100 ml. of methanol at 0°. The mixture was stirred for one hour and allowed to stand at room temperature for one day. A thick deposit of pale yellow crystalline material formed around the walls of the flask. The mixture was then warmed on a water bath at 40–50° for 2 hr., using a Dry Ice–acetone cooling system to condense the ethylene oxide. The ethylene oxide was later removed by evaporation and the methanol-insoluble material was filtered hot and dried, m.p. 246–250°, dec., yield 0.8 g. The methanol filtrate was evaporated to dryness and the residue treated with 100 ml. of ethyl acetate, brought to boil on a steam bath, and filtered hot, leaving a residue which melted at 246–250°, dec., yield 0.2 g. The filtrate of the ethyl acetate on standing for an hour deposited 0.3 g. of material, melting at 202–204°, dec. On two further recrystallizations from ethyl acetate this material melted at 214–216°, the mixture melting point of this product with the starting material was 215°.

After removing the starting material from the ethyl acetate solution and concentrating, 0.3 g. of product melting at 158–162° was obtained, which on subsequent recrystallization from ethyl acetate several times yielded a product melting at 163–164°, 0.15 g. (6.8%), $[\alpha]_D$ +76° (chloroform).

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.89. Found: C, 73.95; H, 9.60; N, 4.15.

The above analysis indicates that the material is the 17-bis(β-hydroxyethyl)amino derivative. It is soluble in alcoholic alkali and the ultraviolet absorption is shifted, showing the free phenolic group: λ_{max} 280 mμ (ε 3600) (neutral alcoholic solution); alcoholic alkaline solution λ_{max} 300 mμ, (ε 3000).

The major reaction product (1.0 g., 50%) was found to be insoluble in the common organic solvents and had a crude melting point of 246–250° dec. It dissolved in boiling dimethylformamide, and recrystallization from this solvent yielded a product melting at 252–254° dec. Analytical data and ultraviolet absorption in alkaline medium suggest this to be the mono-*N*-hydroxyethyl derivative.

Anal. Calcd. for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.57; H, 9.43; N, 4.48.

As the material did not dissolve in alcohol, the ultraviolet absorption in neutral medium was not determined. In alkaline alcoholic medium λ_{max} 300 mμ (ε 2800).

17ξ-Amino-3-methoxy-1,3,5(10)estratriene. Estrone methyl ether (2 g.) was converted to the oxime[14] and reduced with sodium and butanol, as described in several of the earlier reductions of oximes. The hydrochloride (1.2 g.) melted at 276–278°, dec., and the free amine was rather difficult to crystallize. It was obtained as a flaky resin, $[\alpha]_D$ +70.5° (absolute ethanol).

Anal. Calcd. for $C_{19}H_{28}ONCl \cdot H_2O$: C, 67.14; H, 8.90; Cl, 10.43, N, 4.12. Found: C, 67.84; H, 8.25; Cl, 10.55; N, 4.33.

Condensation of the reduction product of the oxime and ethylene oxide. The condensation was carried out with the free amine (1 g.) in methanol and ethylene oxide solution in methanol as described in the earlier condensations. The reaction product was recrystallized from petroleum ether (b.p. 60–110°), 0.75 g., m.p. 136–139°. An analytical sample was obtained by recrystallization from the minimum amount of acetone, m.p. 138–140°, $[\alpha]_D$ +73.5° (chloroform).

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 74.25; H, 9.68; N, 3.94.

Chlorination of 17ξ-Bis(β-hydroxyethyl)amino-3-methoxy-1,3,5(10)estratriene. It was found that chlorination proceeded to completion in the absence of any solvent, i.e., thionyl chloride acted as the solvent. A mixture of the diol (0.5 g.) and thionyl chloride (10 ml.) was boiled under reflux for one hour. The thionyl chloride was removed by distillation under reduced pressure. The dark brown residue was dissolved in 20 ml. of hot absolute ethanol, filtered, and to the filtrate 300 ml. of ether saturated with hydrogen chloride was added. A brown gum separated in 15 min. This gum was removed by filtration and to the resulting filtrate more ether was added. After standing for one day in the refrigerator, a pale yellow crystalline mass separated, m.p. 198–202° dec.

