TABLE VII

MISCELLANEOUS MONOMER–UREA MIXTURES

Monomer	Monomer vol., ml.	Urea, g.	Methanol, ml.	Temp. of complex formation, °C.	Time of complex formation, days	Product[a] weight, g.
Acrolein	2.0	2.0	0.05	−78	8	1.15
Perfluorobutadiene	2.0	2.0	.05	−78	5[b]	
Perfluorobutadiene	2.0	2.0	.05	−55	20[b]	
Ethylene oxide	2.0	2.0	.05	−78	5[b]	
Vinyl acetylene	2.0	2.0	.05	−78	10	0.001[c]
Allyl cyanide	2.0	2.0	.05	−78	10[b]	
Vinyl methyl ether	2.0	2.0	.05	−10	50	0
Vinyl bromide	2.0	5.5	.1	−10	3	0.008
Vinyl bromide	5.0	4.0	.1	−10	35	<.001
Vinyl bromide	5.0	4.0	0	−10	35	<.001
Propylene	3.0	2.0	0.05	−55	7[b]	
Propylene	4.0	2.0	.05	−71	30[b]	
Monoepoxybutadiene	1.0	1.25	.03	−10	8	0
Monoepoxybutadiene	1.0	1.25	.03	−55	8	0
Ethylene	[d]	2.0	[d]	−78	2[b]	
Cyclopropane	1.0	2.0	[e]	−25	2[b]	
Cyclopropane	2.5	2.0	0.04	−55	1	0

[a] The acetone-water insoluble product after irradiation of the complex at −78° with a 2-Mr. dose. [b] A complex did not form. [c] Melting point 135° dec. [d] Ethylene was bubbled through a suspension of urea in 5 ml. of isopropyl alcohol at −78° for 2.5 hours at a rate of 4 ml. per minute. [e] The solvent was 4 ml. of acetone and 3 ml. of water.

and constructive criticisms. Thanks are also due to Mrs. N. R. Young for technical assistance, Mr. J. S. Balwit for the irradiations, Mr. C. A. Hirt and Miss D. V. McClung for the infrared spectra and Mr. H. W. Middleton for the microanalyses.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, QUEEN MARY COLLEGE, UNIVERSITY OF LONDON, LONDON, ENG.]

New Heteroaromatic Compounds. Part VI. Novel Heterocyclic Compounds of Phosphorus

BY M. J. S. DEWAR[1] AND VED P. KUBBA[1]

RECEIVED FEBRUARY 27, 1960

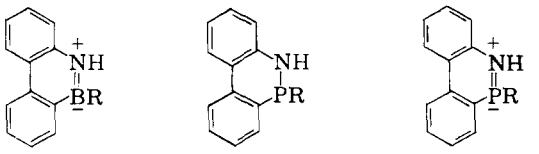
In continuation of previous work we have prepared a number of novel heterocyclic analogs of phenanthrene containing nitrogen and phosphorus in the 9- and 10-positions. The spectra of these compounds resemble those of analogous borazarophenanthrene derivatives, suggesting that they too may be aromatic.

Previous papers[2] of this series have described a number of heteroaromatic boron compounds, each being derived from a normal aromatic by replacement of one carbon atom by the isoelectronic ion B^- and a second by N^+ or O^+, giving a neutral molecule isoconjugate with the normal aromatic.

The equality of bond lengths in the phosphonitrile chloride trimer[3] and the general properties of the phosphonitrile chlorides suggest that these compounds are resonance stabilized. The resonance involves *d*-orbitals of the phosphorus atoms, the π-bonds being of $d\pi$–$p\pi$ type. It occurred to us that we might be able to prepare a series of aromatic phosphorus compounds analogous to the boron compounds we had previously prepared by replacing a carbon atom in an aromatic system by the ion P^- in the configuration $(1s)^2(2s)^2(2p)^6(3s)^2(3p)^3(3d)$; aromatic hydrocarbons contain π-MO's built up by the interaction of singly occupied $2p$-AO's of the individual carbon atoms and P^- with a singly occupied $3d$-AO might be a good substitute.

