765. *The Chemotherapy of Filariasis. Part I. Monoacyl Derivatives of* 1 : 2 : 3 : 4-*Tetrahydroquinoxaline.*

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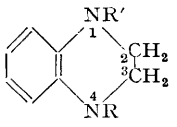
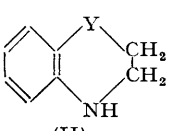
Contrary to previous statements, monoacyl derivatives of tetrahydroquinoxaline may readily be obtained by direct reaction between the base and an acylating agent. At relatively high pH's the yields of monoacyl derivatives (from equimolecular proportions of reactants) exceed 70%. Below pH 5, the yield drops rapidly and disubstitution predominates; this corresponds with a marked increase in ionisation of the base which has been used to interpret the effect. Methylation of the monoacyl derivatives gave the 1-acyl-4-methyl derivatives which were also prepared by acylation of tetrahydro-1-methylquinoxaline.

Apart from the antimonial drugs, the most promising chemicals for treatment of filarial infections have been (*a*) certain derivatives of piperazine (Stewart, Turner, Denton, Kushner, Brancone, McEwen, Hewitt, and Subbarow, *J. Org. Chem.*, 1948, **13**, 134, 144) and (*b*) cyanine dyes and compounds of cyanine-like structure (Welch, Peters, Bueding, Valk, and Higashi, *Science*, 1947, **105**, 486). Of these, the piperazines, especially "Hetrazan" (1-diethylcarbamyl-4-methylpiperazine), have been by far the more useful in the treatment of human cases (for a comparative review of the merits of available canine and human filari-

cides see Otto and Maren, *Amer. J. Hyg.*, 1950, **51**, 385). A series of investigations is therefore planned, designed to throw light on certain features of the piperazine molecule that may be essential for biological activity. Initially, it seemed desirable to evaluate the effect of unsaturation in the piperazine ring on biological activity; the present paper describes the preparation of a tetrahydroquinoxaline analogue (I; R = Me, R′ = CO_2Et) of the active 1-carbethoxy-4-methylpiperazine, where single unsaturation has been introduced at the expense of an additional ring, and of various other monoacyl derivatives of tetrahydroquinoxaline and its *N*-methyl derivative. It is a pleasure to acknowledge the helpful advice and encouragement given by Dr. F. Hawking and Miss W. A. F. Weber of the National Institute for Medical Research, who have kindly undertaken the biological work. The latter will be published later.


(I)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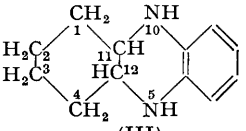
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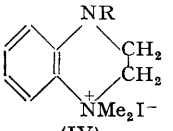
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The preparation of the requisite monoacyltetrahydroquinoxalines (I; R = H, R′ = Acyl) was of interest in that reaction between the base and various acylating agents has been stated to give solely disubstituted products. Thus Meisenheimer and Wieger (*J. pr. Chem.*, 1921, **102**, 49) obtained only diacetyl- and dibenzoyl-tetrahydroquinoxaline. Cavagnol and Wiselogle (*J. Amer. Chem. Soc.*, 1947, **79**, 795) were unable to isolate any of the monosubstituted product on use of acetic anhydride, acetyl chloride, keten, acetamide, or benzoyl chloride under varied conditions; the method of Moore, Boyle, and Thorn (*J.*, 1929, 39) for monocarbethoxylation of piperazines and ethylenediamines at controlled pH led, similarly, only to dicarbethoxytetrahydroquinoxaline and starting material. These results seemed anomalous in the light of experience with piperazine (Moore, Boyle, and Thorn, *loc. cit.*; Baltzly, Buck, Lorz, and Schön, *J. Amer. Chem. Soc.*, 1944, **66**, 263; Brancone *et al.*, *loc. cit.*) on one hand, and dihydrophenazine (following paper) on the other, since in both these cases monosubstitution had been observed under suitable conditions. We therefore reinvestigated the reactions involving tetrahydroquinoxaline, using equimolecular proportions of the base and acylating agent. In all cases, an appreciable amount of monosubstitution was found to take place, a ready separation of the mono- and disubstituted products and unchanged base being possible because of their marked differences in basicity. Acetic anhydride in acetic acid gave 1-acetyl- (I; R = H, R′ = Ac) (47% based on tetrahydroquinoxaline) and 1 : 4-diacetyl-tetrahydroquinoxaline (I; R = R′ = Ac) (15%) and unchanged base (28%); chloroformic ester in ethanol gave 1-carbethoxy- (20%) and 1 : 4-dicarbethoxy-tetrahydroquinoxaline (21·5%) and unchanged base (45%); and benzoyl chloride in aqueous acetone gave 1-benzoyl- (20%) and 1 : 4-dibenzoyltetrahydroquinoxaline (39%) and unchanged base (34%).

