766. *The Chemotherapy of Filariasis. Part II.* Monoacyl Derivatives of* 5 : 10-*Dihydro- and* trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*Octahydrophenazine.*

By J. S. Morley.

At room temperature and with excess of acylating agent, 9 : 10-dihydrophenazine gives solely monoacyl derivatives. In contrast, the degree of acylation of *trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine, like that of tetrahydroquinoxaline, depends upon pH, monoacyl derivatives arising at pH 7 but only diacyl derivatives at pH 3. Details are given of the preparation of phenazine by Ris's method (*Ber.*, 1886, **19**, 2206).

In view of the initial object of these researches, outlined in Part I,* various monoacyl derivatives of di- and *as*-octa-hydrophenazines were of interest. The former may be regarded as doubly, and the latter as singly, unsaturated piperazines (*i.e.*, di- and tetrahydropyrazines), where unsaturation has been introduced at the expense of two additional rings.

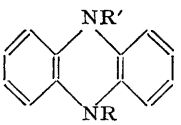
5 : 10-Dihydrophenazine (I; R = R′ = H) is prepared in excellent yield by reduction of phenazine (Claus, *Ber.*, 1875, **8**, 37; Scholl, *Monatsh.*, 1918, **39**, 238) or, more conveniently, by one-stage synthesis from catechol and *o*-phenylenediamine (Ris, *Ber.*, 1886, **19**, 2206; Hinsberg and Garfunkel, *Annalen*, 1896, **292**, 258). The latter reaction appears to

* Part I, preceding paper.

have confused many authors, who have regarded it either as giving a mixture of phenazine and dihydrophenazine, or as giving phenazine directly. Present experience is that dihydrophenazine is the sole product. This compound may be sublimed unchanged in a vacuum or recrystallised in the absence of air, but it is partly oxidised to phenazine by the usual manipulations in air. The most ready conversion into phenazine was by oxidative sublimation; this method gives pure phenazine in excellent overall yield from *o*-phenylenediamine and it is undoubtedly superior to others which have been used for the preparation of this base (cf. the difficulties encountered by Campbell, Le Fèvre, Le Fèvre, and Turner, *J.*, 1938, 408).

Acylation of dihydrophenazine is complicated by the ready tendency of the base to undergo oxidation in solution. It is true that, by the use of an excess of acetic anhydride alone, either a mono- or a di-acetyl derivative may be prepared, according to conditions (see Kehrmann and Havas, *Ber.*, 1913, **46**, 341; Stscherbina, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 613; Puschkareva and Postovski, *J. Gen. Chem. Russia*, 1938, **8**, 158), but with acid chlorides, or with acetic anhydride in a solvent, careful exclusion of air is necessary. When, for example, dihydrophenazine and acetic anhydride (1 mol. each) are stirred together in acetone in air, blue prisms of phenazhydrin (Clemo and McIlwain, *J.*, 1934, 1991) soon separate. However, by working under carbon dioxide, a true comparison of the reactivity of this base in relation to that of analogous diacidic basis may be made. It is then clear that dihydrophenazine is both less reactive and less inclined to give only disubstituted products than either tetrahydroquinoxaline or *trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine. Even with a large excess of acetic anhydride, monoacetyldihydrophenazine (I; R = Ac, R′ = H) is the sole product formed at room temperature (in acetone or without a solvent) and the main product after short boiling; conversion into diacetyldihydrophenazine (I; R = R′ = Ac) is only complete after ½ hour's refluxing with an excess of the reagent. Similarly monobenzoyl- and monocarbethoxy-dihydrophenazine were readily prepared by using an excess of the appropriate acid chloride in either acetone or pyridine; no disubstitution occurred in either case when the reactions were conducted at room temperature.

