TABLE I

Phosphate	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-Bromobenzyl[a] ammonium	97.2[b]	217[c]	$C_7H_{11}NO_4PBr$	29.6	28.9	3.9	3.8	4.9	5.3
p-Bromobenzyl dibrucine		134–135	$C_{53}H_{60}O_{12}N_4PBr$					5.3	5.3
p-Chlorobenzyl[d] ammonium	94.0	210[c]	$C_7H_{11}NO_4PCl$	35.5	35.5	4.6	4.6	5.85	5.9
p-Chlorobenzyl[e]		126–127	$C_7H_8O_4PCl$	37.8	37.1	3.6	3.8	4.9	5.3
p-Chlorobenzyl[f] dibrucine		137–137	$C_{53}H_{60}O_{12}N_4PCl$					5.5	5.5

[a] Contaminated with a small amount of the diammonium salt. [b] Crude material calculated as monoammonium salt. [c] Corrected. [d] R_f values: A, 0.76; B, 0.91; C, 0.80. [e] Calcd. Cl, 15.9; found Cl, 15.8. [f] Hygroscopic.

200 ml. of water) at 50–60°. Stirring was continued until all the oily substance had disappeared. The solution was then cooled, strongly acidified with sulfuric acid and extracted with ether. The ethereal extract was dried with sodium bromide, concentrated to a thick sirup and taken up in absolute ethanol. Concentrated aqueous ammonia was added. After cooling the diammonium salt was filtered and washed with ethanol; yield 60.5 g., m.p. 164–169° dec.; R_f value: A, 0.76; C, 0.73.

Anal. Calcd. for $C_6H_{18}N_2O_4P$: N, 13.4. Found: N, 13.2.

The diammonium salt was dissolved in a minimum amount of water, acidified with sulfuric acid, and extracted with ether. Excess aqueous cyclohexylamine was added to the concentrated ether extract and the separated dicyclohexylamine salt was filtered with suction and recrystallized from hot water; m.p. 214–215° (cor.).

Di-*p*-halobenzyl Hydrogen Phosphate (IVa, b).—Di-*p*-halobenzyl phosphite[12] was suspended in carbon tetrachloride (50 ml.), and sulfuryl chloride (1.7 ml.) was added to the cooled solution (about 15°) with shaking. The clear solution was allowed to stand for 30 minutes at room temperature, and then concentrated *in vacuo*. Acetone (100 ml.) and water (100 ml.) was added in one portion. After 3 hours, water (100 ml.) was added gradually and crystals separated. Almost all the acetone was removed under reduced pressure and the resultant crystals were filtered with suction. IVa was obtained as long needles, m.p. 156° reported[1] 155–156°); R_f: A, 0.97; B, 0.88. The crude IVb (m.p. 134°, yield 82.2%) upon recrystallization from aqueous ethanol gave the same m.p. (136°) as an authentic specimen; R_f: A, 0.95; B, 0.91; C, 0.87.

p-Halobenzyl Dihydrogen Phosphate (Va, b).—The crude IVb (2.0 g.) was dissolved in 25 ml. of ethoxyethanol (saturated with lithium chloride); IVa (2.0 g.) was dissolved in 20 ml. of ethoxyethanol (saturated with lithium chloride). The solution was heated for 1.5 hours at 120°,[13] acidified with sulfuric acid and extracted with ether. The ether was removed from the extract, and ethanol (50 ml.) and concentrated ammonia (5 ml.) added. The separated monoammonium salt was filtered with suction, washed with ethanol, and dried over phosphorus pentoxide *in vacuo*. The analytical results are reported in Table I.

N-Methylmorpholine on Di-*p*-bromobenzyl Phosphate.—Di-*p*-bromobenzyl phosphate (0.6 g.) in N-methylmorpholine (1 ml.) was heated at 105° for 3 hours; the mixture was acidified with dilute sulfuric acid and extracted with ether. The ethereal extract was concentrated under reduced pressure, and chromatographed. A small spot of the starting material (R_f: A, 0.97) and a small but distinct spot of mono-*p*-bromobenzyl phosphate (R_f: A, 0.79) were identified.

