

ROBERT ROBINSON

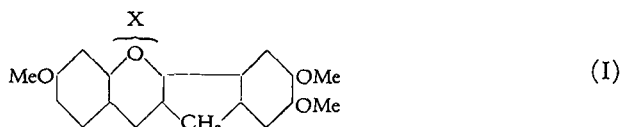
Some polycyclic natural products

Nobel Lecture, December 12, 1947

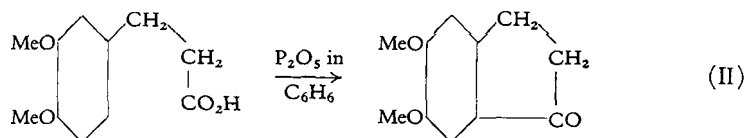
In dealing with this subject I do not propose to attempt any full description of a part of my researches in the fields of the alkaloids, plant colouring matters, or on the methods of synthesis of steroids, but rather to indicate some connecting threads and perhaps, in some places, to go a little behind the scenes. In 1905, I was privileged to be given a place in the private laboratory of my revered teacher, Professor W. H. Perkin, Jr. at the University of Manchester. The synthesis of limonene had just been completed and sylvestrene was the next objective. Such work involved long and laborious preparations and would not have suited my case. It was indeed a fortunate chance that Perkin introduced me instead to the catechol derivatives which, together with their cousins of the *meta* and *para* series, have befriended so many organic chemists, myself among them, by reason of the numerous colour reactions that they exhibit and by the versatility of their transformations. Perkin's idea was to prepare a series of hydroxylated coumarins from ethyl piperonylacetate and to study their dyeing properties. "My brother Arthur", he said, "is a dabhand with natural dyes and will help us". I made the desired ester, by adapting Claisen's elegant method for ethyl benzoylacetate, but not the coumarins, because of the interest that I very soon took in the brazilin problem. At that time experimental study was concentrated on brazilin and its derivatives. This was in the hands of one Johann Engels, supposed by the students to be a retired manufacturer working for his own satisfaction; he inhabited some subterranean cavern of the laboratory but emerged from time to time bringing gifts of most beautiful orange and crimson crystals to the private laboratory.

It seemed that the materials in my hands could be used in the brazilin investigation and I sought and obtained permission to turn in that direction. We soon encountered highly characteristic methylated brazylum salts, related to the isobrazilein sulphate of Hummel and A. G. Perkin (1882) and on the basis of the current brazilin structure of Perkin these were formulated as (I). There was no known method that could be applied to the synthesis of (I), except, perhaps, that of Billow. Attempts to devise a new process led to the

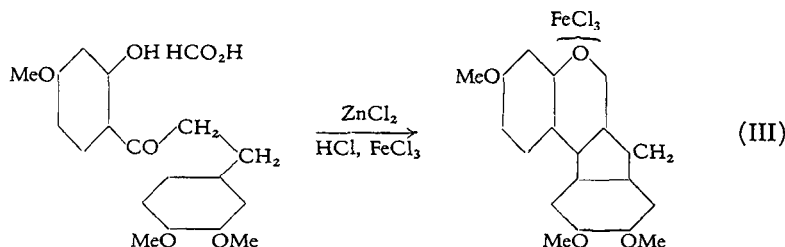
discovery of the condensation between salicylaldehydes and keto-methylenes in the presence of hydrogen chloride. This synthesis of pyrylium salts was independently and simultaneously described by Decker and Fellenberg (1907).



Applying it, *p*-methoxy-salicylaldehyde and 5:6dimethoxy- α -hydrindone (II) gave a chloride (and ferrichloride) corresponding to (I) and these salts were not identical with the isomerides derived from brazilin.