5-Acetyl- (I; R = Ac, R′ = Me), 5-carbethoxy- (I; R = CO_2Et, R′ = Me), and 5-benzoyl-5 : 10-dihydro-10-methylphenazine (I; R = Bz, R′ = Me) were prepared from 5 : 10-dihydro-5-methylphenazine (I; R = Me, R′ = H) by standard methods in an inert atmosphere, but none of these was converted into the corresponding quaternary salts by methyl toluene-*p*-sulphonate or methyl iodide, alone or in various solvents. In each case the starting material was recovered unchanged, or else oxidised to green amorphous products. As in the case of tetrahydroquinoxaline (preceding paper), neither (I; R = R′ = H) nor (I; R = Me, R′ = H) could be induced to react with diethylcarbamyl chloride.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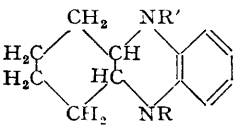
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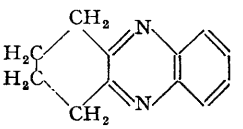
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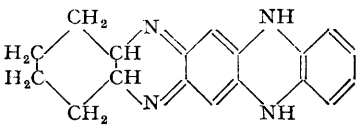
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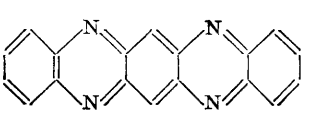
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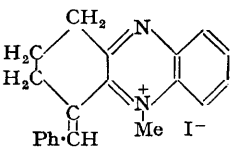
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trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-Octahydrophenazine (II; R = R′ = H) was prepared by reduction of 1 : 2 : 3 : 4-tetrahydrophenazine (III) (Clemo and McIlwain, *J.*, 1936, 258, 1698) which, in turn, results in 60—70% yield by condensation between *cyclo*hexane-1 : 2-dione and *o*-phenylenediamine in sodium acetate–acetic acid (Clemo and McIlwain, *J.*, 1934, 1991). Two by-products have been isolated in the latter reaction: one, obtained always in less than 1% yield, has been previously isolated and identified as *cis*-

1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine *idem, ibid.*; the other, formed in 12—15% yield, is a high-melting base, $C_{18}H_{18}N_4$, which forms a dihydrochloride and a diacetyl derivative. When the known susceptibility of *o*-phenylene-diamines to oxidative attack in the 4 : 5-positions (cf. the oxidation of *o*-phenylenediamine itself to diaminophenazine) is borne in mind, and also the experimental evidence for an oxidative process in the reaction (in the isolation of an octahydrophenazine), (IV) seemed a possible structure. Dehydrogenation to the parent quinoxalinophenazine (V) (Dutt, *J.*, 1926, 1180; see, however, Badger and Pettit, *J.*, 1951, 3211) could not, however, be accomplished; the structure of the base therefore remains in doubt pending synthetic approaches which are in progress.

In reactivity towards acylating agents, the octahydrophenazine was intermediate between 1 : 2 : 3 : 4-tetrahydroquinoxaline and 5 : 10-dihydrophenazine. For example, when each base is treated with a 9-molar excess of acetic anhydride in acetone (48 hours at room temperature), tetrahydroquinoxaline gives only diacetyltetrahydroquinoxaline, dihydrophenazine gives only monoacetyldihydrophenazine, whilst the octahydrophenazine gives a mixture of its monoacetyl (II; R = Ac, R′ = H) (30%) and diacetyl (II; R = R′ = Ac) (54%) derivatives. Other examples may be found in the Experimental section. On the other hand there is a tendency towards disubstitution (particularly when acid chlorides are used) which is equal to that shown by tetrahydroquinoxaline. Indeed only 5 : 10-dicarbethoxy-*trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine (II; R = R′ = CO_2Et) could at first be isolated by reaction between equimolar proportions of the base and chloroformic ester in various solvents. When, later, the importance of pH was disclosed in the tetrahydroquinoxaline series (Part I, preceding paper), analogy suggested that the failure to isolate monocarbethoxyoctahydrophenazine might be due to a relatively low reaction pH (because of hydrogen chloride liberated from the chloroformic ester during reaction and hydrolysis). In conformity, at a controlled pH of 7, 5-carbethoxy-*trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine was the exclusive product. At pH 3, only the dicarbethoxy-derivative was formed. Mono- and di-benzoyloctahydrophenazine were prepared likewise. Since the pK_a values of the octahydrophenazine and its monoacyl derivatives correspond approximately with those of tetrahydroquinoxaline (see Part I), these results lend additional support to the arguments advanced in Part I.