The situation is in fact more complicated than this simple argument implies since phosphorus has a number of *d*-orbitals available for π-bonding, and it seems very likely[4] that in the phosphonitrile chlorides each phosphorus atom uses two different *d*-orbitals to form $d\pi$–$p\pi$ bonds to the adjacent nitrogen atoms. In that case the phosphonitrile chlorides should not be classed as aromatic; for the π-electrons in them occupy isolated three-center π-MO's rather than the cyclic many-center π-MO's characteristic of aromatic systems.

Nevertheless it seemed of interest to prepare heterocyclic compounds of the type indicated above and to study their properties. The phenanthrene system was an obvious choice since we already had a number of analogous borazarophenanthrenes (I) to provide comparison spectra, etc., and since the synthetic difficulties were likely to be less.[2a] We therefore decided to prepare compounds of the type indicated in II; the relation of these to I is indicated by the possibility of writing dipolar resonance structures, *e.g.*, III, in which the double bond to phosphorus is a $d\pi$–$p\pi$ bond.



I II III

For reasons indicated above we decided to synthesize derivatives of 9,10-dihydro-9,10-azaphos-

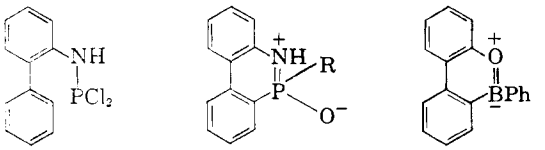
(1) Department of Chemistry, University of Chicago, Chicago, Ill.

(2) (a) M. J. S. Dewar, Ved P. Kubba and R. Pettit, *J. Chem. Soc.*, 3073 (1958); (b) 3076 (1958); (c) M. J. S. Dewar and R. Dietz, *ibid.*, 2728 (1959); (d) M. J. S. Dewar and Ved P. Kubba, *Tetrahedron*, **7**, 213 (1959); (e) M. J. S. Dewar and R. Dietz, *Tetrahedron Letters*, No. 14, 21 (1959); *J. Chem. Soc.*, 1344 (1960).

(3) L. O. Brockway and W. M. Bright, THIS JOURNAL, **65**, 1551 (1943).

(4) M. J. S. Dewar, E. A. C. Lucken and A. R. Whitehead, *J. Chem. Soc.*, 2423 (1960).

phaphenanthrene (II). Following the method used to prepare 10-chloro-10,9-borazarophenanthrene (I, R = Cl) we allowed 2-aminobiphenyl to react with phosphorus trichloride in dry benzene, hydrogen chloride being evolved. The crystalline product, probably N-(2-biphenylyl)-phosphoramidous dichloride (IV), was cyclized without purification by heating to 210–220° with a catalytic amount of aluminum chloride, giving 10-chloro-9,10-dihydro-9,10-azaphosphaphenanthrene (II, R = Cl) in good yield. The structure of this compound was indicated by elementary analysis, by the method of synthesis, by the fact that it could be sublimed at 180–190°(0.05 mm.)(indicating that it could not be dimeric or polymeric), and by the fact that on hydrolysis (see below) it gave no 2-amino-biphenyl (indicating that a phosphorus-carbon bond must have been formed).



IV V VI

Reaction of the chloro compound with phenylmagnesium bromide gave 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene (II, R = Ph) whose spectrum (Fig. 1) resembled that of 10-phenyl-10,9-borazarophenanthrene (I, R = Ph). This resemblance indicates that both compounds have similar electronic structures and that the phosphorus compound may, like the boron compound, show aromatic properties.

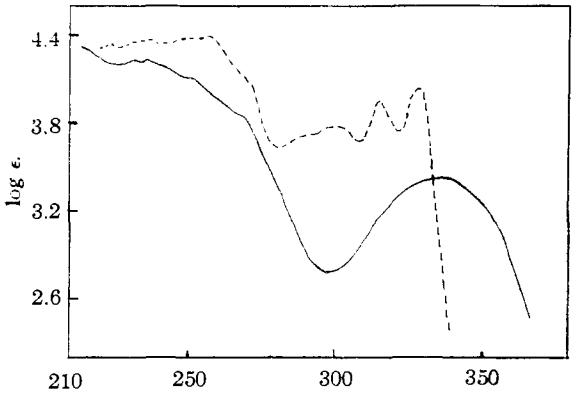


Fig. 1.—Spectra of 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene (——) and of 10-phenyl-10,9-borazarophenanthrene (. . . . . .).