The effect of solvent was next studied, in the carbethoxylation and acetylation reactions (see Table I). In the reaction with chloroformic ester, the proportion of mono- to dicarbethoxytetrahydroquinoxaline remains fairly constant but undergoes a slight, yet significant, decrease in passing towards a more acidic solvent. The same decrease is evident on comparing the reaction with acetic anhydride in ethanol with that in acetic acid.

At first sight, these results appeared surprising since the suggestion that a lower pH

TABLE I. *Carbethoxylation and acetylation of tetrahydroquinoxaline.*

Carbethoxylation			Acetylation			Carbethoxylation		
	Substitution (%) *		Reagent	Substitution (%) *			Substitution (%) †	
Solvent	Mono	Di	and solvent	Mono	Di	pH	Mono	Di
C_5H_5N	54	46	Ac_2O–EtOH	100	0	7	75	0
$COMe_2$	50	50	Ac_2O–AcOH	72	28	6	75	0
EtOH	50	50	AcCl–EtOH	38	62	5	75	Trace
AcOH	33	67	AcCl–AcOH	32	68	4	30	51
						3	25	58

* As % (wt.) of total acylated product isolated. † Yields, based on tetrahydroquinoxaline.

favours disubstitution is the reverse of what is generally believed to hold in the piperazine series (cf., *e.g.*, Moore, Boyle, and Thorn, *loc. cit.*), the explanation there advanced being that a decrease in pH increases the ionisation of the monosubstituted piperazine, yielding a cation which is resistant to further substitution. Nevertheless, our results were supported by the fact that the yields of monosubstituted tetrahydroquinoxaline in those acylations involving the elimination of halogen acid (carbethoxylation and benzoylation) were much lower than in those involving acetic anhydride. The latter point was strikingly illustrated by substituting acetyl chloride for acetic anhydride in the acetylation reaction under otherwise identical conditions (see Table I). Final test, by conducting the carbethoxylation at various controlled pH's (Table I) proved conclusively that monosubstitution is at its maximum at relatively high pH's. Not only does the proportion of mono- to di-carbethoxytetrahydroquinoxaline fall off rapidly below pH 5, but the actual yield of monocarbethoxytetrahydroquinoxaline may be increased to 75% provided that the pH of the reaction does not fall below 5, as against the yields of about 25% obtained in the original reactions where the pH was not controlled. The same conclusion has also been shown to apply to the benzoylation and the acetylation reaction.

Now, it had been surmised qualitatively that there was a marked drop in basicity of tetrahydroquinoxaline on monoacylation and potentiometric determination of pK_a values in 50% ethanol (Table 2) confirmed this quantitatively. From the results, the degree of ionisation of the various compounds concerned was calculated for different pH values. Between pH 3 and 5 there is a marked change in ionisation of tetrahydroquinoxaline itself, but the ionisation of its monacyl derivatives is virtually unaffected (almost complete non-ionisation); for the latter the change occurs between pH 1 and 3. Of the species involved in the acylation reactions, those predominant are B (un-ionised tetrahydroquinoxaline) and BX (un-ionised monoacyltetrahydroquinoxaline) above pH 4·5, and BX and BH^+ (the tetrahydroquinoxalinium ion) between pH 2 and 4·5. Now, it seems reasonable to assume that the reactivity (towards acylating agents) of the species will fall off in the order: $B > BX > BH^+$. In conformity, the drain of electrons from the potentially reacting NH group (see II) would, at any rate, be expected to be greatest in BH^+ (II; Y = $>NH_2^+$) less in BX (II; Y = >N·Acyl), and smallest in B (II; Y = >NH). This being so, reaction above pH 4·5 will involve, primarily, the species B (leading to monosubstitution), whilst below pH 4·5 reaction with species BX (leading to disubstitution) will be more favoured.