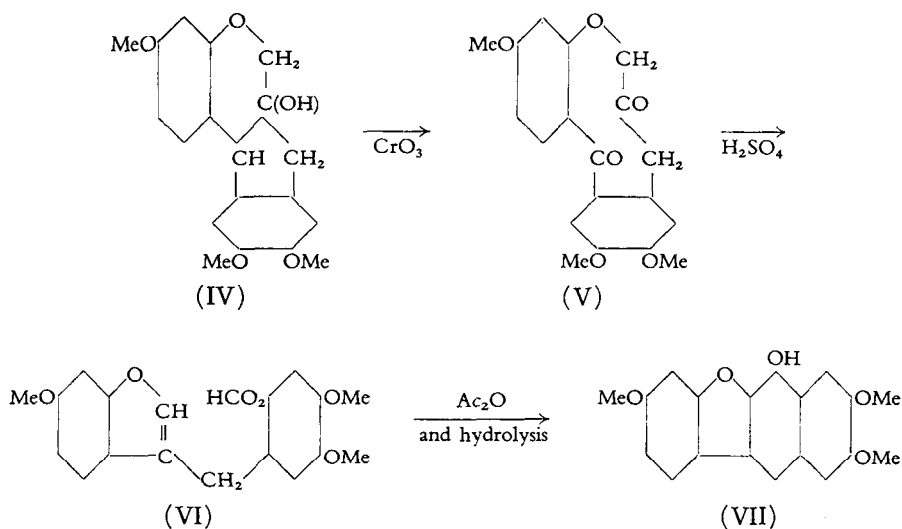
The accepted constitution of brazilin was established by syntheses of anhydrobrazilic acid and brazilinic acid (1908), deoxytrimethylbrazilone and trimethylbrazilone (1926-1928); parallel work by P. Pfeiffer), trimethoxy-brazyhum salts (with 'H. G. Crabtree, 1918) and certain of the hazmatoxylin analogues. The first synthesis of a substance containing the ring skeleton was that of trimethoxybrazylium ferrichloride (III).



The manifold and intriguing transformations of the brazilin molecule, particularly those of trimethylbrazilone (V), may now be said to be well understood but synthetical confirmation has not always been obtained.

Only this year my collaborator, K. W. Bentley, synthesized *b*-anhydro-trimethylbrazilone (VII) obtained from trimethylbrazilin (IV) by the stages (v) and (vi).

The study of brazilin and hazmatoxylin is by no means finished and in this



connexion I would like to make a general observation. The synthesis of brazilin would have no industrial value; its biological importance is problematical, but it is worth while to attempt it for the sufficient reason that we have no idea how to accomplish the task. There is a close analogy between organic chemistry in its relation to biochemistry and pure mathematics in its relation to physics. In both disciplines it is in the course of attack of the most difficult problems, without consideration of eventual applications, that new fundamental knowledge is most certainly garnered.

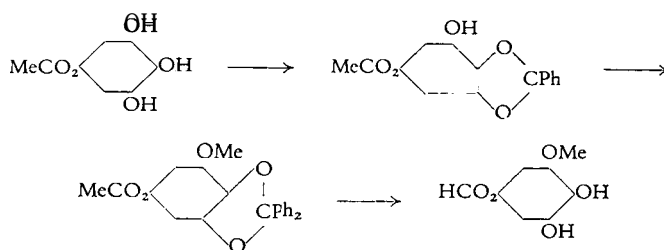
From the incidents of the brazilin investigation two fresh topics developed. In the first place the pyrylium salt synthesis led to the much later extension to the synthesis of anthocyanidins and still later to that of the anthocyanins (see below). Secondly the facile ring closure of *o*-3:4-dimethoxyphenylpropionic acid to the ketone (II) suggested an application to the synthesis of papaverine. That was actually accomplished but not published owing to anticipation by Pictet and Gams (1909). Otto Wallach was in Manchester for a few days at that time and advised publication nevertheless. We did not act on this advice because our final intermediate was an oil and Pictet and Gams had crystallized it. Thirty years later I found that these crystals do not consist of the required compound, and Pictet and Gams must also have used the oil for the synthesis of papaverine.

A side-issue was that, as a small consolation for this disappointment, a new oxazole synthesis was developed by dehydration of the acylamino-ketones, prepared as models in the papaverine work. It was natural also to turn to

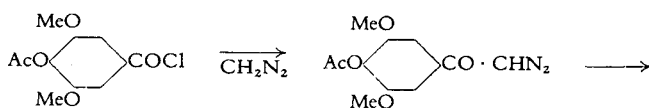
other members of the isoquinoline group of the alkaloids and this led in stages to the syntheses of narcotine, hydrastine and berberine, and to a general wider concern with alkaloid chemistry.

