1,3,2-Diazaphosphorinane 2-Oxides. II.[1] Synthesis of Some 1,3-Bis(aralkyl)-2-(N-arylamino)-1,3,2-diazaphosphorinane 2-Oxides[2]

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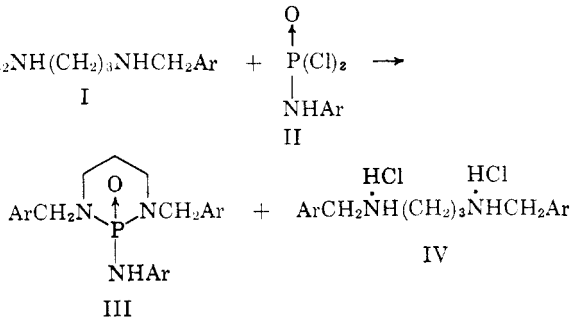
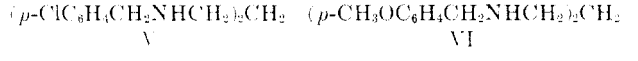
Nine 1,3-bis(aralkyl)-2-(N-arylamino)-1,3,2-diazaphosphorinane 2-oxides (III) have been synthesized as part of a study of 1,2,3-substituted 1,3,2-diazaphosphorinane 2-oxides as antitumor agents. Heterocyclic phosphorus compounds of this type, that is, with aralkyl substituents on the 1,3-nitrogen atoms, have not been previously reported.

These compounds were synthesized by allowing 2 moles of secondary diamine I to react, in benzene, with 1 mole of a phosphoramidic dichloride II. This furnishes 1 mole of the desired product III and 1 mole of the dihydrochloride of the starting diamine IV.



Two different diamines were employed as intermediates in the preparation of the compounds listed in Table I. They were N,N′-bis(*p*-chlorobenzyl)-1,3-diaminopropane (V) and N,N′-bis(*p*-methoxybenzyl)-1,3-diaminopropane (VI). Their synthesis, through the reduction of the corresponding benzylidene di-Schiff base, has been reported.[4]



Biological Results.—The compounds listed in Table I have all been screened for antitumor activity against Carcinoma 755, Sarcoma 180, Leukemia 1210, and a cell culture system.[5] The results of these tests indicate that the compounds have no cytotoxic activity.

Experimental

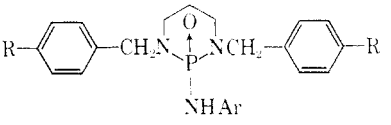
N,N′-Bis(*p*-chlorobenzyl)-1,3-diaminopropane (V) and N,N′-Bis(*p*-methoxybenzyl)-1,3-diaminopropane (VI).—The preparation of these intermediates, and other similar secondary 1,3-diamines, has been reported.[4,6]

N-Arylphosphoramidic Dichlorides.—These intermediates were prepared by refluxing phosphorus oxychloride with the arylamine hydrochloride, a method previously described by Michaelis and Schulze.[7]

1,3-Bis(aralkyl)-2-(N-arylamino)-1,3,2-diazaphosphorinane 2-Oxides (Table I).—The preparation of these compounds is typified in the synthesis of 2-(*m*-toluidino)-1,3-bis(*p*-chlorobenzyl)-1,3,2-diazophosphorinane 2-oxide. A 64.4-g. (0.2-mole) sample of N,N′-bis(*p*-chlorobenzyl)-1,3-diaminopropane was dissolved in 500 ml. of dry benzene. This solution was stirred and a solution of 22.4 g. (0.1 mole) of N-(*m*-tolyl)phosphoramidic dichloride in 500 ml. of benzene was added over a 2-hr. period. The temperature of the reaction mixture remained at 30–35° during this time. The mixture was stirred for an additional 0.5 hr. and then brought to reflux for 15 min. It was filtered through a Büchner funnel, while hot, to remove the precipitated diamine dihydrochloride. The benzene was removed from the filtrate with a rotary evaporator on a 60° water bath. A perfectly clear, light yellow gum was left. Acetonitrile (20 ml.) was added to the gum, and the mixture was stirred well. This caused the formation of a white solid and the stirring was continued until there was no evidence of remaining gum. The mixture was cooled, then the solid was collected and dried. There was obtained 19.65 g. of material, m.p. 138.5–148.0° (uncor.). An additional 1.62 g. of white solid, m.p. 137–148° (uncor.), was obtained from the mother liquor by evaporation