Since 1 : 2 : 3 : 4-tetrahydrophenazine (III) may be regarded as a 2 : 3-dialkylquinoxaline, the methylene groups in the 1 and 4 positions were expected to be reactive; condensation between the corresponding methiodide and *p*-dimethylaminobenzaldehyde readily took place, yielding the deep blue cyanine-like compound (VI).

Experimental

M. p.s are uncorrected.

5 : 10-*Dihydrophenazine*.—Commercial catechol (25 g.) and *o*-phenylenediamine (24 g.) were heated in a sealed tube at 200—210° for 35—40 hours; the product was digested rapidly with water at 60° (400 ml. in all), giving a greenish residue of crude 5 : 10-dihydrophenazine (33 g., 82% based on *o*-phenylenediamine), which was dried over solid sodium hydroxide *in vacuo* and stored under dry carbon dioxide. Portions of this material were purified as required (usually in 5-g. batches) by dissolution in cold acetone and filtration (charcoal); partial evaporation of the filtrate and addition of light petroleum (b. p. 40—60°) gave colourless leaflets (with a slight green sheen) of pure dihydrophenazine (80% recovery) (all operations under dry carbon dioxide), m. p. 280° (decomp.; vac.). Identical material was obtained by reduction of phenazine (Claus, *Annalen*, 1873, **168**, 8). Dihydrophenazine sublimes unchanged in a vacuum and is almost insoluble in air-free alcohol, benzene, and chloroform.

Phenazine.—For sublimation, the crude dihydrophenazine (33 g.), obtained as above, was placed in a 250-ml. wide-armed retort fitted with an oxygen lead, and contained in an air-oven so that ¾ of the arm of the retort projected out of the oven. A slow stream of dry oxygen was then passed through the retort and the temperature was raised to 210—220°. Almost pure phenazine (22·1 g., 55% based on *o*-phenylenediamine), m. p. 169—170°, sublimed into the side-arm during 5—7 hours. Recrystallisation from ethanol (*ca.* 250 ml.) gave massive, yellow prismatic needles (20·3 g.) of pure phenazine, m. p. 171—172°.

Acetylation of 5 : 10-*Dihydrophenazine*.—(*a*) Dihydrophenazine (0·25 g.) was dissolved in

acetone (7·5 ml.) under dry carbon dioxide, acetic anhydride (1·4 ml., 10 mols.) added, and the solution left stoppered under carbon dioxide at room temperature for 48 hours. 5-Acetyl-5 : 10-dihydrophenazine (0·2 g.), m. p. 253—254° (decomp.), was isolated by filtration, and a further crop (40 mg.) by evaporation of the filtrate; recrystallisation from acetone gave snow-white cubes, m. p. 254—255° (decomp.) (Tichwinski and Wolochowitsch, *J. Russ. Phys. Chem. Soc.*, 1905, **37**, 8, and Stscherbina, *loc. cit.*, give m. p. 255°; Puschkareva and Postovski, *loc. cit.*, give m. p. 153·5—154°) (Found: C, 74·9; H, 5·3, N, 12·3. Calc. for $C_{14}H_{12}ON_2$: C, 75·0; H, 5·4; N, 12·5%). When equimolar quantities of the reactants were used under otherwise identical conditions, 60% of the dihydrophenazine was recovered unchanged.

(*b*) Dihydrophenazine (0·5 g.) and acetic anhydride (5 ml.) were boiled gently for a few seconds until solution occurred; colourless prismatic needles of the above monoacetyldihydrophenazine (0·51 g.), m. p. 254—255° (decomp.), separated on cooling, which were isolated by filtration followed by washing with ether. The same product was obtained after a paste of dihydrophenazine (1 mol.) and acetic anhydride (2 mols.) had been left at room temperature for 2 days, or a suspension of these reactants had been warmed in acetic acid (3 parts by vol.) for 5 minutes at 95°.