Anal. Calcd. for $C_{23}H_{34}ONCl_3$: C, 61.81; H, 7.67; N, 3.14; Cl, 23.80. Found: C, 61.61; H, 7.82; N, 3.36; Cl, 23.91.

PHILADELPHIA 4, PA.

(14) B. M. Regan and F. N. Hayes, *J. Am. Chem. Soc.*, 78, 639 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Sulfur Analogs of δ-Aminolevulinic Acid. I. Phthalimide Derivatives[1]

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The chloromethyl sulfide of methyl β-mercaptopropionate has been prepared. A phthalimide derivative of this ester has been made and hydrolyzed to the phthalimido acid and the (*o*-carboxy)benzamido acid. From these products of hydrolysis phthalimidomethyl β-carboxyethyl sulfone and (*o*-carboxy)benzamidomethyl β-carboxyethyl sulfoxide have been prepared. β,β'-Dithiodipropionyl chloride and methylene bis(β-thiopropionyl chloride) have been made and converted to chloromethyl ketones using diazomethane and hydrogen chloride. Treatment of the chloromethyl ketones with potassium phthalimide effected hydrogen elimination and cleavage of the sulfur-carbon bond.

As the compound δ-aminolevulinic acid has recently[3] been assigned a significant role as an intermediate in the metabolism of porphyrins, the synthesis of sulfur analogs has been undertaken which might possibly show interesting biological activity *e.g.*, as anticancer agents.

A. $H_2NCH_2SCH_2CH_2COOH$ (also, the sulfoxide and the sulfone)

B. $H_2NCH_2COCH_2CH_2SO_2NH_2$

EXPERIMENTAL

Chloromethyl β-carbomethoxyethyl sulfide (II). A solution of 0.15 mole (4.9 g.) of formaldehyde in water and 0.15 mole

(1) Supported by U.S.P.H.S. Grant No. CY-2714.

(2) Abstracted from the Ph.D. dissertation of Mae L. Beck, University of Pennsylvania, 1960.

(3) D. Shemin, *The Succinate-Glycine Cycle*, in Ciba Foundation *Symposium on Porphyrin Biosynthesis and Metabolism*, Little Brown and Co., Boston, Mass., 1955.

(18 g.) of methyl β-mercaptopropionate was cooled to 0° and dry hydrogen chloride gas was passed in for 3 hr. (until homogeneity was reached). The solution was diluted with 80 ml. of ethyl ether, washed once with 14 ml. of ice water and three times with 8-ml. portions of ice water. The aqueous extracts were then washed with 20 ml. of ethyl ether and this ether extract with 3-ml. portions of cold water. The combined ether extracts were dried over phosphorus pentoxide (10 g.) which was added cautiously with stirring to prevent charring. After filtration and removal of the ether under reduced pressure, the oil was distilled to yield 8.8 g. (35%), b.p. 88° (1 mm.).

Anal. Calcd. for $C_5H_9O_2ClS$: C, 35.70; H, 5.34; Cl, 21.08; S, 19.00. Found: C, 35.86; H, 5.60; Cl, 20.98; S, 19.27.

The distillation residue, which weighed 15 g., was saponified to the known acid, methylene bis(β-thiopropionic acid), m.p. 142°.

