Experimental

Rearrangement of Diethyl Dithiodiglycolate (I).—To sodium methoxide prepared by the addition of 2.3 g. (0.1 g.-atom) of sodium to methanol was added 250 ml. of absolute ether. To the stirred mixture was added at −20° a solution of 23.8 g. (0.1 mole) of diethyl dithioglycolate. The mixture immediately turned deep yellow in color and a small amount of solid precipitated. To obtain the free mercaptan, a mixture of ice, 20 ml. of concd. hydrochloric acid, and water was added to the cold reaction mixture. The organic layer was separated and dried over anhydrous magnesium sulfate. Removal of the solvent by vacuum distillation gave a pale yellow oil possessing a mercaptan odor. When the material was distilled rapidly through a short head still, a fraction was obtained, b.p. 103–104° (0.10 mm.), $n^{25}D$ 1.5042, which possessed a penetrating mercaptan odor.

Anal. Calcd. for $C_8H_{14}O_4S_2$: C, 40.31; H, 5.92; S, 26.91; mol. wt., 238. Found: C, 39.68; H, 5.53; S, 29.95; mol. wt., 208.

The infrared absorption spectrum possessed a band at 3.95 μ, which is characteristic of the mercaptan group.

The product (109 g., 92%) from a similar reaction using five times the above quantities was subjected to a slow precision distillation through an 18-in. column. The distillate, b.p. 28–30° (0.4 mm.) (pot temperature, 110°), weighed 42 g. The residue (51 g.) did not distill up to 170° (0.4 mm.) and was a liquid polymer of ethyl thioglyoxylate The distillate was redistilled, b.p. 60–61° (21 mm.), and was ethyl mercaptoacetate.

Anal. Calcd. for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 40.08; H, 6.79; S, 26.60.

Addition of diethyl dithiodiglycolate to either 20% aqueous sodium hydroxide at 25° or 30% aqueous sodium hydroxide at 0° gave the characteristic intense yellow color of the anion II.

Methylation of the Sodium Salt of Diethyl 2-Mercapto-3-Thiaglutarate (II).—The rearranged product from 71.5 g. (0.3 mole) of diethyl dithiodiglycolate and 0.33 mole of sodium ethoxide was stirred vigorously at −30°. When 47 g. (0.33 mole) of methyl iodide was added, the temperature rose to −10°. After 1 hr. at 0° and 2 hr. at 30°, the mixture was poured into water. The organic layer was taken up in ether, washed with dilute aqueous sodium hydroxide and water, and dried over anhydrous magnesium sulfate. The fraction (42 g.) boiling between 40 and 150° was rectified by precision distillation through an 8-in. spinning-band column using a reflux ratio of 10:1. The product weighed 21 g. (28%), b.p. 116–118° (0.40 mm.), $n^{25}D$ 1.4990 to 1.5033, proved to be diethyl 2-methylmercapto-3-thiaglutarate (IV). A center cut of this fraction, 4.6 g., b.p. 117–118° (0.40 mm.), $n^{25}D$ 1.4990, was analyzed.

Anal. Calcd. for $C_9H_{16}S_2O_4$: C, 42.84; H, 6.39; mol. wt., 252. Found: C, 42.89; H, 6.45; mol. wt., 250.

Amperometric titration with silver nitrate indicated the presence of less than 0.7% mercaptan group. The infrared absorption spectrum resembled that of compound III except that there was no characteristic band for the mercaptan group. Also the 7.3-μ band for methyl was stronger.