Reaction of *p*-Chlorobenzyl Alcohol and Phosphorus Oxychloride.—A mixture of *p*-chlorobenzyl alcohol (22.7 g., 1 mole) and pyridine (12.6 g., 1 mole) was added dropwise to a stirred solution of phosphorus oxychloride (24.4 g., 1 mole) in ether (10 ml.) at about 10°; stirring was continued for 20 minutes after the addition was complete. The reaction mixture was washed with dilute sulfuric acid (40 ml.), dried with calcium chloride, and concentrated under reduced pressure; 23.1 g. (90%), m.p. and mixed m.p. with authentic *p*-chlorobenzyl chloride 28°.

(12) Bromobenzyl compound, 8.2 g.; chlorobenzyl, 6.4 g.

(13) After a few minutes heating the fine white needles of the lithium salt of the starting material, which began to separate, disappeared and a yellow amorphous solid was deposited. Heating of IVb to 100° for 2 hours resulted in a poor yield of the desired product.

ANJÔ, AICHI-KEN, JAPAN

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES, THE LUBRIZOL CORPORATION]

The Preparation and Reactions of Diphenylphosphinous Chloride

BY CARL STUEBE, W. M. LESUER AND G. R. NORMAN

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A new preparation of diphenylphosphinous chloride, based on the reduction of diphenylphosphoranetrioic trichloride with elemental phosphorus, is described. Certain esters of the diphenylphosphinate and phosphinite type, as well as phosphines and their oxidation products, derived from diphenylphosphinous chloride are reported.

The preparation of diphenylphosphinous chloride has been a subject of investigation in several laboratories.[1] The best methods developed previously are outlined in the following reactions. Yields of the desired product are relatively low in all cases.

$$C_6H_5PCl_2 + (C_6H_5)_2Hg \longrightarrow (C_6H_5)_2PCl + C_6H_5HgCl^{1a} \quad (1)$$

$$C_6H_5H + PCl_3 \xrightarrow{AlCl_3} (C_6H_5)_2PCl + C_6H_5PCl_2 + HCl^{1b} \quad (2)$$

$$(C_6H_5)_3PCl_2 \xrightarrow{\text{distn.}} (C_6H_5)_2PCl + C_6H_5Cl^{1c} \quad (3)$$

(1) (a) F. G. Mann and I. T. Millar, *J. Chem. Soc.*, 4453 (1952); (b) G. M. Kosolapoff and W. F. Huber, THIS JOURNAL, **69**, 2020 (1947); (c) A. Michaelis and H. Soden, *Ann.*, **229**, 303 (1885).

In reaction (2) above the diphenylphosphinous chloride was not isolated, but was used directly in the formation of an ester, following breakdown of the aluminum chloride complex.

A new method has been developed for the preparation of diphenylphosphinous chloride in good yield, utilizing the readily available diphenylphosphinodithioic acid as a starting material. The preparation of diphenylphosphinodithioic acid from the reaction of phosphorus pentasulfide and benzene in the presence of aluminum trichloride has been reported recently.[2] Dried crude diphenylphosphinodithioic acid obtained after hydrolysis of the reac-

(2) W. A. Higgins, P. W. Vogel and W. G. Craig, THIS JOURNAL, **77**, 1864 (1955).