TABLE I

1,3-BIS(ARALKYL)-2-(N-ARYLAMINO)-1,3,2-DIAZAPHOSPHORINANE 2-OXIDES



Ar	R	Yield (% pure)	M.p., °C. (cor.)	Nitrogen, %[b] Calcd.	Nitrogen, %[b] Found
p-$CH_3OC_6H_4$[a]	CH_3O	26	154.5–155.5	8.86	8.73
C_6H_5[b]	CH_3O	37	154.4–155	9.32	9.51
p-ClC_6H_4[a,c]	CH_3O	21	188–189	8.65	8.72
p-$CH_3OC_6H_4$[b]	Cl	15	143–144	8.57	8.65
C_6H_5[d]	Cl	20	128.5–130	9.13	9.07
p-ClC_6H_4[d]	Cl	17	166.5–168	8.50	8.20
p-$CH_3C_6H_4$[e]	Cl	29	164.5–166	8.87	8.69
m-$CH_3C_6H_4$[f]	Cl	41	150–150.5	8.87	9.04
o-ClC_6H_4[f,g]	Cl	49	86.5–87.5	8.50	8.37

[a] Recrystallized from absolute EtOH. [b] Recrystallized from EtOAc. [c] Mol. wt.: calcd., 486; found, 510 (Rast-camphor by Bernhardt, Mulheim). [d] Recrystallized from 80% CH_3CN–20% absolute EtOH. [e] Recrystallized from CH_3CN–MeOH. [f] Recrystallized from CH_3CN. [g] Mol. wt: calcd., 495; found, 516 (Rast-camphor by Bernhardt, Mülheim). [h] Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

(1) Paper I: J. H. Billman, J. L. Meisenheimer, and R. A. Awl, *J. Med. Chem.*, **7**, 366 (1964).

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(3) National Institutes of Health Fellow, 1961–1963.

(4) J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **6**, 682 (1963).

(5) Antitumor screening was accomplished by the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md.

(6) J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **7**, 115 (1964).

(7) A. Michaelis and G. Schulze, *Ber.*, **26** 2937 (1893).

of one-half of the solvent and subsequent cooling. The total crude yield was, therefore, 21.27 g. (45.0%). The crude material was recrystallized twice from acetonitrile, and 19.3 g. (41%) of pure product, m.p. 150.0–150.5° (cor.), was obtained.

Anal. Calcd. for $C_{24}H_{26}Cl_2N_3OP$: N, 8.87. Found: N, 9.04.

Acknowledgments.—The authors wish to acknowledge the assistance of Mr. Richard A. Awl and Mr. Stephen C. Johnson in preparing some of the intermediates. Thanks are also due Drs. H. W. Bond, R. B. Ross, and J. E. Leiter of the CCNSC for their cooperation and for making the screening data available.

Hexahydro-11H-pyrrolo[2,1-*a*]-β-carbolines and Tetrahydro-13H-isoindolo[1,2-*a*]-β-carbolines

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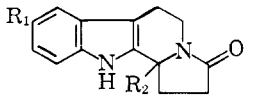
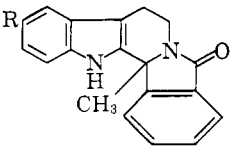
In previous work[2] the preparation of 1-substituted β-carbolines from DL-tryptophan and tryptamines and various phthaldehydic acids for testing as hypotensive agents has been described. The reaction has now been extended to various tryptamines and γ-keto acids. This type of reaction has, thus far, been reported only for cyclohexanone-2-acetic acid and tryptamine,[3] and α-ketoglutaric acid and 5-methoxytryptamine.[4]

The condensation of tryptamine, 5-methoxytryptamine, and 5-chlorotryptamine, with levulinic acid in refluxing technical xylene and with β-benzoylpropionic acid in refluxing *p*-cymene (b.p. 175°), gave the substituted 1,2,3,5,6,11b-hexahydro-3-oxo-11H-pyrrolo-[2,1-*a*]carbolines (Ia–f) in yields of 40–70%. The corresponding condensation of the three amines with *o*-acetylbenzoic acid in xylene gave higher yields of the substituted 5,7,8,13b-tetrahydro-5-oxo-13H-isoindolo-[1,2-*a*]-β-carbolines (IIa–c), required less vigorous