Phthalimidomethyl β-carbomethoxyethyl sulfide (IV). A mixture of 7.1 g. (0.042 mole) of chloromethyl β-carbomethoxyethyl sulfide (II) and 7.75 g. (0.042 mole) of potassium phthalimide in 25 ml. of dimethylformamide was stirred for 0.5 hr. at room temperature and for 1 hr. at 60–70°, finally cooling to room temperature during 0.5 hr. Chloroform (40 ml.) was added and the resulting mixture was poured into 100 ml. of water. The layers were separated and the water was extracted with 10 ml. of chloroform. The combined chloroform extracts were washed with 20 ml. of water; acidification of the water layer deposited no precipitate. The chloroform solution was dried over anhydrous sodium sulfate, filtered, and the solvent removed under reduced pressure. The solid remaining was taken up in hot absolute ethanol and upon cooling crystals appeared, which were collected and dried in a vacuum desiccator to afford 5.0 g. (43%) of product melting at 86–93°. After recrystallization from absolute ethanol, an analytically pure sample was obtained which melted at 96.5–97.5°.

Anal. Calcd. for $C_{13}H_{13}O_4SN$: C, 55.80; H, 4.65; N, 5.02; S, 11.50. Found: C, 56.05; H, 4.74; N, 5.12; S, 11.64.

Phthalimidomethyl β-carboxyethyl sulfide (V). An Erlenmeyer flask containing 3.0 g. of phthalimidomethyl β-carbomethoxyethyl sulfide (IV) and 30 ml. of hydrochloric acid (6N) was heated on a steam bath for 2 hr. The mixture was cooled to 5° and the crystals filtered through a sintered-glass funnel and washed with a minimum of cold water. The product, which did not need further purification, was dried for several hours in a vacuum oven at 60°, whereupon it melted at 163.5–164.5° and weighed 2.43 g. (86%).

Anal. Calcd. for $C_{12}H_{11}O_4NS$: C, 54.30; H, 4.15; N, 5.28; S, 12.05. Found: C, 54.21; H, 4.17; N, 5.09; S, 12.23.

(o-Carboxy)benzamidomethyl β-carboxyethyl sulfide (VII). A flask containing 2.24 g. (0.00845 mole) of phthalimidomethyl β-carboxyethyl sulfide (V) in 200 ml. of ethanol was maintained at 18°. To the stirred solution was added one drop of phenolphthalein, and from a buret, at a rate slow enough to maintain the temperature at 18° and keep the pink color at a minimum, was added 0.0169 equivalents of sodium hydroxide (169 ml. of 0.1*N*). The solution was allowed to stand for 18 hr. The temperature was again lowered and the free acid was liberated from the sodium salt with 16.9 ml. of standard 1*N* hydrochloric acid, added slowly in order to maintain the temperature at 10–15°. The solution was concentrated under reduced pressure over a steam bath to a volume of 15–20 ml. Upon cooling, a precipitate formed, which was filtered and washed with the minimal amount of cold water. The dried crystals weighed 1.68 g., m.p. 135–136°. An additional crop was obtained from the mother liquor weighing 0.5 g. and melting at 119–135°.

Anal. Calcd. for $C_{12}H_{13}O_5NS$: C, 50.80; H, 4.59; N, 4.94; S, 11.30. Found: C, 50.62; H, 4.35; N, 4.70; S, 11.31.

(o-Carboxy)benzamidomethyl β-carboxyethyl sulfoxide (VIII). To a flask containing 0.2 g. of (o-carboxy)benzamidomethyl β-carboxyethyl sulfide in 30 ml. of acetone was added 0.1–0.2 ml. of 30% hydrogen peroxide. After 3 hr. at room temperature, the acetone was allowed to evaporate at room temperature. The hygroscopic product was taken up in several milliliters of absolute ethanol to which was added 2 ml. of a 1:1 acetone-ether mixture to induce crystallization. The crystals, after drying, weighed 0.15 g. (70%), m.p. 138–139°.

Anal. Calcd. for $C_{12}H_{13}O_6NS$: C, 48.10; H, 4.34; N, 4.68; S, 10.70. Found: C, 47.90; H, 4.44; N, 4.83; S, 10.60.

