materials to be treated were introduced into 50-ml. Erlenmeyer flasks, and an equal volume of 0.2 *N* hydrochloric acid, 0.2 *N* sodium hydroxide, or 2% sodium hydroxide were added. The flasks were stoppered and held for twenty-four hours at room temperature in the case of the 0.1 *N* acid and alkali and at 40° in the case of the 1% sodium hydroxide. The samples were then neutralized with an equivalent amount of alkali or acid, and inorganic orthophosphate determinations were made on aliquots of the solutions.

The data obtained included only a part of the inorganic metaphosphate that may have been liberated. Control experiments with sodium metaphosphate indicated that 0.1 *N* sodium hydroxide and hydrochloric acid hydrolyzed only 11 and 22%, respectively, to orthophosphate at 23° in twenty-four hours; 28% was converted by 1% sodium hydroxide at 40° in the same length of time.

Summary

Proteins reacted with phosphoric acid containing excess phosphorus pentoxide (78% total phosphorus pentoxide) for three days at room temperature. After neutralization and dialysis, the products contained considerable amounts of phosphorus, much of which could be removed by dialysis against 10% sodium chloride solution. The remaining stably-bound phosphate was found to be present as esters of ortho- and metaphosphoric acids on the hydroxyl groups of the serine, threonine, and hydroxyproline residues. Possibly part of the phenolic hydroxyl groups, but probably no other type of protein group, participate in the stable fixation of phosphate.

The stability of the protein phosphate bonds in neutral and dilute acid and alkaline solutions has been determined.

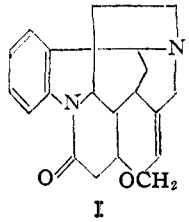
ALBANY 6, CALIFORNIA RECEIVED JANUARY 28, 1948

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

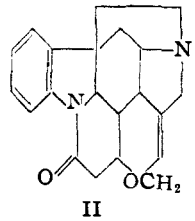
The Structure of Strychnine. Formulation of the *Neo* Bases

BY R. B. WOODWARD AND WARREN J. BREHM

Some years ago we were led to the view that strychnine was best represented by the expression[1] (I), rather than that (II) generally accepted at that time.[2] We considered *i.e.*: (i) that (I) was preferable on biogenetic grounds[3]; (ii) that (I) contains the skeletons of the main products of the drastic degradation of strychnine, *viz.*, tryptamine,[4] carbazole[5] and in particular, β-collidine,[4b,6] while the last could be formed from (II) only by rearrangement; (iii) that in any event little direct evidence was available concerning the mode of attachment of N^b to the carbazole ring.

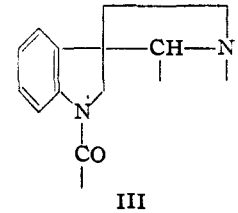


I



II

Since we have recently been able to provide evidence that the part structure (III) is present in the strychnine molecule,[7] only one major barrier



III

has remained in the way of the final acceptance of the expression (I) for strychnine. It will be clear that many of the reactions of the alkaloid will be as readily interpretable on the basis of (I) as of (II).[8] On the other hand, the acceptance of (I) has definite consequences in respect to the formulation of the *neo* series of strychnine derivatives, and the previous knowledge of the reactions of the *neo* bases has indicated strongly that these consequences did not obtain. In this communication, we describe experiments which provide conclusive proof in favor of particular expressions for relevant portions of the molecules of the *neo* bases, and show that the expressions derived are those to be expected if strychnine be formulated as (I).

The first of the *neo* bases, methoxymethyldihydro*neo*strychnidine, $C_{21}H_{24}ON(NCH_3)(OCH_3)$, was formed when strychnidine methosulfate was treated with methyl alcoholic potassium hydrox-

(1) This structure was proposed and discussed at length in the lectures by the senior author on the Chemistry of Natural Products during the summer term of 1944. It was discussed with Sir Robert Robinson in August of 1945, and since that time, investigations have been proceeding independently in the Oxford and Harvard Laboratories with the objective of final clarification of the structural situation. Professor Robinson has very generously kept us informed from time to time of the more important results of his program through private communications, and we in turn have let him know of ours.

(2) Holmes and Robinson, *J. Chem. Soc.*, 603 (1939).

(3) Woodward, *Nature*, in press.

(4) Kotake, *Proc. Imp. Acad. Tokyo*, **12**, 99 (1936); Clemo, *J. Chem. Soc.*, 1695 (1936).

(5) Perkin and Robinson, *J. Chem. Soc.*, 305 (1910); Clemo, Perkin and Robinson, *ibid.*, 1589 (1927).

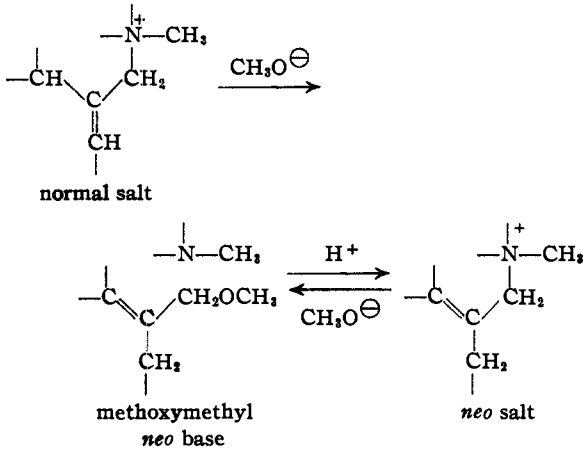
(6) Clemo and Metcalfe, *ibid.*, 1519 (1937); Oechsner de Coninck, *Ann. chim.*, [5] **27**, 507 (1882); *Bull. soc. chim.*, [2] **42**, 102 (1884).

(7) Woodward, Brehm and Nelson, THIS JOURNAL, **69**, 2250 1947).

(8) A review of the enormous literature on the subject is outside the scope of this paper. An outline of the main facts is given in Henry's "Plant Alkaloids" (Blakiston's Son, 1939) and an excellent and very complete review by Professor H. L. Holmes will appear in the first volume of the forthcoming series of monographs on alkaloids, to be published by the Academic Press under the general editorship of Dr. R. H. F. Manske.

