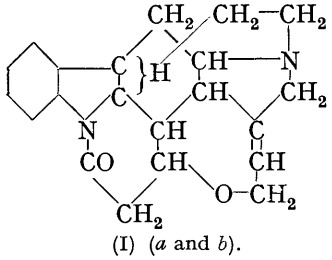
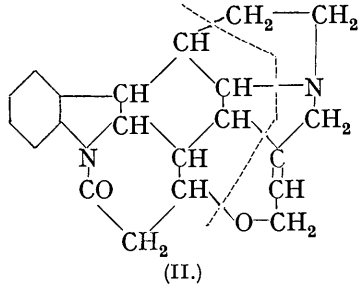
192. *Strychnine and Brucine. Part XXXVI. Preliminary Synthetical Experiments.*

By H. T. Openshaw and Robert Robinson.

The interpretation of the properties and transformations of strychnine advanced in this series of papers is represented by the expression (I) and it has been repeatedly pointed out



(I) (*a* and *b*).



(II.)

that no clear evidence is available as to which of the alternatives should be preferred.* The slight modification (II) later advocated by Leuchs was the first formula of this type

* Apart from the degradation to carbazole (at relatively high temperatures) the evidence does not exclude a third formula, namely (I*b*), in which the methylene group of the carbazole skeleton is brought down from the β- to the α-position in the indole nucleus. The resulting constitution does not of course contain a carbazole skeleton, but such could readily be formed by migration from the α- to the β-position. The advantage gained by this modification is that the β-position of the indole nucleus bears a hydrogen atom and the chief disadvantage is that it does not look right. The structure, however, like (I*a*) and (I*b*), can be set up on the models without strain.

to be considered by us (J., 1932, 2307), but it was rejected chiefly because strychnine and its derivatives do not exhibit the behaviour of dihydroindoles bearing hydrogen atoms in both α- and β-positions.

The experiments described in the present communication confirm us in the view that the hydroindole nucleus of strychnine is blocked by *gem*-substitution in the α- or β-positions, because we have prepared a substance in the molecule of which methylene replaces carbonyl (that is, it is analogous to strychnidine) and the groups to the right of the dotted line in (II) are replaced by hydrogen atoms; unlike strychnidine, this base may be dehydrogenated with ease and with formation of an aromatic indole derivative.

Before discussing the details of these experiments the opportunity may be taken to reply to the criticisms of M. Kotake (*Proc. Imp. Acad. Tokyo*, 1936, **12**, 99) which are based on the interesting discovery, independently made by Clemo (J., 1936, 1695), that strychninolone, strychninonic acid, or strychnine yields β-indolylethylamine (tryptamine) on fusion with potassium hydroxide. So far from affording material for reasonable doubt of the validity of the structures (I*a*; bridge to the α-position), (I*b*; bridge to the β-position), and (II) it would appear that these observations can be accommodated by any of the three constitutions; the tryptamine skeleton occurs in them all.* The explanation of the degradation of (II) to tryptamine offers the greatest difficulty, but (I*b*) can yield the base by a series of fissions all of which are in accord with analogy. They involve only rupture of C·N links or detachment of substituents from the indole nucleus and both types of reaction are known. The formation of tryptamine from (I*a*) might be the result of migration or of straightforward degradation.

The facts that strychninolone gives the best yield of tryptamine (17%) and methylstrychnine gives none at all (Kotake, Mori, and Mitsuwa, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 129) will doubtless be eventually significant, but at the moment cannot be brought to bear on the structural problem. In terms of *any* strychnine formula the latter observation shows that the course of the degradation of the molecule is profoundly modified when N–b is alkylated, but there is nothing surprising in this and there is no relevance to the discussion of the merits or demerits of (I*a*) or (I*b*). It is easy, especially on the basis of (I*a*), to devise a plausible explanation of the failure of methylstrychnine to yield tryptamine on fusion with alkali, but such speculations cannot be pursued with much profit.

The new partial structures actually put forward by Kotake are quite unacceptable, not for any abstruse reason but because they fail to take account of some of the most clearly established features of the chemistry of the alkaloids. It is, for example, unnecessary to elaborate the insuperable objections to Kotake's view that the functions of N(a) and N(b), as shown in (I) and (II), should be transposed and that the salt-forming nitrogen atom of strychnine is directly attached to the aromatic nucleus.