Phthalimidoethyl β-carboxyethyl sulfone (VI). To a warm solution of phthalimidoethyl β-carboxyethyl sulfide (0.5 g.) in 15–20 ml. of acetic acid bromine water was added until a permanent yellow color was maintained. The solution was concentrated under reduced pressure over a steam bath to about 50 ml. and cooled in an ice bath. The colorless needles were recrystallized from ethanol, m.p. 163.5–164°, yield 0.3 g. (60%).

Anal. Calcd. for $C_{12}H_{11}O_6NS$: C, 48.50; H, 3.70; N, 4.71; S, 10.77. Found: C, 48.10; H, 3.91; N, 4.50; S, 10.72.

The infrared spectrum (Table I) indicated that the phthalimide ring was intact.

TABLE I

INFRARED SPECTRA OF PHTHALIMIDE AND (o-CARBOXY)-BENZAMIDO DERIVATIVES

Compound	CO Stretching Frequency (Cm.$^{-1}$)	SO_2 Stretching Frequency (Cm.$^{-1}$)	SO Stretching Frequency (Cm.$^{-1}$)	Medium
V	1765 (M)			
	1700 (S)			
	1620 (W)			KBr
VI	1770 (M)	1325 (S)		
	1715 (S)	1135 (S)		
	1630 (W)			KBr
VII	1695 (S)			
	1630 (S)			
	1540 (S)			KBr
VIII	1720 (S)			
	1650 (S)			
	1550 (S)		995 (S)	KBr

β,β′-Dithiodipropionic acid (IX). Several drops of ferrous sulfate (0.01 molar) in sulfuric acid were added to 80 g. of β-mercaptopropionic acid in 270 ml. of water. With ice cooling and stirring, 290 g. of 5% hydrogen peroxide was added. After the initial exothermic reaction was complete and the temperature began to fall, the ice bath was removed and the solution was allowed to continue stirring for 3 hr. at room temperature. The solid acid was collected on a coarse sintered-glass funnel and washed several times with small portions of cold water (50 ml.). The test for hydrogen peroxide was negative after the last washing. After drying overnight in a 70° vacuum oven there remained 72 g. (90%) of product having a melting point of 153–154° (lit.[6] m.p. 155°). The principle infrared bands were (potassium bromide) 1700 cm.$^{-1}$ (S), 1425 cm.$^{-1}$ (M), 1220 cm.$^{-1}$ (S).

β,β′-Dithiodipropionyl chloride. To 24 g. (0.114 mole) of β,β′-dithiodipropionic acid (IX) was added 72 g. of thionyl chloride in a flask fitted with a condenser. The mixture was allowed to reflux for 3 hr. After cooling, the excess thionyl chloride was removed by aspiration with a stream of nitrogen gas. The weight of the clear light yellow oil was 27.5 g.; the theory is 28.2 g. The product was used without further purification for the next step.

Bis(4-chloro-3-ketobutyl) disulfide (X). An ethereal solution of diazomethane containing about 0.2 mole was prepared using the procedure developed by Arndt[4] which employs *N*-methyl-*N*-nitrosourea as starting material. This was cooled to −5° and a precooled (to 0°) solution of β,β′-dithiodipropionyl chloride containing 0.1 mole of acid chloride in 100

(4) F. G. Arndt, *Org. Syntheses*, Coll. Vol. II, 165 (1940).

ml. of ethyl ether was added over 0.5 hr. Stirring was continued at 0° for 2 hr., after which the solution was allowed to warm to room temperature. A small amount of precipitate had formed which dissolved quickly upon the addition of gaseous hydrogen chloride. The heat of the reaction brought the ether to reflux temperature during the course of the hydrogen chloride addition. After 1 hr. the addition of hydrogen chloride gas was stopped and the product was stored in the refrigerator overnight. A yellow precipitate had formed which weighed 10 g. (39%). After one recrystallization from carbon tetrachloride and another from chloroform, 7.5 g. of product was obtained having a m.p. of 81.0–81.5°.