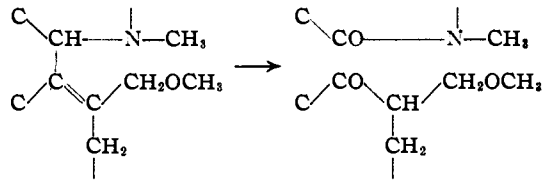
ide.[9] On boiling with dilute acids, the methoxy group of the new base was lost, and a new quaternary salt, isomeric with the original strychnidinium derivative, was formed.[9,10] The chloride of the new series, methyl *neo*strychnidinium chloride, lost methyl chloride on pyrolysis with the formation of *neo*strychnidine, an isomer of strychnidine.[9,10] Further, the methyl *neo*strychnidinium salts, on treatment with methyl alcoholic potassium hydroxide, were reconverted to the same methoxymethyldihydro*neo*strychnidine from which they were formed.[9,10] Subsequently, exactly parallel transformations were effected in the strychnine series,[11] and the important observations were made that *neo*strychnidine[10] and *neo*strychnine[11] could be reduced catalytically to dihydro derivatives identical with those obtained by the hydrogenation, respectively, of strychnidine and strychnine.[12]

From these observations, it was clear that in the formation of the *neo* bases, no rearrangement of the carbon skeleton had occurred, and that the double bond of the normal series had migrated to a new position. Further, the cleavage of the quaternary salts of both series, as well as the ready reconstitution of the quaternary salts of the *neo* series, was explicable if the double bond present were assumed to be in the β,γ (*i. e.*, allylic) position with respect to the quaternary nitrogen atom, and the fundamental changes outlined above were formulated in this sense



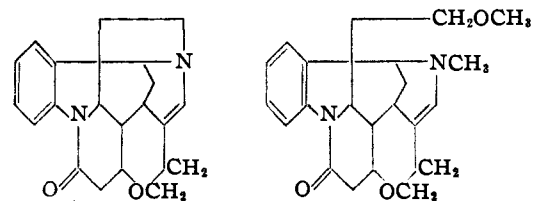
Support for this view was found in the relatively sluggish cyclization (to quaternary salts) of those methoxymethyl derivatives in which the double bond had been saturated.[13]

The validity of this scheme was challenged by facts which emerged from the further study of methoxymethyldihydro*neo*strychnine. It was found that the latter was converted by perbenzoic acid in excellent yield, with addition of two oxygen atoms, to a *neutral* oxidation product (named methoxymethyl*chano*dihydrostrychnone) containing a carbonyl group. It was clear that the new substance contained the group $-N^b(-)CO-$, and its formation was assumed to involve the change[13,14]:



When methoxymethyl*chano*dihydrostrychnone was reduced by the Clemmensen method, the oxygen atom of its carbonyl function appeared to be replaced by two hydrogen atoms, and a new substance, methoxymethyl*chano*dihydrostrychnane, was formed, which on Kuhn–Roth oxidation gave one mole of acetic acid.[15] This fact was explained by assuming that the new methylene group (C—CH_2—C) appeared as acetic acid during the Kuhn–Roth procedure; the assumption was hardly tenable in view of the fact that no such change had been observed even in more likely cases.[16] The simple inference from the above facts was that methoxymethyl*chano*dihydrostrychnone contained an aldehyde group (thus, —C(—)—CHO ⟶ —C(—)—CH_3), and although negative evidence was brought forward against that view,[13] no really convincing formulation of the substance was advanced; the recent demonstration[17] that the double bond in the *neo* series is adjacent to N^b served only further to compound the difficulty of the matter.

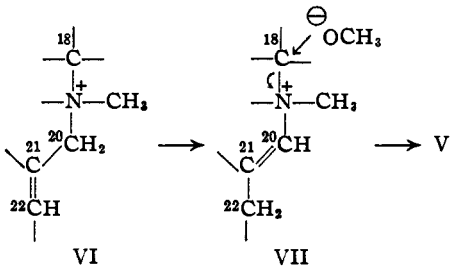
We turn now to a consideration of the structure of the *neo* bases in the light of the new strychnine



(9) Clemo, Perkin and Robinson, *J. Chem. Soc.*, 1589 (1927).
(10) Achmatowicz, Perkin and Robinson, *ibid.*, 486(1932).
(11) Achmatowicz, Clemo and Perkin, *ibid.*, 767 (1932).
(12) *Neo* bases have been prepared by other methods, of less structural interest, but of more preparative value. Kotake and Yokohama (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, **31**, 321 (1937)) isomerized strychnine to *neo*strychnine by heating with selenium. Recently Robinson and Chakravarti (*J. Chem. Soc.*, 78 (1947)) have confirmed Kotake's observation, and have shown that the strychnos alkaloids are smoothly converted to the corresponding *neo* isomers when heated in xylene in the presence of Raney nickel. This elegant method makes the *neo* bases readily accessible in quantity for the first time.
(13) Reynolds and Robinson, *J. Chem. Soc.*, 936 (1935).
(14) Briggs and Robinson, *ibid.*, 590 (1934).
(15) Reynolds and Robinson, *ibid.*, 592 (1934).
(16) *Cf.* Kuhn and L'Orsa, *Z. angew. Chem.*, **44**, 852 (1931), who show that even the methylene groups of malonic acid and 5,5-dimethyldihydroresorcinol (dimedon), do not appear as acetic acid in the C-methyl determination.
(17) Briggs, Openshaw and Robinson, *J. Chem. Soc.*, 903 (1946).

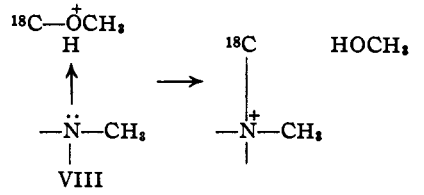
formula (I). It may be deduced at once that only one likely position is available for the double bond in the *neo* series if (I) be accepted.[18] Steric considerations prohibit the placement of unsaturation at Δ^{14-21}, Δ^{13-14}, Δ^{14-15}, or Δ^{15-16}, and no reasonable path is available for the migration of a double bond from Δ^{21-22} to Δ^{8-13} or Δ^{17-18}. Only Δ^{20-21} remains, and on the basis of (I), *neo*strychnine must be represented as (IV).

If *neo*strychnine be (IV), the views outlined above in connection with the formation of the methoxymethyl derivatives must be abandoned. An alternate scheme is available in the following terms: (i) the double bond of the methyl strychninium salt (VI) migrates into juxtaposition with the quaternary nitrogen atom[19] (*cf.* VII); (ii)



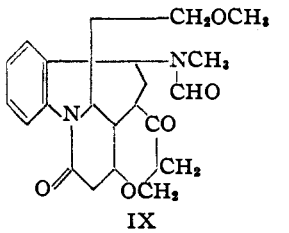
VI VII

the double bond in the new position facilitates[20] a direct bimolecular cleavage reaction (S_N2) involving attack by methoxide ion at C.18 (VII, arrows) to give (V).[21] The greater ease of reconstitution of quaternary salts from the unsaturated, as compared with the saturated methoxymethyl derivatives must be attributed to the lowering of the basicity of N^b in the former by the adjacent double bond. Thus the attack of N^b on C.18, with release of methyl alcohol (VIII, arrows) will be more or less facile as a smaller or greater proportion of the molecules contain a proton attached to N^b.