(*c*) When dihydrophenazine (0·5 g.) or monoacetyldihydrophenazine (0·5 g.) and acetic anhydride (5 ml.) were heated gently under reflux for ½ hour or 3 hours, the sole product (0·62 g.) was 5 : 10-diacetyl-5 : 10-dihydrophenazine, which separated in colourless prisms, m. p. 179—180° (165—170° on admixture with monoacetyldihydrophenazine), after decomposition of the excess of anhydride with hot water (20 ml.); this was very appreciably more soluble than the monoacetyl compound in alcohol, acetic acid, or acetone.

Phenazhydrin.—When acetic anhydride (0·28 ml.) was stirred into a solution of dihydrophenazine (0·5 g.) in acetone (15 ml.) in the presence of air, blue prisms of phenazhydrin (0·25 g.), m. p. 225° (decomp.), separated after 1 hour, which could be recrystallised from ethanol without change in m. p. (Found: C, 79·7; H, 4·8; N, 15·3. Calc. for $C_{12}H_8N_2$,$C_{12}H_{10}N_2$: C, 79·55; H, 5·0; N, 15·45%). A specimen prepared by mixing of solutions of dihydrophenazine (0·1 g.) and phenazine (0·1 g.) in acetone was a darker blue and had m. p. 210° (decomp.) [Clemo and McIlwain, *J.*, 1934, 1991, give m. p. 209° (decomp.); Schlenk and Bergmann, *Annalen*, 1928, **463**, 306, give m. p. 224—226°]; there was, however, no depression in m. p. on admixture, and the two specimens were otherwise identical. (The existence of two forms of phenazhydrin has been discussed by Dufraise, Étienne, and Toromanoff, *Compt. rend.*, 1951, **232**, 2379.) Both specimens (100 mg.), when dissolved in hot benzene (10 ml.) and quickly cooled, gave colourless crystals of dihydrophenazine (30 mg.) (identified by m. p. and mixed m. p. determinations, and by conversion into monoacetyldihydrophenazine); evaporation of the filtrate and addition of light petroleum (b. p. 40—60°) gave yellow needles (55 mg.) of phenazine, m. p. and mixed m. p. 170—171°.

Monobenzoyl- and *Monocarbethoxy-dihydrophenazine.*—These compounds were the sole products isolated from the reaction between dihydrophenazine and an equivalent or excess of the appropriate acid chloride in acetone or pyridine at room temperature (all reactions under dry carbon dioxide). For comparative purposes, the following details of the cases involving equimolar proportions of reactants are given. (*a*) Air-free acetone (15 ml.), dihydrophenazine (0·5 g.), and freshly distilled benzoyl chloride (0·32 ml.) were left under carbon dioxide for 3 days. The solid, which separated, was digested with hot acetone (20 ml. in all), and the digests (after filtration in the cold) were then evaporated, yielding *5-benzoyl-5 : 10-dihydrophenazine* (0·13 g.), after crystallisation from acetone–light petroleum (charcoal); this formed soft, colourless plates from benzene, or colourless prismatic needles from aqueous acetone; both forms had m. p. 224—225° (Found: N, 9·8. $C_{19}H_{14}ON_2$ requires N, 9·8%). A further crop (0·27 g.; total yield, 51%) was obtained from the original mother-liquors. Chloroformic ester (0·25 ml.) and a reaction time of 16 hours gave *5-carbethoxy-5 : 10-dihydrophenazine* (0·12 g., 17%) (isolated by dilution with water, basification, and extraction with benzene), which separated from light petroleum (b. p. 40—60°) containing a little ethanol or acetone (very long solubility lag) in pale yellow prisms, m. p. 109—110° (Found: N, 10·9. $C_{15}H_{14}O_2N_2$ requires, N, 11·0%). (*b*) Specimens identical in m. p. and mixed m. p. with the above were obtained when pyridine (5 ml.), dihydrophenazine (0·25 g.), and benzoyl chloride (0·16 ml.) or chloroformic ester (0·25 ml.) were left under carbon dioxide for 24 hours. The yield of crude benzoyl derivative, which separated on dilution with water (20 ml.), was 0·15 g. (38%); the carbethoxy-derivative (yield 66%) was similarly obtained as an oil, which solidified during a week at room temperature.