The Synthesis of Tetrahydropalmatrubine[1]

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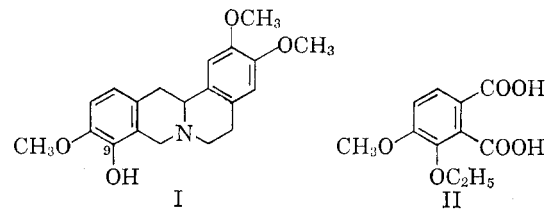
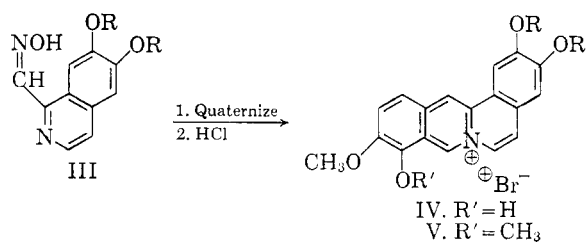
The chloride salt of the berberine alkaloid palmatine undergoes monodemethylation to yield a red compound, palmatrubine.[2] Späth and Burger[3] reduced palmatrubine to tetrahydropalmatrubine (I), and by ethylation, followed by oxidation to 3-ethoxy-4-methoxybenzene-1,2-dicarboxylic acid (II), established beyond doubt that the free hydroxyl group must have been at position 9.



Since it has been shown that the aromatic cyclodehydration method makes possible the formation of the dehydroberberinium nucleus under very mild conditions,[4–6] it seemed probable that the first unequivocal synthesis of the tetrahydrapalmatrubine nucleus could be effected.

Crude 2-hydroxy-3-methoxybenzyl bromide formed with 6,7-dimethoxyisoquinoline-1-carboxaldoxime[6] (III. R = CH_3), a quaternary salt which cyclized in concentrated hydrochloric acid at 100° in only a few minutes to afford the new dehydropalmatrubinium bromide (IV. R = CH_3). Catalytic reduction of the bromide salt gave tetrahydropalmatrubine[1]:



Dehydroberberubinium bromide (IV. R—R = —CH_2—) and its acetate were prepared also. A comparison of the ultraviolet absorption spectra of the new dehydro systems (IV) with those of the related dehydroberberinium salts (V)[5,6] is shown in Table I.

(1) This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

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(7) All melting points are uncorrected. The ultraviolet absorption spectra were determined in 95% ethanol using the Warren Spectracord spectrophotometer with 1-cm. silica cells.

(8) N. Mauthner, *J. prakt. Chem.*, **158**, 321 (1941).

TABLE I
COMPARISON OF ULTRAVIOLET ABSORPTION SPECTRA OF DEHYDRORUBINIUM (IV) WITH ANALOGOUS DEHYDROBERBERINIUM SYSTEMS (V)

Dehydro-	max, mμ[a]					min, mμ			
Palmatrubinium	248	281		354	477	263		337	412
Palmatinium	246	285	328	355	464	268	306	344	404
Berberubinium	249	281		352	470	268		334	415
Berberinium[b]	246	278	310	348	460	257	290.5	332	405

[a] Except as noted, bromides were used. [b] As chloride.

Experimental[7]

3-Methoxy-2-hydroxybenzyl alcohol[8] (prepared in 68% yield by sodium borohydride reduction of the aldehyde) was converted to the bromide by treatment with phosphorus tribromide. The crude 3-methoxy-2-hydroxybenzyl bromide was not purified.

Dehydropalmatrubinium (IV. R = CH_3) Bromide.—One gram of 6,7-dimethoxyisoquinoline-1-carboxaldoxime[6] was allowed to react with 1 g. of crude 3-methoxy-2-hydroxybenzyl bromide in 7 ml. of dimethylformamide, at first for a few minutes in the steam bath, and then at room temperature for 24 hr. The yellow crystals of the crude quaternary salt were collected, washed with ether, and then cyclized by heating on the steam bath with 12 ml. of concd. hydrochloric acid. After only 10 min. red crystals started to precipitate. The mixture was cooled and the product collected and recrystallized from methanol–ethyl acetate as red needles, m.p. 218–220° dec. (sealed tube), yield 2 g. (100%).

Anal. Calcd. for $C_{20}H_{18}BrNO_4 \cdot 2H_2O$: C, 53.10; H, 4.86; N, 3.10. Found: C, 53.50; H, 4.69; N, 3.32.

The Perchlorate (IV. R = CH_3) crystallized from dimethyformamide-methanol as red needles, m.p. 313–314° dec. (sealed tube).

Anal. Calcd. for: $C_{20}H_{18}ClNO_8 \cdot 2H_2O$: C, 50.90; H, 4.66; N, 3.00. Found: C, 51.22; H, 4.86; N, 3.16.