VIII

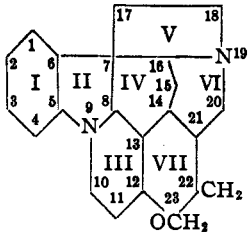
Ample analogy is now available[22] for the cleavage $-\overset{|}{N}-\overset{|}{C}=\overset{|}{C}- \longrightarrow -\overset{|}{N}-\overset{|}{C}O\ O\overset{|}{C}-$ by perbenzoic acid, and if (V) be methoxymethyldihydro*neo*strychnine, the expression (IX) must be accepted for methoxymethyl*chano*dihydrostrychnone. The facts hitherto available could only with the greatest difficulty be so construed as to commend this



IX

view. On the one hand it was necessary to assume that a formamide system survived boiling for twenty-eight hours with concentrated hydrochloric acid[15] (in the Clemmensen reduction of the strychnone), as well as heating for four hours with concentrated methyl alcoholic barium hydroxide[18] sodium ethoxide in ethanol for a few hours. Further, the ease of these reactions has a sound basis in theory, in that the breaking of the C—N bond will be facilitated as the environment of the nitrogen atom is such that the latter more readily accepts the released electron pair. The low basicity of nitrogen atoms attached to double bonds, and the ultraviolet absorption characteristics of such systems (*cf.* Bowden, Braude, Jones and Weedon, *J. Chem. Soc.*, 50 (1946)) are attributable to the same effect, which has its origin in the resonance $-\overset{|}{C}=\overset{|}{C}-\overset{|}{N}- \longleftrightarrow -\overset{|}{C}-\overset{|}{C}=\overset{|}{N}-$.

(18) The following numbering of the strychnine skeleton is used in the sequel, and we should like to propose that it be adopted generally. Following general practice contiguous rings are numbered consecutively; the particular choice adopted has the distinct menmonic advantage that the designations of rings. V, VI and VII are identical with the respective ring sizes. The atoms have then been numbered consecutively, beginning with ring I, *etc.*



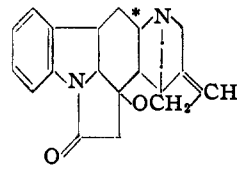
(19) The change is formally analogous in some respects to the well-known shift $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}H-\overset{|}{C}O \longrightarrow -\overset{|}{C}H-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}O$, since the carbon atom of —CO bears a considerable formal charge. On the other hand, the first order conjugation effects present in the carbonyl system cannot be operative in the case described above, since $\equiv N^+$ is saturated. However, it may not be doubted that the positive charge in $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}H-\overset{+}{N}\equiv$ will facilitate the first step in the process, *vis.*, proton release from C*; the operation of the same effect is seen in the very ready elimination of hydrogen bromide from $BrCH_2CH_2N^+(CH_3)_3$ (Renshaw, THIS JOURNAL, 34, 1618 (1912); Schmidt and Bode, *Ann.*, 267, 311 (1892)).

(20) No relevant information is available for analogous simple unsaturated systems. However, it is abundantly clear that in the case in which a phenyl group replaces the C.20–C.21 double bond of (VII). cleavage analogous to that outlined above takes place with particular ease (von Braun and Seemann, *Ber.*, 55, 3820 (1922); *cf. Ann. Rep. Chem. Soc.*, 103 (1920) for collected references to v. Braun's results). Cases strikingly analogous to that discussed above were studied by Vorländer and Spreckels (*Ber.*, 52, 309 (1919)), who showed that the change $C_6H_5N^+R_3 + {}^-OEt \rightarrow C_6H_5NR_2 + ROEt$ was readily brought about when the quaternary salt was heated with

(21) There is no direct evidence bearing on the point of attachment of the methoxyl group. It seems probable that a bimolecular substitution reaction of the type outlined above would take place most readily at C.18, which is primary, and possibly otherwise less hindered, than the alternative position (C.16). In any event, the point has no special relevance in connection with the demonstration which follows.

(22) Witkop, private communication. Dr. Witkop has made available to us a proof copy of a communication by himself and Fiedler which was submitted in 1946 for publication in the *Annalen:* we have been unable to determine whether it has appeared. In it the very smooth oxidation of a series of indole derivatives to o-acylaminophenyl ketones by perbenzoic acid is described.

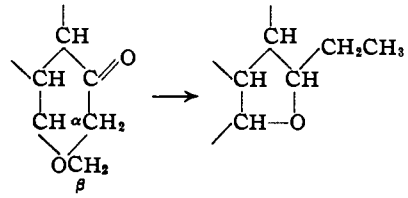
(in the transformation of methoxymethyl*chano*-dihydrostrychnane to the corresponding strychnanic acid, *by cleavage of the N^a lactam link*). On the other hand, the presence of the group $-\overset{|}{\underset{|}{C}}-CH_3$ in the Clemmensen reduction product of the strychnone suggested that the carbonyl group of the latter was present as $-\overset{|}{\underset{|}{C}}-CHO$. The obvious inference from these facts was that the *neo* bases contained $-N^{b}-\underset{|}{C}=CH-C$ and indeed, these, taken with other considerations, led recently to the proposal of a strychnine formula (X) which permitted this feature[23] (double bond at * in the *neo* series).



X

We have now subjected these substances to further study. Methoxymethyl*chano*dihydrostrychnone was converted by ethyl mercaptan in the presence of hydrochloric and acetic acids to the corresponding mercaptal ($-\overset{|}{\underset{|}{C}}=O \longrightarrow -\overset{|}{\underset{|}{C}}(SEt)_2$). Removal of the mercapto groups by treatment in alcohol with Raney nickel ($-\overset{|}{\underset{|}{C}}(SEt)_2 \longrightarrow -\overset{|}{\underset{|}{C}}H_2$) gave a substance, $C_{23}H_{30}O_4N_2$, m. p. 136–139°, different from, but isomeric with methoxymethyl*chano*dihydrostrychnane (m. p. 163°). *The new compound contained no* $-\overset{|}{\underset{|}{C}}-CH_3$ *group.*

It is now clear that methoxymethyl*chano*dihydrostrychnone contains the group $C-\overset{|}{\underset{|}{C}}=O$, and that the formation of methoxymethyl*chano*dihydrostrychnane[24] must be accompanied by rearrangement. It is not difficult to envisage the nature of this change. Thus, in the part structure (XI), present in the strychnone, the opportunity exists for: (i) reductive cleavage of the ether linkage in the reactive β-position to a carbonyl group (this change may well proceed through β-elimination, followed by reduction of the resultant α,β-unsaturated carbonyl system); (ii) reduction of $-\overset{|}{\underset{|}{C}}=O$ to $-\overset{|}{\underset{|}{C}}HOH$; (iii) ether formation involving the two hydroxyl groups formed in (i) and (ii). The strychnane, then, contains the part structure (XII), and the presence of $-\overset{|}{\underset{|}{C}}-CH_3$ no longer constitutes a problem.