5 : 10-*Dihydro-5-methylphenazine.*—A solution of pure phenazine (5 g.) in nitrobenzene (25 ml.) was heated at the b. p. for a few seconds in order to expel traces of moisture, the solution

allowed to cool to 120°, and methyl sulphate (3·8 ml.) added with stirring. After 15 minutes at 100—110°, the suspension was cooled, diluted to 250 ml. with dry ether, and filtered; after washing of the residue with dry ether, almost pure methyl 5-methylphenazonium sulphate (6·1 g.) was obtained, which was used without further purification. Recrystallisation from 80% aqueous ethanol–ether gave glittering, yellow-brown needles; their m. p. (rapid heating) 198° (decomp.) varied according to the rate of heating. A solution of this salt (3 g.) in 3N-hydrochloric acid (150 ml.), containing a trace of platinum chloride, was stirred under benzene (100 ml.), carbon dioxide was bubbled into the solution, and zinc dust (12 g.) was added in portions. When the aqueous phase was colourless (up to ½ hour; warming may be necessary towards the end of the reaction), the benzene layer was quickly run off and combined with two benzene extracts of the aqueous phase. After washing with water, drying (K_2CO_3), evaporation and addition of light petroleum (b. p. 60—80°) (all operations under dry carbon dioxide), 5 : 10-dihydro-5-methylphenazine separated in colourless needles (1·6—2·0 g.), m. p. 163—164° (vac.) (Hantzsch, *Ber.*, 1916, **49**, 511, gives m. p. 164° under carbon dioxide). Treatment with benzoyl chloride or chloroformic ester in pyridine (16 hours at room temperature under carbon dioxide) gave *5-benzoyl-5 : 10-dihydro-10-methylphenazine* (crude yield, 80%; prisms from aqueous acetic acid, which retained a yellow-green colour after repeated recrystallisation), m. p. 164—165° (Found: C, 78·8; H, 5·45; N, 9·9. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·4; N, 9·3%), and *5-carbethoxy-5 : 10-dihydro-10-methylphenazine* (crude yield, 90%; colourless needles from aqueous acetic acid), m. p. 84—85° (Found: C, 71·5; H, 6·09; N, 10·8. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·45%).

1 : 2 : 3 : 4-*Tetrahydrophenazine.*—*cyclo*Hexane-1 : 2-dione (10·5 g.), *o*-phenylenediamine (11 g.), freshly fused sodium acetate (15 g.), and glacial acetic acid (45 ml.) were heated under reflux for 2 hours. The hot solution was then poured into water (250 ml.), giving crude 1 : 2 : 3 : 4-tetrahydrophenazine (11·5 g., 67%), m. p. 88—90°, which separated from light petroleum (b. p. 40—60°) in almost colourless prisms, m. p. 92—93° (Clemo and McIlwain, *J.*, 1934, 1991, give m. p. 92·5°). Basification of the mother-liquors (aqueous ammonia) gave a gum, which yielded a granular *base* (? IV) (2·15 g.) when digested with acetone (100 ml.) (digests A). For purification, this, and a further crop (1·4 g.), which separated slowly on addition of excess of 20% aqueous sodium hydroxide to the basified mother-liquors, were first converted into the corresponding *dihydrochloride* (colourless needles from dilute hydrochloric acid or aqueous acetone), m. p. 320—322° (decomp.), by recrystallisation from 4N-hydrochloric acid (Found: C, 54·05; H, 6·0; N, 14·1; Cl, 18·0. $C_{18}H_{18}N_4,2HCl,2H_2O$ requires C, 54·15; H, 6·1; N, 14·0; Cl, 17·8%). The regenerated base separated from aqueous ethanol in small, colourless prisms, m. p. 264—265° [Found: C, 74·5; H, 6·1; N, 19·15%; *M* (ebullioscopic in ethanol), 290. $C_{18}H_{18}N_4$ requires C, 74·45; H, 6·25; N, 19·3%; *M*, 290], which yielded a *diacetyl* derivative (clusters of small, colourless needles from pyridine), m. p. 245—247° (decomp.), with boiling acetic anhydride (5 parts by volume), alone or in ethanol (Found: C, 70·75; H, 5·5; N, 14·85. $C_{22}H_{22}O_2N_2$ requires C, 70·6; H, 5·9; N, 14·95%). *cis*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-Octahydrophenazine (0·1 g.), m. p. 146—147° alone and on admixture with an authentic specimen (Clemo and McIlwain, *J.*, 1936, 1698), was obtained from the acetone digests A by evaporation and recrystallisation of the residual oil from light petroleum (b. p. 40—60°).

