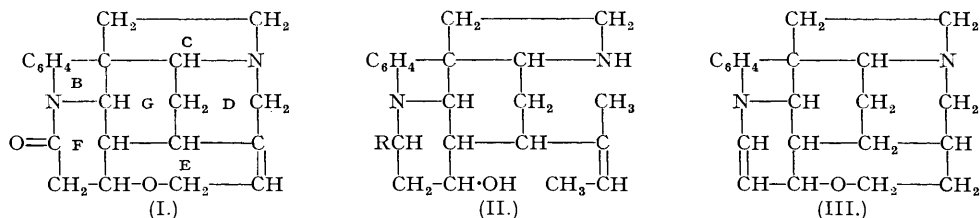


336. Strychnine. Part III. Some New Reduction Products.

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The reduction of strychnine and three of its derivatives by sodium in liquid ammonia is investigated and partial structures are assigned to the products.

THE emphasis of recent work on the structure of strychnine, particularly in this country, by Robinson and his collaborators, has been upon the relationship of the strychnine and *neostrychnine* double bond to N(b), and upon the possible point of attachment of the nitrogen atom to the carbazole residue now almost universally assumed to be present in the alkaloid. The present work has been undertaken with the object of obtaining evidence of the structure of the lactam and ether rings of strychnine. Little work has been done on this point in recent years, and, although early work sufficed for a structure of these rings to be postulated, a more rigorous proof is desirable. The structure generally thought to be the most probable for strychnine is (I). The structures of the compounds described below will be illustrated on the basis of this formulation for convenience and not from conviction that the rings (E and F) are indeed seven- and six-membered respectively.



When one considers the chemistry of the two rings E and F of strychnine (I), it appears that the double bond in ring E and the nitrogen and carbon atoms which form the lactam group interact in a profound way. Thus dihydrostrychnidine is considerably more basic than strychnidine; strychnine is much more readily reduced than strychnidine; and the lactam ring, comparatively readily opened in strychnine, cannot be opened to give dihydrostrychnic acid (Oxford, Perkin, and Robinson, *J.*, 1927, 2389). The distance of the double bond from the

lactam grouping renders explanation of these facts difficult, and, to our knowledge, no satisfactory explanation has been made. A further important reaction, the nature of which is quite obscure, is the change of strychnine to *isostrychnine*. Irrefutable evidence of the structure of rings E and F might throw light on these unsolved problems. We thus consider it is highly desirable to establish (i) the size of the lactam ring, (ii) whether the ether oxygen of strychnine is attached to a secondary or a tertiary carbon atom.

The relationship of the lactam group to the point of attachment of the ethereal oxygen is indicated by the ready hydrolysis of strychninolic acid (Leuchs and Schneider, *Ber.*, 1909, **42**, 2495), and a proof of the secondary nature of the alcohol in a compound such as (II) would virtually prove the six-membered nature of ring F. Conversely, if the hydroxyl group in such a compound should prove tertiary, the lactam ring must be considered as five-membered, and drastic changes made in the proposed formula for strychnine. Work on *isonitrosostrychnine* (Wieland and Kaziro, *Annalen*, 1933, **506**, 60) does indeed point to the secondary nature of such an alcohol, but the proof is not as rigorous as could be desired.

A fission of ring E in which the oxygen atom remains attached to ring F, followed by oxidation to a ketone, would afford the simplest and most direct proof of the secondary nature of the attachment of the oxygen. Raper and Clemo (*J.*, 1946, 891) have suggested that such a fission occurs when strychnine is reduced at high temperature and pressure in methanol solution over Raney nickel. A hydroxyl group is certainly present in the product (termed Base D), but it is not possible to say with certainty that this is attached to ring F; there seems no activating group which would justify us in assuming that fission would take place preferentially in the desired direction, and fission may have occurred in a manner to separate the oxygen from ring F. The double bond in ring E in strychnine cannot facilitate the fission, as we have shown that quantitative conversion of strychnine into dihydrostrychnine occurs over Raney nickel at 100°/100 atm. long before ring fission can take place. Again, it is possible that, under the conditions of the reaction, a change to the *isostrychnine* series is involved in the production of Base D, as dihydro*isostrychnine* can be prepared by heating dihydrostrychnine to 145° in methanol in the presence of a base (Oxford, Perkin, and Robinson, *loc. cit.*), and the fact that in our hands the drastic reduction of dihydro*isostrychnine* does not give Base D does little to discredit the hypothesis. It thus appeared that unless confirmatory evidence for the structure of Base D could be obtained, the secondary or tertiary nature of its hydroxyl group could have no significance.