Some further connexions between apparently unrelated investigations are mentioned below although there have certainly been several fresh points of departure. Electronic theories of chemical reactions are not part of my present topic but it may be recalled that the condensation reactions of pseudo bases (carbinol-amines) and the C-alkylation of unsaturated amines were among the experimental foundations of my theoretical system and they arose from early work on alkaloids.

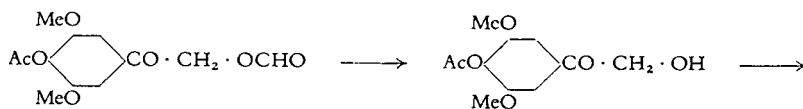
Anthocyanins. The general pyrylium salt synthesis, mentioned already, was found (with D.D. Pratt, 1922 etc.) to be applicable to the synthesis of the anthocyanidins. Then (with A. Robertson, 1926 etc.) it was first shown that glucosidylflavylium salts could be prepared and then some of the simpler anthocyanins were synthesized. It became chiefly a question of preparation of the necessary intermediates and this depended largely on the use of appropriate protecting groups. The following illustrates some special devices :



(with W. Bradley and G. Schwarzenbach, 1930)



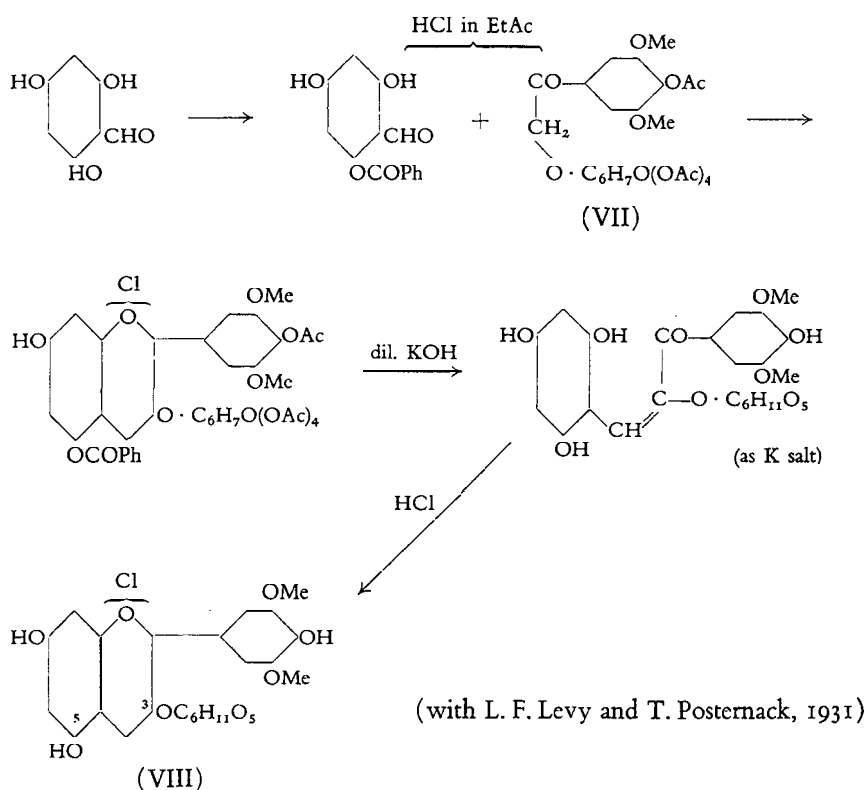
(with W. Bradley, 1928)



→ (VII, see p. 170)

