[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

7-METHYLMERCAPTO-1-TETRALONE, AND ITS USE IN PREPARING SULFUR-CONTAINING CARBAZOLES AND ACRIDINES[1]

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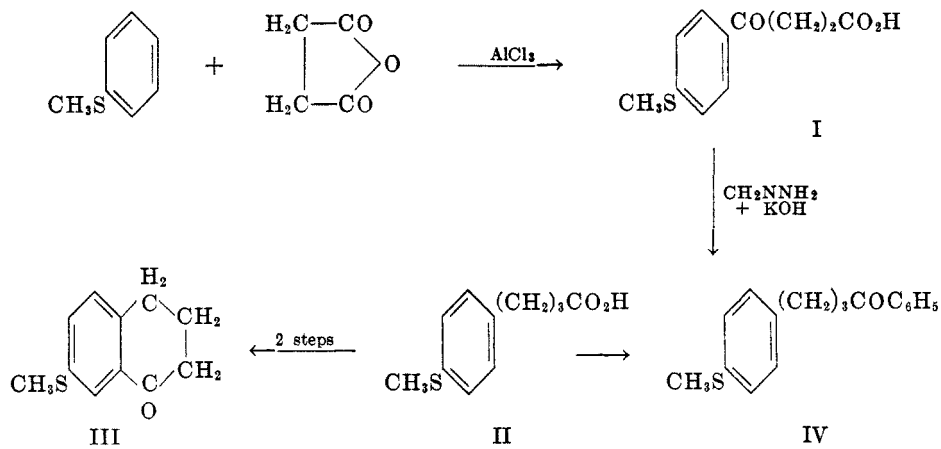
Sulfur-containing organic molecules have frequently been linked to the cancer problem, in respect either to the mechanism (1) or to the inhibition (2) of chemical carcinogenesis. In view of the activity of angular benzocarbazoles and dibenzocarbazoles as tumor-producing agents (3), derivatives of these bearing thioether groups have now been synthesized for biological investigation.[2]

From results published in previous papers of this series (4), 7-methylmercapto-1-tetralone (III) was deemed a particularly convenient intermediate for such syntheses. We prepared this hitherto unknown ketone very easily by the following sequence of reactions: (a) Friedel-Crafts' condensation of succinic anhydride with thioanisole, to give β-(4-methylmercaptobenzoyl)propionic acid (I); (b) reduction of the foregoing compound to γ-(4-methylmercaptophenyl)butyric acid (II) by the Wolff-Kishner reaction, using the convenient modified technique of Huang-Minlon (5); (c) conversion of the acid (II) into its *chloride* by thionyl chloride and cyclization of the latter with aluminum chloride into 7-methylmercapto-1-tetralone (III).

Each of these reactions was achieved with high yields, but it was found in the final stage that the use of benzene as a solvent for cyclization resulted in poor yields of the cyclic ketone (II), owing to the competitive formation of 4-(methylmercaptophenylbutyryl)benzene (IV). As no similar side-reaction was observed to any extent in the cyclization in benzene medium of γ-phenylbutyryl chloride

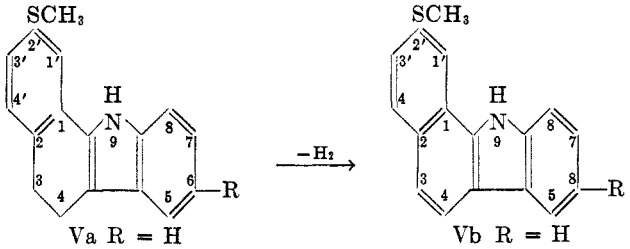


[1] This paper is Part V of a series of articles entitled: "Carcinogenic Derivatives of Carbazole."

[2] The substances described in this paper are under biological investigation in this Institute by Professor A. Lacassagne. The work here reported was carried out under a grant from the U. S. Public Health Service (Federal Security Agency). The authors convey their gratitude to the authorities concerned.

(6), it can be assumed that the thioether substituent exerted a deactivating influence on *meta* positions. This is parallel to what has already been observed in respect to the *meta*-deactivating effect of methoxyl groups (7). It may also be noted that the condensation of succinic anhydride with thioanisole apparently yielded none of the *ortho*-isomer.

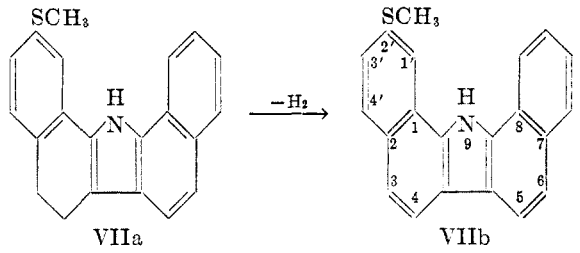
The indolization of 7-methylmercapto-1-tetralone phenylhydrazone was achieved as usual by hydrogen chloride in acetic acid; the 2′-methylmercapto-3,4-dihydro-1,2-benzocarbazole (Va) thus obtained was smoothly dehydrogenated into 2′-methylmercapto-1,2-benzocarbazole (Vb) with chloranil. From