The Leuchs degradation indicates that strychnine is an allyl ether, and one very convenient method for the fission of allyl ethers involves reduction by sodium in liquid ammonia in the presence of a suitable proton donor, usually an alcohol. If fission of the ether link in strychnine should occur under these conditions, it would be reasonable to assume that no rearrangement had taken place and that the hydroxyl group in the product would be attached as desired to ring F. We have shown that rearrangement is most unlikely during such a reduction by recovering strychnine, dihydrostrychnine, Base D, and strychnidine from solution of sodium methoxide in liquid ammonia in nearly quantitative yields.

A factor greatly influencing the course and speed of the reduction of strychnine and its derivatives with sodium in liquid ammonia is their low solubility in this solvent, which results in the comparatively slow reaction of sodium with the added alcohol, the speed being comparable to that of dissolution of the base; it also limits the scale upon which the reaction can be carried out, 1—2 g. of the alkaloid being as much as can be successfully reduced using vessels of 100 ml. capacity. Increase of the amount of base used without increase of the amount of solvent leads to the necessity of a wasteful separation of product from unchanged material.

Reduction of strychnine itself, using the amounts of sodium and alcohol necessary for the fission of the ether linkage, was disappointing; in some experiments a small amount of pure product was isolated, but not until at least six mols. of added alcohol and sodium were used could consistent results be obtained. The process described in the experimental section was eventually standardised and proved reliable and satisfactory.

The primary *product* (II, R = OH)—subsequently referred to as Base E—isolated from strychnine was a colourless compound, stable in neutral or alkaline solution, containing at least one atom of active hydrogen, as shown by acetylation and by the Zerewitinoff method: this had been formed by the addition to strychnine of six hydrogen atoms instead of the expected two. On treatment in the cold with mineral acid a yellow solution was obtained which, on basification, gave an amorphous yellow solid of indeterminate melting point which was almost certainly a mixture. Its empirical formula showed, however, that it had been formed from Base E by elimination of water, the resulting double bond presumably being responsible for the colour.

Boiling of Base E with dilute mineral acids brought about still further decomposition, giving a dark red solution from which basification produced only a red resinous material. The colour reactions of this series of compounds resemble those of strychnidine rather than strychnine (*e.g.*, no Otto reaction could be detected), and thus it appeared that the lactam group had been modified.

The reduction of the lactam group and the ether linkage would account for the uptake of four hydrogen atoms, and the presence of two further atoms we attribute to the fission of the allylamino-group also present in the molecule. For this to be true, Base E should contain a secondary amino-group in addition to a hydroxyl group, and should give at least two active hydrogens in a Zerewitinoff determination. In practice, only one active hydrogen could be detected, and only a monoacetyl derivative was obtained on acetylation. This latter evidence is not, however, very significant, as the instability of Base E to acids prevented vigorous acetylation conditions being employed. The low active-hydrogen determination is also discounted as evidence, because two active hydrogen atoms are definitely present in the compound obtained by catalytic reduction of Base E, where the modified lactam group has been removed. Interaction between this group and the hydroxyl group is considered to be responsible for the low active hydrogen content. It is interesting to note that Base D, in which a hydroxyl group is also present, gives no active hydrogen in a Zerewitinoff determination, although the corresponding strychnidine derivative gives one active hydrogen atom.

The reduction of tertiary amides with sodium in ammonia has not been previously reported, and a model experiment was undertaken with *N*-methylacetanilide in the hope that light might be thrown on the nature of the alteration of the lactam group. Acetaldehyde was isolated in fair yield, after treatment of the crude product with acid, as its 2 : 4-dinitrophenylhydrazone. This reaction, constituting a new method of preparation of aldehydes from derivatives of the corresponding acids, was further investigated. However, dialkylamides were not reduced, and experiments with a wide range of anilides were disappointing, the above reduction to give acetaldehyde being the most successful. The reaction may, however, be of use in the hydrolysis of alkylanilides when groups in the remainder of the molecule make the use of strongly acid or alkaline reagents undesirable.