The object of the present experiments is to approach the strychnine skeleton as closely as may be in the hope that some degradation product may be synthesised. We have not yet developed a method for the preparation of derivatives of hexahydrocarbazole analogous to (I*a*), but a beginning has been made in the synthesis of a part of the skeleton of (I*b*). Proceeding a few stages further along the lines laid down by Leuchs in his brilliant researches, it should be possible to convert strychninonic acid into the base (III), which is here formulated on the assumption that (I*b*) is the constitution of strychnine, and the synthesis of such a base is our objective.

The action of boiling dilute sulphuric acid on the phenylhydrazone of *cyclo*hexanone-2-β-propionic acid resulted in both indole and indolenine ring closure; the products were the

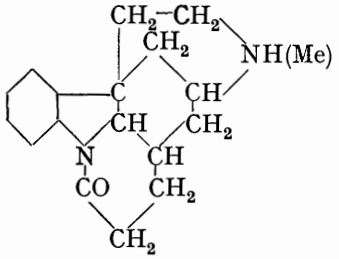
* In connection with Kotake's criticism of our formulations based on the isolation of tryptamine from strychnine, the following quotations from earlier parts of this series are not without interest.

J., 1932, 2308.—" The particular development of the idea adopted in formula (II) was selected (i) because it gives a tryptophan nucleus and beyond this a continuous block of carbon atoms, and (ii) because the arrangement is strainless." Formula (II) is (I*b*).

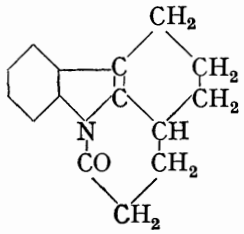
J., 1934, 1491.—Referring to a formula proposed by Kotake and Mitsuwa—" Although the argument will not have universal appeal, some chemists, including the writer, would reject the formula on the sole ground that it does not contain the tryptophan skeleton."

lactam of *tetrahydrocarbazole*-1-β-*propionic acid* (IV) and *tetrahydrocarbazolenine*-11-β-*propionic acid* (V).

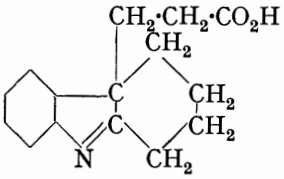
(III.)



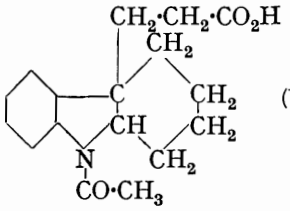
(IV.)



(V.)

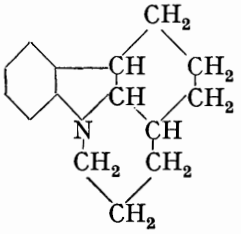


(VI.)

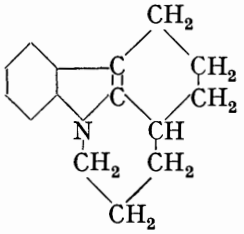


On reduction and acetylation, (V) afforded an *acid* (VI), which exhibited a characteristic Otto reaction. Attempts to reduce the double bond alone in (IV) were unsuccessful, but on electrolytic reduction the *base* (VII) was obtained.

(VII.)



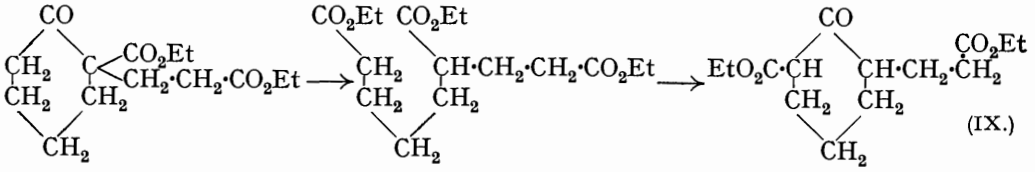
(VIII.)



This *trimethylenehexahydrocarbazole* gives strong strychnidine-type reactions and is readily dehydrogenated on heating with palladised charcoal with formation of *trimethylenetetrahydrocarbazole* (VIII). This substance shows no colour reactions like those of strychnine or strychnidine, but resembles tetrahydrocarbazole in its behaviour.