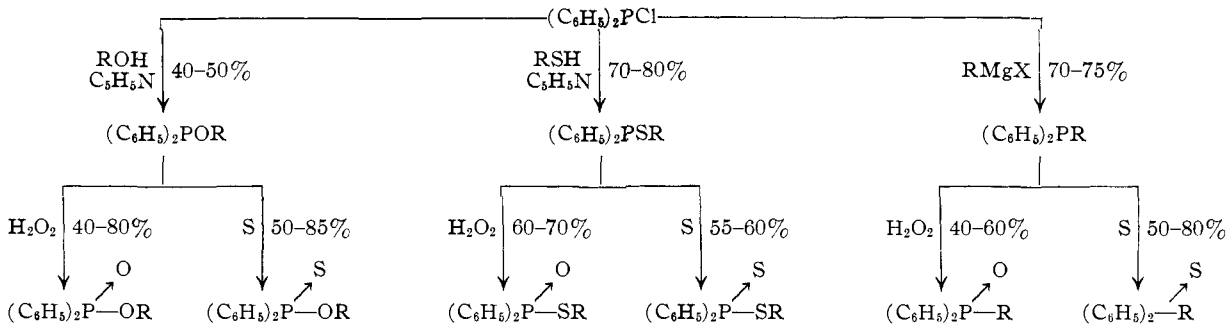

Fig. 1.—Reaction methods.

tion mixture is satisfactory as a starting material in the preparation of diphenylphosphinous chloride. Chlorination of this acid in benzene at 30–40° yields diphenylphosphoranetrioic trichloride and sulfur chlorides. The diphenylphosphoranetrioic trichloride, after removal of the sulfur halide, is treated with elemental red phosphorus in petroleum ether, yielding diphenylphosphinous chloride and phosphorus trichloride. Phosphorus trichloride codistils with petroleum ether as the temperature is increased and the product is readily purified by fractionation. The method affords overall yields of 70% of theory, based on starting diphenylphosphinodithioic acid.

$$(C_6H_5)_2PS_2H + 3Cl_2 \xrightarrow{\text{benzene}} (C_6H_5)_2PCl_3 + S_2Cl_2 + HCl$$

$$3(C_6H_5)_2PCl_3 + 2P \xrightarrow[70\text{–}200°]{\text{pet. ether}} 3(C_6H_5)_2PCl + 2PCl_3$$

Walsh, *et al.*,[3] recently reported a very similar reduction, that of the PCl_5–styrene reaction product with yellow phosphorus (iodine catalyst) yielding styrylphosphonous dichloride as the product. In the present work, red phosphorus has been chosen as the most desirable allotrope, although both the red and yellow forms give the same product. Red phosphorus can be employed in excess in the reaction with diphenylphosphoranetrioic trichloride, and the unreacted phosphorus removed by filtration. No fire hazard or phosphorus codistillation problem is present during fractionation of the product. The use of excess yellow phosphorus in a similar reduction leads to purification problems, since the excess yellow phosphorus is soluble in the final reaction mixture. The presence of elemental yellow phosphorus in a mixture to be fractionated leads to frequent fires, a contaminated product, or both. If a lower than stoichiometric amount of yellow phosphorus is employed, there is the problem of separating diphenylphosphinous chloride from the starting material, diphenylphosphoranetrioic trichloride. The one known advantage of utilizing yellow phosphorus, that of allowing a lower reaction temperature, appears to be definitely overshadowed by the disadvantages in its use in this particular application.

The diphenylphosphinous chloride was employed as an intermediate in the preparation of a series of phosphorus compounds as follows: (a) phosphines; (b) phosphine oxides and sulfides; (c) diphenylphosphinites and diphenylphosphinothioite esters; and (d) diphenylphosphinate, diphenylphosphinothiolate, diphenylphosphinothionate, and diphenylphosphinodithioate esters. The reaction methods are outlined in Fig. 1.

The following comments on the methods utilized are in order.

Phosphines.—Diphenylphosphinous chloride reacts readily with Grignard reagents to give tertiary phosphines in good yield.

Phosphinite and Phosphinothioite Esters.—In the presence of tertiary amines, alcohols and mercaptans react readily with diphenylphosphinous chloride yielding the corresponding phosphinite and phosphinothioite esters.[4] The relatively low yield of phosphinite esters is probably due to a large extent to their facile isomerization to the corresponding tertiary phosphine oxide, and to a lesser extent to hydrolysis and subsequent oxidation of the hydrolysis product to diphenylphosphinic acid. This isomerization is a much greater problem with the oxygen-containing esters than with the sulfur-containing esters. In the reaction of *n*-hexyl bromide with *n*-hexyl diphenylphosphinite, a 74% yield of the corresponding phosphine oxide, hexyldiphenylphosphine oxide, was obtained. No phosphine sulfide was isolated in a similar reaction of *n*-hexyl bromide with hexyl diphenylphosphinothioite.