The model experiment left no doubt that Base E contained a potential aldehyde group, and this was confirmed by its ready reaction with hydroxylamine. The presence of an unmodified aldehyde group is inherently unlikely, and the compound exhibited no reducing action or aldehyde colour reactions; the comparative difficulty of reduction of this compound is also against its formulation as an aldehyde. We consider the most likely formulation of Base E to be (II, R = OH) (hydroxytetrahydrodichanostrychnidine), that is, an aldehyde ammonia or *pseudo*-base, and the formulation affords an explanation of the acid-catalysed change previously mentioned. Acid treatment would presumably give the true base, as with the *pseudo*-bases of the quinoline series; wandering of the double bond into the five-membered ring might occur, basification leading to further bond migration of an indeterminate nature. A double bond which had so wandered into the central part of the molecule might be expected to be resistant to reduction for purely steric reasons, and so the observation that the yellow base (anhydrohydroxytetrahydrodichanostrychnidine) retains its colour and so presumably its double bond on reduction at 150°/100 atm. over Raney nickel adds support to this interpretation. The only alternative to formulation as the *pseudo*-base is formulation as the corresponding anhydro-base. However, this would necessitate Base E having a molecule of water of crystallisation. We have been quite unable to eliminate water from the base without decomposition. Water is in fact evolved quantitatively on melting, but the resulting melt cannot be reconverted into Base E by treatment with water or aqueous solvents. The loss of water is indeed the first result of treating Base E with acetic anhydride; acetylation of the anhydro-base then takes place slowly.

A compound of the structure we attribute to Base E should be oxidisable to the lactam with alkaline ferricyanide, but under the conditions attempted by us no such oxidation could be accomplished. This failure is significant in that it raised doubts as to the validity of the evidence for the existence of the group $\text{>C-N}(b)\text{<}$ in strychnine, based as it is on the non-oxidation under similar conditions of *pseudostrychnine*.

Reduction of the double bond in Base E, using Adams's catalyst, was unsuccessful. Reduction over Raney nickel at 100°/80 atm., however, reduced both double bond and the *pseudo*-basic hydroxyl group to give a *compound*, which we call hexahydrodichanostrychnidine, containing two active hydrogen atoms. This shows no aldehydic properties, nor is it sensitive to acid; it is clearly a derivative of strychnidine.

The reduction of dihydrostrychnine was next attempted and again a colourless compound (Base F) was obtained, unstable to acids, with which it formed yellow compounds, almost certainly mixtures. In this case there can be little doubt as to the partial structure of the reduction product. Analysis indicated the presence of one oxygen only, and, as vigorous catalytic reduction produced dihydrostrychnidine, the only acceptable structure is (III), which may be called dehydrodihydrostrychnidine. The occurrence of this compound as the anhydro-base need not decide us against formulating Base E as the *pseudo*-base, as quite small changes in the molecule might be expected to alter the relative stability of *pseudo*-base to *anhydro*-base.

Reduction of Base D gave a *product* having the characteristic acid sensitivity and composition for a *pseudo*-basic structure analogous to that of Base E. The melting point with effervescence was very similar to that of Base E, and both these compounds are probably closely related. That no skeletal changes had taken place during the reduction is shown by the catalytic reduction of the compound to the strychnidine derivative obtained by electrolytic reduction of Base D.

Strychnidine was readily reduced in good yield by the standard technique. The reduction was not complicated by the presence of the amido-grouping, and the structure of the *product* as (II, R = H) is virtually certain. The compound is unchanged by acid and has two active hydrogen atoms. Only a monoacetyl derivative could be obtained, which however still contained active hydrogen, and it is perhaps interesting to note that the hydroxyl group of Base D is very resistant to acetylation. The presence of a secondary amino-group in this compound was demonstrated as follows. Straightforward nitrosation was complicated by the reaction of nitrous acid with the aromatic nucleus, and the crude product did not give a Liebermann colour reaction showing the presence of a *N*-nitroso-group. Nitrosation was thus attempted on the compound prepared by condensation of the base with benzenediazonium chloride, in which the benzene nucleus should be protected from attack. The product from this nitrosation gave a positive Liebermann reaction which was not given when a similar series of reactions was applied to strychnidine itself.

Further reduction of the base proved surprisingly difficult. Reduction at room temperature was unsuccessful, and after attempted reduction over Raney nickel at 100°/100 atm. the starting material was recovered nearly quantitatively. However, more vigorous conditions, *i.e.*, 150°/100 atm. resulted in reduction. The *product*, however, was formed by the addition to the base of six atoms of hydrogen instead of the expected two atoms. The same product was later obtained in good yield by the reduction under the same conditions of Base E.