XI XII

We turned next to an examination of the nature of the amide function in methoxymethyl*chano*dihydrostrychnone. Since this compound undergoes deep-seated changes in the presence of acid or base, it seemed unlikely that the isolation or characterization of simple hydrolysis products would be possible. (We attribute these changes to the presence of the labile system $-COCH_2CH_2O-$, which can readily suffer elimination, with the formation of the very reactive grouping $-COCH=CH_2$). Consequently, we studied the behavior with hydrolytic reagents of (*a*) methoxymethyl*chano*dihydrostrychnane, (*b*) desoxomethoxymethyl*chano*dihydrostrychnone, m. p. 136–139°, from the Raney nickel desulfurization (see above), and (*c*) a dihydroderivative ($-\overset{|}{\underset{|}{C}}=O \longrightarrow -\overset{|}{\underset{|}{C}}HOH$) m. p. 225–226°, obtained by the catalytic hydrogenation of the strychnone. As might have been expected from earlier work with the strychnane, none of these substances liberated formic acid even on prolonged treatment with concentrated bases. On the other hand, *each of them readily gave exactly one mole of formic acid on hydrolysis with 2N sulfuric acid.* After hydrolysis of methoxymethyl*chano*dihydrostrychnane ($C_{23}H_{30}$-

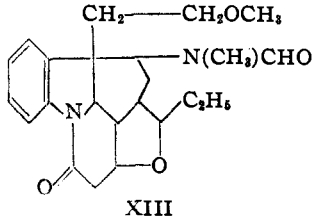
(23) Robinson, *Nature*, **159**, 263 (1947). The supporting evidence involved the formation from the *neo* bases of oxidation products containing one additional oxygen atom by the action of bromine and water. The products are basic, and contain a carbonyl group; the change was assumed to be $-N-\underset{|}{C}=CH-C \longrightarrow -N-CH-CO-C$. In a still more recent note, Robinson and Chakravarti (*Nature*, **160**, 18 (1947)) indicate that the substances are aldehydes, and that a rearrangement accompanies their formation. The opinion is further expressed that while the new evidence does not exclude the structure (X) (presumably in view of the possibility $-N-\underset{|}{C}=CH-C \longrightarrow -N-\underset{|}{\overset{|}{C}}-CHO$), it removes the necessity for its proposal in so far as the oxidation reaction is concerned (since $-N-CH=\underset{|}{C}-$ is transformable with rearrangement to $-N\ OHC-\underset{|}{C}-$). In these circumstances, Robinson and Chakravarti, as "the best hypothesis to guide future work," revert to the expression (I), which for some years has been under consideration independently in the Harvard and in the Oxford laboratories.

(24) Actually the new substance, m. p. 136–139°, now properly deserves this name, but the adoption of the change would create unnecessary confusion. Consequently, we propose the designation desoxomethoxymethyl*chano*dihydrostrychnone for the new isomer.

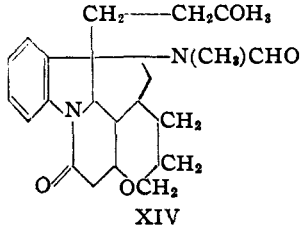
O_4N_2), the corresponding base, $C_{22}H_{30}O_3N$, m. p. 86–86.5° was isolated. In view of the special circumstances *vis-a-vis* the stability of $-\overset{|b}{N}-CO$ in these substances, it was necessary to eliminate the possibility that the formic acid owed its origin to an acid-catalyzed rearrangement (*e. g.*, of an α-hydroxy (*or* alkoxy) amide). This was done by formylating the above base, m. p. 85–86°, through treatment with anhydrous formic acid and acetic anhydride. The formylation product was identical in all respects with methoxymethyl*chano*dihydrostrychnane.

These facts are explicable only if in all of these compounds the presence of the group $-\overset{|b}{N}-CHO$ be accepted. The marked resistance to alkaline cleavage must be attributed to steric hindrance of the approach of hydroxide ion (models indicate the plausibility of this view), while the stability under the strongly acid conditions of the Clemmensen reduction is probably a consequence of the relatively low activity of water in highly acid and concentrated salt (in this case zinc chloride) solutions.[25]

Taken all together our new observations provide conclusive proof of the presence of $-\overset{|b}{N}-CH=\overset{C}{\overset{|}{C}}-C$ in the *neo* bases; we may now assign with confidence the structures (IV), (V), (IX), (XIII) and (XIV),[21] respectively, to *neo*strychnine, methoxymethyldihydro*neo*strychnine, methoxymethyl*chano*dihydrostrychnone, methoxymethyl*chano*dihydrostrychnane and desoxomethoxymethyl*chano*dihydrostrychnone. Since these are precisely the expressions required by the structure (I) for



XIII

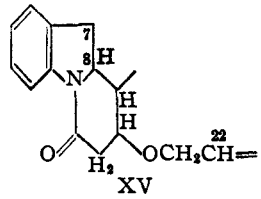


XIV

strychnine, it is clear that the last major barrier in the way of the acceptance of (I) has collapsed.

(25) In any event, the slowing down of amide hydrolysis as the acid concentration is increased beyond a certain point appears to be a general phenomenon. *Cf.* Hammett, "Physical Organic Chemistry," p. 365 (McGraw-Hill Book Co., Inc., 1940). Further it should be mentioned that the formamide link of the strychnane is not completely stable under the above conditions, since we have been able to isolate some of the base $C_{21}H_{30}O_1N_2$ from Clemmensen reduction reaction-mixtures.

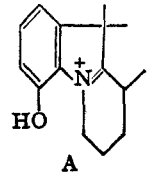
It is therefore now pertinent to examine the general situation in order to determine whether the formula (I) represents a necessary as well as a sufficient solution to the structural problem. We take as the basis for the structural discussion the expression (XV), which follows from (i) the presence in strychnine of an *o*-substituted N-acylaniline system[8]; (ii) Robinson's deduction, from the Leuchs degradations, of the nature of ring III and of the presence of the chain $-OCH_2CH=$ at C.12[26]; (iii) the presence of a dihydroindole sys-



XV

tem, suggested by a number of independent lines of evidence,[8] and definitely confirmed by our recent elucidation of the changes accompanying the formation of strychnone.[7] We now examine evidence which necessitates the elaboration of three independent chains of atoms, each of which originates at N^b and terminates at some atom of (XV): (*a*) the nature of the changes involved in the formation of strychnone requires[7] that in strychnine the β position of the dihydroindole ring be linked by a methine bridge to N^b; (*b*) the formation of tryptamine by the alkaline degradation of strychnine necessitates a chain of two carbon atoms between C.7 and N^b. *We make the reasonable assumption that this chain bears four hydrogen atoms*[27]; (*c*) the results of the present