The phosphorus compound was less stable to oxidation than the boron analog (I, R = Ph). On standing in air it was gradually converted to an oxidation product (A) analyzing as $C_{18}H_{14}O_2NP$. A second oxidation product (B) was also formed in small quantities when the preparation of II (R = Ph) was carried out in air; B analyzed as $C_{18}H_{14}ONP$. Unexpectedly B was formed in good yield when 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene was heated with bromobenzene and aluminum chloride (see below). The ultraviolet spectra of A and B were almost superposable

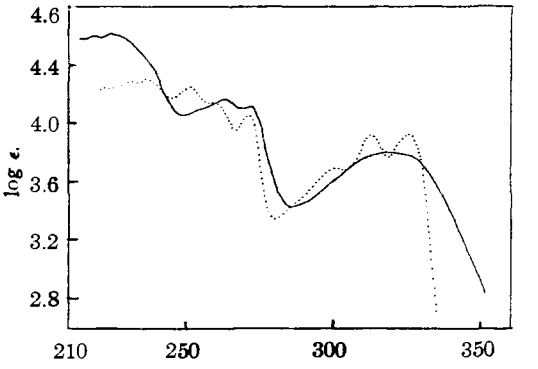


Fig. 2.—Spectra of 10-phenyl- or 10-phenoxy-9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxide(——) and of 10-hydroxy-10,9-borazarophenanthrene (. . . . . .).

and resembled (Fig. 2) that of 10-hydroxy-10,9-borazarophenanthrene (I, R = Ph), indicating that both contained the azaphosphaphenanthrene ring system intact. That they were not identical was indicated by a large depression of mixed m.p. and by their very different elementary compositions. It seems very likely that B is 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxide (V, R = Ph), its formation being analogous to the well-known oxidations of phosphines to phosphine oxides. The available evidence suggests that A must have been the corresponding 10-phenoxy derivative (V, R = OPh) although its formation by oxidation of II(R = Ph) seems surprising, and although attempts to hydrolyze A gave no recognizable products. If we have formulated A correctly, this unusual reaction would certainly imply an unusual resonance interaction in the dihydroazaphosphaphenanthrene ring.

Hydrolysis of the chloro compound II(R = Cl) took place very readily, giving a product which was at first formulated as 10-hydroxy-9,10-dihydro-9,10-azaphosphophenanthrene (II, R = OH). However the infrared spectrum showed no hydroxyl band and the ultraviolet spectrum was very similar (Fig. 3) to that of the phenoxyoxide (VII, R = OPh). The isomeric structure 9,10-dihydro-9,10-azaphosphophenanthrene 10-oxide (V, R = H) therefore seems more likely. This is not surprising. Hydroxy derivatives of trivalent phosphorus normally exist in the isomeric phosphine oxide form and here there are no special factors that favor a planar configuration of the phosphorus since only its *d*-orbitals are involved in the resonating system.

The oxide V(R = H) was not converted to 2-aminobiphenyl by boiling with strong alkali, but the spectrum in even dilute alkali differed markedly from that in alcohol (Fig. 3).

This suggested that the nitrogen–phosphorus bond had undergone hydrolysis, and indeed the solution gave a strong color on acidification, diazotization and coupling with β-naphthol, implying formation of a free amino group. The boron–oxygen bond in the boroxarophenanthrene system (2e) is stable to alkali.

When we tried to make 10-methyl-9,10-dihydro-9,10-azaphosphaphenanthrene (II, R = Me) from the corresponding chloro compound and

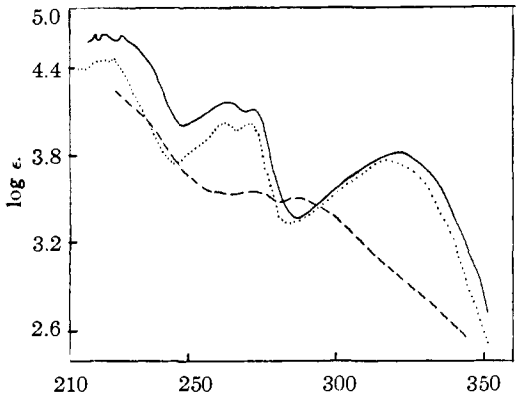


Fig. 3.—Spectra of 10-phenoxy-9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxide (——) and of 9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxide in alcohol (. . . . . .) and in 10% NaOH solution (--------).