Oxidations and Sulfurizations.—Phosphines, phosphinite esters and phosphinothioite esters were oxidized with hydrogen peroxide or sulfurized with elemental sulfur[5] to yield tertiary phosphine oxides and sulfides, and a series of phosphinate, phosphinothiolate, phosphinothionate and phosphinodithioate esters.

Yields, physical constants and analyses of the products obtained are reported in Table I.

Experimental[6,7]

Diphenylphosphinous Chloride.—Crude diphenylphosphinodithioic acid[2] (500 g., 2 moles) was dissolved in 500 ml. of benzene and the stirred solution held at 25–50° (cold water-bath) during the addition of 477 g. (6.3 moles) of chlorine gas (required four hours). After the chlorination was completed, 400 ml. of petroleum ether (80–100°) was added to the stirred suspension to complete precipitation of the diphenylphosphoranetrioic trichloride. The crystalline

(3) E. N. Walsh, T. M. Beck and W. H. Woodstock, "Abstract of Papers," 125th Meeting, American Chemical Society, Kansas City, Mo., p. 2N.

(4) A. E. Arbuzov and A. I. Razumov, *Izvest. Akad. Nauk S.S.S.R., o. kh. n.*, 167 (1945).

(5) F. G. Mann and J. Watson, *J. Org. Chem.*, **13**, 502 (1948).

(6) Yields, physical constants and analyses of the products obtained are reported in Table I.

(7) All melting points are uncorrected.

TABLE I

Compound	Yield, %	B.p. °C.	Mm.	M.p., °C.	$n^{20}D$	d^{20}_4	P, % Found	P, % Theory	S, % Found	S, % Theory
$(C_6H_5)_2$P-*n*-hexyl	71	136–141	0.2		1.5766	0.9989	11.2	11.5		
$(C_6H_5)_2$P-*n*-octyl	75	178–179	1.4		1.5655	0.9791	10.3	10.38		
$(C_6H_5)_2$(*n*-hexyl)PO	44			61–62	....	....	10.72	10.82		
$(C_6H_5)_2$(*n*-octyl)PO	52			64–65	....	....	9.5	9.85		
$(C_6H_5)_2$(*n*-hexyl)PS	52			51–52	....	....	10.05	10.24	10.8	10.6
$(C_6H_5)_2$(*n*-octyl)PS	79			14–16	1.5862	1.0473	9.25	9.37	9.57	9.71
$(C_6H_5)_2$PO-*n*-hexyl	49	138–141	0.3		1.5608	1.0140	10.54	10.82		
$(C_6H_5)_2$PO-*n*-octyl	40	156–162	.2		1.5508	1.0066	9.45	9.85		
$(C_6H_5)_2$PS-*n*-hexyl	80	163–165	.3		1.5988	1.0776	10.03	10.24	10.45	10.6
$(C_6H_5)_2$PS-*n*-octyl	71	185–188	.3		1.5828	1.0269	9.38	9.37	9.47	9.71
$(C_6H_5)_2$P(O)O-*n*-hexyl	80	161–165	.1		1.5449	1.0761	9.84	10.26		
$(C_6H_5)_2$P(O)O-*n*-octyl	36	177–182	.2		1.5330	1.0384	9.06	9.4		
$(C_6H_5)_2$P(O)S-*n*-hexyl	62	169–171	.075		1.5800	1.1003	9.5	9.73	9.74	10.07
$(C_6H_5)_2$P(O)S-*n*-octyl	67	197–200	.3		1.5700	1.0702	8.7	8.94	9.1	9.26
$(C_6H_5)_2$P(S)O-*n*-hexyl	54	180–183	.35		1.5792	1.0856	9.44	9.73	10.05	10.07
$(C_6H_5)_2$P(S)O-*n*-octyl	82	180–185	.2		1.5658	1.0521	8.78	8.94	9.02	9.26
$(C_6H_5)_2$P(S)S-*n*-hexyl	60			46–47	....	....	9.65	9.26	19.02	19.17
$(C_6H_5)_2$P(S)S-*n*-octyl	56	195–200	.06		1.5946	1.0866	8.22	8.55	17.27	17.69