TABLE 2. *Determination of basic strength.*

Compound	Derivative	Concn. (mole./l.) × 10^3	Solvent	Temp.	pK_a
Tetrahydroquinoxaline	—	?	H_2O (?)	?	4·84 [a]
,, ...	—	9·02	50% aq. EtOH	24—25°	4·60
,, ...	Monocation	?	H_2O (?)	?	(1·17) [a]
,, ...	1-CO_2Et	6·56	50% aq. EtOH	24—25	2·21 [b]
,, ...	1-SO_2Ph	4·72	,,	,,	1·92
,, ...	1-Ac	8·10	,,	,,	1·84
trans-Octahydrophenazine ...	— *	4·96	50% aq. EtOH	24—25	4·62
,, ...	—	6·22	,,	,,	4·62 [b]
,, ...	5-SO_2Ph *	3·92	,,	,,	2·04
o-Phenylenediamine	—	1·28—10·3	H_2O	20	4·47 [c]
,, ...	—	1·28—5·15	50% aq. MeOH	,,	4·42 [c]
,, ...	Monocation	10·5	H_2O	,,	(0·02) [c]
,, ...	,,	2·63—5·25	50% aq. MeOH	,,	(0·67) [c]

[a] Cavagnol and Wiselogle, *loc. cit.* [b] By titration of the hydrochloride with sodium hydroxide. [c] Kuhn and Zumstein, *Ber.*, 1926, **59**, 488; Kuhn and Wasserman, *Helv. Chim. Acta*, 1928, **11**, 20. * Part II, following paper.

A fairly satisfactory qualitative interpretation of the course of the reactions is thus arrived at (discussion of the rather complicated kinetics does not appear justified in view of the limited experimental data). It may be noted it should apply equally to acylation reactions of other diacidic bases whose pK_a values (of the base and of its acyl derivatives) correspond, approximately, to those of tetrahydroquinoxaline (see Table 2). Preliminary results indicate that this is in fact so in the cases of *trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine (III) and *o*-phenylenediamine.

Methylation of the monoacyl derivatives of tetrahydroquinoxaline gave the compounds (I; R = Me, R′ = Ac, Bz, CO_2Et), identical with specimens prepared by direct acylation of 1-methyltetrahydroquinoxaline. These reacted slowly in ethanol with excess of methyl iodide, giving the quaternary salts (IV; R = Ac or CO_2Et); for biological comparison, the methiodide of "Hetrazan" was prepared.

In contrast with the ready reaction of (I; R = R′ = H or Me) with acetyl chloride, benzoyl chloride, and chloroformic ester, neither compound reacted with diethylcarbamyl chloride under a variety of conditions. This acid chloride reacts smoothly with a variety of piperazines (Brancone *et al.*, *loc. cit.*) and with piperidine (unpublished work), though Hurd and Spence (*J. Amer. Chem. Soc.*, 1927, **49**, 266) report that it does not react with sodium azide in benzene and that only diethylamine hydrochloride is obtained by reaction with hydrazine in methanol. Other routes to (I; R = Me, R′ = $CO{\cdot}NEt_2$) are being investigated.

Experimental

M.p.s are uncorrected.

1 : 2 : 3 : 4-*Tetrahydroquinoxaline*.—This base was prepared in excellent yield by hydrogenation of quinoxaline (Cavagnol and Wiselogle, *loc. cit.*) and also by the one-stage synthesis from catechol and ethylenediamine (Merz and von Ris, *Ber.*, 1887, **20**, 1191; cf. Almond and Mann, *J.*, 1951, 1906). The difficulties experienced by Cavagnol and Wiselogle (*loc. cit.*) in the latter reaction were not encountered; the following procedure gave the stated yield of pure product consistently, and was preferred as a rapid and convenient route to moderate quantities of the base: Commercial catechol (24 g.) and ethylenediamine hydrate (20 ml.) were heated in a sealed tube at 200—210° for 15 hours, and the product was melted into water (250 ml.) with mechanical stirring. The resulting suspension was then extracted thrice with benzene, and the combined extracts were washed with N-sodium hydroxide, then with water, dried (K_2CO_3), and concentrated; addition of light petroleum (b. p. 60—80°) gave pale yellow crystals of almost pure tetrahydroquinoxaline (average yield 47% based on catechol), m. p. 97—98°. A further crop (5%) was obtained by concentration of the mother-liquors. The hydrochloride, prepared by passing dry hydrogen chloride into a solution of the base in dry acetone, separated from ethanol–ether under nitrogen in colourless needles, m. p. 167—169°, slowly becoming pink in air.