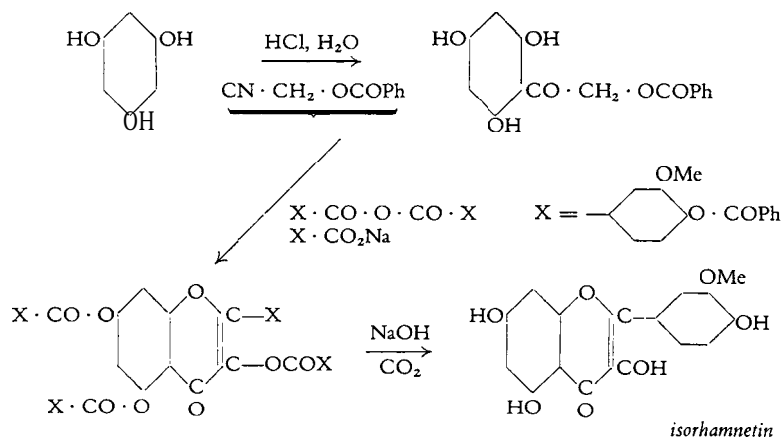
The formation of diazoketones from acid chlorides and diazomethane was first observed in the course of these investigations and found to be of great service.

As the work proceeded the effort was made to reduce the protection of hydroxyl groups to the minimum and, rather as a *tour de force*, it was shown that cyanin could be synthesized even by use of unprotected components. In most cases, monobenzoylphloroglucinaldehyde was an effective starting point and if a sugar residue was required in the phloroglucinol nucleus that was adequate protection in itself. The following scheme, representing the synthesis of oenin chloride (VIII), is an illustrative example.

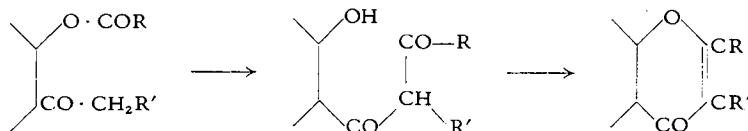


The important 3:5-diglucosides were synthesized in a similar fashion (with A. R. Todd, 1932) from the 2-tetra-acetylglucoside of phloroglucinaldehyde. This was fortunately obtained by direct aceto-glucosidation in acetonitrile solution.

Possession of the pure synthetic specimens of the anthocyanidins and chief anthocyanins enabled my wife and me to devise quick tests for these colouring matters which can be used with the material from a few flower petals. Hence it was possible to make a survey of anthocyanins. As a result one quite



W. Baker has shown that the arylation proceeds in two stages and involves a migration from O to C.



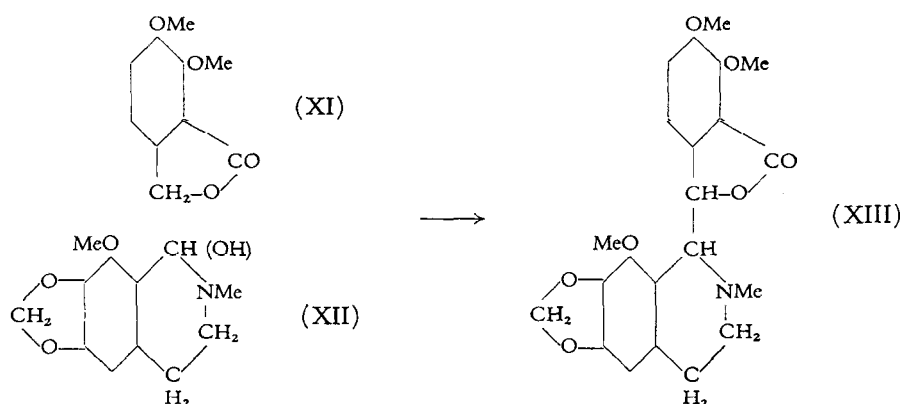
The synthesis of isoflavones, the conversion of catechin into cyanidin, and work on leuco-anthocyanins, cyanomaclurin and peltogynol were by-products of the studies of plant pigments.

I would like to add that no weed crops up in gardens more persistently and regularly than does the idea in the chemical literature that anthocyanins are formed in Nature from anthoxanthins by reduction (or *vice versa* by oxidation). There is no direct evidence that this is so; the statistical evidence opposes the theory, and the genetic studies of *Dahlia* by Lawrence and Scott-Moncrieff give clear indication that the flavones and flavylum compounds are formed by divergent processes, possibly from the same starting point, already, however, considerably elaborated as compared with the primary carbohydrate material.