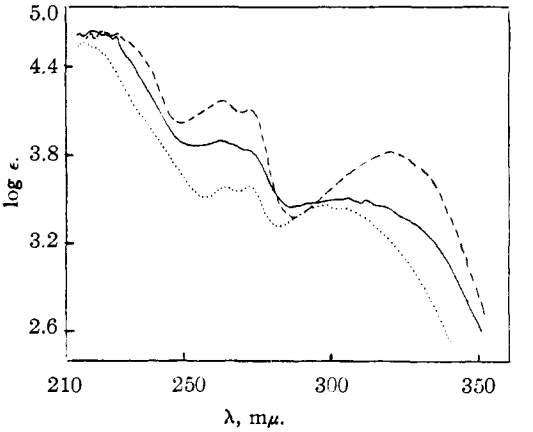
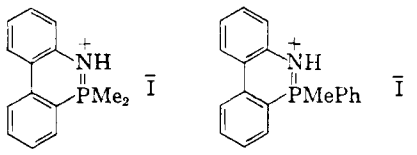


Fig. 4.—Spectra of 10-methyl- (. . . . . .) and 10-phenyl- (——) 9,10-dihydro-9,10-azaphosphaphenanthrene 10-methiodide and of 10-phenoxy-9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxide (--------).

methylmagnesium iodide we obtained instead a water-soluble compound which gave an intermediate precipitate with silver nitrate. We had prepared the Grignard reagent from an excess of methyl iodide and the yield of the new compound was improved when the product from the Grignard reaction was treated with excess methyl iodide before working up. This together with elementary analysis indicated that the compound was 10-methyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-methiodide (VII).



VII VIII

We likewise obtained 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-methiodide (VIII) by treating 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene (II, R = Ph) with methyl iodide. The ultraviolet spectra of these quaternary salts were similar to those of the 9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxides (Fig. 4). The structures of the iodides also were indicated by the n.m.r. spectrum of the dimethyl compound VII which showed only one methyl peak; if the compound had had one methyl attached to phosphorus and one to nitrogen it should have shown two distinct methyl peaks.

We also tried unsuccessfully to prepare 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-pheniodide by heating 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene with bromobenzene in presence of aluminum chloride, following the method of synthesis of quaternary aromatic phosphonium salts devised by Chatt and Mann[5]; the only product isolated (see above) was V (R = Ph).

Conclusions.—The novel heterocyclic compounds described in this paper seem to be of considerable theoretical interest. The similarity of their ultraviolet spectra to those of analogous boron compounds which are known to be aromatic suggests that they may be aromatic too. Further work is needed to clarify their electronic structures and chemical properties; this preliminary study suggests that such an investigation should prove profitable.

(5) J. Chatt and F. G. Mann, *J. Chem. Soc.*, 1192 (1940); F. G. Mann and I. T. Miller, *ibid.*, 3746 (1953).

Experimental

10-Chloro-9,10-dihydro-9,10-azaphosphaphenanthrene (II, R = Cl).—A solution of 2-aminobiphenyl (5 g.) in dry benzene (50 ml.) was added during 20 minutes with stirring to one of phosphorus trichloride (4.1 g.) in dry benzene (500 ml.). The mixture was boiled under reflux until evolution of hydrogen chloride ceased (6 hours) and evaporated, leaving a crystalline residue (6.8 g.). Anhydrous aluminum chloride (0.5 g.) was added and the mixture heated under reflux at 210–220° for 6 hours. The residue, which solidified on cooling, sublimed at 180–190° (0.05 mm.) in white needles (2.9 g., 42%), m.p. 132–134°, which apparently contained traces of a recalcitrant impurity.