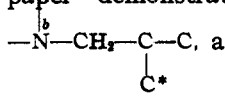
(26) Robinson, *Proc. Roy. Soc.* (*London*), **130**, 431 (1931). The original demonstration did not include the placing of a hydrogen atom at C.8 but, subsequently, Briggs, Openshaw and Robinson (ref. 17, footnote, p. 903) deduced the presence of this feature through the formulation of one of the colorless benzal derivatives of the (*iso*) strychnine series as an (11-) benzyl α-pyridone. Further, the formation of strychnone (ref. 7) requires a hydrogen atom either at C.7 or C.8, and the lack of reactivity toward bromine of diketonucidine (ref. 2) provides evidence against C.7. We reach a similar conclusion through a consideration of certain changes in the vomicine series (part formulation of the salts of the catalytic hydrogenation products from desoxyvomicidine, isovomicidine and dihydrodesoxyvomicidine (Wieland and Huisgen, *Ann.*, **556**, 161, 166 (1944)) as (A)–note



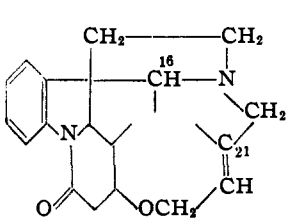
A

that the typical color reactions of the *o*-aminophenol system are not given by these bases with oxidizing agents in weakly acid solution!).

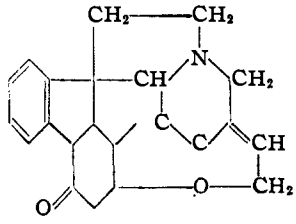
(27) The presence of such a chain $(-\overset{17}{CH_2}\overset{18}{CH_2}-)$ has been accepted generally (*cf.* ref. 8). No conclusive direct proof of that feature is available but it may be considered unlikely that tryptamine (ref. 4) would be a product of degradative processes involving the scission of carbon-carbon bonds to these positions. The presence of $=\overset{18}{CH_2}$ in dimethyl*dess*trychnidine D (Achmatowicz and Dybowski, *J. Chem. Soc.*, 1483 (1938)) has also been put forward as evidence in support of the presence of $-\overset{18}{CH_2}-\overset{|b}{N}-$ in strychnine.

paper demonstrate that strychnine contains  and it is further clear that in order to account for the formation of strychninonic acid, one of the starred carbon atoms must be identical with C.22 (see XV).[28]

These considerations extend the development of the partial structure of strychnine to (XVI). Now Prelog's recent demonstration[29] that ring VI is six-

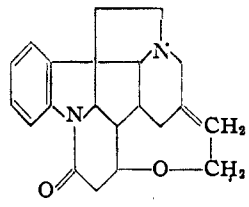


XVI

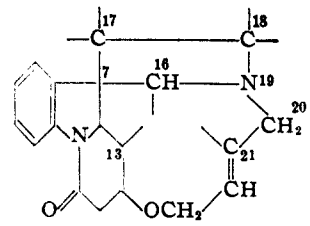


XVII

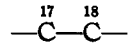
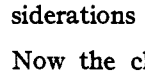
membered, from which a certain amount of ambiguity is removed by our new results,[30] necessitates the incorporation of the two carbon atoms lacking from XVI in a chain bridging C.16 and C.21. The resulting expression (XVII) can be elaborated in only two ways, *viz.*, to (I) or to XVIII, and the latter is excluded in view of the formation from N-methyl*chano*pseudostrychnine of a dibenzal derivative[31] and by the failure of strychninonic acid to be attacked by bromine at the position α to the carbonyl group.[32] It is now clear that (I) provides a unique solution to the structural problem.

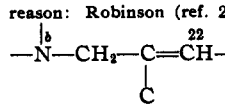


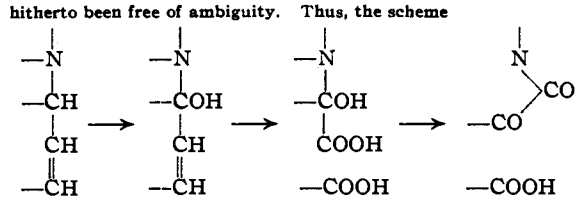
XVIII



XIX

On the other hand, it is necessary to examine the consequences of rejecting the one assumption[27] in the above demonstration for which unambiguous experimental evidence is not available. In that event the structural argument is more complicated, but in our opinion is equally conclusive. Thus, if the four hydrogen atoms at C.17 and C.18 be omitted, it is first possible to show that  cannot be co-extensive with either of the chains of (*a*) or (*c*), above, since: (i) if C.16 were identical with either C.17 or C.18, pseudostrychnine must be a (potential) cyclopropanone or α-iminoketone, and these possibilities may safely be discarded; (ii) C.20 cannot be identical with C.18, since the latter must be contained in a five-membered ring, and it has been shown earlier that C.20 cannot be so situated.[29,30] These considerations lead to the part structure (XIX). Now the chain  must be part of a six-(or seven)-membered ring[29,30]; this ring cannot be constructed from the chain 21-20-19-16-7-17, nor by the interpolation of a bridge containing one or both of the carbon atoms lacking from (XIX) between C.21 and C.17, since in that event the formation and properties of strychninonic acid (and to a greater extent, the formation of the lactam of cunine carboxylic acid[33]) would be inexplicable.[34] Precisely the same circumstances bar construction of the necessary ring by the union of C.13 and C.21. Finally, the ring cannot be constructed by bridging C.21 and C.18 by a chain of two carbon atoms, since in that event, N-methyl*chano*pseudostrychnine could not form a dibenzal derivative,[31] and the stable (and consequently five- or six-membered) N^b-lactam ring of strychnone[7] could not be accounted for. The only remaining possibility, *viz.*, the interpolation of two carbon atoms, to one of which two hydrogen atoms must be attached,[31] between C.16 and

(28) We have presented the situation in the above terms for this reason: Robinson (ref. 26) postulated the presence of the system  (identical with that derived above) on the basis of interpretations of (*a*) the methoxylating cleavage of strychninium salts, and (*b*) the formation of strychninonic acid. It will be clear from the earlier sections of this paper that the considerations involved in (*a*) must now be rejected, but the alternative now adopted yields the same part structure. Beyond that, in our opinion the interpretation of the formation of strychninonic acid has not hitherto been free of ambiguity. Thus, the scheme



is *a priori* in no wise less satisfactory than that originally proposed by Robinson (the concomitant formation of dihydrostrychninonic acid can also be encompassed). The results of the present work, however, permit the unequivocal rejection of the alternative scheme.

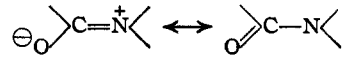
(29) Prelog and Szpilfogel, *Helv. Chim. Acta*, **28**, 1669 (1946).

