XCVI. THE CHEMOTHERAPY OF DERIVATIVES OF HARMINE AND HARMALINE. I.

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THIS investigation had its origin in Gunn and Marshall's [1920] discovery that harmine and harmaline had some therapeutic value in malaria. Further clinical trials of these compounds, however, failed to establish their practical worth as antimalarial agents. Since harmine and harmaline are readily accessible in quantity by extraction from *Peganum harmala*, and their chemical constitution, determined by Perkin and Robinson [1919, 2],

has features in common with those of known antimalarial agents such as quinine and plasmoquin, we thought it of interest to prepare a number of derivatives of these alkaloids in order that they might be tested for antimalarial action. Now, Morgenroth and his collaborators have shown that the bactericidal value of a homologous series of *O*-alkylhydrocupreines increases to a peak value and then falls again. This fact suggested to us that perhaps replacement of the methoxy-group of harmine or harmaline by higher alkyloxy-groups might yield substances of greater antimalarial action. Suitable methods for the demethylation of these alkaloids and subsequent *O*-alkylation of the resulting phenolic compounds, harmol and harmalol, were worked out, and all the members of the homologous normal series from *O*-ethylharmol to *O*-*n*-dodecylharmol (except undecylharmol), several members of the *iso*-series and also *O*-allyl- and *O*-benzylharmol were prepared. A smaller number of the corresponding derivatives of harmalol were also made.

Through the courtesy of the Chemotherapy Committee of the Medical Research Council, two members of the series, namely, *O*-*n*-butylharmol and *O*-*n*-heptylharmol, as well as harmol, harmalol and *O*- β -diethylaminoethylharmol (to which reference will be made later) were tested for activity against bird-malaria under the direction of Prof. Keilin, of the Molteno Institute, Cambridge, but were found to be inactive.

The possibility that some members of these series might have other chemotherapeutic uses was then examined, and it was found that both bactericidal and amoebicidal activity increased, on ascending the homologous series, up to a point and then started to fall. The peak of amoebicidal activity was reached at *O*-*n*-nonylharmol, but the salts of this and other high members of the series were very sparingly soluble in water, and consequently a further series of compounds was prepared with the hope of obtaining more readily soluble compounds. In the first place, the effect of an ω -hydroxy-group was tested by the preparation of *O*- ω -hydroxy-*n*-decylharmol, but the salts of this were also sparingly soluble. A series of *O*- ω -dialkylamino-*n*-alkylharmols was then prepared, and these were found to yield dihydrochlorides readily soluble in water. An account of the investigation of the bactericidal properties of these and the simpler alkylharmols follows. Many of the ω -dialkylamino-*n*-alkylharmols proved to have a very considerable amoebicidal action, when tested *in vitro* by the method of Laidlaw, Dobell and Bishop [1928], and the results obtained in this connection will be reported later. Three members of the series, *O*-*n*-butylharmol, *O*- ω -diethylamino-*n*-heptylharmol, and *O*- ω -diethylamino-*n*-decylharmol were tested for trypanocidal action by Mr W. A. Broom, of Boots Pharmacological Department, but were found to be inactive in doses of approximately 50 % of the lethal dose.

It may be noted that the pharmacology of the *O*-ethyl, *n*-propyl, *n*-amyl, and *n*-nonyl ethers of harmol has been studied by Gunn and Heathcote [1931], Elphick and Gunn [1932], and Gunn and MacKeith [1932].

BACTERICIDAL PROPERTIES.

The methods to be adopted in the examination of new compounds for bactericidal properties call for very careful consideration. It is obviously impracticable to investigate the activity of all of a series of compounds from every point of view, and in the case of homologous series of compounds we have adopted the procedure of exploring the series for "peak" activity by some particular test and later testing out the "peak" compound more thoroughly. In the testing of these compounds for bactericidal efficiency, we have used the Rideal-Walker technique for the preliminary survey, and since it is well known that the "peak" bactericidal activity of a homologous series of compounds differs with the test organism, we have in some cases supplemented our results on *Bacillus typhosus* with others obtained using *Staphylococcus aureus*. These two organisms may, we believe, be taken as representative of two important groups of bacteria, that of the organisms allied to *B. coli*, and that of the Gram positive cocci. Both organisms will grow in the Rideal-Walker broth and may be used for the Rideal-Walker test.

Table I shows the results of our Rideal-Walker (phenol coefficient) tests on the hydrochlorides of these compounds.

It will be observed that in the *n*-alkyl series the peak of bactericidal efficiency is reached at butyl for *B. typhosus*, and at amyl for *S. aureus*, and that where the *n*-members are highly active, corresponding *iso*-members are less so. In the ω -diethylaminoalkyl series the peak for *B. typhosus* is reached at diethylaminononylharmol, and in the dialkylaminodecyl series at the diethylamino-member.

O-*n*-Butylharmol hydrochloride, with a coefficient against *B. typhosus* of 350 and against *S. aureus* of 150, is evidently a germicide of great potency and additional work has been carried out to study its action more fully. The inhibitory effect and the lethal effect in the presence of blood and serum were tested

Table I.

Compound	R.W. coefficients	
	<i>B. typhosus</i>	<i>S. aureus</i>
Harmol	<1	—
Harmine	<1	—
<i>O</i> -Ethylharmol	25	—
<i>O</i> - <i>n</i> -Propylharmol	225	75
<i>O</i> - <i>n</i> -Butylharmol*	350 to 400	150
<i>O</i> - <i>n</i> -Amylharmol	350	250 to 300
<i>O</i> - <i>n</i> -Hexylharmol	50	45 to 50
<i>O</i> - <i>n</i> -Heptylharmol	30 to 35	45 to 50
<i>O</i> - <i>n</i> -Octylharmol	15	35 to 40
<i>O</i> - <i>n</i> -Nonylharmol	10 to 15	15
<i>O</i> - <i>n</i> -Decylharmol	10	—
<i>O</i> - <i>n</i> -Dodecylharmol	5	—
<i>O</i> - <i>iso</i> -Propylharmol	75	—
<i>O</i> - <i>iso</i> -Amylharmol	150 to 200	—
<i>O</i> - <i>sec.</i> -Octylharmol	About 20	—
<i>O</i> - <i>iso</i> -Decylharmol	10	—
<i>O</i> -Allylharmol	110	—
<i>O</i> -Benzylharmol	250	—
<i>O</i> - ω -Hydroxydecylharmol	10 to 15	—
<i>O</i> - β -Diethylaminoethylharmol	5	—
<i>O</i> - ω -Diethylaminoheptylharmol	23	<12
<i>O</i> - ω -Diethylaminooctylharmol	110	†About 100
<i>O</i> - ω -Diethylaminononylharmol	220	†About 200
<i>O</i> - ω -Diethylaminodecylharmol	200	†250 to 300
<i>O</i> - ω -Diethylaminoundecylharmol	160	†About 200
<i>O</i> - ω -Dimethylaminodecylharmol	125	—
<i>O</i> - ω -Dibutylaminodecylharmol	150	—
<i>O</i> - ω -Piperidyldecylharmol	55	—
Harmaline	<1	—
Harmalol	<1	—
<i>O</i> -Ethylharmalol	2-5	—
<i>O</i> - <i>n</i> -Butylharmalol	About 100	—

* *O*-*n*-Butylharmol methochloride had a R.W. coefficient of 50 to *B. typhosus*.