Alkaloid studies. After the papaverine incident it was decided to attempt the synthesis of narcotine (XIII) which could be a condensation product of cotamine (XII) with meconine (XI). Cotamine was thought of as an aldehyde and meconine as a keto-methylene compound $-\text{CO}-\text{C}=\text{C}-\text{CH}_2-$ and we knew that Lapworth had shown the methyl of similarly constituted ethyl

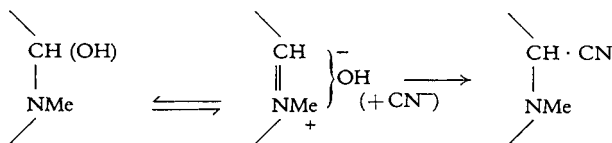
crotonate to be reactive; for example, it could be oxalylated. Therefore an alkaline catalyst was used, potassium carbonate was chosen in order to avoid hydrolysis of the lactone. The reaction gave a small yield of *dl*-narcotine (α -gnoscopine) in boiling alcohol and this racemic substance was resolved, with some difficulty, into *d*- and *l*-narcotine (natural).

The yield was improved by employing halogenated meconines and on dehalogenation, α -gnoscopine was obtained. Condensation of cotarnine with

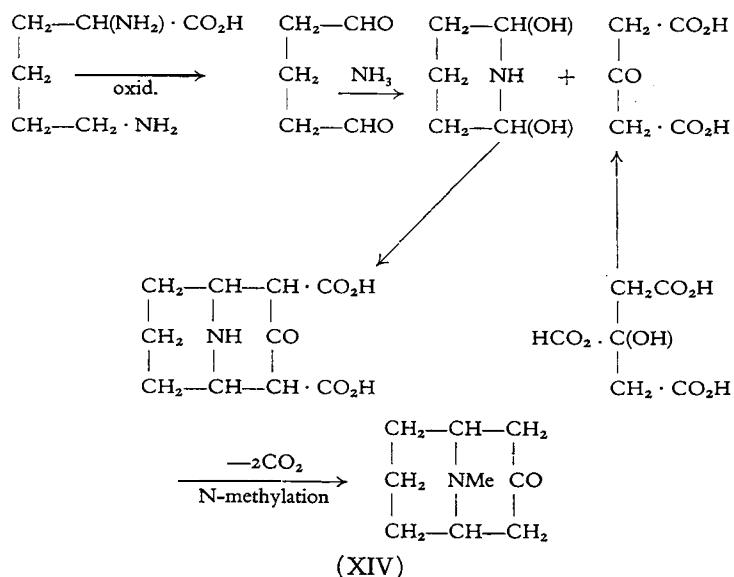


nitro-meconine afforded a nearly quantitative yield of a base recognized as nitro- β -gnoscopine. On removal of the nitro-group ($\text{NO}_2 \rightarrow \text{NH}_2 \rightarrow \text{NH} \cdot$
 $\text{N H}_2 \rightarrow \text{H}$; $\text{N H}_2 \rightarrow \text{I} \rightarrow \text{H}$) β -gnoscopine was produced. This could not be resolved but it was synthesized from *d*- and *b*-narcotines produced by partial racemization of the *d*- and *l*-narcotines. I will not pursue this topic except to mention that hydrastine and bicuculline have been synthesized in similar fashion. Hydrastine does not conform with narcotine in stereochemical configuration.

I have mentioned these researches chiefly because they introduced me to the facile condensation reactions of pseudo-bases, the carbinol-amines, of which cotarnine is very typical. The earlier work of Liebermann, and of Kropf, was greatly extended (with E. Hope, 1913). Cotarnine condenses very readily with alcohols, mercaptans, amides, ketones such as acetone and acetophenone, malonic ester and the like, phenylacetonitrile, indene, fluorene, α -methylindole, nitromethane, 2:4-nitrotoluene, etc., etc. The reactive form is now considered to be the ammonium hydroxide and a typical case is represented by the formation of cyanodihydrocotarnine. The part formulae are:



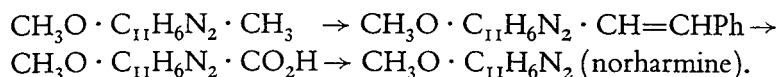
It was impossible not to be impressed with the smooth progress of such reactions and the conviction came that they must be of importance in Nature, especially since carbinol-amines can be regarded as oxidation products of amino-acids. These ideas germinated while still at the University of Manchester and developed during the period of tenure of my first Chair of Chemistry at Sydney, New South Wales. There I wrote down a possible biosynthesis of pseudopelletierine (XIV) from lysine and citric acid, based on pseudo-base condensations.