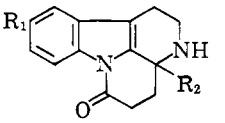
Ia, R_1 = H; R_2 = CH_3
b, R_1 = H; R_2 = C_6H_5
c, R_1 = OCH_3; R_2 = CH_3
d, R_1 = OCH_3; R_2 = C_6H_5
e, R_1 = Cl; R_2 = CH_3
f, R_1 = Cl; R_2 = C_6H_5

IIa, R = H
b, R = OCH_3
c, R = Cl

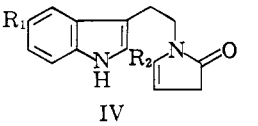
condition, and gave cleaner products than the condensation involving levulinic and β-benzoylpropionic acids. The water formed had to be removed to obtain a successful reaction and amounted to 2 moles.

An extensive investigation to obtain optimum conditions for the condensation was not carried out, but when the product yield was low, the time and/or temperature of the reaction were increased until no significant improvement in the yield was noted.

The position of the lactam ring was demonstrated by the lack of basicity of the condensation products. Lactam formation at the indole nitrogen would give the pyrido[1,2,3-*l*,*m*]-β-carboline (III), which would form salts with dilute acids. The indole nitrogen will



III



IV

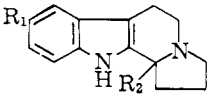
not form salts under these conditions. Structures I and II are further substantiated by the ultraviolet spectra which are similar to that of indole derivatives and unlike the spectra of N-acylindoles.[5]

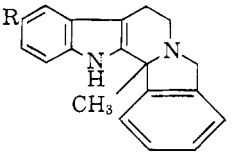
Compounds I and II did not give the Ehrlich's test in agreement with their β-carboline structure.

A precursor of this structure (IV) was isolated when β-benzoylpropionic acid and tryptamine were refluxed together for 8 hr. in toluene. The product (IV) after extensive purification gave a positive Ehrlich test and showed infrared bands at 1680 and 1645 cm.$^{-1}$ corresponding to the lactam carbonyl and enamine absorptions, respectively.

The same condensation in Butyl Cellosolve gave the lactam (Ib) and only small amounts of IV.

The lactams I and II were reduced to the corresponding tertiary amines V and VI with lithium aluminum hydride in 46–81% yields. These compounds (V and VI) were sensitive to air and precautions against oxidation were necessary to obtain good yields.





Va, R_1 = H; R_2 = CH_3
b, R_1 = H; R_2 = C_6H_5
c, R_1 = OCH_3; R_2 = CH_3
d, R_1 = OCH_3; R_2 = C_6H_5
e, R_1 = Cl; R_2 = CH_3
f, R_1 = Cl; R_2 = C_6H_5

VIa, R = H
b, R = OCH_3
c, R = Cl

The tertiary amine structure (Vc) was confirmed further by forming the methiodide; only one methyl group was introduced.

In rat dose range studies, compounds Ic and Ie in a 300-mg./kg. (*p.o.*) dose produced a moderate decrease in motor activity. Moderate hypersensitivity and slight hypertonicity were also observed in the rats treated with compound Ie. The remaining lactams in the series I and II produced no overt effects at dosage levels of 200–300 mg./kg.

Compound Ia in oral doses up to 300 mg./kg. did not produce ptosis or depletion of adrenal catechol amines in mice and hence does not resemble reserpine in these actions.

At oral doses of 200–300 mg./kg. in the rat, compounds Vb, Vd, and VIb produced signs of central stimulation. Convulsions occurred in the animals treated with similar doses of the other members of series V and VI.

(1) (a) Abstracted in part from the Ph.D. Thesis of J. D. Nordstrom, February 1963. (b) National Science Foundation Predoctoral Fellow, 1960–1962.

(2) S. Wawzonek and G. E. Nelson, *J. Org. Chem.*, **27**, 1377 (1962).

(3) A. Mondon and G. Hasselmeyer, *Chem. Ber.*, **92**, 2552 (1959).

(4) R. G. Taborsky and W. M. McIssac, *J. Med. Chem.*, **7**, 135 (1964).

(5) M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960).