(30) Thus, the work of the Swiss workers indicated that *strychninonic acid* contains a six (or seven) membered ring. The considerations advanced in ref. 28 indicate that hitherto the possibility was definitely present that a five-membered ring in strychnine itself might be transformed into a six-membered ring in strychninonic acid.

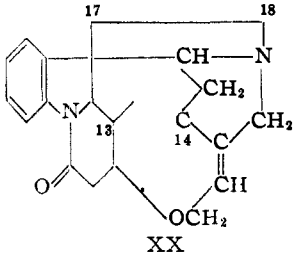
(31) Blount and Robinson, *J. Chem. Soc.*, 2305 (1932).

(32) Leuchs, *Ber.*, **72**, 1588 (1939); *cf.* also Robinson, ref. 2, and Leuchs and Grunow, *Ber.*, **72**, 679 (1939). The phenomenon is explicable on the basis of (I) through the steric blocking of enolization, which necessitates a double bond at C.14–C.21. It is worthy of note that pseudostrychnine does not form anhydro salts (—C=N⁺—) for a similar reason ($\Delta^{14\cdot 19}$ impossible).

(33) Holmes, Openshaw and Robinson, *J. Chem. Soc.*, 908 (1946).

(34) Since the amide link is stabilized by the resonance  amides do not form at the bridgeheads of bicyclic systems which prohibit double bonds to the bridgehead atoms; further, were such an amide obtainable by indirect means, it would be expected to open very readily and *irreversibly* to the corresponding amino acid. The situation is discussed in detail by one of us (R. B. W.) in Chapter XV of the forthcoming monograph on the chemistry of penicillin (Princeton University Press).

C.21, leads to (XX). Now bonds between C.14 and C.17 or C.18 are excluded by considerations already advanced.[34] Only three possibilities remain; of these, the first is I, and those obtained by linking C.13 to C.17 or to C.18 are excluded by the fact that strychninonic acid is not attacked by bromine at the position α to the carbonyl group,[32] and by the failure of pseudostrychnine to form anhydro salts.[35]



XX

We conclude that the structure (I) for strychnine is established.

Experimental

Methylstrychnine.—The method[36] employing strychnine and dimethyl sulfate in the absence of a solvent was found to be superior to the alternate method involving preliminary isolation of pure crystalline strychnine methosulfate.[37]

Methoxymethyldihydro*neo*strychnine (V).—Since, in our hands, both the yield and purity of product were similar whether methylstrychnine was treated with methanolic sodium methoxide or with sodium amalgam in methanol,[11] we favor the former method because of its greater simplicity.

In an early preparative attempt, before any material with the reported melting point of 143° had been obtained, there was isolated a white crystalline substance of m. p. 115–117°. Subsequent to the successful preparation of material with the higher melting point, this material was recrystallized and gave material, m. p. 139–141°, identical with the higher melting sample obtained directly from the reaction-mixture. Hence this is apparently a case of polymorphism.

Methoxymethyl*chano*dihydrostrychnone (IX).—This compound was prepared[14] in almost quantitative yield by treating a boiling ethereal solution of methoxymethyldihydro*neo*strychnine (V) with perbenzoic acid in ether. Ten recrystallizations from ethyl acetate–ether and acetone–ether were required to obtain a sample melting at 189–191°. This is in accord with the observations of the original workers. However, material melting at about 160° (after two recrystallizations from benzene–ligroin) was found to be suitable for use in subsequent reactions.

When (IX) was heated with concentrated sulfuric acid, carbon monoxide was detected in the evolved gases by the production of black metallic palladium from a neutral palladous chloride solution. Under the conditions the gases from strychnine itself caused no reduction. *Anal.* Calcd. for $C_{23}H_{28}O_5N_2$: mol. wt., 412.5. Found (method of isothermal distillation):[38] 433.

Methoxymethyl*chano*dihydrostrychnone Semicarbazone.—Methoxymethyl*chano*dihydrostrychnone (IX) (2.0 g.), dissolved in the minimum amount of hot water (steam-bath), was treated with an aqueous solution of 2.0 g. of anhydrous sodium acetate. After heating for one hour the solution was concentrated *in vacuo;* a yellowish gum precipitated. After a week crystals appeared, 0.65 g., m. p. 238–242°. After recrystallization from methanol the white needles melted at 242–244° (dec.). *Anal.* Calcd. for $C_{24}H_{31}O_5N_5$: C, 61.30; H, 6.60; N, 14.90. Found: C, 61.33; H, 6.70; N, 14.40.

Methoxymethyl*chano*dihydrostrychnol.—Methoxymethyl*chano*dihydrostrychnone (IX) (0.995 g.) was dissolved in 75 cc. of ethanol and was stirred with 0.04 g. of pre-reduced Adams catalyst in an atmosphere of hydrogen. In twenty-four hours only 13.5 cc. of hydrogen was absorbed. After addition of 0.25 g. of pre-reduced catalyst 42.7 cc. of hydrogen was consumed in eleven hours, followed by 6.2 cc. in four hours (theoretical consumption, 54 cc.). The solution was filtered through charcoal and concentrated *in vacuo*. When the concentrated solution was diluted with ether, crystallization occurred; 0.67 g. of white crystals, m. p. 223–226°. After two recrystallizations from ethanol–ether, 0.41 g. of short white needles, m. p. 225.5–226.5°, were obtained. *Anal.* Calcd. for $C_{23}H_{30}O_5N_2$: C, 66.64; H, 7.30; N, 6.76. Found: C, 66.37; H, 7.30; N, 6.73.

When a repetition of this preparation was attempted on a larger scale using a more concentrated ethanolic solution, a larger excess of hydrogen was consumed and only an amorphous product was obtained. This would not crystallize under the conditions described above even with seeding. Similarly, none of the eluted fractions from a chromatographic adsorption of this material could be made to crystallize.

Methoxymethyl*chano*dihydrostrychnone Diethylmercaptal.—Methoxymethyl*chano*dihydrostrychnone (IX) (4.12 g.), dissolved in 30 cc. of glacial acetic acid and 0.3 cc. of concentrated hydrochloric acid and cooled in ice, was treated with 4.4 g. of ethyl mercaptan. After standing in the refrigerator for three days the volatile materials were removed *in vacuo*. The yellowish oily residue crystallized to a pasty mass on standing. After crystallization from ethanol there was 2.6 g., m. p. 177–181°. After recrystallizations from benzene–ligroin, carbon tetrachloride and ethanol the white prisms melted at 183–184.5°. *Anal.* Calcd. for $C_{27}H_{38}O_4N_2S_2$: C, 62.51; H, 7.38; N, 5.40; S, 12.36. Found: C, 61.83; H, 7.64; N, 5.21; S, 12.35.