In the lower ring-homologous series the position of the carboxyl group of ecgonine seemed to give support to the hypothesis. On returning to England the opportunity arose at the University of Liverpool to test the scheme experimentally. We were in the midst of the First Great War and a shortage of atropine was threatened.

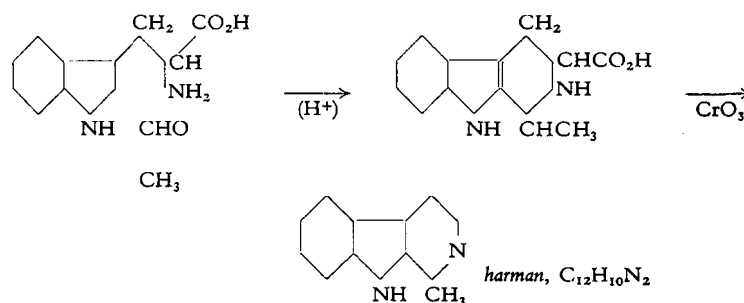
I found that succindialdehyde, methylamine, and acetonedicarboxylic acid or its calcium salt, mixed in aqueous solution at the ordinary temperature, gave a notable yield of tropinone (XV) after acidification. C. Schöpf has

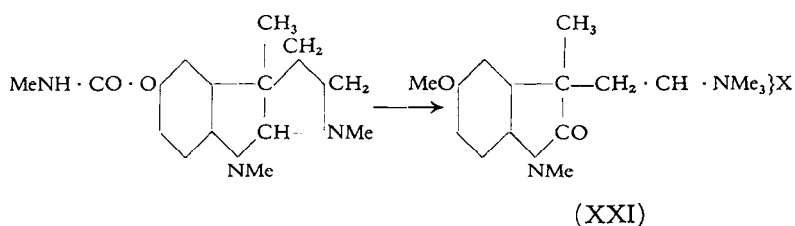
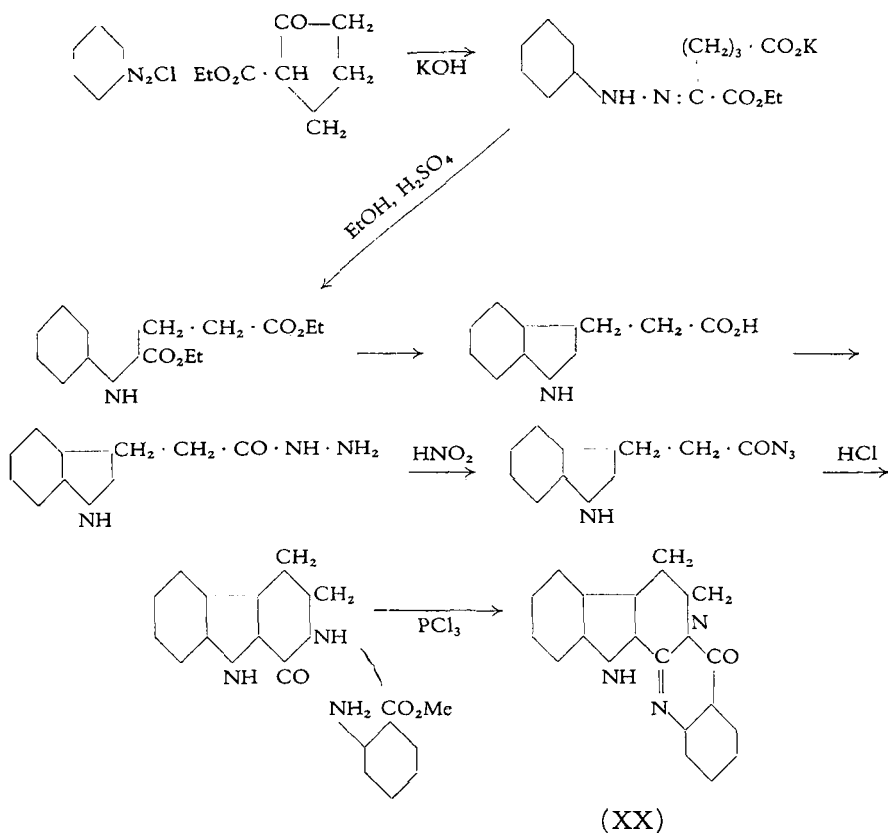
stance. A great many of them would be methyl derivatives, $C_{11}H_7N_2 \cdot CH_3$, of $C_{11}H_8N_2$ which is the formula of a tricyclic aromatic substance containing benzene, pyrrole, and pyridine nuclei. Hence in 1912 we sought, and found, this methyl group, and also eliminated it. This was made easy by the fact that harmine, like quinaldine, forms a benzylidene derivative:



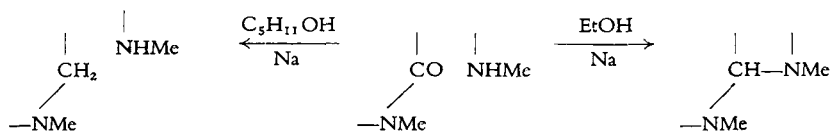
Later, norharman, $C_{11}H_8N_2$, was prepared by removing the methoxyl group from norharmine or the methyl group from harman.

It seems incredible that the next step was not taken until some years had elapsed. One day, when in Liverpool, I happened to wish to refer to Richter's Lexicon for the melting point of a methylnaphthiminazole, $C_{12}H_{10}N_2$. It was interesting to see an old friend, harman, as No. 16 and a little further I noticed (No. 19) Verbindung (aus Tryptophan) and a Zentralblatt reference of 1903. The paucity of the information and the coincidence induced me to read the original (Hopkins and Cole, 1902). The base from tryptophan had m.p. 238° which was a few degrees higher than that attributed to harman but otherwise the properties of the two substances, especially the characteristic fluorescence in acid solution, were identical. Later the m.p. of harman was raised to 238° and direct comparison with a specimen of Hopkins' base proved the identity. The mystery of the formation of a C_{12} base by oxidation of tryptophan (C_{11} and loss of CO_2H occurs) with aqueous ferric chloride was easily resolved. The mixture had been extracted with ether and left for a few days; there is little doubt that alcohol in the ether was a source of acetaldehyde. It was in fact possible to synthesize harman by condensation of tryptophan with acetaldehyde followed by oxidation, or by joint oxidation of tryptophan and alanine.

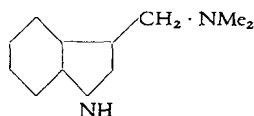




The complete synthesis of eserine was accomplished by Julian and Piki (1925). We missed it because we used sodium and amyl alcohol for a reduction which was carried beyond the desired stage.

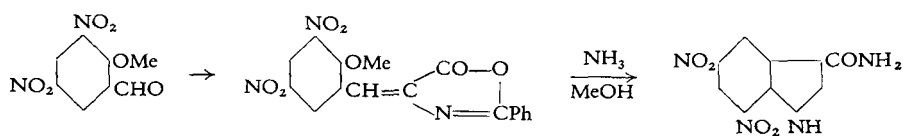
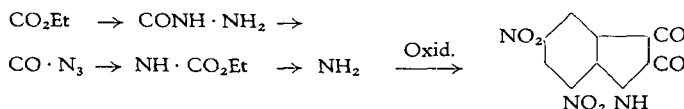
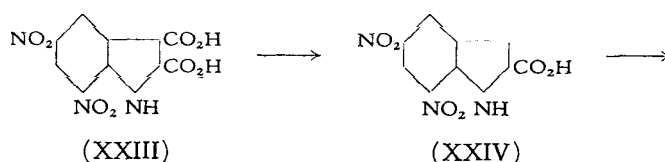