† In our hands the *S. aureus* coefficients of these four compounds differ widely from test to test. The results quoted were obtained in tests put on at one time.

using cocci and *Bacillus coli*. In all cases where a test against cocci is described the test culture was prepared by mixing, immediately before use, 24-hour broth cultures of all the available strains of *S. aureus* and of streptococci. The following results are of interest.

(1) Inhibition tests.

A. In broth (prepared by tryptic digestion of ox-heart).

B. coli was inhibited by 1 in 10,000 to 1 in 25,000.

Cocci were inhibited by 1 in 50,000 to 1 in 100,000.

Aspergillus (Sterigmatocystis) niger was inhibited by 1 in 25,000 to 1 in 75,000.

Using phenol under the same conditions the figures were, for *B. coli*, 1 in 500; for cocci, 1 in 250; and for *A. niger*, 1 in 1200.

B. In broth with glucose 1% and ox-serum 20%.

B. coli was inhibited by 1 in 5000 to 1 in 10,000.

Cocci were inhibited by 1 in 2500 to 1 in 7500.

Using phenol under the same conditions the figures were, for *B. coli*, 1 in 400; and for cocci, 1 in 200.

C. Using the serum-agar cup test of Himebaugh [Allen and Wright, 1931].

With *S. aureus*, and allowing 24 hours' contact, 1 in 500 *O*-*n*-butylharmol hydrochloride gave a "halo" of similar extent to that produced by 5% phenol.

(2) *Tests to indicate the lethal efficiency in blood or in serum.*A. *Germicidal effect in the presence of serum.*

(0.5 cc. of equal parts of broth culture of cocci and ox-serum added to 5 cc. of the germicide dilution in equal parts of serum and saline.)

A dilution of 1 in 500 killed in about 4 hours.

1 in 1000 did not kill in 48 hours.

Corresponding dilutions of phenol:

1 in 50 killed in under 4 hours.

1 in 100 killed in 24 hours, not in 8.

B. *Germicidal effect in the presence of blood.*

(1 cc. of equal parts of culture and citrated blood added to 5 cc. of germicide solution.)

Using cocci as previously described complete sterilisation was obtained in less than 5 minutes with dilutions of 1 in 1000 to 1 in 2500.

Of a number of germicides tested in this way, none was as efficient as *O-n*-butylharmol hydrochloride. To effect sterilisation in 5 minutes the following concentrations were necessary.

<i>O-n</i> -Butylharmol hydrochloride	...	...	1-1000 to 1-2500
Brilliant green	...	...	1-200
Mercuric iodide	...	...	1-200
Silver nitrate	...	...	1-200
Neutral acriflavine	...	...	1-100
Lysol	...	...	1-50
Phenol	...	...	1-25

C. *Action on phagocytosis.*

Fleming [1931], has shown that the addition of most germicides to living blood reduces the efficiency of the antibacterial action of the leucocytes long before the germicide is in sufficient concentration to exert any bacteriostatic action. We have carried out a number of "slide cell" tests [Wright, Colebrook and Storer, 1923], in which dilutions of germicides in Ringer's solution were added to *Streptococcus faecalis* in fresh citrated rabbit blood and, slide cells being prepared and incubated, the developing colonies read off after incubation.

Our tests indicate that *O-n*-butylharmol hydrochloride also is more toxic to leucocytes than to bacteria. In a typical result, a control, in which the leucocytes were inactivated by strong saline, showed 35 colonies, another control to which Ringer's solution only was added showed 1 colony; the following figures indicate the colonies developed in the presence of different concentrations of *O-n*-butylharmol hydrochloride.

1-1750	...	...	...	...	0 colonies
1-3500	...	...	...	...	30 colonies
1-7000	...	...	...	...	0 colonies
1-14,000	...	...	...	...	0 colonies

From a consideration of this bacteriological work it appears that this compound does not possess the power of acting in extreme dilution, whether blood-serum be present or not, so characteristic of acriflavine.

On the other hand, none of the germicides we have tested approaches *O-n*-butylharmol hydrochloride in the efficiency and rapidity of its action against cocci in the presence of blood, and it appears possible that the compound might have some application in the disinfection of discharges containing blood where the action of phagocytes was unimportant.

Preparation of harmol and harmalol.

Harmol and harmalol have been prepared by the demethylation of harmine and harmaline respectively using hydrochloric acid under pressure [Fischer and Täuber, 1885; Fischer, 1889], and in the former case by means of boiling hydriodic acid also [Perkin and Robinson, 1919, 2]. They can be prepared more conveniently by boiling with diluted sulphuric acid [Boots Pure Drug Co., Ltd., Pyman and Levene, 1932, 1]. A nearly theoretical yield of harmol can be obtained by boiling harmine with sulphuric acid of 35 to 60 % strength, the

time required for the hydrolysis decreasing with the strength of acid from 100 to about 2 hours. When stronger sulphuric acid is employed, the product is contaminated with harmolsulphonic acid.

Harmol. Harmine (120 g.), is boiled with a mixture of sulphuric acid (1200 g.), and water (800 cc.) until a test portion is completely soluble in aqueous sodium hydroxide (about 2 hours). On cooling harmol sulphate crystallises. It is collected, suspended in hot water and mixed with sodium carbonate, yielding pure harmol (109 g., *i.e.* nearly theoretical yield, m.p. 320° decomp.).

The *hydrochloride* crystallises from water in minute colourless needles with $\frac{1}{2}$ H₂O, which do not melt below 350°. It is soluble in 23 parts of cold water, giving a colourless fluorescent neutral solution. (Found, in air-dried salt: loss at 100°, 3.9; N, 11.5; Cl, 14.7 %. C₁₂H₁₀ON₂, HCl, $\frac{1}{2}$ H₂O requires H₂O, 3.7; N, 11.5; Cl, 14.6 %.) The *lactate* crystallises from moist acetone in colourless needles, m.p. 207–208° (corr.). It is soluble in 4 parts of cold water. (Found: C, 62.7; H, 5.7 %. C₁₂H₁₀ON₂, C₃H₆O₃ requires C, 62.5; H, 5.6 %.)