Dehydrogenation Experiments.—Tetrahydrophenazine was recovered unchanged after prolonged heating under reflux in sulphur-free xylene with Raney nickel (cf. Badcock and Pausacker, *J.*, 1951, 1373); no useful product was obtained after 2 hours' refluxing in xylene with chloranil. On the other hand, phenazine was formed in quantitative yield when a mixture of the tetrahydrophenazine or *cis*- or *trans*-octahydrophenazine was heated with 30% palladium–charcoal (Baker, McOmie, and Norman, *J.*, 1951, 1117) for ½ hour at 245—250°. Under similar conditions the base, m. p. 264—265°, was unchanged; even after prolonged heating at temperatures ranging from 230° to 300° the loss of hydrogen corresponded to less than 4 atoms per mole of base.

Reactions of Tetrahydrophenazine Methiodide.—(*a*) When the methiodide (0·8 g.) (McIlwain, *J.*, 1937, 1701) in cold pyridine (3 ml.) was treated with *p*-dimethylaminobenzaldehyde (0·4 g.) in acetic anhydride (3 ml.), the colour, initially red, rapidly became green and within 2 minutes was a very deep blue; 1-p-*dimethylaminobenzylidene*-1 : 2 : 3 : 4-*tetrahydrophenazine methiodide* (1·0 g.), which was precipitated by addition of dry ether, formed small, deep maroon-coloured needles, m. p. (variable) 160—180° (decomp.) after marked previous sintering, from ethanol–ether; this gave intense blue colours to water, ethanol, or acetic acid, destroyed by addition of mineral acids (Found: C, 58·4; H, 5·4; N, 9·15. $C_{22}H_{24}N_3I$ requires C, 57·8; H, 5·3; N, 9·2%).

(*b*) The methiodide yielded the dehydro-base (McIlwain, *loc. cit.*), b. p. 169—170°/1 mm., on basification, but neither compound gave a useful product after reduction with sodium in boiling ethanol.

trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*Octahydrophenazine*.—Sodium (20 g.) was added gradually to a gently refluxing solution of crude tetrahydrophenazine (3·6 g.) in absolute ethanol (150 ml.). When all the sodium had reacted, the now colourless solution was decanted into water (300 ml.), and the precipitate of crude octahydrophenazine (2·8—3·0 g.) collected and washed with water. The products from four such runs were dissolved in hot ethanol (100—150 ml.) and concentrated hydrochloric acid added; the *monohydrochloride*, which separated on cooling, formed colourless prisms, m. p. 315° (decomp.), when recrystallised from water under nitrogen (in the presence of air, the crystals become pink) (Found: C, 63·7; H, 7·6; N, 12·5. $C_{12}H_{16}N_2$,HCl requires C, 64·1; H, 7·6; N, 12·5%); it gave the pure base (10·5—11·5 g., 71—78%), m. p. 155—156° (Clemo and McIlwain, *J.*, 1936, 258, give m. p. 156°), on neutralisation with aqueous ammonia. The hydrochloride was only sparingly soluble in ethanol.