precipitate was allowed to settle for one hour and the supernatant liquid was siphoned from the mixture through a glass wool plug. The residue was then washed four times with 500-ml. portions of petroleum ether to remove sulfur monochloride. Red phosphorus (62 g., 2.0 moles) was added to the crystalline mush containing petroleum ether. The stirred mixture was then slowly heated to 180°, allowing the volatile phosphorus trichloride and petroleum ether to distil continuously. The residual liquid was filtered in a nitrogen atmosphere to remove unreacted red phosphorus, and the filtrate fractionated yielding 320 g. (72%) of diphenylphosphinous chloride, b.p. 111–112° (0.3 mm.), $n^{20}D$ 1.6361.

Anal. Calcd. for $C_{12}H_{10}PCl$: P, 14.05; Cl, 16.09. Found: P, 13.78; Cl, 16.06.

Hexyldiphenylphosphine.[8]—A solution of *n*-hexylmagnesium chloride (0.825 mole) in 200 ml. of anhydrous ether was stirred at 10° (nitrogen atmosphere) and 110 g. (0.5 mole) of diphenylphosphinous chloride was added dropwise over a two-hour period, maintaining the temperature at 10–20° throughout. After the addition was complete, the mixture was heated at reflux for two hours, and the complex then hydrolyzed in aqueous ammonium chloride solution. The organic layer was extracted with 300 ml. of ethyl ether, the extract washed three times with water and dried with anhydrous $MgSO_4$. The ether was removed by distillation on a steam-bath, and the residual product purified by fractionation *in vacuo*.

Hexyldiphenylphosphine Oxide.—A stirred solution of 27 g. (0.1 mole) of hexyldiphenylphosphine in 150 ml. of acetone, held at 40°, was treated with 37.5 g. (0.11 mole) of 10% aqueous hydrogen peroxide solution over a two-hour period. The temperature was maintained at 40–50° throughout the addition. The mixture was then heated at reflux temperature for two hours, cooled to 30°, and poured into 300 ml. of water. The product was extracted with ether and the ether layer water washed and dried with anhydrous $MgSO_4$. The crude product obtained after removal of the ether was purified through two recrystallizations from naphtha.

This phosphine oxide can also be obtained, but in lower yield, by aqueous potassium permanganate oxidation of hexyldiphenylphosphine in basic solution.

Hexyldiphenylphosphine Sulfide.—A solution of 13.5 g. (0.05 mole) of hexyldiphenylphosphine in 100 ml. of benzene was stirred at 28° and 2 g. (0.062 mole) of sulfur was added. Heat of reaction caused a temperature rise to 40°. The mixture was then heated one hour at 40–50°, and filtered. The product crystallized after removal of the solvent. The pure product was obtained after two recrystallizations from absolute ethanol.

Hexyl Diphenylphosphinite.—A solution of 110 g. (0.5 mole) of diphenylphosphinous chloride in 200 ml. of naphtha (30–60°) was added dropwise over a three-hour period to a stirred solution containing 61 g. (0.6 mole) of *n*-hexyl alcohol, 44 g. (0.55 mole) of pyridine and 100 ml. of naphtha. The reaction mixture was held at 5–10° throughout the addition. After the addition was complete, the mixture was stirred at reflux for three hours, then poured into 500-ml. of water. The naphtha layer was thoroughly water washed, dried over anhydrous $MgSO_4$, and the solvent removed on a steam-bath. The crude liquid residue was fractionated *in vacuo*, yielding the desired ester. The phosphinite esters are readily oxidized, and must be stored in an inert atmosphere.