Harmolsulphonic acid is obtained together with harmol by heating harmine with sulphuric acid of more than 70 % strength at 150°, the proportion of sulphonic acid increasing rapidly with increasing concentration of acid. The solution is heated until a sample is completely soluble in caustic soda. The concentration of sulphuric acid is then reduced to 50 % by adding water, and on cooling harmol sulphate crystallises out at once with a little harmolsulphonic acid, the bulk of the sulphonic acid coming down on standing. The crude acid is freed from harmol by adding sodium acetate and dilute acetic acid and is then recrystallised from much boiling water, when it separates in greyish needles with 4H₂O. It does not melt below 300°, is sparingly soluble in water, and its sodium and ammonium salts are also sparingly soluble in water. (Found, in air-dried substance: loss at 120°, 20.7; S, 9.1 %. C₁₂H₁₀O₄N₂S, 4H₂O requires H₂O, 20.6; S, 9.2 %.)

Harmalol is readily made by boiling harmaline under reflux with 20–55 % sulphuric acid, the operation requiring approximately 100 and 4 hours in the extreme cases. With stronger sulphuric acid, the product is contaminated with harmalolsulphonic acid. Harmalol is most conveniently made by gently boiling harmaline with 20 parts by weight of 50 % sulphuric acid, until a test sample is completely soluble in aqueous sodium hydroxide (6 to 8 hours). On cooling, harmalol sulphate crystallises. It is collected and mixed with hot water and ammonia, when the pure base is obtained in nearly theoretical yield, and has the properties described by previous authors. The *lactate* crystallises from alcohol in bright yellow microscopic leaflets containing 1H₂O. m.p. (air-dried) 116–120° (corr.); (anhydrous) 174–176° (corr.). It is soluble in an equal weight of water, and is readily soluble in alcohol. (Found: loss at 100°, 5.9; C, 58.4; H, 6.6; N, 9.3 %. C₁₂H₁₂ON₂, C₃H₆O₃, H₂O requires H₂O, 5.9; C, 58.5; H, 6.5; N, 9.1 %.)

Harmalolsulphonic acid is obtained together with harmalol by heating harmaline with sulphuric acid exceeding 60 % in strength, at 150–160°. It can be isolated by repeatedly extracting the mixture of crude harmalol sulphate and sulphonic acid with hot dilute aqueous ammonia, and acidifying the solution. It is thus obtained as a crystalline yellow powder, containing 1H₂O. It does not melt below 300°, and is sparingly soluble in water. (Found, in air-dried substance: loss at 100°, 6.5; S, 10.8 %. C₁₂H₁₂O₄N₂S, H₂O requires H₂O, 6.1; S, 10.8 %.)

Alkylation of harmol and harmalol.

Harmol and harmalol present two points of attack to alkylating agents and can give *O*-alkyl, *N*-alkyl, and *ON*-dialkyl derivatives. In the case of harmine, the formulae of these substances are given on p. 732.

Formulae II and III arise by a molecular rearrangement which has been explained by Perkin and Robinson [1919, 1].

The results of alkylation depend upon the conditions employed. On alkylating harmol in alcoholic solution in the presence of sodium carbonate with butyl *p*-toluenesulphonate (1 mol.) for example much harmol is recovered unchanged, and *ON*-dibutylharmol is formed, identical with the product obtained by heating the dry sodium salt of harmol with butyl *p*-toluenesulphonate (2 mols.) in the absence of a solvent.

If however harmol is heated under reflux in alcoholic solution with sodium hydroxide (1 mol.) and an alkyl or aralkyl salt (1 mol.) the main product of the reaction is an *O*-alkyl or aralkyl ether of harmol [Boots Pure Drug Co., Ltd., Pyman and Levene, 1932, 2].

The alkyl salts usually employed were bromides, but other salts were used in some cases, *e.g.* allyl and octyl iodides, benzyl chloride, butyl *p*-toluenesulphonate. The product of the reaction was worked up by distilling off the alcohol, and mixing the residue with dilute aqueous sodium hydroxide to remove unchanged harmol and the *N*-alkylharmol. The insoluble residue—a solid or with the higher aliphatic derivatives an oil which rapidly crystallised—was yellow in colour owing to the presence of a small proportion of the *ON*-dialkyl derivative. Purification was best effected by recrystallising the hydrochloride from alcoholic hydrochloric acid, with the lower members of the series, or from alcohol-acetone with the higher members. The bases were best obtained pure by adding excess ammonia to a hot dilute solution of the hydrochloride in dilute alcohol.

The *O*-alkylharmols crystallise from dilute alcohol in the form of colourless needles which are anhydrous. They are almost insoluble in water, but readily soluble in alcohol and chloroform, and slightly soluble in ether and benzene. They form colourless hydrochlorides crystallising in needles, some with and others without water of crystallisation and are moderately or slightly soluble in water, the solutions being colourless, fluorescent and neutral to litmus. The behaviour of the hydrochlorides of the members of the *n*-series from butyl upwards is peculiar. In the case of the butyl ether and the near higher homologues, a hot strong aqueous solution gelatinises on cooling. From the *n*-octyl ether upwards, the salts are sparingly soluble even in hot water but become gelatinous on contact with water. The amyl derivative and its higher homologues gradually hydrolyse in solution, depositing crystals of the base. The lactates are far more soluble than the hydrochlorides, do not gelatinise so readily and—possibly because of their increased concentration—show little or no hydrolysis even on prolonged standing.

N-alkylated derivatives, e.g. metho- or buto-chlorides do not gelatinise in the same way as the hydrochlorides and are also moderately or sparingly soluble in water. They can be made by the action of an alkyl halide on the alkyl ether in benzene solution.

Harmalol was alkylated in exactly the same way as harmol. The *O*-alkyl ethers of harmalol form yellow salts, which are considerably more soluble than the corresponding harmol derivatives, their solutions being yellow, highly fluorescent and neutral to litmus.

O-Ethylharmol. Harmol (8 g.), ethyl bromide (4.5 g.), aqueous 5*N* sodium hydroxide (8.1 cc.), and 99 % alcohol (200 cc.) were heated under reflux for 2 hours. After distilling off the alcohol the residue was washed with dilute aqueous sodium hydroxide to remove phenolic bases. The washings were acidified with acetic acid and then basified with ammonia, giving 2.6 g. of a somewhat tarry precipitate, mainly harmol. The residue insoluble in aqueous sodium hydroxide was a powdery solid (6.1 g.), pale yellow in colour due to the presence of some *ON*-diethylharmol. It was dissolved in hot alcohol (18 cc.), and concentrated hydrochloric acid (9 cc.) was added; on cooling, the crude hydrochloride (6.6 g.) crystallised.

After recrystallisation from very dilute hydrochloric acid, using charcoal, the pure *hydrochloride* was obtained as a mass of colourless, anhydrous needles, m.p. 313° (corr.) after sintering from 306°. It is soluble in 12 parts of water at 80°, or 18 parts at 24°. (Found: Cl, 13.5 %, $C_{14}H_{14}ON_2$, HCl requires Cl, 13.5 %.)