Acetylation.—(*a*) A solution of the above octahydrophenazine (0·5 g.) and acetic anhydride (2·8 ml., 10 mols.) in acetone (15 ml.) was set aside at room temperature for 48 hours (unchanged octahydrophenazine was present after 24 hours). Addition of dry ether saturated with hydrogen chloride then gave 5-*acetyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine hydrochloride* (0·21 g., 30%), which formed soft, colourless needles, m. p. 292—294° (decomp.), from dry ethanol–ether, easily soluble in warm ethanol (cf. octahydrophenazine hydrochloride) (Found: C, 62·7; H, 7·05; N, 11·0. $C_{14}H_{18}ON_2$,HCl requires C, 63·0; H, 7·17; N, 10·5%); the corresponding *base* separated from light petroleum (b. p. 40—60°) in rosettes of colourless needles, m. p. 118—119° (Found: C, 72·95; H, 7·7; N, 12·2. $C_{14}H_{18}ON_2$ requires C, 73·0; H, 7·9; N, 12·2%). The original mother-liquors were basified (dilute aqueous ammonia), and the organic layer separated, combined with two ether-extracts of the aqueous layer, dried, and evaporated, giving 5 : 10-*diacetyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine* (0·39 g., 54%), which formed colourless prisms, m. p. 175—176°, when recrystallised from acetone–light petroleum (Found: C, 70·75; H, 6·6; N, 10·7. $C_{16}H_{20}O_2N_2$ requires C, 70·55; H, 7·4; N, 10·3%).

(*b*) The octahydrophenazine (2 g.), dissolved in ethanol, (50 ml.) was treated with stirring at 45—50° with acetic anhydride (2·2 ml., equiv. to 2 mols.), added dropwise during 5 minutes. After 1½ hours at this temperature, the solution was diluted with water (100 ml.), then basified (aqueous ammonia), and the unchanged octahydrophenazine (0·84 g., 42%) collected by filtration; only monoacetyloctahydrophenazine, m. p. 118—119°, alone and on admixture with the above specimen, remained in the filtrate, from which it was isolated *via* the hydrochloride (1·1 g., 39%) obtained by ether-extraction, evaporation of the extracts, and addition of dry ethereal hydrogen chloride to a solution of the residue in acetone.

(*c*) Diacetyloctahydrophenazine, m. p. 175—176°, was the sole product obtained after dissolution of octahydrophenazine (0·3 g.) in warm acetic anhydride (2 ml.) followed by immediate cooling, or after refluxing of the reactants for 2 hours.

Carbethoxylation and Benzoylation at Controlled pH.—(*a*) Equimolar proportions of chloroformic ester (0·51 ml.) and octahydrophenazine (1 g.) were allowed to react at pH 7 under conditions described in Part I (preceding paper) except for the omission of buffering; by substitution of water (100 ml.), in place of the buffer solution, the pH could be controlled within ±0·2 unit, as against ±0·02 unit when a buffer is used. Reaction was less rapid than in the case of tetrahydroquinoxaline, as shown by the longer time required for the pH to reach equilibrium and by appreciable hydrolysis of the acid chloride. When, finally, there was no tendency for the pH to fall, the alcohol was partly removed on the steam-bath under reduced pressure, then the solution was cooled, made acid to Congo-red with hydrochloric acid, and extracted with ether. Evaporation of the dried extracts, followed by addition of dry ether saturated with hydrogen chloride to a solution of the residue in dry acetone (10 ml.), gave, slowly, 5-*carbethoxy*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine hydrochloride* (0·5 g., 32%), which formed colourless clusters of needles, m. p. 228—230° (slight decomp.), from dry ethanol–ether (Found: N, 9·45. $C_{15}H_{20}O_2N_4$,HCl requires N, 9·4%); the dicarbethoxy-derivative (see below) was not detected in the mother-liquors. On contact with water, this hydrochloride dissociated into the corresponding *base*, which, after drying, separated from light petroleum (b. p. 60—80°) in compact pale brown prisms (almost colourless when pulverised), m. p. 98—99° (Found: C, 69·0; H, 8·0; N, 10·5. $C_{15}H_{20}O_2N_2$ requires C, 69·2; H, 7·75; N, 10·75%). The aqueous phase from the above ether-extraction contained unchanged octahydrophenazine (0·34 g.) isolated by basification (aqueous ammonia) and further evaporation.

