1024000	1 : 2048000	1 : 1000	1 : 2000
(7) Benzoyldecyltriethylammonium bromide ..	1 : 256000	1 : 51200	No inhibition	
(8) Benzyldecyltriethylammonium bromide ..	1 : 2048000	1 : 4096000	„	
(9) 1-(4′-Aminobenzoyl)-10-diethylaminopropane HBr	1 : 1000	1 : 2000	„	
(10) 1-(4′-Aminobenzyl)-10-diethylaminopropane HBr	1 : 2000	1 : 4000	„	
(11) 4′-Aminobenzoylpropyltriethylammonium bromide	1 : 4000	1 : 8000	„	
(12) 4′-Aminobenzylpropyltriethylammonium bromide	1 : 128000	1 : 256000	„	

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