Anal. Calcd. for $C_8H_{12}O_2Cl_2S_2$: C, 34.86; H, 4.37; Cl, 25.80; S, 23.26. Found: C, 34.64; H, 4.38; Cl, 26.06; S, 23.56.

Compound $C_{12}H_{11}O_5N$. A mixture of 0.25 g. of bis(4-chloro-3-ketobutyl)disulfide and 0.185 g. of potassium phthalimide in 3 ml. of dimethylformamide was stirred for 45 min. at room temperature and 15 min. at 50–60°. The solution was cooled, 10 ml. of chloroform was added and the contents were poured into 30 ml. of water. The chloroform layer was washed twice with 5 ml. of water and the combined water extracts were then washed with 5 ml. of chloroform. This chloroform extract was washed with 1 ml. of water and added to the original chloroform solution, which was then dried over anhydrous sodium sulfate. The solution was filtered and the solvent was removed under reduced pressure over a water bath. Upon the addition of 5 ml. of hot benzene some of the solid dissolved, and the solution was stored for several hours at 5°. After filtration, 0.1 g. of a solid melting at 227–229° was obtained, which upon admixture with phthalimide represented 50% of the amount of potassium phthalimide used.

After the removal of the benzene from the filtrate under reduced pressure, a solid weighing 0.1 g. resulted. After recrystallization from ethanol the solid melted at 113–114°.

Anal. Calcd. for $C_{12}H_{11}O_5N$: C, 57.80; H, 4.42; N, 5.62. Found: C, 57.85; H, 4.66; N, 5.55; S, none.

This compound had a *p*H of 7.1 which rose to 8.0 upon the addition of one drop of 0.01*N* sodium hydroxide. No carbonyl derivative such as the 2,4-dinitrophenylhydrazone could be made. The infrared spectrum showed the phthalimide ring to be intact and that there was no free hydroxyl band.

The compound $C_{12}H_{11}O_5N$ also arose when methylene bis-(4-chloro-3-ketobutyl sulfide) was treated with potassium phthalimide using the same procedure.

The melting point of the compound obtained from the thioformal, mentioned above, showed no depression upon admixture which the compound obtained from the disulfide. The infrared spectra of the two compounds were identical.

Methylenebis(β-thiopropionic acid) (XI) was obtained by saponification of methyl methylenebis(β-thiopropionate) (III) formed as a by-product in the chloromethylation of methyl β-mercaptopropionate (I), m.p. 141–142° (lit.[5] m.p. 142°). The neutralization equivalent was 110 (the calculated value is 112).

Methylenebis(β-thiopropionyl chloride). A 22.5-g. sample of the thioformal acid prepared above was treated with 60 g. of thionyl chloride and the mixture was allowed to reflux for 1 hr. After 18 hr. at room temperature, the excess thionyl chloride was removed under reduced pressure and the colorless oil was distilled, b.p. 108° (18 mm.), 13 g. (54%). A *dianilide* derivative was prepared and recrystallized twice from absolute ethanol, m.p. 158–159°.

Anal. Calcd. for $C_{19}H_{22}O_2S_2N_2$: C, 61.00; H, 5.90; S, 17.10; N, 7.50. Found: C, 60.90; H, 6.06; S, 17.02; N, 7.37.

Methylenebis(4-chloro-3-ketobutyl) sulfide (XII). An ethereal solution (300 ml.) containing 0.071 mole of diazomethane was cooled to −5°, followed by the addition of a precooled ether solution (20 ml.) containing 0.035 mole of methylenebis(β-thiopropionyl chloride). The solution was allowed to warm to room temperature overnight. Anhydrous hydrogen chloride was then added over a period of 1 hr., during which time the heat of the reaction caused the ether to reflux. The solution was stored at 5° for 18 hr. After warming to room temperature, the hydrogen chloride and ether were removed with a stream of nitrogen gas. When the volume had concentrated to 100 ml., 75 ml. of carbon tetrachloride was added and the solution was concentrated again, this time to 50 ml. Dark green insoluble globules formed, which were removed occasionally by filtration during the concentration process. The amber carbon tetrachloride solution which remained was cooled at 5° for 18 hr. A precipitate had formed which weighed 1.15 g. (10%), m.p. 71–78°. The impure solid gave rise to two products upon careful separation. The first was obtained by recrystallization from 1:1 chloroform–carbon tetrachloride in which the other was soluble. After several recrystallizations, a sample was obtained melting at 88.5–89.5°.