Acetylation with Acetic Anhydride.—(*a*) To a solution of tetrahydroquinoxaline (5 g.) in glacial acetic acid (25 ml.) at 27—30° acetic anhydride (3·53 ml.) was aed droddpwise during 5 minutes with mechanical stirring and cooling as necessary. After ½ hour's stirring at room temperature, the solution was diluted with water (100 ml.) and made alkaline (litmus) with concentrated aqueous ammonia, the pH brought to 4—5 by dropwise addition of concentrated hydrochloric acid, and the resulting suspension extracted with ether (3 × 85 ml.). The ethereal extracts were washed with 20% aqueous acetic acid (4 × 25 ml.) and once with water (25 ml.) (combined washings A), dried, and neutralised (K_2CO_3), then evaporated to 10 ml., giving 1-*acetyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (3·10 g.), m. p. 108—109°, which formed brittle, pale ginger-coloured prisms, m. p. 109—110°, from dry benzene–light petroleum (b. p. 60—80°); the mixed m. p. with tetrahydroquinoxaline was 72—74° (Found: C, 67·95; H, 6·7; N, 16·1. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·9; N, 15·9%). This monoacetyl derivative was moderately soluble in hot water and gave colourless prisms on cooling; it was more soluble in cold dilute hydrochloric acid than in water.

The original aqueous phase from the ether-extraction was made acid to Congo-red with concentrated hydrochloric acid and extracted with benzene (extracts B), then basified with sodium hydroxide, and re-extracted with benzene (extracts C). Extracts B, after drying (K_2CO_3) and evaporation, gave a colourless residue of 1 : 4-diacetyltetrahydroquinoxaline (0·58 g., 7·15%), m. p. and mixed m. p. 143—144°. Extracts C contained only a little oil (0·3 g.) which was mostly tetrahydroquinoxaline. The bulk of the unchanged tetrahydroquinoxaline was present in the washings A, and was isolated by basification and extraction with benzene; the residual oil (2·4 g.) from the evaporated extracts gave tetrahydroquinoxaline hydrochloride (1·8 g., 28·4%) by treatment with dry hydrogen chloride in ethanol.

By bringing the basified reaction mixture directly to pH 3 with concentrated hydrochloric acid and extraction with benzene, the yield of diacetyltetrahydroquinoxaline in this reaction was ascertained as 15·4%.

(*b*) In ethanol (50 ml.), under conditions otherwise identical with those described in (*a*),

the sole product was the monoacetyltetrahydroquinoxaline (6·3 g., 96%), m. p. and mixed m. p. 107—109°, isolated by dilution with water (150 ml.), basification (sodium hydroxide), and extraction with benzene.

(*c*) When tetrahydroquinoxaline (1 g.) was added in portions to acetic anhydride (1·50 ml., equiv. to 2 moles per mole of base) at 35—40°, and left for 2 hours at room temperature, the product, isolated by basification and extraction with benzene, was wholly 1 : 4-diacetyl-1 : 2 : 3 : 4-tetrahydroquinoxaline (1·05 g.), which formed small colourless warts (from ethyl acetate), m. p. 143—144° (Ris, *Ber.*, 1888, **21**, 378, gives m. p. 144°; Cavagnol and Wiselogle, *loc. cit.*, give m. p. 147—147·5°) [Found: C, 66·05; H, 6·45; N, 12·7%; *M* (ebullioscopic), 209. Calc. for $C_{12}H_{14}O_2N_2$: C, 66·0; H, 6·5; N, 12·8%; *M*, 218). This compound was easily soluble in hot water and in organic solvents other than ether and light petroleum; it was, curiously, appreciably more soluble in dilute acids than in water.

(*d*) The diacetyl compound (1·08 g.), m. p. 143—144°, and a further crop (0·18 g.) separating gradually from the mother-liquors, were likewise obtained by refluxing of tetrahydroquinoxaline (1 g.) and acetic anhydride (1·5 ml.) for 5 minutes, and followed by addition to aqueous ammonia.