The *free base* is obtained in long, anhydrous needles, m.p. 193° (corr.) on adding ammonia to a hot dilute solution of the hydrochloride in aqueous alcohol. (Found: C, 74.1; H, 6.3 %. $C_{14}H_{14}ON_2$ requires C, 74.3; H, 6.2 %.) The *lactate* crystallises from moist acetone in anhydrous needles, m.p. 174–175° (corr.), which are soluble in 3 parts of cold water. (Found: C, 64.3; H, 6.5 %. $C_{15}H_{16}ON_2$, $C_3H_5O_3$ requires C, 64.5; H, 6.3 %.)

The following homologues of *O*-ethylharmol were prepared similarly.

O-n-Propylharmol, thick needles, m.p. 203–204° (corr.). (Found: C, 74.6; H, 6.8 %. $C_{15}H_{16}ON_2$ requires C, 75.0; H, 6.7 %.) The *hydrochloride*, minute needles, m.p. 259–261° (corr.) soluble in 48 parts of water at 20°. (Found, in air-dried salt: loss at 100°, 3.2 %. $C_{15}H_{16}ON_2$, HCl, $\frac{1}{2}H_2O$ requires H_2O , 3.2 %. Found, in dried salt: Cl, 12.7 %. $C_{15}H_{16}ON_2$, HCl requires Cl, 12.8 %.) The *lactate*, long anhydrous needles, m.p. 164–166° (corr.), soluble in 2 parts of cold water. (Found: C, 65.5; H, 6.8 %. $C_{15}H_{16}ON_2$, $C_3H_5O_3$ requires C, 65.4; H, 6.7 %.)

O-iso-Propylharmol, feathery needles, m.p. 181° (corr.). (Found: C, 75.2; H, 6.8 %. $C_{15}H_{16}ON_2$ requires C, 75.0; H, 6.7 %.) The *hydrochloride*, fine needles, m.p. 277–278° (corr.) after drying at 100°, soluble in 5 parts of water at 75° and 60 parts at 20°. (Found, in air-dried salt: loss at 100°, 6.1 %. $C_{15}H_{16}ON_2$, HCl, H_2O requires H_2O , 6.1 %. Found, in dried salt: Cl, 12.9 %. $C_{15}H_{16}ON_2$, HCl requires Cl, 12.8 %.)

O-Allylharmol, needles, m.p. 166–167° (corr.). (Found: C, 75.5; H, 6.0 %. $C_{15}H_{14}ON_2$ requires C, 75.6; H, 5.9 %.) The *hydrochloride*, small needles, m.p. 233° (corr.) when air-dried and m.p. 221–222° (corr.) after drying at 110°, soluble in 10 parts of cold water. (Found, in air-dried salt: loss at 110°, 6.2 %. $C_{15}H_{14}ON_2$, HCl, H_2O requires H_2O , 6.1 %.)

O-n-Butylharmol, thick rhombs, m.p. 220–221° (corr.). (Found: C, 75.3; H, 7.2 %. $C_{16}H_{18}ON_2$ requires C, 75.6; H, 7.1 %.) The *hydrochloride*, rhombs, m.p. 232–234° (corr.), is soluble in 25 parts of hot water giving a solution which sets to a firm gel on cooling. At 15° a 0.8 % solution can be poured. (Found: Cl, 12.3 %. $C_{16}H_{18}ON_2$, HCl requires Cl, 12.3 %.) The *lactate*, slender anhydrous needles, m.p. 160–163° (corr.) is soluble in 20 parts of cold water. The *methiodide*, obtained by heating the base with methyl iodide in benzene as a cream-coloured crystalline precipitate, m.p. 247° (corr.), is sparingly soluble in water, and gives, when boiled with an aqueous suspension of silver chloride, the *methochloride*, clusters of needles, m.p. 279° (corr.). (Found: Cl, 11.8 %. $C_{17}H_{21}ON_2Cl$ requires Cl, 11.7 %.) The methochloride is soluble in 10 parts of water at 70°, and this solution does not gelatinise but deposits crystals on cooling, the solubility of the salt at 31° being only 0.8 %. It yields with ammonia the corresponding base, *N*-methyl-*O*-*n*-butylharmol, which crystallises from alcohol in glistening dark green needles, m.p. 144° (decomp.).

ON-Di-n-butylharmol, prepared by heating harmol with butyl *p*-toluenesulphonate in the presence of sodium carbonate or by heating the sodium salt of harmol with butyl *p*-toluenesulphonate (2 mols.) crystallised from alcohol in yellow needles, m.p. 113° (corr.). (Found: C, 69.1; H, 8.4 %. $C_{20}H_{26}ON_2$, $2H_2O$ requires C, 69.3; H, 8.6 %.) Its *hydrochloride* or *O*-*n*-butyl-

harmol n-butochloride crystallised from water in colourless needles, containing $2\text{H}_2\text{O}$ lost at 100° . M.P. 68° (corr.). (Found: Cl, 9.25; loss, 9.44 %. $\text{C}_{20}\text{H}_{27}\text{ON}_2\text{Cl}$, $2\text{H}_2\text{O}$ requires Cl, 9.30; loss, 9.35 %. The anhydrous salt melts at $185\text{--}186^\circ$ (corr.).

O-n-*Amylharmol*, needles, M.P. $204\text{--}206^\circ$ (corr.). (Found: C, 75.9; H, 7.5 %. $\text{C}_{17}\text{H}_{20}\text{ON}_2$ requires C, 76.1; H, 7.5 %.) The *hydrochloride*, long silky needles, M.P. $192\text{--}194^\circ$ (corr.) after drying at 50° , is soluble in 10 parts of hot water, the solution gelatinising on cooling, sparingly soluble in cold water. (Found, in air-dried salt: loss at 50° , 5.2 %. $\text{C}_{17}\text{H}_{20}\text{ON}_2$, HCl, H_2O requires H_2O , 5.5 %. Found, in dried salt: Cl, 11.4 %. $\text{C}_{17}\text{H}_{20}\text{ON}_2$, HCl requires Cl, 11.7 %.) The *lactate*, colourless needles, M.P. $130\text{--}132^\circ$ (corr.), sparingly soluble in cold water.

O-iso-*Amylharmol*, thick rhombs, M.P. $236\text{--}237^\circ$ (corr.). (Found: C, 76.4; H, 7.6 %. $\text{C}_{17}\text{H}_{20}\text{ON}_2$ requires C, 76.1; H, 7.5 %.) The *hydrochloride*, needles, M.P. $206\text{--}208^\circ$ (corr.) after drying, soluble in 20 parts of water at 80° . Strong solutions gelatinise on cooling, but the gel soon passes into a mass of small crystals. Sparingly soluble in cold water. (Found, in air-dried salt: loss at 100° , nil; at 120° , 5.6 %. $\text{C}_{17}\text{H}_{20}\text{ON}_2$, HCl, H_2O requires H_2O , 5.6 %. Found, in dried salt: Cl, 11.9 %. $\text{C}_{17}\text{H}_{20}\text{ON}_2$, HCl requires Cl, 11.7 %.)