In order to combine the structural features of (VI) and (VII), we required cyclo*hexanone*-2 : 6-ββ′-*dipropionic acid* and the preparation of this substance proved difficult. Ultimately an excellent method was discovered and this is dependent on a molecular rearrangement which is probably general. The process should be applicable to the synthesis of a variety of 2 : 6-disubstituted *cyclo*hexanones.

Ethyl 2-carbethoxy*cyclo*hexanone-2-β-propionate is transformed by boiling alcoholic sodium ethoxide into *ethyl* 6-*carbethoxy*cyclo*hexanone*-2-β-*propionate* (IX), the mechanism being obviously alcoholysis and ring-closure in a new position as shown below :

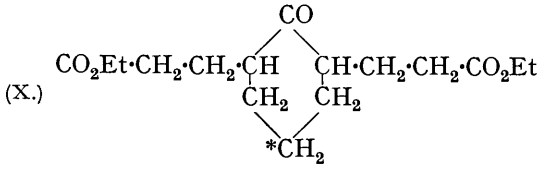


(IX.)

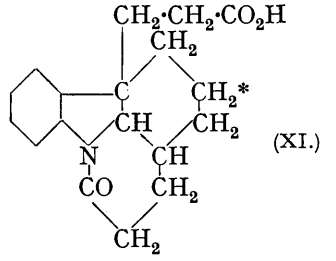
A second propionic acid residue could then be introduced in the usual manner and after hydrolysis and esterification the *ethyl* ester (X) of the required acid was obtained.

The product of the action of alcoholic hydrogen chloride on the phenylhydrazone of (X)

could not be purified, but, after reduction, the *lactam* of *hexahydrocarbazole*-1 : 11-ββ′-*dipropionic acid* (XI) was isolated. This substance exhibits an Otto reaction.



(X.)



(XI.)

We are now attempting to introduce a carboxyl group at the positions denoted by asterisks in (X) and (XI), and if this proves to be possible the final stages in the synthesis of (III) will be a double Curtius reaction and a pentamethylenediamine–piperidine ring closure.

Experimental.

Ethyl 2-*Carbethoxy*cyclo*hexanone*-2-β-*propionate*.—R. D. Haworth (J., 1933, 1012) obtained this ester (b. p. 199—202°/15 mm.) in 60% yield, and the following conditions have effected some improvement. A solution of sodium ethoxide (from 10 g. of sodium) in alcohol (250 c.c.) was slowly added with shaking to a mixture of ethyl *cyclo*hexanone-2-carboxylate (75 g.), ethyl β-chloropropionate (60 g.), absolute alcohol (150 c.c.), and sodium iodide (1 g.), with cooling in a bath of cold water. The reaction was allowed to proceed at room temperature for 2 hours, and after refluxing for a further 2 hours the greater part of the alcohol was evaporated. The residue was poured into ice-water (2000 c.c.), and the precipitated oil isolated by means of ether. On distillation ethyl carbethoxy*cyclo*hexanonepropionate was collected at 184—185°/13 mm. as an almost colourless oil, giving a negative ferric reaction (yield, 95 g. or 80%) (Found: C, 62·2; H, 8·2. Calc. for $C_{14}H_{22}O_5$: C, 62·2; H, 8·1%).

cyclo*Hexanone*-2-β-*propionic Acid*.—The foregoing ester (10 g.) was hydrolysed by refluxing with concentrated hydrochloric acid (60 c.c.). Solution was complete after 2—3 hours, and after boiling a further hour, the liquid was concentrated to a small bulk under reduced pressure, and diluted with saturated ammonium sulphate solution; an oil then separated, which was collected by means of ether. The extract was dried and evaporated; the residual oil crystallised, on cooling, in minute colourless prisms (5·8 g. or 90%). A sample recrystallised from light petroleum (b. p. 40—60°) had the recorded m. p. 55°.

Haworth (*loc. cit.*) carried out this hydrolysis with methyl-alcoholic potassium hydroxide, and obtained the acid, together with the anhydride of heptane-1 : 3 : 7-tricarboxylic acid.