Hexyl Diphenylphosphinate.—Acetone (200 ml.) containing 28.6 g. (0.1 mole) of hexyl diphenylphosphinite was stirred at 30–35° while 24 g. (0.106 mole) of 15% aqueous hydrogen peroxide was added dropwise over a one-hour period. After the addition was complete, the solution was heated for three hours at 50–60° and then poured into 300 ml. of water. The organic material was extracted with ether, and the extract washed successively with water, 5% aqueous $NaHCO_3$ solution and water again until neutral. The dried ether layer was stripped of solvent, and the crude phosphinate ester purified by fractionation.

Hexyl Diphenylphosphinothionate.—A stirred solution of 28.6 g. (0.1 mole) of hexyl diphenylphosphinite in 100 ml. of benzene was stirred at 27° and 3.2 g. (0.1 mole) of sulfur was added portionwise over a ten-minute period, causing a temperature rise to 35°. The sulfur went completely into solution. The solution was then heated at reflux for two hours, and the solvent removed by distillation under vacuum. The residual ester was purified by fractionation *in vacuo*.

Hexyldiphenylphosphine Oxide (by Isomerization of Hexyl Diphenylphosphinite with *n*-Hexyl Bromide).—A solution of 21.45 g. (0.075 mole) of hexyl diphenylphosphinite and 12.35 g. (0.075 mole) of *n*-hexyl bromide was stirred for five hours at 150–160°. Three grams of an unsaturated hydrocarbon, probably hexene, was collected in a Dry Ice trap. The reaction mixture was cooled and dissolved in 150 ml. of benzene. The benzene solution was washed with 10% $NaHCO_3$ solution, and then with water until neutral. The benzene was removed from the dried solution by distillation under reduced pressure. The crude residue crystallized on standing, and was purified by recrystallizing four times from naphtha, yield 16 g. (74%) of the desired product, m.p. 60–61°.

The $NaHCO_3$ extract on acidification with hydrochloric acid yielded 1.0 g. of diphenylphosphinic acid, m.p. 187–188°, neutral equivalent 217 (calculated neutral equivalent for diphenylphosphinic acid 218).

Hexyl Diphenylphosphinothioite.—This material was prepared from 118 g. (1.0 mole) of *n*-hexyl mercaptan, 40 g. (0.5 mole) of pyridine and 110 g. (0.5 mole) of diphenylphosphinous chloride by the procedure previously described for hexyl diphenylphosphinite.

Hexyl Diphenylphosphinothiolate.—This ester was prepared from 30.2 g. (0.1 mole) of hexyl diphenylphosphinothioite and 24 g. (0.106 mole) of 15% aqueous hydrogen

(8) The procedure for the hexyl derivative will be described for each type of compound. The octyl derivatives are prepared by the same procedure.

peroxide by the procedure previously described for hexyl diphenylphosphinate.

Hexyl Diphenylphosphinodithioate.—This material was prepared from 30.2 g. (0.1 mole) of hexyl diphenylphosphinothioite and 3.2 g. (0.1 mole) of sulfur by the procedure described previously for hexyl diphenylphosphinothionate. The crude product, a crystalline solid, was purified by recrystallization from naphtha.

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CLEVELAND, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

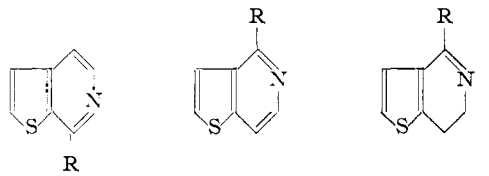
Sulfur Analogs of Isoquinolines. IV. The Pictet–Gams Reaction and Attempts to Prepare Analogs of Papaverine[1,2]

BY WERNER HERZ AND LIN TSAI

RECEIVED DECEMBER 18, 1954

The Bischler–Napieralski and Pictet–Gams reactions in the thiophene series have been found to proceed satisfactorily. However, attempts to prepare papaverine analogs were not successful. Introduction of a methoxy group into the thiophene ring in order to facilitate cyclization resulted in demethylation; the resulting compounds appear to exist in the thiolactone form.