O-n-*Hexylharmol*, long needles, M.P. $143\text{--}144^\circ$ (corr.). The *hydrochloride*, felted needles, M.P. $212\text{--}213^\circ$ (corr.). (Found: Cl, 10.9 %. $\text{C}_{18}\text{H}_{22}\text{ON}_2$, HCl requires Cl, 11.1 %.)

O-n-*Heptylharmol*, large anhydrous leaflets, M.P. $131\text{--}132^\circ$ (corr.) after sintering at 110° . (Found: C, 76.8; H, 8.1 %. $\text{C}_{19}\text{H}_{24}\text{ON}_2$ requires C, 77.0; H, 8.1 %.) The *hydrochloride*, needles, M.P. $228\text{--}229^\circ$ (corr.). (Found: N, 8.3; Cl, 10.6 %. $\text{C}_{19}\text{H}_{24}\text{ON}_2$, HCl requires N, 8.4; Cl, 10.7 %.) The *methiodide*, minute glistening needles, M.P. $239\text{--}240^\circ$ (corr.) gives on double decomposition with silver chloride in aqueous solution the *methochloride*, colourless tablets, M.P. $251\text{--}252^\circ$ (corr.). This gives a bright but gelatinous 1 % solution in cold water. (Found: Cl, 10.1 %. $\text{C}_{20}\text{H}_{27}\text{ON}_2\text{Cl}$ requires Cl, 10.2 %.) It yields with ammonia O-n-*heptyl-N-methylharmol*, pale yellow needles, M.P. 227° (corr.) after darkening at 120° , insoluble in water, but very readily soluble in alcohol giving an intensely yellow solution. (Found: C, 77.5; H, 8.4 %. $\text{C}_{20}\text{H}_{28}\text{ON}_2$ requires C, 77.4; H, 8.4 %.)

O-n-*Octylharmol*, needles, M.P. $98\text{--}100^\circ$ (corr.). (Found: C, 76.9; H, 8.4 %. $\text{C}_{20}\text{H}_{28}\text{ON}_2$ requires C, 77.3; H, 8.4 %.) The *hydrochloride*, thick needles, M.P. $217\text{--}218^\circ$ (corr.) after drying. (Found, in air-dried salt: loss at 100° , 5.1 %. $\text{C}_{20}\text{H}_{28}\text{ON}_2$, HCl, H_2O requires H_2O , 4.9 %. Found, in dried salt: Cl, 10.1 %; $\text{C}_{20}\text{H}_{28}\text{ON}_2$, HCl requires Cl, 10.2 %.)

O-sec-*Octylharmol hydrochloride* (prepared by means of α -methylheptyl iodide), short prisms, M.P. $254\text{--}255^\circ$ (corr.) after drying. (Found, in air-dried salt: loss at 100° , 11.6, 11.3; Cl, 10.4 %. $\text{C}_{20}\text{H}_{28}\text{ON}_2$, HCl, $2\frac{1}{2}\text{H}_2\text{O}$ requires H_{20} , 11.5; Cl, 10.2 %.) This salt is readily soluble in hot water, and the solution crystallises on cooling and does not set to a gel. The solubility in cold water is 1 in 28.

O-n-*Nonylharmol*, long needles, M.P. 115° (corr.). (Found: C, 77.5; H, 8.6 %. $\text{C}_{21}\text{H}_{28}\text{ON}_2$ requires C, 77.7; H, 8.6 %.) The *hydrochloride* crystallises from a mixture of alcohol and acetone in anhydrous leaflets, M.P. $205\text{--}207^\circ$ (corr.). It is readily soluble in alcohol, and dissolves in 20 parts of water at 45° giving a turbid solution, which does not gelatinise on cooling but yields an amorphous deposit; after filtering, an opalescent solution is obtained containing about 1 part of the salt in 140. (Found: N, 7.7; Cl, 9.8 %. $\text{C}_{21}\text{H}_{28}\text{ON}_2$, HCl requires N, 7.8; Cl, 9.8 %.)

O-n-*Decylharmol*, needles, M.P. $105\text{--}107^\circ$ (corr.). (Found: C, 78.1; H, 8.8 %. $\text{C}_{22}\text{H}_{30}\text{ON}_2$ requires C, 78.1; H, 8.9 %.) The *hydrochloride*, leaflets, M.P. 208° (corr.), after drying. (Found, in air-dried salt: loss at 100° , 2.4 %. $\text{C}_{22}\text{H}_{30}\text{ON}_2$, HCl, $\frac{1}{2}\text{H}_2\text{O}$ requires H_2O , 2.3 %. Found, in dried salt: Cl, 9.3 %. $\text{C}_{22}\text{H}_{30}\text{ON}_2$, HCl requires Cl, 9.5 %.)

O-iso-*Decylharmol* (O- β -n-*Butyl-n-hexylharmol*) was prepared by means of β -n-*butyl-n-hexyl bromide* (B.P. $108\text{--}109^\circ/14\text{ mm.}$; d , 1.073 at 16° . Found: Br, 35.9 %. $\text{C}_{10}\text{H}_{21}\text{Br}$ requires Br, 36.2 %) which resulted from the action of hydrogen bromide upon β -n-*butyl-n-hexyl alcohol* (B.P. $213\text{--}216^\circ$), prepared by reducing ethyl di-n-butyl acetate with sodium and alcohol. O-iso-*Decylharmol*, flocks of needles, M.P. $101\text{--}104^\circ$ (corr.). (Found: C, 78.1; H, 8.9 %. $\text{C}_{22}\text{H}_{30}\text{ON}_2$ requires C, 78.1; H, 8.9 %.) The *hydrochloride*, needles containing $2\text{H}_2\text{O}$, M.P. hydrated $88\text{--}90^\circ$; anhydrous $210\text{--}212^\circ$ (corr.). (Found: loss at 100° , 8.5 %. $\text{C}_{22}\text{H}_{31}\text{ON}_2\text{Cl}$, $2\text{H}_2\text{O}$ requires H_2O , 8.8 %. Found, in dried salt: Cl, 9.6 %. $\text{C}_{22}\text{H}_{31}\text{ON}_2\text{Cl}$ requires Cl, 9.5 %.)

O-n-*Dodecylharmol*, needles, M.P. $119\text{--}120^\circ$ (corr.). (Found: C, 78.5; H, 9.4 %. $\text{C}_{24}\text{H}_{34}\text{ON}_2$ requires C, 78.7; H, 9.3 %.) The *hydrochloride*, nacreous leaflets, M.P. 208.5° (corr.). (Found: Cl, 8.8 %. $\text{C}_{24}\text{H}_{34}\text{ON}_2$, HCl requires Cl, 8.8 %.)

O-Benzylharmol, minute needles, m.p. 213° (corr.) after sintering from 195°. (Found: C, 79.2; H, 5.6%. $C_{19}H_{16}ON_2$ requires C, 79.2; H, 5.6%.) The *hydrochloride*, needles, m.p. 256–257° (corr.) gives a 2% solution in hot water, which gelatinises on cooling. (Found: Cl, 11.2%. $C_{19}H_{16}ON_2$, HCl requires Cl, 11.0%.)