Anal. Calcd. for $C_8H_{13}O_3ClS_2$: C, 37.62; H, 5.09; Cl, 13.80; S, 24.80. Found: C, 37.40; H, 5.05; Cl, 13.80; S, 24.80.

The second compound was obtained when the mother liquor from the first was concentrated. After recrystallization from carbon tetrachloride a sample having a m.p. of 80–81° resulted. The infrared spectrum for this compound showed principle peaks at 1720 cm.$^{-1}$ (S), 1405 cm.$^{-1}$ (M), 1345 cm.$^{-1}$ (M), and 1078 cm.$^{-1}$ (M).

The oil which remained weighed 8 g. and appeared to be a mixture of products and unchanged diacid chloride, which defied separation. The oil decomposed upon heating when an effort was made to distil it.

The first product, m.p. 89°, corresponds to the half-acid, half-chloromethyl ketone (infrared bands at 1720 and 1690 cm.$^{-1}$); whereas the second product, m.p. 81°, corresponds to the expected methylenebis(4-chloro-3-ketobutyl sulfide) on the basis of the infrared data. The spectrum of the thioformal chloromethyl ketone was nearly identical with that of the chloromethyl ketone made from the disulfide with principle bands occurring at 1720 cm.$^{-1}$, 1405 cm.$^{-1}$, and 1345 cm.$^{-1}$; these compounds differ only by a methylene group. There was not a large enough sample of the second product to send for an elemental analysis.

DISCUSSION

Diagram A outlines the procedures used to prepare δ-aminolevulinic acid analogs of general structure A. It was found necessary to esterify β-mercaptopropionic acid before chloromethylation since the free acid gave only the formal XI.

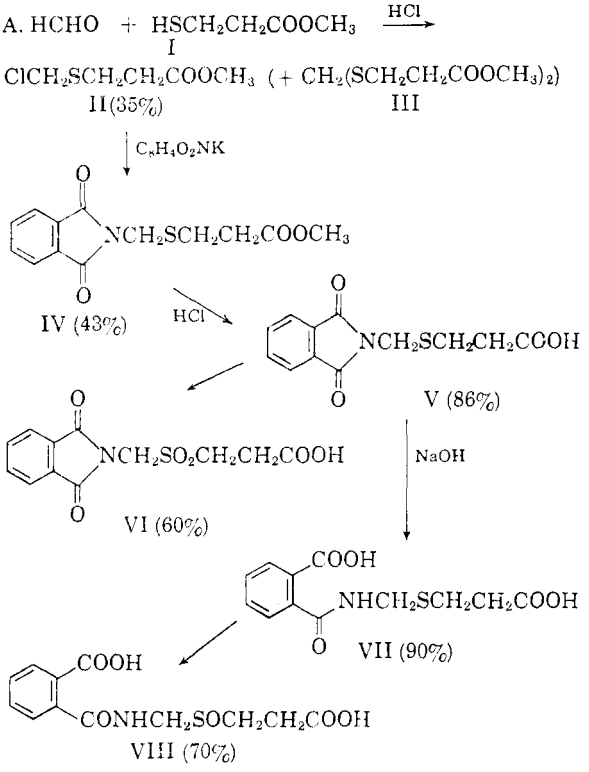
The phthalimido ester IV was extremely sensitive to base hydrolysis, liberating mercaptan, but careful acid hydrolysis cleaved the methyl ester linkage successfully to produce the acid V. In determining the neutral equivalent for this acid, it was found that the end-point faded rapidly until two equivalents had been added. Acidification at this point produced an excellent yield of the *o*-carboxyphthalamide VII. The opening of the phthalimide ring is confirmed by the infrared spectrum (Table I).