Carbethoxylation.—Ethyl chloroformate (4·76 ml., 0·05 mol.) was added dropwise during ¼ hour with mechanical stirring to a suspension of tetrahydroquinoxaline (6·7 g., 0·05 mol.) in ethanol (50 ml.); the temperature, originally 15°, was allowed to rise to 20—22°, and kept within these limits by occasional cooling. The solution was then stirred for 1 hour at room temperature (during which the temperature dropped to 15°), water (5 ml.) was added, and the stirring continued for ½ hour at 30°. Dilution with water (100 ml.) and extraction with ether (3 × 125 ml.) left an aqueous phase which, after basification with sodium hydroxide, gave unchanged tetrahydroquinoxaline (3·02 g., 45%), m. p. 90—92°, isolated by exhaustive extraction with benzene. The combined ethereal extracts were washed with water (2 × 25 ml.; these washings were combined with the aqueous phase above), dried ($MgSO_4$), and evaporated, giving an oil, which was dissolved in benzene (50 ml.) and treated with an excess of hydrogen chloride in dry ether. 1-*Carbethoxy*-1 : 2 : 3 : 4-*tetrahydroquinoxaline hydrochloride* (2·5 g., 20·6%), m. p. 149—150°, was thereby precipitated as an oil which rapidly crystallised when scratched; the pure compound formed clusters of soft colourless needles, m. p. 151—152°, from ethanol–ether (Found: C, 54·4; H, 6·0; N, 11·6. $C_{11}H_{14}O_2N_2$,HCl requires C, 54·45; H, 6·2; N, 11·55%); this dissociated into the base (an oil) when suspended in water. The benzene–ether mother-liquors from this hydrochloride were then shaken with 2N-aqueous ammonia, and the organic layer was combined with two extracts of the aqueous layer with ether; after being washed with water and dried (K_2CO_3), the extracts were evaporated, yielding an oil, which distilled almost completely at 176°/0·3 mm. The distillate (3·0 g., 21·5%) crystallised after being scratched under light petroleum (b. p. 40—60°), giving 1 : 4-dicarbethoxy-1 : 2 : 3 : 4-tetrahydroquinoxaline (2·8 g.) m. p. 40—41°, which formed large, colourless prisms [from light petroleum (b. p. 40—60°)], m. p. 40·5—42°, unchanged after recrystallisation from water (in which the compound was only sparingly soluble) [Cavagnol and Wiselogle, *loc. cit.*, give m. p. 42—44° (anhyd.), and describe a trihydrate as an oil] (Found: C, 60·6; H, 6·4; N, 10·0. Calc. for $C_{14}H_{18}O_4N_2$: C, 60·4; H, 6·5; N, 10·05%).

In other experiments when the chloroformic ester was added at 18—30°, the solution stirred for ½ hour at 20—30°, then for 10 minutes at 35—40°, and a further ¼ hour with water (5 ml.) at 35—40°, the yield of monocarbethoxy-derivative was 24%.

The reactions in solvents other than ethanol were carried out similarly, and the products were separated by application of the same principles.

Carbethoxylation at Controlled pH.—The reaction vessel consisted of a 400-ml. beaker, fitted with mechanical stirring and a thermometer, into which projected sealed glass and dip-type calomel electrodes working in conjunction with a Cambridge Instrument Company pH meter (bench type). After standardisation, tetrahydroquinoxaline (1 g.), dissolved in ethanol (100 ml.) and B.D.H. Universal Buffer Solution (100 ml.), was added, and the pH of the solution brought to the desired value by addition of concentrated alkali or acid. An equimolar proportion of chloroformic ester (0·71 ml.) was then added, dropwise, with stirring, through a microburette (time of addition *ca.* ½ hour; temp. 25°); reaction was rapid but the desired pH was easily maintained within ±0·02 unit, by cautious addition of 2N-sodium hydroxide while each drop of acid chloride was reacting. The solution was finally stirred for a further ¼ hour, whereafter the pH was brought to 2—3 by addition of concentrated hydrochloric acid and the products were isolated as described in the previous experiment.

Benzoylation.—A solution of tetrahydroquinoxaline (5·0 g.) in acetone (50 ml.) and water (10 ml.) was stirred and treated dropwise during ¼ hour at 25—30° with freshly distilled benzoyl

chloride (4·30 ml.). Water (10 ml.) was added, the suspension stirred for a further ¼ hour at room temperature and then filtered, giving pure 1 : 4-dibenzoyl-1 : 2 : 3 : 4-tetrahydroquinoxaline (5·0 g., 39%), which formed colourless cubes, m. p. 204—205°, from acetone [Meisenheimer and Wieger (*loc. cit.*) give m. p. 201—202°; Cavagnol and Wiselogle (*loc. cit.*) give m. p. 206—207°] (Found: N, 8·3. Calc. for $C_{22}H_{18}O_2N_2$: N, 8·2%).