O-ω-Hydroxy-n-decylharmol, prepared from ακ-decylenechlorohydrin, formed needles, m.p. 174–175° (corr.). (Found: C, 74.5; H, 8.5%. $C_{22}H_{30}O_2N_2$ requires C, 74.6; H, 8.5%.) The *hydrochloride*, needles, m.p. 180° (corr.) after drying is sparingly soluble in water. (Found, in air-dried salt: loss at 100°, 4.2%. $C_{22}H_{30}O_2N_2$, HCl, H_2O requires H_2O , 4.4%. Found, in dried salt, Cl, 9.1%. $C_{22}H_{30}O_2N_2$, HCl requires Cl, 9.1%.) The lactate is soluble in 10 parts of hot water, but separates in gelatinous masses on cooling.

ω-Dialkylaminoalkyl ethers of harmol.

These were prepared by boiling alcoholic solutions of harmol (1 mol.), aqueous (5*N*) sodium hydroxide (2 mols.), and the appropriate ω-dialkylaminoalkyl chloride hydrochloride (1 mol.). Substances of the latter class were made by the action of thionyl chloride in chloroform upon the corresponding ω-dialkylaminoalkyl alcohols [Gough and King, 1928]. Except in the case of the undecyl derivatives these alcohols were prepared by heating dialkylamines with the corresponding chlorohydrins. Several of the latter were prepared in a crude state by boiling the appropriate glycol with concentrated hydrochloric acid, but were contaminated with much of the corresponding dichlorides, so that on treatment with dialkylamines mixtures of ω-dialkylaminoalkyl alcohols and bis-dialkylaminoparaffins resulted. On the appearance of Bennett and Mosses's work [1931] the chlorohydrins were made in a purer state by their method. These reactions may be outlined as follows:

The λ-dialkylaminoundecyl chlorides were made by a different method. Ethyl κ-bromoundecate was condensed with dialkylamines, and the amino-esters reduced to the amino-alcohols which were then treated with thionyl chloride.

ω-Dialkylaminoalkyl alcohols.

η-Diethylaminoheptyl alcohol. η-Chloroheptyl alcohol (39 g.) and diethylamine (39 g.) were heated under reflux at 70° for 48 hours, more diethylamine being added from time to time to replace that lost by evaporation. The solid mass was mixed with aqueous sodium hydroxide and extracted with ether. This was distilled into hydrochloric acid to recover diethylamine, and the non-volatile residue was separated by means of acid into unchanged chlorohydrin (8.4 g.) and η-diethylaminoheptyl alcohol (32.7 g. = 90% on chlorohydrin used up; b.p. 139–141°/25 mm.). (Found: C, 70.7; H, 13.4%. $C_{11}H_{25}ON$ requires C, 70.6; H, 13.3%.)

The following alcohols were prepared similarly:

θ-Diethylaminooctyl alcohol, yield 89%, b.p. 187–190°/72 mm. (Found: C, 71.5; H, 13.5%. $C_{12}H_{27}ON$ requires C, 71.7; H, 13.4%.)

ι-Diethylaminononyl alcohol, yield 72%, b.p. 171–173°/23 mm. (Found: C, 72.6; H, 13.6%. $C_{13}H_{29}ON$ requires C, 72.6; H, 13.5%.)

κ-Dimethylaminodecyl alcohol, yield 64%, b.p. 202–204°/30 mm. (Made in a sealed tube at 100°.) (Found: C, 71.6; H, 13.4%. $C_{12}H_{27}ON$ requires C, 71.7; H, 13.4%.)

κ-Diethylaminodecyl alcohol, yield 80%, b.p. 193–196°/50 mm. (Found: C, 73.5; H, 13.4%. $C_{14}H_{31}ON$ requires C, 73.3; H, 13.5%.) The *picrate* had m.p. 145°.

κ-Dibutylaminodecyl alcohol, yield 91%, b.p. 233–235°/50 mm. (Found: C, 75.6; H, 13.7%. $C_{18}H_{39}ON$ requires C, 75.7; H, 13.7%.)

κ -Di-*n*-amylaminodecyl alcohol, yield 62 %, B.P. 227–229°/17 mm. (Found: C, 76.6; H, 13.8 %. $C_{20}H_{43}ON$ requires C, 76.7; H, 13.8 %.)

κ -Piperidyldecyl alcohol, yield 89 %, B.P. 210–211°/25 mm., M.P. 55–56°. (Found: C, 74.7; H, 12.7 %. $C_{15}H_{31}ON$ requires C, 74.7; H, 12.7 %.)

λ -Diethylaminoundecyl alcohol. Ethyl κ -bromoundecoate (147 g.) and diethylamine (80 g.) were heated under reflux for 2 days. The product was worked up similarly to the products of the interaction of diethylamine with the chlorohydrins, and gave ethyl κ -diethylaminoundecoate (103 g. = 73 %, B.P. 210–212°/50 mm.). (Found: C, 71.4; H, 12.2 %. $C_{17}H_{35}O_2N$ requires C, 71.6; H, 12.3 %.) On reducing the amino-ester with sodium and alcohol under the conditions employed by Bennett and Mosses [1931] for reducing esters of dicarboxylic acids to glycols, λ -diethylaminoundecyl alcohol was obtained in 71 % yield, B.P. 219–220°/72 mm. (Found: C, 73.9; H, 13.8 %. $C_{15}H_{33}ON$ requires C, 74.1; H, 13.6 %.) Ethyl κ -di-*n*-butylaminoundecoate, yield 75 %, B.P. 210°/25 mm. (Found: C, 73.8; H, 12.6 %. $C_{21}H_{43}O_2N$ requires C, 73.8; H, 12.6 %), similarly gave on reduction λ -di-*n*-butylaminoundecyl alcohol, yield 62 %, B.P. 215°/17 mm. (Found: C, 76.2; H, 13.8 %. $C_{19}H_{41}ON$ requires C, 76.2; H, 13.7 %) and ethyl κ -di-*n*-heptylaminoundecoate, yield 78 %, B.P. 246–250°/4 mm. (Found: C, 76.1; H, 12.9 %. $C_{27}H_{55}O_2N$ requires C, 76.3; H, 13.1 %) gave λ -di-*n*-heptylaminoundecyl alcohol, yield 70 %, B.P. 236–238°/4 mm. (Found: C, 78.3; H, 13.9 %. $C_{25}H_{53}ON$ requires C, 78.5; H, 13.8 %.)

ω -Dialkylaminoalkyl chlorides.

These were prepared by the method of Gough and King [1928] and isolated as hydrochlorides in yields of 80–100 %. The lower members of the series separated from absolute alcohol or mixtures of absolute alcohol with anhydrous ether in colourless needles, usually anhydrous, which were very readily soluble in water, alcohol or acetone, but insoluble in dry ether.