The indole group now includes many types varying from the remarkably simple gramine (donaxine) (XXII) of von Euler and collaborators (1932) to the complex ergot alkaloids, yohimbine, rauwolfine, calycanthine, etc., which I must be content to merely mention. The fact that strychnine and brucine are indole derivatives was first definitely proved by the examination



(XXII)

of dinitro-strycholcarboxylic acid (XXIII), which was obtained by Tafel by simultaneous oxidation and nitration of strychnine. It was systematically degraded to dinitro-isatin (with K. N. Menon, 1931), and dinitrostrychol (XXIV) was later synthesized (with P. Hill, 1933).



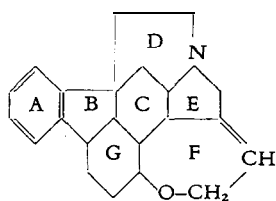
The interlocking developments of the chemistry of strychnine and brucine cannot be usefully summarized and demand separate treatment. This is a most fascinating molecule and with its seven fused rings it is a kind of organic chemist's playground. For many years to come it will provide material for degradative studies. Nevertheless I believe that the problem of its constitu-

tion is finally solved in every detail. For a long time the formula (XXV) seemed satisfactory but in 1945 Prelog and Szpilfogel gave good reasons for supposing that ring E is six-membered. Other evidence in the same direction has since accumulated. The chemistry of neostrychnine, an isomeride depending on a change in position of a double bond, created some temporary difficulties. These have been overcome by the recognition that neostrychnine

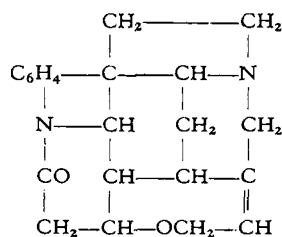
contains $\text{N}-\overset{\alpha}{\text{C}}\text{H}=\overset{\beta}{\text{C}}$, which can be oxidized by perbenzoic acid to $\text{N}\cdot\text{CHOCO}$, and changed by bromine to a bromo-hydrobromide

which in warm water becomes $\text{N}-\overset{\beta}{\text{C}}-\overset{\alpha}{\text{C}}\text{H}\text{O}$, HBr (with R. N. Chakravarti, 1945-1946). After careful and prolonged consideration I am satisfied that strychnine is (XXVI) (*Experientia*, 1946) and that no alternative can now be entertained.

A tribute must be paid here to the memory of Hermann Leuchs whose brilliant experimental work is admired by all students of this subject.



(XXV)



(XXVI)

Synthesis in the steroid groups. This investigation sprang from a new point of departure and was at first a survey of the methods applicable to the building of the ring skeletons of the steroid hormones. Again it cannot be shortly summarized and I will speak of a few sections only. The early methods (with E. Schlittler and J. Walker, 1935-1937) encountered stereochemical obstacles when directed towards oestrone; Bachmann made much better use of these routes in his synthesis of equilenin. We always tried to shorten the synthesis by coupling together two components and one promising device (with W. Rapson and D. A. Peak, 1936-1937) is shown in the scheme:

A second precedent investigation is that on the reduction of 2-methoxynaphthalene. With sodium and alcohol this gives a dihydro-derivative, easily hydrolysed by acids to 2-tetralone (with J. W. Cornforth and Mrs. R.H. Cornforth, 1942) (see scheme at bottom of p. 182).

The synthesis shown on p. 184 represents the high-water mark of our achievement in this field and was only made possible by the skill and pertinacity of Dr. J. W. Cornforth.

This last substance from (+) *B* is completely identical with a tricyclic diketone made from a degradation product of desoxycholic acid by H. Reich (1945). The fusion of rings A : B is *cis* and that of B : C is *trans*; hence the prospect for the complete synthesis of coprosterol (and therefore of cholesterol) is a bright one.

I conclude with an expression of deepest gratitude and appreciation to all of my numerous co-workers; any success which I have had was due to their unsparing efforts. Though it might be invidious to mention individuals, yet I may be allowed to say how much I owe to the constant help of my wife, not quite my first, but much my most consistent collaborator, and over the longest period of years.