The Condensation of cyclo*Hexanone*-2-β-*propionic Acid with Phenylhydrazine*.—A mixture of the keto-acid (27·5 g.) and phenylhydrazine (17·5 g.) was gently heated until reaction commenced; the oily phenylhydrazone was then formed with liberation of heat. The product was treated with boiling dilute sulphuric acid (300 c.c. of 20%) for 10 minutes with shaking; the brownish oil thus obtained crystallised on cooling. It was collected, washed with water, and recrystallised from alcohol. The *lactam* of *tetrahydrocarbazole*-1-β-*propionic acid* (IV) separated in hexagonal plates with a faint bluish tinge, m. p. 121° (20 g.). Two further crystallisations from alcohol or glacial acetic acid raised the m. p. to 126° (Found: C, 80·0; H, 6·7; N, 6·3. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7; N, 6·2%).

The aqueous filtrate from the reaction mixture was washed twice with ether, made weakly alkaline with dilute aqueous ammonia, and neutralised with acetic acid; the liquid became turbid, and on stirring deposited a pale yellow, crystalline solid (9 g.). On recrystallisation from a moderately large volume of alcohol, *tetrahydrocarbazolenine*-11-β-*propionic acid* separated in nearly colourless prisms, m. p. 226°. For analysis, the substance was crystallised twice more from alcohol without raising the m. p. (Found: C, 74·3; H, 6·9. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0%). The compound is insoluble in water, ether and benzene; it dissolves readily in dilute acids or alkalis.

Reduction of the Lactam of Tetrahydrocarbazole-1-β-*propionic Acid*.—Attempts to reduce this substance with hydrogen and platinum, with tin and aqueous-alcoholic hydrochloric acid, and with sodium and ethyl or *iso*amyl alcohol were unsuccessful; it was readily reduced electrolytically at a lead cathode.

The lactam (10 g.) was dissolved in warm glacial acetic acid (300 c.c.), and the solution was diluted with 15% sulphuric acid (100 c.c.) and placed in the cathode chamber of the usual apparatus. A current of 5 ampères was passed for 24 hours; the liquid, which was stirred occasionally, maintained itself at 40°. The colourless solution was filtered, diluted with water, and mixed with dilute aqueous potassium hydroxide. A white crystalline solid was precipitated before the liquid had become alkaline, and this was collected, washed with water, and dried (10 g.). The compound was freely soluble in cold light petroleum, benzene or ethyl acetate. It was crystallised from a little hot acetic acid, 1 : 9-*trimethylenehexahydrocarbazole* (VII) being obtained in lozenge-shaped, glistening, colourless plates, m. p. 81—82°. For analysis, a specimen was crystallised from methyl alcohol; the m. p. was unchanged (Found : C, 84·6; H, 8·7; N, 6·7. $C_{15}H_{19}N$ requires C, 84·5; H, 8·9; N, 6·6%). This base is readily soluble in 5% hydrochloric acid, and on the addition of a trace of ferric chloride, an intense red coloration which is stable for several hours is produced.

Dehydrogenation of 1 : 9-*Trimethylenehexahydrocarbazole*.—(A) The substance (1 g.) was dissolved in glacial acetic acid (15 c.c.), cooled to room temperature, and mixed with a solution of mercuric acetate (6 g.) in 10% aqueous acetic acid (15 c.c.). The heterogeneous mixture, kept at room temperature, at first developed a bright red colour, but after 24 hours this had changed to a yellowish-brown, and the bulk of the insoluble matter had increased considerably. The solid was collected, washed with 50% acetic acid, and pressed as dry as possible (7 g.). The slightly sticky solid thus obtained was suspended in a hot mixture of 50% acetic acid (20 c.c.) and acetone (30 c.c.), saturated with hydrogen sulphide, and filtered hot from the mercury sulphide, which was washed with hot acetone. The filtrate and washings were combined and evaporated until a turbidity appeared; on cooling, a sticky solid (occasionally an oil) separated. This was isolated, washed with dilute acetic acid, then with water, and dissolved in concentrated hydrochloric acid. The filtered solution was diluted with twice its volume of water; a brownish solid then separated. This was collected and washed with dilute hydrochloric acid. It was crystallised from methyl alcohol (norit), pale yellow, lozenge-shaped leaflets of 1 : 9-*trimethylene*-1 : 2 : 3 : 4-*tetrahydrocarbazole*, m. p. 85—86°, being obtained (0·1 g.). Further crystallisation raised the m. p. to 86—87°. The compound was insoluble in dilute hydrochloric acid, and gave no colour with ferric chloride and dilute acid. A mixture with trimethylenehexahydrocarbazole melted at 68—71°. Basification of the last acid filtrate afforded 0·2—0·3 g. of the initial material. The following process is the more convenient and gives a better yield.