The empirical formula indicates that either the benzene ring has been saturated or two further rings have undergone fission. It is very unlikely that a benzene ring would be reduced while an isolated double bond was unchanged, and all our present evidence is against such a hypothesis. Thus the new base seems to contain a primary amino-group indicating fission of one ring, insufficient hydrogen then being available for saturation of the benzene ring, and an active hydrogen determination gives a value of three per molecule, a result which could not be explained by a simple reduction of the ring. We must therefore suppose that reduction is accompanied by the fission of two more rings. Present evidence is insufficient for us to formulate this very interesting degradation product, but further work on the constitution of this and of the other new degradation products here described is being pursued.

EXPERIMENTAL.

The reductions in ammonia were carried out in an unsilvered Dewar vessel (100 ml.) without rigorous exclusion of moisture. Melting points are uncorrected.

Hydroxytetrahydrodichanostrychnidine (Base E) (II, R = OH).—Sodium (*ca.* 100 mg.) was added with stirring to a suspension of finely powdered strychnine (1 g.) in liquid ammonia (80 ml.) containing excess (1 ml.) of ethanol. Similar additions were made each time the blue colour disappeared until the colour from one such addition persisted for 15 minutes (total time of reduction $\frac{3}{4}$ —1 hour). The resulting suspension was cautiously acidified by the addition of ammonium chloride, poured into an open beaker, and allowed to evaporate spontaneously. The dry residue was washed (2*N*-sodium hydroxide, 50 ml.) collected at the pump, washed with water, dried in a vacuum, and recrystallised from boiling ethyl acetate (*ca.* 100 ml.). The *product* separated as colourless radiating clumps of needles (0.53 g., 53%), very soluble in alcohols, less so in acetone, benzene, and ethyl acetate, insoluble in water and light petroleum, *m. p.* 165° (efferv.) (Found: C, 74.15; H, 8.15; N, 8.5; active hydrogen 0.96. $C_{21}H_{28}O_2N_2$ requires C, 74.1; H, 8.2; N, 8.2%). The compound did not give the Otto reaction, but gave the colour reactions with oxidising agents characteristic of strychnidine derivatives.

Attempted Ferricyanide Oxidation.—(1) Base E (0.5 g.) suspended in aqueous dioxan (25 ml., 20%) containing potassium ferricyanide (1 g.) and sodium hydroxide (1.5 ml. of 2*N*), was shaken for 48 hours at room temperature. Filtration gave 0.35 g. of Base E, and dilution of the mother liquors liberated a further 0.05 g. (2) The reaction mixture as in (1) was heated on the steam-bath for 4 hours; dilution and filtration gave 0.45 g. of an impure solid from which 0.1 g. of pure Base E was isolated. No further pure

product could be obtained. A model experiment under similar conditions omitting the ferricyanide produced a similar decomposition.

Oximino-Base E.—Base E (0.34 g., 1 mol.) and hydroxylamine hydrochloride (0.07 g., 1 mol.) in water (20 ml.) were refluxed for 1 hour, excess of sodium carbonate solution was added, and the resulting precipitate collected and dried in a vacuum. The very pale yellow *product* was purified by precipitation with light petroleum (b. p. 60–80°) from benzene, and obtained as a microcrystalline powder (0.16 g., m. p. 122°) (Found: N, 11.2. $C_{21}H_{29}O_2N_3$ requires N, 11.8%). Treatment with acid immediately caused hydrolysis with formation of anhydro-Base E.

Action of Acetic Anhydride on Base E.—(a) Dissolution of Base E in acetic anhydride for a short time (15 minutes) followed by basification gave a precipitate, m. p. 170° (decomp.), with the composition of the corresponding *anhydro*-base (Found: C, 77.7; H, 8.35. $C_{21}H_{28}ON_2$ requires C, 78.2; H, 8.1%). The poor quality of the analyses in this series is attributed to the instability of the compounds and to the difficulty of purifying them.

(b) Base E (0.1 g.) was added to acetic anhydride (1 c.c.); the solid passed slowly into solution during 1 hour at room temperature. After 4 more hours the solution was added to excess of aqueous sodium hydrogen carbonate. The precipitated *acetyl* derivative did not crystallise from any of the usual solvents and was finally obtained by precipitation with water from its alcoholic solution as a colourless powder, m. p. 175° (decomp.). It was extremely unstable to acids (Found: C, 76.4; H, 8.0. $C_{23}H_{28}O_2N_2$ requires C, 75.8; H, 7.7%). More vigorous conditions lead to decomposition with the formation of yellow compounds.