The filtrate was evaporated under reduced pressure on the steam-bath until a turbidity set in, water added to bring the volume to 120 ml., and the suspension extracted with benzene. The combined extracts were washed with water (washings A), followed by N-sodium hydroxide, and finally water, dried (K_2CO_3), and evaporated to 20 ml. under reduced pressure; *1-benzoyl-1 : 2 : 3 : 4-tetrahydroquinoxaline* (1·1 g.), m. p. 147—148°, separated on cooling, and a further crop (0·7 g.; total yield of crude product, 20%) after addition of light petroleum (b. p. 40—60°) to the mother-liquors. The pure compound formed colourless prisms, m. p. 152—153°, from benzene, which were very much more soluble in acetone than the dibenzoyl derivative (Found: N, 12·1. $C_{15}H_{14}ON_2$ requires N, 11·75%).

Unchanged tetrahydroquinoxaline (1·7 g., 34%) was recovered from the acid aqueous phase from the above extraction and from washings A, by basification with sodium hydroxide and extraction with benzene.

1 : 2 : 3 : 4-*Tetrahydro-1-methylquinoxaline*.—Finely-powdered tetrahydro-1-methyl-4-phenylsulphonylquinoxaline (15 g.) [Cavagnol and Wiselogle (*loc. cit.*)] was added portionwise to concentrated sulphuric acid (15 ml.) with stirring at 45—50°, and the stirring continued at room temperature until all the solid had dissolved. The blue-green solution was then warmed on the steam-bath for 10 minutes and basified in the cold with ice and 40% sodium hydroxide solution, enough water was added to redissolve precipitated inorganic salts, and the mixture extracted with benzene. Distillation of the residue from the dried (K_2CO_3), evaporated extracts gave tetrahydro-1-methylquinoxaline (6·4 g., 83%), b. p. 108°/2 mm., which slowly darkened in air. When a solution in acetone (150 ml.) was saturated with dry hydrogen chloride, the *monohydrochloride* (8·0 g.) was precipitated as a colourless solid, which formed large, prismatic needles, m. p. 173—174°, when recrystallised from ethanol–ether under nitrogen (Found: C, 58·6; H, 6·9. $C_9H_{12}N_2$,HCl requires C, 58·55; H, 7·1%); in air, the solution suddenly became red during the recrystallisation, and the crystals were tinged red.

1-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-4-*methylquinoxaline*.—(*a*) Tetrahydro-1-methylquinoxaline (0·8 g.) and acetic anhydride (3 ml.) were gently refluxed for ¼ hour, the excess of anhydride was decomposed with water, and the solution basified with aqueous ammonia; the acetyl compound, isolated by ether-extraction, was a colourless oil which, when dissolved in dry benzene (20 ml.) and treated with dry hydrogen chloride, gave a *monohydrochloride* (0·7 g.), which crystallised from ethanol–ether in colourless prisms, m. p. 154—155° (Found: C, 57·95; H, 6·5; N, 12·1. $C_{11}H_{14}ON_2$,HCl requires, C, 58·25; H, 6·7; N, 12·35%).

(*b*) 1-Acetyltetrahydroquinoxaline (1 g.), anhydrous sodium carbonate (1·2 g.), and methyl iodide (0·71 ml.) were gently refluxed in ethanol (10 ml.) for 5 hours under nitrogen at a slight positive pressure (5 cm. mercury). The ethanol was then removed and the residue digested with dry benzene (4 × 10 ml.); 1 acetyltetrahydro-4-methylquinoxaline (0·91 g.) was obtained as an oil from the filtered and evaporated digests, and gave a hydrochloride identical with that prepared by method (*a*).

1-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-4 : 4-*dimethylquinoxalinium Iodide*.—(*a*) When the above acetyl derivative (0·8 g.) was heated under gentle reflux with methyl iodide (3 ml.) in ethanol (5 ml.) for 7 hours, the pure *methiodide* (0·32 g.) separated in the hot, forming soft, colourless, prismatic needles, m. p. 184—185° (decomp.), from ethanol (Found: C, 43·05; H, 5·1. $C_{12}H_{17}ON_2I$ requires C, 43·4; H, 5·2%).