η -Diethylaminoheptyl chloride hydrochloride, contains $\frac{1}{2}H_2O$, and has M.P. (hydrated) 82–84°; dried *in vacuo* 76–78°. (Found, in air-dried salt: loss *in vacuo*, 3.3 %. $C_{11}H_{24}NCl$, $\frac{1}{2}H_2O$ requires H_2O , 3.6 %. Found, in salt dried *in vacuo*: C, 52.3; H, 10.5; Cl, 29.0 %. $C_{11}H_{24}NCl$, HCl requires C, 52.6; H, 10.4; Cl, 29.3 %.)

θ -Diethylaminoethyl chloride hydrochloride, M.P. 73°. (Found: N, 5.4; Cl, 27.5 %. $C_{12}H_{26}NCl$, HCl requires N, 5.5; Cl, 27.7 %.)

ι -Diethylaminononyl chloride hydrochloride, M.P. 85–86° (corr.).

κ -Dimethylaminodecyl chloride hydrochloride, M.P. 136–138° (corr.). (Found: Cl, 27.6 %. $C_{12}H_{26}NCl$, HCl requires Cl, 27.7 %.)

κ -Diethylaminodecyl chloride hydrochloride, M.P. 80–82° (corr.). (Found: C, 59.1; H, 11.1; Cl, 24.8 %. $C_{14}H_{26}NCl$, HCl requires C, 59.2; H, 10.9; Cl, 25.0 %.)

κ -Piperidyldecyl chloride hydrochloride, M.P. 127–128° (anhyd.). (Found: C, 60.8; H, 10.6; Cl, 23.9 %. $C_{15}H_{30}NCl$, HCl requires C, 60.8; H, 10.45; Cl, 24.0 %.)

λ -Diethylaminoundecyl chloride hydrochloride, M.P. 84–86° (corr.). (Found: C, 60.2; H, 11.05 %. $C_{15}H_{32}NCl$, HCl requires C, 60.3; H, 11.05 %.)

κ -Di-*n*-butylaminodecyl chloride hydrochloride, κ -di-*n*-amylaminodecyl chloride hydrochloride, λ -di-*n*-butylaminoundecyl chloride hydrochloride and λ -di-*n*-heptylaminoundecyl chloride hydrochloride were obtained—and used as alkylating agents—in the form of syrups, which did not crystallise.

Tetraethyldiaminoalkylenes.

In two preliminary experiments chlorohydrins heavily contaminated with the corresponding dichlorides were caused to react with diethylamine and the resulting crude amino-alcohols were treated with thionyl chloride. The crude mixtures of diethylaminoalkyl chloride hydrochloride and tetraethyldiaminoalkylene dihydrochloride were dissolved in absolute alcohol and could be separated sharply by fractional precipitation with ether, the diamino-derivative precipitating last.

η -Tetraethyldiaminoheptane dihydrochloride, colourless hygroscopic crystals (containing $1H_2O$). (Found: H_2O , 5.6 %. Calc.: H_2O , 5.4 %), M.P. 226° (corr.), after drying at 105° was readily soluble in water or alcohol, but insoluble in ether. (Found, in dried salt: C, 56.9; H, 11.5; Cl, 22.9 %. $C_{15}H_{34}N_2$, 2HCl requires C, 57.2; H, 11.4; Cl, 22.6 %.)

κ -Tetraethyldiaminodecane dihydrochloride, colourless hygroscopic needles, m.p. 210–212° (corr.). (Found: Cl, 19.7 %. $C_{18}H_{40}N_2$, 2HCl requires Cl, 20.0 %.)

O- ω -Dialkylaminoalkylharmols.

These were prepared as indicated upon p. 735. They were isolated as dihydrochlorides, which crystallised in colourless needles, more or less readily soluble in water yielding neutral solutions which did not gelatinise. The corresponding bases were obtained by adding ammonia to hot dilute alcoholic solutions of the dihydrochloride, and crystallised from alcohol in colourless needles. Most of those which were analysed contained 2H₂O.

O- β -Diethylaminoethylharmol, m.p. 167–168° (corr.); the *dihydrochloride*, m.p. 295° (corr. decomp.). (Found: C, 51.0; H, 7.4; N, 9.9; Cl, 16.8 %. $C_{18}H_{23}ON_3$, 2HCl, 3H₂O requires C, 50.9; H, 7.3; N, 9.9; Cl, 16.7 %.)

O- η -Diethylaminoethylharmol, m.p. 109–111° (corr.); the *dihydrochloride* crystallises from a mixture of alcohol and acetone in thick needles containing 3H₂O, of which 2 mols. are lost in a vacuum over H₂SO₄ and the third at 100°. The air-dried salt has m.p. 144–146° (corr.); the dried salt has m.p. 138–140°. (Found, in air-dried salt: loss in a vacuum, 6.4; total loss at 100°, 10.7; C, 56.2; H, 8.32 %. $C_{23}H_{33}ON_3$, 2HCl, 3H₂O requires 3H₂O, 10.9; C, 56.0; H, 8.32 %. Found, in dried salt: Cl, 16.2 %. $C_{23}H_{33}ON_3$, 2HCl requires Cl, 16.2 %.)

O- θ -Diethylaminooctylharmol, m.p. 98–99° (corr.); contains 2H₂O. (Found: C, 69.3; H, 9.36 %. $C_{24}H_{35}ON_3$, 2H₂O requires C, 69.0; H, 9.34 %.) The *dihydrochloride* crystallises from aqueous acetone with 1½H₂O which is lost at 80°. The air-dried salt has m.p. 97–100°, and the dried salt 88°. It is soluble in 8 parts of cold water. (Found, in air-dried salt: loss at 80°, 5.4 %. $C_{24}H_{35}ON_3$, 2HCl, 1½H₂O requires H₂O, 5.6 %. Found, in dried salt: Cl, 15.5 %. $C_{24}H_{35}ON_3$, 2HCl requires Cl, 15.6 %.)

O- ι -Diethylaminononylharmol, m.p. 92° (corr.); its *dihydrochloride* crystallises from dilute hydrochloric acid with 3H₂O, which is lost at 100°. m.p. (air-dried) 162–167°; (anhydrous) 168° (corr.). It is soluble in 30 parts of cold water. (Found, in air-dried salt: loss at 100°, 10.3; C, 57.6; H, 8.66 %. $C_{25}H_{37}ON_3$, 2HCl, 3H₂O requires H₂O, 10.5; C, 57.5; H, 8.63 %. Found, in dried salt: Cl, 15.1 %. $C_{25}H_{37}ON_3$, 2HCl requires Cl, 15.3 %.)

O- κ -Dimethylaminodecylharmol, m.p. 91–94° (corr.); its *dihydrochloride*, needles from alcohol, m.p. 180–182° (corr.) contain 2½H₂O which is lost at 100°, soluble in 18 parts of cold water. (Found, in air-dried salt: loss at 100°, 9.08; C, 57.5; H, 8.62 %. $C_{24}H_{35}ON_3$, 2HCl, 2½H₂O requires H₂O, 9.02; C, 57.8; H, 8.43 %. Found, in dried salt: Cl, 15.6 %. $C_{24}H_{35}ON_3$, 2HCl requires Cl, 15.7 %.)