Anal. Calcd. for $C_{12}H_9NPCL$: C, 61.7; H, 3.8; N, 5.9; Cl, 15.2; P, 13.3. Found: C, 60.7; H, 4.0; N, 6.2; Cl, 15.6; P, 12.4.

10-Phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene (II, R = Ph).—To a solution of crude (unsublimed) 10-chloro-9,10-dihydro-9,10-azaphosphaphenanthrene, prepared exactly as above, in dry methylene chloride at room temperature was added a solution of phenylmagnesium bromide prepared from magnesium (0.9 g.) and bromobenzene (5.8 g.) under nitrogen. After boiling under reflux for 6 hours and pouring on ice, evaporation of the organic layer and recrystallization of the residue from methylene chloride gave white rosettes (3.9 g., 58%), m.p. 178–179°.

Anal. Calcd. for $C_{18}H_{14}NP$: C, 78.5; H, 5.1; N, 5.1; P, 11.2; mol. wt., 275. Found: C, 78.5; H, 5.2; N, 5.2; P, 11.4; mol. wt., (by Rast method), 259.

10-Phenoxy-9,10-dihydro-9,10-azaphosphaphenanthrene-10-Oxide (V, R = OPh).—After standing in air for 6 weeks 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene was converted to V(R = OPh) which crystallized from methylene chloride in colorless prisms, m.p. 288–289°. The same oxidation product was obtained in varying amounts as a by-product if the preparation of II(R = Ph) was carried out in air.

Anal. Calcd. for $C_{18}H_{14}O_2NP$: C, 70.4; H, 4.6; N, 4.6; P, 10.1. Found: C, 70.7; H, 4.8; N, 4.8; P, 10.7.

10-Phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-Oxide (V, R = Ph).—A mixture of 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene (1 g.), anhydrous aluminum chloride (0.97 g.) and bromobenzene (1.15 g.) was heated in a current of nitrogen at 210–220° for 4 hours. Addition of water to the cold product and extraction with benzene gave VII(R = Ph) which crystallized from alcohol in

prisms (0.42 g., 40%), m.p. 283°, mixed m.p. with 10-phenoxy-9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxide, 244–250°. The same compound was isolated in some cases from the mother liquors from the recrystallization of II (R = Ph).

Anal. Calcd. for $C_{18}H_{14}ONP$: C, 74.2; H, 4.8; N, 4.8; P, 10.7. Found: C, 74.3; H, 4.9; N, 5.0; P, 10.9.

9,10-Dihydro-9,10-azaphosphaphenanthrene 10-Oxide.—Crude 10-chloro-9,10-dihydro-9,10-azaphosphaphenanthrene (6 g.) was shaken with water and methylene chloride. The residue from evaporation of the organic layer crystallized from methylene chloride in stout white prisms (3.9 g., 71%), m.p. 193–194°.

Anal. Calcd. for $C_{12}H_{10}ONP$: C, 67.0; H, 4.6; N, 6.5; P, 14.4. Found: C, 67.1; H, 4.6; N, 6.5; P, 14.0.

10-Methyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-Methiodide (VII).—To a solution of crude 10-chloro-9,10-dihydro-9:10-azaphosphaphenanthrene, prepared from 2-aminobiphenyl (8.2 g.), in methylene chloride (500 ml.) was added one of methylmagnesium iodide, prepared from magnesium (1.8 g.) and methyl iodide (10.3 g.) in ether. Methyl iodide (10.5 g.) was then added and the solution boiled under reflux for 8 hours. Ice was added and the residue from evaporation of the organic layer crystallized from methylene chloride in light yellow prisms (11.2 g., 65%), m.p. 230–233° dec.

Anal. Calcd. for $C_{14}H_{15}NPI$: C, 47.3; H, 4.2; N, 3.9; P, 8.7; I, 35.8. Found: C, 47.5; H, 4.3; N, 3.9; P, 9.0; I, 35.4.

10-Phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene Methiodide (VIII).—A solution of 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene (1 g.) and methyl iodide (1.9 g.) in dry benzene (100 ml.) was boiled under reflux for 6 hours when X separated in almost theoretical yield. It crystallized from methylene chloride in light yellow prisms, m.p. 214°.