Anhydro-Base E.—Base E dissolved rapidly in the cold in dilute mineral acids with formation of a yellow solution from which aqueous sodium carbonate precipitated an amorphous yellow solid of indeterminate m. p. ca. 280° (decomp.). This was partially purified by precipitation from ethanolic solution with water, but later evidence indicated that it was probably a mixture. Its constitution corresponded to its formation from Base E by loss of water (Found: C, 78.1; H, 7.8. $C_{21}H_{28}ON_2$ requires C, 78.2; H, 8.1%).

Reduction at ordinary pressures and temperatures over Adams's catalyst in acetic acid resulted in a very slow absorption of hydrogen, no definite end point being observed, and the yellow products could not be purified. Reduction at 150°/90 atm. in alcohol over Raney nickel gave a yellow solution, showing that the chromophoric double bond is very resistant to reduction.

Hexahydrodichanostrychnidine.—Base E (0.235 g.) in ethanol (120 ml.) was stirred with hydrogen at 100°/80 atm. and Raney nickel (0.1 g.) for 2 hours. After removal of the catalyst and solvent the gummy residue was triturated with benzene; the *product* crystallised from ethyl acetate as well-defined colourless prisms, m. p. 247°. It dissolved unchanged in acids and gave colour reactions of the strychnidine type (Found: C, 77.7, 77.3; H, 9.3, 8.9; active hydrogen, 1.96. $C_{21}H_{30}ON_2$ requires C, 77.3; H, 9.2%).

If the temperature of the reduction was allowed to rise much above 100° a small quantity of a higher-melting product was formed (see later).

Dehydrodihydrostrychnidine (Base F) (III).—Dihydrostrychnine (prepared by stirring strychnine with hydrogen at 100°/100 atm. and Raney nickel for 15 minutes) was reduced with sodium and liquid ammonia in the same way as strychnine, methanol being added instead of ethanol, by the use of which considerable quantities of dihydrostrychnine were sometimes recovered. The crude *product*, m. p. 246°, isolated as before, was obtained pure (0.65 g., m. p. 254°) by crystallisation from ethyl acetate (Found: C, 78.5; H, 8.0. $C_{21}H_{28}ON_2$ requires C, 78.25; H, 8.1%). The solubility of the crude product varied considerably from preparation to preparation, probably owing to the presence of small quantities of impurities. The crystal form of the compound also varied; although it usually formed massive hexagonal prisms, one preparation yielded a product separating as long colourless leaflets. The m. p., however, was always 254°. The pure product was sparingly soluble in cold acetone, benzene, and ethyl acetate, readily soluble in alcohol, and insoluble in water and light petroleum.

Base F gave yellow solutions with acids; the yellow base obtained on neutralisation of the acid solution of 0.5 g. was dissolved in much benzene and fractionated on an alumina column. The appearance of four diffuse bands demonstrated its complexity.

Further reduction of Base F in liquid ammonia proved impossible, the compound being recovered almost quantitatively.

Base F (0.250 g.) in ethanol (120 c.c.) was stirred with Raney nickel and hydrogen at 100°/90 atm. for 1 hour. After removal of catalyst and solvent, the residue crystallised from ethyl acetate as well-defined colourless glistening tablets (0.165 g., m. p. 212–214° alone and mixed with an authentic specimen of dihydrostrychnidine).

Reduction of Base D.—Base D (1 g.) was treated as in the reductions of strychnine and dihydrostrychnine previously described. The crude product was best purified, although with poor recovery, by crystallisation from a large volume (ca. 250 ml.) of ethyl acetate, in which it is only very sparingly soluble. The pure *product* formed colourless needles (34%), decomp. 160°, soluble in alcohols but very sparingly soluble in cold acetone, benzene, and ethyl acetate. The m. p. was not depressed by admixture with Base E, but subsequent reduction showed the individuality of the compound (Found: C, 74.4; H, 8.5. $C_{21}H_{28}O_2N_2$ requires C, 74.1; H, 8.2%). Treatment with acid gave a yellow compound.