(B) Trimethylenehexahydrocarbazole (0·8 g.) was heated at 170—195° with palladised charcoal (prepared according to Ruzicka) for 7½ hours; hydrogen (63 c.c.; theoretical, 90 c.c.) was slowly evolved. After cooling, the product was dissolved in warm concentrated hydrochloric acid (7 c.c.) and filtered from the catalyst. The yellow solution was diluted with 2—3 times its volume of water, a white crystalline precipitate being formed. After stirring and standing for a short time, the 1 : 9-trimethylenetetrahydrocarbazole was collected, washed with dilute hydrochloric acid, then with water, and dried (0·5 g.). It was recrystallised from methyl alcohol, yielding almost colourless leaflets, m. p. 87—88°, not raised by further recrystallisation (Found : C, 85·1; H, 8·2; N, 6·7. $C_{15}H_{17}N$ requires C, 85·3; H, 8·1; N, 6·6%). When the acid filtrate was made alkaline, a quantity of the initial material was recovered.

With Ehrlich's reagent on boiling, a bluish-green coloration is produced. This fades to yellow on cooling and the changes may be repeated as often as desired. This behaviour is similar to that of other 2 : 3-substituted indoles.

N-*Acetylhexahydrocarbazole*-11-β-*propionic Acid* (VI).—A mixture of tetrahydrocarbazolenine-11-β-propionic acid (4 g.), concentrated hydrochloric acid (10 c.c.), and granulated tin (4 g.) was refluxed for 8 hours; on dilution of the hot filtered solution a colourless gum separated. This was detinned in aqueous suspension in the usual way, and the filtrate boiled to expel hydrogen sulphide, cooled, and neutralised by means of ammonia and acetic acid. The gum that separated could not be crystallised; it was mixed with acetic anhydride (15 c.c.), and the solution refluxed for 5 hours. On keeping, the product obtained after decomposition of the acetic anhydride with water crystallised and the *substance* separated from alcohol in colourless prisms, m. p. 202° (Found : C, 71·1; H, 7·4. $C_{17}H_{21}O_3N$ requires C, 71·1; H, 7·3%). A suspension of the substance in 60% sulphuric acid gave an intense reddish-purple coloration on the addition of a trace of potassium dichromate; the colour rapidly faded through red to brownish-yellow.

Ethyl 6-*Carbethoxy*cyclo*hexanone*-2-β-*propionate* (IX).—A mixture of ethyl 2-carbethoxy*cyclo*hexanone-2-β-propionate (52 g.) and alcoholic sodium ethoxide (70 c.c.; 4·8 g. of sodium) was refluxed for 8 hours. The ester was then isolated in the usual manner and distilled, b. p. 189—192°/11 mm. (30·6 g.). The fraction, b. p. 120—188°/11 mm., gave a further 6·2 g. on redistilla-

tion, making the yield 70%. The *product* distilled again at 189—190°/11 mm. (Found: C, 62·3; H, 8·3. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·1%). The ferric reaction in alcoholic solution was a deep violet coloration.