Desoxomethoxymethyl*chano*dihydrostrychnone (XIV).—About 5 g. of Raney nickel, suspended in 50 cc. of ethanol, was added to a boiling solution of 0.25 g. of methoxymethyl*chano*dihydrostrychnone diethylmercaptal in 50 cc. of ethanol. The reaction-mixture was boiled for thirty minutes and the nickel was filtered off and washed with fresh ethanol. When the solvent had been removed in an air stream on the steam-bath the residue weighed 0.13 g. This was dissolved in benzene and the solution diluted with ligroin. On standing, rosettes of crystals appeared, 100 mg., m. p. 140–143°. The melting point of a mixture with methoxymethyl*chano*dihydrostrychnane (XIII) was 129–131°. After recrystallizations from benzene–ligroin the white prisms melted at 136–139°. *Anal.* Calcd. for $C_{23}H_{30}O_4N_2$: C, 69.32; H, 7.59; N, 7.03; C—CH_3, 0.0. Found: C, 69.73; H, 7.73; N, 6.73; C—CH_3, 0.12.

Methoxymethyl*chano*dihydrostrychnane (XIII).—This material was prepared as reported[15] by the Clemmensen reduction of methoxymethyl*chano*dihydrostrychnone (IX). By strict adherence to the published procedure the reported yield was never obtained although the preparation was repeated many times (from 10 g. of IX yields were 0.2–0.9 g. instead of 3.5 g.). Better yields were obtained when the period of heating was shortened to five hours or when mechanical stirring of the reaction mixture was employed (1.0 and 1.9 g., respectively). However, in these cases, the reported difficulty in purification was observed. This had not been previously encountered in the reactions which gave lower yields. *Anal.* Calcd. for $C_{23}H_{30}O_4N_2$: C—CH_3, 6.8. Found: C—CH_3, 6.1, 6.0.

The acidic mother liquor from the Clemmensen reduction of 6.0 g. of methoxymethyl*chano*dihydrostrychnone

(35) Leuchs, Grunow and Tessmar, *Ber.*, **70**, 1701 (1937). *Cf.* also ref. 32.

(36) Clemo, Perkin and Robinson, *J. Chem. Soc.*, 1624 (1927).

(37) Clemo, Perkin and Robinson, *ibid.*, 1599 (1927).

(38) Clark, "Semimicro Quantitative Organic Analysis," Academic Press, New York, N. Y., 1943, p. 78.

Compound	Amount	Volume (in cc.) of 0.0137 *N* alkali consumed: 1st fraction	2nd fraction	Total	No. of N—CHO groups
N-Formylpenicillamine	0.0737 mmole. (13.0 mg.)	3.56	1.18	4.85 (4 fractions)	0.91
Methoxymethyl*chano*dihydrostrychnane (XIII)	0.0397 mmole. (15.8 mg.)	0.14[a]	..	....	..
Desoxomethoxymethyl*chano*dihydrostrychnone (XIV)	0.0482 mmole. (19.2 mg.)	0.14	0.14	0.79 (5 fractions)	0.22
Methoxymethyl*chano*dihydrostrychnol	0.0487 mmole. (20.2 mg.)	0.27	0.38	3.05 (9 fractions)	0.86
Desoxomethoxymethyl*chano*dihydrostrychnone (XIV)	0.0461 mmole. (18.4 mg.)	0.25[b]	0.34	2.39 (7 fractions)	0.71

[a] Here the amount of base consumed by the first fraction was so small that extra acid was added, and the solution refluxed for a while so as to bring about acidic hydrolysis of the amide linkage. [b] In this determination the hydrolysis mixture was refluxed overnight before acidification and distillation.

Compound	Amount	Volume (in cc.) of 0.0137 *N* alkali consumed: 1st fraction	2nd fraction	Total	No. of N—CHO groups
Desoxomethoxymethyl*chano*dihydrostrychnone (XIV)	0.0446 mmole. (18.0 mg.)	1.53	0.65	3.23 (4 fractions)	0.99
Methoxymethyl*chano*dihydrostrychnane (XIII)	0.0479 mmole. (19.1 mg.)	2.07	0.85	3.45 (6 fractions)	0.99
Methoxymethyl*chano*dihydrostrychnol	0.0397 mmole. (15.8 mg.)	1.91	0.86	3.06 (4 fractions)	1.03
Methoxymethyl*chano*dihydrostrychnone (IX)	0.0514 mmole. (21.2 mg.)	1.73	0.95	3.08 (4 fractions)[a]	0.56

[a] In this determination 0.00937 *N* alkali was used.

(IX) (after extraction of the desired product (XIII) with chloroform) was poured into excess concentrated ammonium hydroxide and extracted continuously with 300 cc. of ether. On evaporation the ether solution was found to contain 2.4 g. of orange-brown oil. In benzene solution this was chromatographed over alumina. Fractional elution with various solvents gave: (1) benzene, 0.67 g.; (2) benzene–ether (1:1), 0.37 g.; (3) ether, 0.20 g.; (4) methanol–ether (1:1), 1.09 g.; (5) methanol, 0.06 g.; (6) methanol–water (1:1), 0.10 g. None of these eluates was crystalline. On treating ethanolic solutions of fractions 2, 3 and 4 with an ethanolic solution of picric acid there was obtained a crystalline picrate, 0.55 g.; after recrystallizations from benzene and ethanol, 0.14 g., m. p. 174–177°. This showed no depression on mixed melting point determination with the picrate of desformylmethoxymethyl*chano*dihydrostrychnane (see below).

Desformylmethoxymethyl*chano*dihydrostrychnane.— Methoxymethyl*chano*dihydrostrychnane (XIII) (0.25 g.) was refluxed for five hours with 15 cc. of 3 *N* sulfuric acid. After cooling, the solution was extracted with chloroform to remove any unchanged starting material. The aqueous solution was made basic with 10 cc. of concentrated ammonium hydroxide, causing the precipitation of a whitish oil. This was extracted with chloroform. The second chloroform extract was dried over sodium sulfate and evaporated to dryness. The residual red oil was boiled with ligroin (b. p. 70–90°). After concentrating the ligroin solution crystallization was induced by cooling in Dry Ice and scratching the sides of the vessel with a glass rod. However, this material was still gummy, and it was found better to remove all the ligroin, dissolve the oil in ethanol and treat the solution with picric acid in ethanol. This gave 0.11 g. of picrate, m. p. 172.5–174°. After recrystallizations from benzene and ethanol the bright yellow wooly needles melted at 176–178°. *Anal.* Calcd. for $C_{28}H_{32}O_{10}N_6$: C, 56.09; H, 5.55; N, 11.68. Found: C, 55.91; H, 5.86; N, 11.92.