The feasibility of preparing analogs of isoquinolines in which the benzene moiety is replaced by a thiophene nucleus has been demonstrated.[2,3] Earlier work indicated that the Bischler–Napieralski and the Pomeranz–Fritsch reactions could be applied successfully to derivatives of thiophene to give thieno(2,3-c)- (I) and thieno(3,2-c)pyridines (II). The present paper describes our attempts to extend this work, particularly to the preparation of analogs of papaverine, in order to produce compounds whose pharmacological properties would be of interest.



I II III

Because 2-(2-thienyl)-ethylamine is the key intermediate in the synthesis of compounds of type II by the Bischler–Napieralski reaction, attempts were made to improve its preparation from 2-thienylacetonitrile. These are described in the experimental part. A significant improvement in the yield obtained by reduction by means of lithium aluminum hydride was observed when the contact time with the basic medium was shortened. For the synthesis of 3,4-dihydro(3,2-c)pyridine (III, R = H) the amine was formylated by ethyl formate.[4] Cyclization with polyphosphoric acid–phosphorus oxychloride, the best procedure found, gave only an 8% yield of III (R = H), whereas the cyclization of N-formyl-2-phenylethylamine reportedly furnishes 31% of 3,4-dihydroisoquinoline.[5]

With the purpose of synthesizing a sulfur analog resembling papaverine, N-homoveratroyl-2-(2-thienyl)-ethylamine was prepared, but all attempts to cyclize the amide were fruitless. This was not entirely surprising since Kondo[6] failed to obtain 1-veratryl-3,4-dihydroisoquinoline under similar conditions. Bischler–Napieralski cyclizations of N-homoveratroyl derivatives appear to be successful only when the phenyl ring is activated by the presence of one or more hydroxy or alkoxy substituents.[7]

A route to the desired papaverine analog which in view of previously published reports[7] offered greater prospects of success, while avoiding the dehydrogenation step which lowers the yield of 1-alkylthieno-(3,2-c)pyridines,[3] is the method of Pictet and Gams. Its several modifications utilize a 2-hydroxy- or 2-methoxy-2-phenylethylamide whose cyclization leads directly to an isoquinoline derivative. Although 2-hydroxy-2-(2-thienyl)-ethylamine was not accessible through adaptations of standard methods,[8] the corresponding methoxy derivative was prepared in fair yield by reaction of β-2-nitrovinylthiophene with sodium methoxide followed by reduction with lithium aluminum hydride.

The acetyl derivative of this amine was subjected to widely varied cyclization conditions. After extensive experimentation, 1-methylthieno(3,2-c)pyridine (II, R = CH_3) was prepared in an over-all yield of 22.5%, based on the amine. The cyclization was favored by mild conditions (phosphorus oxychloride at room temperature for 30 days). This thienopyridine has previously been prepared in lower yield by aromatization of 1-methyl-3,4-dihydrothieno(3,2-c)pyridine (III, R = $-CH_3$).[8] Since we were also interested in developing a synthetic method for the preparation of 1,2,3,4-tetrahydrothienopyridines, the methiodide of the latter compound was reduced[9] to 1,2-dimethyl-1,2,3,4-tetra-

(1) Supported in part by grant RC-3097 from the United States Public Health Service, Department of Health, Education and Welfare.

(2) Previous paper, W. Herz and L. Tsai, THIS JOURNAL, **75**, 5122 (1953).

(3) W. Herz, *ibid.*, **73**, 351 (1951).

(4) This derivative was reported by G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938), but no analysis was given. The authors stated that they were unable to cyclize this amide.

(5) H. R. Snyder and F. Y. Werber, THIS JOURNAL, **72**, 2962 (1950).

(6) J. Kondo, *J. Pharm. Soc. Japan*, No. 519, 429 (1925).

(7) Pertinent work on this and related subjects is reviewed by W. M. Whaley and T. R. Govindachari, as well as by W. J. Gensler in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 74, 151 and 191.

(8) The nitrosation of 2-acetylthiophene has been recorded[4] but we were not able to reduce this compound successfully to the β-hydroxyethylamine. Similarly we were unable to prepare the cyanohydrin of 2-thiophenealdehyde whose reduction was expected to lead to the desired compound.

(9) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 960 (1949).