In an exactly similar manner, benzoyl chloride (0·55 ml.) and octahydrophenazine (0·9 g.)

gave 5-*benzoyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine hydrochloride* (0·35 g., 22%) (colourless needles from ethanol–ether), which melted slowly, with decomp., between 280° and 310°, after marked sintering above 230° (Found : N, 8·5. $C_{19}H_{20}ON_2$,HCl requires N, 8·5%), and the corresponding *base* (pale brown prisms from benzene–light petroleum), m. p. 155—156° (Found : C, 78·2; H, 7·1; N, 9·85. $C_{19}H_{20}ON_2$ requires C, 78·05; H, 6·9; N, 9·6%). The recovery of unchanged octahydrophenazine was 45%, and of benzoyl chloride (as ethyl benzoate) 30—40%.

(*b*) When the above reactions were conducted at pH 3±0·2, the ethereal residues did not yield a hydrochloride, which indicated the absence of monosubstitution; in both cases, recrystallisation of the residue from aqueous acetic acid gave the appropriate, almost pure diacyl derivative. There were so obtained 5 : 10-*dicarbethoxy*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine* (11—15%, based on octahydrophenazine), in colourless needles, m. p. 76—77° (65—70° when mixed with the monocarbethoxy-derivative) (Found : C, 69·95; H, 7·0; N, 8·45. $C_{18}H_{24}O_4N_2$ requires C, 65·05; H, 7·3; N, 8·45%), and the *dibenzoyl* derivative (10—12%) in flesh-coloured needles (prismatic needles from benzene–light petroleum), m. p. 168—169° (131—138° when mixed with the monobenzoyl derivative) (Found : C, 78·9; H, 6·2; N, 6·85. $C_{26}H_{24}O_2N_2$ requires C, 78·8; H, 6·1; N, 7·05%). The recovery of unchanged base was 40—60%. The same products were obtained when equimolar proportions of octahydrophenazine and acid chloride were allowed to react in pyridine, ethanol, or acetone at various temperatures without reference to the pH of the medium, or when excess of the acid chloride was used in pyridine.

Benzenesulphonylation.—(*a*) Benzenesulphonyl chloride (0·34 ml., 1 mol.) was added dropwise to a solution of octahydrophenazine (0·5 g., 1 mol.) in pyridine (5 ml.) at 20—25° (mechanical stirring). After 14 hours at room temperature, the crude product (0·65 g.), obtained by dilution with water (15 ml.), was dissolved in acetone (25 ml.) and treated with dry ether saturated with hydrogen chloride; the hydrochloride (0·68 g., 70%) so precipitated gave 5-*benzenesulphonyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine* (0·43 g., 50%) on basification [aqueous ammonia in ethanol (20 ml.) and water (5 ml.)], which formed colourless needles, m. p. 150—151°, from aqueous ethanol or benzene–light petroleum (Found : C, 65·65; H, 6·0; N, 8·6. $C_{18}H_{20}O_2N_2S$ requires C, 65·85; H, 6·1; N, 8·5%).

(*b*) With excess of the acid chloride (4 mols.) the product was 5 : 10-*dibenzenesulphonyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine* (crude yield, 98%), which separated from ethanol in large, colourless, prismatic needles, m. p. 169—170° (or, occasionally, in colourless prisms, m. p. 185—186°) (Found : C, 61·5; H, 5·1; N, 6·1. $C_{24}H_{24}O_4N_2S_2$ requires C, 61·5; H, 5·16; N, 6·0%).

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