The above product (0.250 g.) was stirred in ethanol (120 ml.) with Raney nickel and hydrogen at 100°/90 atm. for 1 hour. Removal of catalyst and solvent left a crystalline residue, purified from benzene, m. p. 217° alone and mixed with the product of the electrolytic reduction product of Base D (cf. Clemons and Raper, *loc. cit.*).

Tetrahydrodichanostrychnidine (II, R = H).—Strychnidine (1 g.) was reduced with methanol as a proton donor, as in the reduction of the previous strychnine derivatives. The crude *product* crystallised from a small volume of boiling benzene in well-defined rectangular tablets (0.63 g., m. p. 192°, b. p. 200°/14 mm., 63%). The m. p. is depressed by admixture with the dihydroisostrychnidine of similar melting point described by Oxford, Perkin, and Robinson (*loc. cit.*) (Found: C, 77.8; H, 8.8; active hydrogen, 2.1. $C_{21}H_{28}ON_2$ requires C, 77.8; H, 8.7%). The compound is readily soluble in alcohols, moderately so in acetone and ethyl acetate, insoluble in light petroleum and water. It crystallises with

benzene of crystallisation in which it dissolves if rapidly heated to about 140°; prolonged drying at 130° or distillation are necessary to remove all traces of solvent. It was recovered unchanged from its solution in acids. The *picrate monohydrate* separated slowly on the addition of water to its ethanolic solution as a microcrystalline powder, m. p. 127° (decomp.) (Found: C, 56.5; H, 5.8. $C_{21}H_{28}ON_2 \cdot C_6H_3O_7 \cdot N_3 \cdot H_2O$ requires C, 56.7; H, 5.8%); attempts to dehydrate the salt led to its decomposition.

Acetyl tetrahydrodichanostrychnidine.—This reduction product of strychnidine (0.3 g.) was refluxed for 2 hours with acetic anhydride (10 ml.) containing sodium acetate (0.5 g.). Excess of anhydride was decomposed with water, and the whole neutralised (2*N*-sodium carbonate). The tarry matter which separated was removed, and the solution basified with ammonia. A colourless amorphous *derivative* (0.26 g.) separated, and after being dried in a vacuum was either crystallised from a small volume of light petroleum (b. p. 60–80°), in which it is very soluble, or sublimed at 190°/14 mm. to form stout colourless needles, m. p. 158–160° (Found: C, 75.2; H, 8.1. $C_{22}H_{30}O_2N_2$ requires C, 75.4; H, 8.3%).

Decahydrotrichanostrychnidine.—The reduction product of strychnidine (0.5 g.) in ethanol (100 c.c.) was reduced over Raney nickel at 150°/100 atm. for 2 hours. Removal of solvent and catalyst left a gummy residue which crystallised on trituration with ethyl acetate. The crude *product* (0.25 g.) crystallised from ethyl acetate in long silky needles, m. p. 258–260° (Found: C, 75.9, 75.9, 76.8, 76.4; H, 10.2, 10.3, 10.3; active hydrogen, 2.9. $C_{21}H_{34}ON_2$ requires C, 76.4; H, 10.3%). The compound was very soluble in alcohols, less so in acetone and benzene, insoluble in water and light petroleum. When it is treated with nitrous acid a gas is evolved; this is taken to indicate the presence of a primary amino-group. With chromic acid in sulphuric acid or ferric chloride in acid solution an orange-red colour was produced, very much less intense than that obtained from strychnidine under the same conditions.

In the preparation of this compound, Base E can take the place of the strychnidine reduction product without significant alteration in the yield of the decahydro-derivative.

Reduction of N-Methylacetanilide.—*N*-Methylacetanilide (1.5 g.) was reduced by sodium (0.6 g., 2 atoms) in liquid ammonia containing excess of ethanol (1 ml.). The dry solid obtained after acidification with ammonium chloride and evaporation of the solvent was treated with 2*N*-hydrochloric acid (100 ml.). The pale yellow solution smelled strongly of acetaldehyde. One-fifth of it was treated with excess of a saturated solution of 2:4-dinitrophenylhydrazine hydrochloride in 2*N*-hydrochloric acid. The yellow crystalline precipitate (0.250 g., 56%) was identified after recrystallisation as acetaldehyde 2:4-dinitrophenylhydrazone (m. p. 167°, not depressed by admixture with an authentic specimen).

Half the original solution was concentrated to 5 ml. under reduced pressure, basified, and the liberated oil isolated with ether and distilled. A nearly quantitative yield of methylaniline was obtained (0.51 g., 96%).

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