Tetrahydropalmatrubine (I).—A suspension containing 200 mg. of dehydropalmatrubinium bromide in 150 ml. of methanol was hydrogenated at atmospheric pressure for 2 days in the presence of 40 mg. of platinum oxide catalyst. The colorless solution was concentrated under reduced pressure and the residue treated with a dilute solution of sodium carbonate and then extracted with ether. The residue obtained by evaporation of the ether was crystallized twice from dilute methanol as colorless prisms, m.p. 148° (lit.,[3] m.p. 148–149°). The base slowly develops color on storage.

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.38; H, 6.74; N, 4.10. Found: C, 70.33; H, 6.93; N, 3.95.

Dehydroberberubinium (IV. R—R= —CH_2—) Bromide.—Quaternization of 1.1 g. of 6,7-methylenedioxyisoquinoline-1-carboxaldoxime[5] with 1.1 g. of crude 3-methoxy-2-hydroxybenzyl bromide was carried out in 9 ml. of dimethylformamide and the product cyclized as in the case of dehydropalmatrubine. Two grams (100%) of red needles were obtained, m.p. 203–205° dec.

Anal. Calcd. for $C_{19}H_{14}BrNO_4$: C, 57.00; H, 3.50; N, 3.50. Found: C, 56.83; H, 3.63; N, 3.35.

The perchlorate (IV. R—R = —CH_2—) crystallized from dimethylformamide–methanol as red needles, m.p. 338° dec.

Anal. Calcd. for $C_{19}H_{14}NClO_8$: C, 54.35; H, 3.33; N, 3.33. Found: C, 54.48; H, 3.46; N, 3.40.

Acetyldehydroberberubinium Bromide.—Dehydroberberubinium bromide was acetylated by refluxing for 3 hr. in acetic anhydride. The product crystallized from methanol as yellow prisms, m.p. 145–146°, and slowly turned to a buff color on keeping.

Anal. Calcd. for $C_{21}H_{16}BrNO_5$: C, 57.01; H, 3.61; N, 3.16. Found: C, 57.32; H, 3.90; N, 3.15.

Diisothiocyanates and Derivatives[1]

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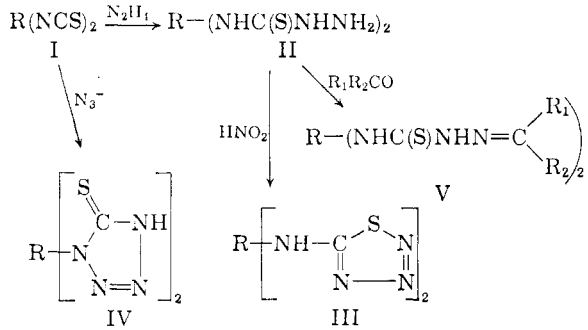
The present investigation relates to the synthesis of difunctional compounds of the aminothiatriazole and tetrazolinethione series.[4,5] For this purpose, diisothiocyanates (I) were prepared from diamines and their conversion to di-thiosemicarbazides (II), -aminothiotriazoles (III), and -tetrazoline-5-thione (IV) studied. Most of the compounds thus prepared have not been previously reported. Thiosemicarbazones (V) were prepared to characterize II.



The infrared absorption spectra of I, II, III, and IV were determined. All of the diisothiocyanates show a strong or medium band, near 2040 cm.$^{-1}$ or between 2062–2105 cm.$^{-1}$. The 2040-cm.$^{-1}$ band is slightly lower than the characteristic vibrational frequencies for the monofunctional isothiocyanates.[6] It has been suggested that the bands in the 1000–1100-cm.$^{-1}$ region are due to the isothiocyanate stretching vibration.[6] As in the monofunctional compounds[7] the S—H band (2600–

(1) The authors gratefully acknowledge the support of this investigation by the U. S. Army Research Office.

(2) To whom all correspondence should be addressed.

(3) Abstracted from the M.S. Thesis, DePaul University, Chicago, Ill., 1961.

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