(*b*) The crude methiodide (0·18 g.) separated slowly after 1-acetyltetrahydroquinoxaline (0·75 g.) had been heated with methyl iodide (3 ml.) in methanol (10 ml.) under reflux for 13 hours; recrystallisation from ethanol (20 ml.) (charcoal) gave the pure compounds (0·11 g.), identical in m. p. and mixed m. p. with the above specimen.

1-*Carbethoxy*-1 : 2 : 3 : 4-*tetrahydro*-4-*methylquinoxaline*.—(*a*) Tetrahydro-1-methylquinoxaline hydrochloride (1 g.), ethyl chloroformate (0·60 ml., rather more than one mol.), and sodium hydrogen carbonate (1·4 g., 3 mols.) in ethanol (10 ml.) were gently refluxed for 4 hours under nitrogen at a slight positive pressure (5 cm. mercury). The ethanol was then evaporated off, the residue extracted with benzene (5 × 10 ml.), and the combined, filtered extracts were evaporated, yielding an oil, which was dissolved in acetone (5 ml.) and saturated with dry hydrogen chloride at 0°; addition of dry ether (5 ml.) gave colourless needles (0·94 g., after ether-washing) of 1-*carbethoxy*-1 : 2 : 3 : 4-*tetrahydro*-4-*methylquinoxaline hydrochloride*, m. p.

133—134°, not raised after further recrystallisations from ethanol–ether or acetone–ether under nitrogen (Found: C, 55·9; H, 6·9; N, 10·6. $C_{12}H_{16}O_2N_2$,HCl requires C, 56·4; H, 6·7; N, 10·9%). The hydrochloride dissociated in distilled water, yielding the oily base.

(*b*) 1-Carbethoxytetrahydroquinoxaline hydrochloride (0·9 g., rather less than 0·004 mol.), anhydrous sodium carbonate (1·24 g., 0·012 mol.), and methyl iodide (0·5 ml., 0·008 mol.), in ethanol (10 ml.) were gently refluxed for 5 hours under nitrogen. The product, obtained by the procedure described in (*a*), was an oil (0·65 g.), which gave a hydrochloride (0·45 g.), identical in m. p. and mixed m. p. with that described in (*a*). Digestion of the benzene-insoluble fraction with hot ethanol gave the methiodide (0·3 g.) described below.

1-*Carbethoxy*-1 : 2 : 3 : 4-*tetrahydro*-4 : 4-*dimethylquinoxalinium Iodide*.—The crude mixture of mono- and di-carbethoxytetrahydroquinoxaline from the reaction of ethyl chloroformate (2·38 ml.) with tetrahydroquinoxaline (3·35 g.), was heated under reflux with methyl iodide (5 ml.) in ethanol (50 ml.) for 10 hours. After evaporation of the excess of methyl iodide, the crude *iodide* (1·07 g.), m. p. 166—167°, separated slowly, yielding colourless prismatic needles, m. p. 172—173° (decomp.), from ethanol (Found: C, 43·5; H, 5·5; N, 7·3. $C_{13}H_{19}O_2N_2I$ requires C, 43·1; H, 5·3; N, 7·7%).

"*Hetrazan*" *Methiodide*.—"Hetrazan" (1-diethylcarbamyl-4-methylpiperazine) (1 g.), ethanol (5 ml.), and methyl iodide (2 ml.) were gently refluxed for 4 hours. The crude *iodide*, precipitated by the addition of dry ether, formed colourless, brittle, needles, m. p. 159—160° (decomp.), from ethanol–ether, which were easily soluble in cold water (Found: C, 39·0; H, 7·2; N, 12·2. $C_{11}H_{24}ON_3I$ requires C, 38·7; H, 7·1; N, 12·3%).

Determination of pK_a *Values*.—The values given in Table 2 were obtained by the potentiometric method, under the conditions described by Morley and Simpson (*J.*, 1949, 1014), save that ionic strength corrections were applied in each case. At the concentrations employed these are small (0·01—0·04 unit) and were calculated from the approximate formulæ pK_a (corrected) = pK_a (observed) − 0·5 $\sqrt{\mu}$ where μ = the ionic strength of the solution.

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