As we are unaware of the isolation of stable α-amino sulfides, the stability of VII and VIII is of interest.

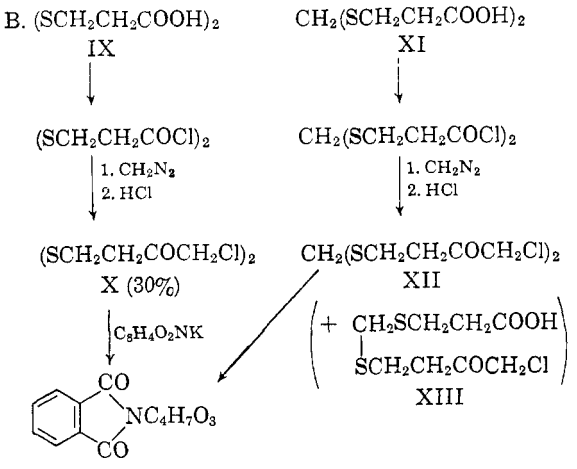
Diagram B outlines the procedures employed in

(5) G. G. Stoner and G. Dougherty, *J. Am. Chem. Soc.*, **63**, 988 (1941).

an effort to prepare δ-aminolevulinic acid analog B. These were patterned after the successful synthesis



of δ-aminolevulinic acid.[6] The effort proved abortive when it was found that both chloromethyl ketones X and XII, on reaction with phthalimide, produced the same sulfur-free compound, $C_{12}H_{11}O_5N$. The structure of this compound has not been established, but the infrared spectra show the phthalimido ring system to be present. The absence of a carboxyl group was indicated by titration and the infrared spectrum. The latter also suggest there are no free hydroxyl groups.



PHILADELPHIA 4, PA.

(6) A. Neuberger and J. J. Scott, *J. Chem. Soc.*, 1820 (1954).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Cyclopropanes Derived from Diaryldiazomethanes. II. 3-Azabicyclo[3.1.0]-hexanes and Their Azaspiroquaternary Salts[1]

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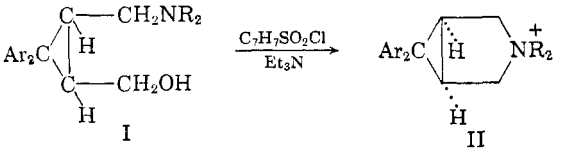
The 6,6-diaryl-3-azabicyclo[3.1.0]hexane ring system can be prepared by alternative routes: through addition of diaryldiazomethanes to *N*-substituted maleimides and citraconimides followed by reduction, and by cyclization of 1,1-diaryl-2-hydroxymethyl-3-*cis*-*t*-aminomethylcyclopropanes by the action of *p*-toluenesulfonyl chloride. The latter route affords access to *N*-spiroquaternary ammonium salts.

In the course of an investigation of the amino-alcohols of the formula I[5] several such compounds



were allowed to react with *p*-toluenesulfonyl chloride in the presence of tertiary bases (pyridine or preferably triethylamine). No sulfonic esters could be isolated; either the starting amino alcohol was recovered or the entire product had the properties of a quaternary salt. It seems reasonable to suppose that the sulfonic ester III is actually formed

(1) A portion of this material was presented by Dr. Mehta before the Organic Division of the American Chemical Society, Boston Meeting, April 1959.

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(5) R. Baltzly, N. B. Mehta, P. B. Russell, R. E. Brooks, E. M. Grivsky, and A. M. Steinberg, *J. Org. Chem.*, 26, 3669 (1961).