O- κ -Diethylaminodecylharmol, m.p. (air-dried); 117–118° (corr.); (anhydrous) 137° (corr.). (Found, in air-dried substance: loss *in vacuo* over P₂O₅, 7.9 %. $C_{26}H_{39}ON_3$, 2H₂O requires H₂O, 8.1 %.) Its *dihydrochloride* crystallises from alcohol-acetone with 1H₂O, which is lost at 100°. m.p. (air-dried) 134–135°; (anhydrous) 149–150° (corr.). It is soluble in about 5 parts of cold water. (Found, in air-dried salt: loss at 100°, 3.4 %. $C_{26}H_{39}ON_3$, 2HCl, H₂O requires H₂O, 3.6 %. Found, in dried salt: C, 64.8; H, 8.6; N, 8.5; Cl, 14.7 %. $C_{26}H_{39}ON_3$ HCl requires C, 64.8; H, 8.5; N, 8.7; Cl, 14.2 %.)

O- κ -Di-n-butylaminodecylharmol, m.p. 59–60° (corr.), contains 2H₂O. (Found: C, 72.0; H, 10.0 %. $C_{30}H_{47}ON_3$, 2H₂O requires C, 71.9; H, 10.2 %.) The *dihydrochloride* crystallises from alcohol-acetone in needles, which rapidly darken in moist air. The vacuum-dried salt melts at 98–99° and contains 1½H₂O which is lost at 80°. It is soluble in 13 parts of cold water. (Found: loss, 4.9 %. $C_{30}H_{47}ON_3$, 2HCl, 1½H₂O requires H₂O, 4.8 %. Found, in dried salt: Cl, 13.0 %. $C_{30}H_{47}ON_3$, 2HCl requires Cl, 13.2 %.)

O- κ -Piperidyldecylharmol, m.p. 109–111° (corr.). (Found: C, 76.6; H, 9.3 %. $C_{27}H_{39}ON_3$ requires C, 76.7; N, 9.2 %.) The *dihydrochloride* crystallises from water with 4H₂O which is lost at 100°. m.p. (air-dried) 116–118°; (anhydrous) 117–118°. It is soluble in 200 parts of cold water. (Found, in air-dried salt: loss at 100°, 12.45; Cl, 12.45 %. $C_{27}H_{39}ON_3$, 2HCl, 4H₂O requires H₂O, 12.7; Cl, 12.55 %.)

O- λ -Diethylaminoundecylharmol, m.p. 82–84° (corr.), contains 2H₂O. (Found: C, 70.4; H, 9.9 %. $C_{27}H_{41}ON_3$, 2H₂O requires C, 70.5; H, 9.8 %.) The *dihydrochloride* crystallises from alcohol-acetone with 1H₂O, which is lost at 80°, m.p. (air-dried) 94–97°; (anhydrous) 99–101° (corr.).

It is soluble in 3 parts of cold water. (Found, in air-dried salt: loss at 80°, 3·7; Cl, 13·8 %. $C_{27}H_{41}ON_3 \cdot 2HCl \cdot H_2O$ requires H_2O , 3·6; Cl, 13·8 %.)

λ -*Di-n-butylaminoundecylharmol*, m.p. 65–67° (corr.); its *dihydrochloride* crystallises from water with $3H_2O$, of which two are lost at 100° and the rest at 115°. m.p. (air-dried) 138° (corr.), sinters at 135°; (anhydrous) 138–139° (corr.). It is soluble in 80 parts of cold water. (Found, in air-dried salt: loss at 115°, 9·17 %. $C_{31}H_{54}ON_3 \cdot 2HCl \cdot 3H_2O$ requires 6·68 and 9·22 % for loss of $2H_2O$ and $3H_2O$ respectively. Found, in dried salt, Cl, 12·9 %. $C_{31}H_{54}ON_3 \cdot 2HCl$ requires Cl, 12·85 %.)

Alkylharmalols.

These were prepared by the action of alkyl bromides on harmalol in aqueous-alcoholic sodium hydroxide (1 mol.) and worked up in the same way as the alkylharmols.

O-Ethylharmalol was precipitated by ammonia from an alcoholic solution of the hydrochloride in pale brown needles, m.p. 237–239° (corr.). (Found: C, 73·7; H, 7·1 %. $C_{14}H_{18}ON_2$ requires C, 73·7; H, 7·0 %.) The *hydrochloride* crystallises from 5 parts of hot water in bright yellow needles containing $1H_2O$, which is lost at 100°. m.p. (hydrated) 265–268° (corr.); (anhydrous) 263–264° (corr.). It is soluble in 30 parts of cold water. (Found, in air-dried salt; loss at 100°, 6·1 %. $C_{14}H_{18}ON_2 \cdot HCl \cdot H_2O$ requires H_2O , 6·4 %. Found, in dried salt: Cl, 13·4 %. $C_{14}H_{18}ON_2 \cdot HCl$ requires Cl, 13·4 %.)

O-n-Propylharmalol crystallises from moist alcohol in long brown flattened needles, m.p. 195–197° (corr.). (Found: C, 74·5; H, 7·6 %. $C_{15}H_{18}ON_2$ requires C, 74·4; H, 7·4 %.) The *hydrochloride* crystallises from water or moist alcohol in pale yellow needles, m.p. 232–234° (corr.). It is soluble in 9 parts of cold water. (Found: Cl, 12·7 %. $C_{15}H_{18}ON_2 \cdot HCl$ requires Cl, 12·8 %.)

O-n-Butylharmalol crystallises from alcohol in colourless slender needles, m.p. 173° (corr.). (Found: C, 75·0; H, 7·9 %. $C_{16}H_{20}ON_2$ requires C, 75·0; H, 7·8 %.) The *hydrochloride* crystallises from water or alcohol in minute yellow needles, m.p. 213–214° (corr.). It is soluble in 70 parts of water at 35°. (Found: Cl, 12·3 %. $C_{16}H_{20}ON_2 \cdot HCl$ requires Cl, 12·2 %.)

SUMMARY.

1. A convenient method for preparing harmol and harmalol is described.
2. A long series of *O*-alkyl and substituted *O*-alkyl ethers of harmol has been prepared by the alkylation of harmol.
3. In the *n*-alkyl series, the peak of bactericidal activity is found at *n*-butyl- for *B. typhosus* and at *n*-amyl- for *S. aureus*, whilst the peak of amoebicidal activity is found at *n*-nonyl-harmol.
4. In the ω -diethylaminoalkyl series, the peak of bactericidal activity to *B. typhosus* is found at ω -diethylaminononylharmol.
5. Several members of these series were tested for antimalarial or trypanocidal activity, but none gave a positive result.

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