The picrate was suspended in benzene and extracted with dilute ammonium hydroxide. The benzene solution on evaporation gave 60 mg. of colorless oil. This was crystallized from ligroin, 50 mg., m. p. 84.8–86°. After recrystallization from ligroin the white needles melted at 86.0–86.6°. *Anal.* Calcd. for $C_{22}H_{30}O_3N_2$: C, 71.32; H, 8.16; N, 7.56. Found: C, 70.80; H, 8.08; N, 7.66.

When 40 mg. of this base was warmed with 2 cc. of 2 *N* perchloric acid, a crystalline perchlorate precipitated on cooling, 40 mg., m. p. 195–201°. After recrystallization from absolute ethanol, the white needles melted at 244.5–245.5°. *Anal.* Calcd. for $C_{22}H_{31}O_7N_2Cl$: C, 56.10; H, 6.64; N, 5.95; Cl, 7.53. Found: C, 56.58; H, 6.86; N, 6.05; Cl, 7.29.

Formylation of Desformylmethoxymethyl*chano*dihydrostrychnane.— Desformylmethoxymethyl*chano*dihydrostrychnane (40 mg., m. p. 83–84°) was dissolved in 10 cc. of anhydrous formic acid[39] and 4 cc. of acetic anhydride. After refluxing for fourteen hours the volatile materials were removed *in vacuo*, and the residue was dissolved in benzene. The benzene solution was twice extracted with dilute hydrochloric acid and then with water. After drying over sodium sulfate the benzene was evaporated leaving a tan-colored oily residue, 10 mg. This was dissolved in a little benzene, treated with charcoal, filtered and diluted with petroleum ether (b. p. 30–60°). On standing the cloudy solution deposited rosette-shaped clumps of crystals, m. p. 160–161.5° after washing with fresh petroleum ether. A sample, mixed with some methoxymethyl*chano*dihydrostrychnane of m. p. 163–164.5°, had a melting point of 161–162°.

An earlier attempt to effect this reaction omitting the use of acetic anhydride resulted in the isolation only of unchanged starting material.

N-Formyl Determinations.—About 20 mg. of the compound to be analyzed was refluxed for one hour with 2 cc. of reagent grade methanol, 1 cc. of 5 *N* sodium hydroxide and 2 cc. of water. The mixture was diluted with 5 cc. of water and the methanol distilled off. After acidification with 1 cc. of 33% sulfuric acid distillation was continued, and the volatile acid in the distillate determined by titration with standard alkali. The distillate was collected in 20-cc. fractions, water being added to the reaction-mixture at intervals to maintain its volume. These fractions were titrated separately, and the process continued until there was detected only a small constant

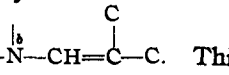
(39) Lorin, *Bull. soc. chim.*, [2] **5**, 10 (1866).

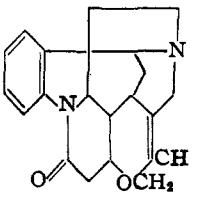
quantity of volatile acid consistent with that obtained from a blank determination.

The small volume of acid in the first fraction, and the constancy of the amount in successive fractions of distillate, led to the conclusion that hydrolysis of the amide linkage was occurring at the same time as the acid produced was being distilled.

When acidic hydrolysis was employed the sample was refluxed for two hours with 2 *N* sulfuric acid before distillation was started. Here again the collection of fractions of distillate was continued until they contained constant amounts of volatile acid of the same size as was found in a blank determination.

Summary

It has been shown that the *neo* bases derived from the strychnos alkaloids contain the part structure  . This demonstration resolves previous difficulties in the way of the acceptance of the structure (I) for strychnine. The general situation has now advanced to the point at which it is conclusive in favor of the expression (I), and the structure of the major strychnos alkaloids is regarded as established.



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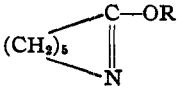
Chemical Reactions of Caprolactam

BY RICHARD E. BENSON AND THEODORE L. CAIRNS

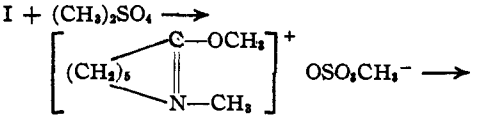
This paper reports the results of a general investigation of the chemistry of caprolactam with emphasis on the O-alkyl imino ethers and their reactions, and on nitrogen-substituted derivatives obtainable by alkylation and acylation. The general reactivity of caprolactam parallels that of related open-chain amides but several unusual transformations were observed and some discrepancies in the literature were clarified.

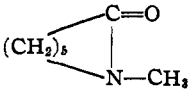
The preparation of O-methylcaprolactim (I) was accomplished by the direct action of dimethyl sulfate on caprolactam in benzene solution.[1a] Dur-



I, R = CH_3
II, R = C_2H_5

ing this preparative work, it was noticed that the proportion of N-methylcaprolactam formed along with the O-methylcaprolactim increased as the scale of the preparation was increased and that, in particular, the amount of N-methyl derivative formed was very much greater when all the dimethyl sulfate was added at once compared with the amount formed when a gradual addition over a long period of time was used. These observations lead to the hypothesis that dimethyl sulfate reacts with I to convert it to N-methylcaprolactam as shown in the equation





That this may actually be the case is demonstrated by the fact that treatment of O-methylcaprolactim in benzene solution with 0.1 mole equivalent of dimethyl sulfate brought about its conversion to N-methylcaprolactam in 80% yield. In addition, the action of excess dimethyl sulfate on the lactam gave the N-methyl derivative in 70% yield. The report[2] that the interaction of dimethyl sulfate and caprolactam leads only to the N-methyl derivative may well be accounted for by the assumption that a slight excess of the alkylating agent was used. O-Ethylcaprolactim (II)[1b] was prepared in an analogous fashion. It was found that heating caused rearrangement of both I and II to the corresponding N-alkyl compounds in a manner similar to that reported for open-chain imino ethers.[3]

O-Methylcaprolactim was found to be a water-insoluble basic material that could be converted by the action of boiling water into a mixture of caprolactam and ε-aminocaproic acid. Treatment of the imino ether with amines led to the corresponding amidines; these are listed in Table I. In the case of the unsubstituted amidine it was found that the action of ammonia on the imino ether was not a satisfactory preparative method, while the use of ammonium chloride readily yielded the desired amidine as the hydrochloride, in accord with the experience of Knorr[4]

(1) (a) Schlack, U. S. Patent 2,356,622. Other methods for the preparation of this and related imino ethers may be found in (b) French Patent 673,628; Schmidt and Zutavern, German Patents 532,969 and 531,403.

(2) Prochazka, *Chem. Listy*, **37**, 208 (1943); *C. A.*, **40**, 2113 (1946).

(3) Chapman, *J. Chem. Soc.*, 1992 (1925).

(4) Knorr, *Ber.*, **50**, 229 (1917).