Anal. Calcd. for $C_{19}H_{17}NPI$: C, 54.6; H, 4.1; N, 3.4; P, 7.4; I, 30.4. Found: C, 54.7; H, 4.1; N, 3.3; P, 7.2; I, 30.1.

Acknowledgments.—We are grateful to Albright and Wilson Ltd. for the award of a Fellowship to V. P. K. and to Dr. P. M. Maitlis for helpful discussion.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY]

Some Hypotensive Amino Steroid Glycosides[1]

BY R. A. LUCAS, D. F. DICKEL, R. L. DZIEMIAN, M. J. CEGLOWSKI, B. L. HENSLE AND H. B. MACPHILLAMY

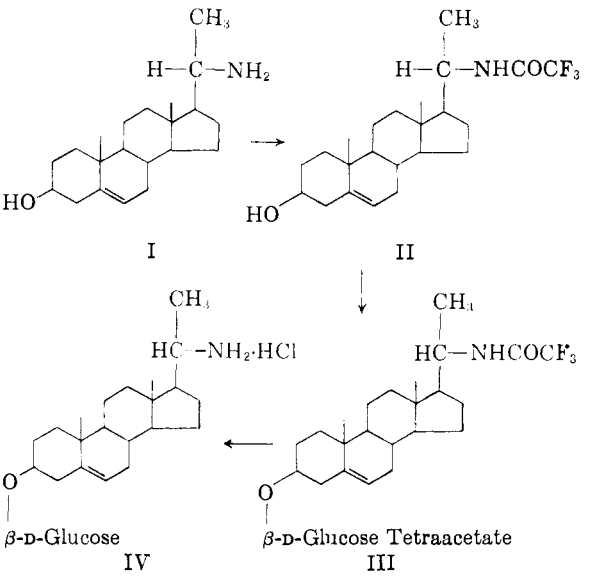
RECEIVED FEBRUARY 25, 1960

A new hypotensive amino steroid glycoside has been isolated from the roots of *Conopharyngia pachysiphon*. Degradation experiments have demonstrated that this substance is 20α-amino-5-pregnen-3β-yl β-D-glucoside hydrochloride. This has been confirmed by synthesis and a number of related compounds have been prepared. Several of these substances have shown considerable hypotensive activity on intravenous administration.

In a previous communication[2] we reported the isolation of the substance responsible for the hypotensive action of a methanol extract of the roots of *Conopharyngia pachysiphon*.[3] It was found to have the empirical formula $C_{27}H_{45}NO_6 \cdot HCl$. Acid hydrolysis yielded two aglycons which were identified as 20α-amino-5-pregnen-3β-ol and its dehydration product, 3,5-pregnadiene-20α-amine. The sugar moiety also resulting from this hydrolysis was shown to be D-glucose. On the basis of these data the active substance was assigned the structure 20α-amino-5-pregnen-3β-yl β-D-glucose hydrochloride (IV). This was confirmed by the synthesis outlined in chart I.

In spite of the high intravenous activity of IV (Table I) it demonstrated little if any hypotensive effect on oral administration. This fact led us to synthesize a number of related amino steroid glycosides in the hope that an effective orally active substance could be produced. In general they were prepared by suitable modification of the above synthetic scheme and the results are tabulated in Table I. It is evident that in no case was our goal achieved although several of the products were quite active when given intravenously.

CHART I



Further paper chromatographic study of *C. pachysiphon* root and bark extracts has demonstrated the presence of several other alkaloids. However, none of these on preliminary examination have shown activity nor do they seem to resemble chemically those recently reported from *C. durissima*.[4] They are now under further investigation.

(1) Presented in part before the Division of Medicinal Chemistry at the Atlantic City Meeting of the American Chemical Society, September 15, 1959.

(2) D. Dickel, R. Lucas and H. MacPhillamy, THIS JOURNAL, **81**, 3154 (1959).

(3) Prof. F. J. Simmonds, Imperial College of Tropical Agriculture, Trinidad, B.W.I., has recently informed us that this material originally came from the Island of Principé, Portugese West Africa.

(4) U. Renner, D. A. Prins and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1572 (1959).