Ethyl 6-*Carbethoxy*cyclo*hexanone*-2 : 6-ββ′-*dipropionate*.—The foregoing keto-ester (36·8 g.) was added to a suspension of sodium powder (3·1 g.) in benzene (80 c.c.); the solution of the sodium was completed by refluxing for 2 hours. The orange liquid was cooled, and ethyl β-chloropropionate (18·5 g.) introduced. As there was no sign of immediate reaction, the mixture was refluxed for 5 hours; no solid, however, was precipitated from the slightly turbid solution. The reaction product was mixed with water and a few drops of hydrochloric acid and the ester was isolated by means of ether and distilled, b. p. 195—197°/0·4 mm. (yield, 38·1 g. or 75%). A sample was redistilled, b. p. 182—183°/0·2 mm. (Found: C, 61·3; H, 8·1. $C_{19}H_{30}O_7$ requires C, 61·6; H, 8·1%). The condensation in alcoholic solution gave a poor yield of the desired *product*, and a considerable quantity of *ethyl heptane*-1 : 3 : 7-*tricarboxylate*, b. p. 147—148°/0·15 mm., was formed as the result of alcoholysis (Found: C, 61·0; H, 8·8. $C_{18}H_{28}O_6$ requires C, 60·8; H, 8·9%). When this ester was treated with sodium in benzene with a trace of alcohol, and subsequently with ethyl β-chloropropionate, an 80% yield of ethyl carbethoxy-*cyclo*hexanonedipropionate was obtained.

cyclo*Hexanone*-2 : 6-ββ′-*dipropionic Acid and its Ethyl Ester* (X).—A mixture of ethyl carbethoxy*cyclo*hexanonedipropionate (38 g.) and concentrated hydrochloric acid (250 c.c.) was refluxed for 30 minutes and the clear solution was then evaporated to dryness, finally under diminished pressure. The residue crystallised (24·5 g. or 98%) and the solid was collected, washed with saturated aqueous ammonium sulphate and then with a little water, and dried at 100°. Crystallisation from ethyl acetate afforded colourless prisms (14·5 g.), m. p. 145° (Found: C, 59·4; H, 7·4. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·4%), and the gummy acid in the mother-liquor was set aside for combination with another batch and for recovery by esterification.

The crystallised acid (14·5 g.) was treated in an automatic separation apparatus (" Organic Syntheses," Coll. Vol. I, 256) with alcohol (10 c.c.), carbon tetrachloride (30 c.c.), and two drops of concentrated sulphuric acid; separation of water ceased after an hour. The *ester* was isolated in the usual way and crystallised on cooling (17 g. or 95%). It separated from light petroleum in colourless prisms, m. p. 60—61° (Found: C, 64·5; H, 8·8. $C_{16}H_{26}O_5$ requires C, 64·4; H, 8·7%).

The Lactam of Hexahydrocarbazole-1 : 11-ββ′-*dipropionic Acid* (XI).—The foregoing ester (5 g.) and phenylhydrazine (1·8 g.) were melted together, a few drops of glacial acetic acid added, and the mixture kept for ½ hour at 60—70°. Reaction occurred with separation of water. The oily phenylhydrazone was taken up in ether, washed with water, dried with potassium carbonate, and recovered as an orange-coloured oil which could not be crystallised.

This phenylhydrazone was dissolved in alcohol (10 c.c.), and the solution was saturated with dry hydrogen chloride at first with cooling in ice, but after 5 minutes the bath was removed and the mixture then heated itself to about 70°. A precipitate of ammonium chloride was rapidly formed. The mixture was allowed to cool, concentrated hydrochloric acid (25 c.c.) and tin (5 g.) added, and the whole gently boiled in an open flask so that the alcohol might be evaporated. After an hour, the boiling was continued under reflux for a further 4 hours; the tin had then almost completely disappeared. The cooled solution was diluted with water (75 c.c.); the colourless oil then precipitated became crystalline on stirring and keeping. It was collected, washed with water, and treated with warm aqueous sodium carbonate. The solution was filtered and on acidification yielded a white solid (0·5 g.). This was dried at 100°, dissolved in a small quantity of hot glacial acetic acid, and diluted with an equal volume of water. On cooling, the *lactam* of *hexahydrocarbazole*-1 : 11-ββ′-*dipropionic acid* separated in colourless, elongated prisms, m. p. 269—270°. Recrystallisation from 50% aqueous acetic acid raised the m. p. to 271°, with previous sintering (Found: C, 72·1; H, 7·0; N, 4·7. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·0; N, 4·7%).

A solution of the substance in 60% sulphuric acid gave a transient deep purple coloration on the addition of a trace of aqueous potassium dichromate. The colour faded through rose-red to yellow and was inherently unstable, because the addition of more dichromate to the yellow solution gave again a purple coloration.

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 6th*, 1937.]