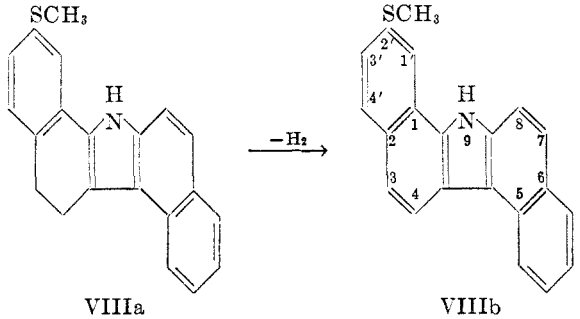
Va R = H
VIa R = CH_3

Vb R = H
VIb R = CH_3

7-methylmercapto-1-tetralone *p*-tolylhydrazone, 2′-methylmercapto-6-methyl-1,2-benzocarbazole (VIb) was similarly synthesized *via* the corresponding 3,4-dihydro intermediate (VIa). Indolization of the α and β-naphthylhydrazones of 7-methylmercapto-1-tetralone was also easily performed and yielded 2′-methylmercapto-3,4-dihydro-1,2,7,8-dibenzocarbazole (VIIa) and 2′-methylmercapto-3,4-dihydro-1,2,5,6-dibenzocarbazole (VIIIa); these relatively stable



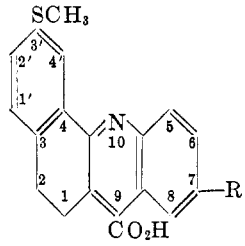
VIIa VIIb



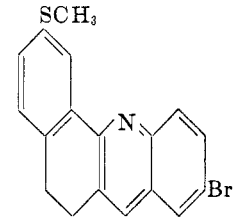
VIIIa VIIIb

compounds were dehydrogenated by chloranil as usual into 2′-methylmercapto-1,2,7,8-dibenzocarbazole (Vb) and 2′-methylmercapto-1,2,5,6-dibenzocarbazole (VIIIb).

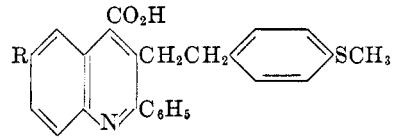
In view of the biological significance of certain 3,4-benzacridine derivatives either as carcinogens (8) or as strychnine-like drugs (9), some related compounds were prepared from 7-methylmercapto-1-tetralone. Pfitzinger condensation of the latter with isatin, 5-methylisatin, and 5-bromoisatin, readily yielded respectively, 3′-methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (IX), and 7-methyl- (X) and 7-bromo-3′-methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (XI); from the latter, 7-bromo-3′-methylmercapto-1,2-dihydro-3,4-benzacridine (XII) could be obtained by thermal decarboxylation.



IX R = H
X R = CH_3
XI R = Br



XII



XIII R = H
XIV R = Br

4-(Methylmercaptophenylbutyryl)benzene (IV) responded also to the Pfitzinger reaction, giving 2-phenyl-3-[β-(*p*-methylmercaptophenyl)ethyl]cinchoninic acid (XIII) with isatin and the 7-bromo derivative (XIV) of the latter with 5-bromoisatin.

EXPERIMENTAL

β-(4-Methylmercaptobenzoyl)propionic acid (I). To an ice-cooled well-stirred mixture of 182 g. of freshly distilled thioanisole (prepared from thiophenol with dimethyl sulphate and potassium hydroxide) and 150 g. of succinic anhydride with 1000 ml. of dry nitrobenzene, 330 g. of powdered aluminum chloride was added in small portions. The mixture was kept overnight at room temperature, poured on to ice, and the nitrobenzene completely removed with steam. The hard crust formed after cooling was powdered and treated with a hot aqueous solution of sodium carbonate; after filtration and acidification with dilute hydrochloric acid, 235 g. of the solid crude acid (I) was obtained; recrystallization from xylene or chlorobenzene yielded shiny colorless needles, melting at 157°.

Anal. Calc'd for $C_{11}H_{12}O_3S$: C, 58.9; H, 5.3.
Found: C, 58.9; H, 5.6.

γ-(4-Methylmercaptophenyl)butyric acid (II). A solution of 100 g. of the foregoing acid in a mixture of 100 g. (very large excess) of 70% hydrazine hydrate, potassium hydroxide (90 g.), and diethylene glycol (300 ml.) was heated with removal of water until the temperature reached 190–195° (*circa* five hours); the greater part of the diethylene glycol was removed by vacuum-distillation. The residue was dissolved in water, and yielded on acidification with dilute hydrochloric acid an oil which quickly solidified. This was crystallized from boiling water; glistening colorless leaflets, m.p. 54°, were obtained (yield, 95%). This compound distilled *in vacuo* without decomposition and had an unpleasant odor reminiscent of γ-phenylbutyric acid.

Anal. Calc'd for $C_{11}H_{14}O_2S$: C, 62.8; H, 6.6.
Found: C, 62.5; H, 6.8.

7-Methylmercapto-1-tetralone (III). A mixture of 180 g. of the acid (II) and 120 g. of thionyl chloride was kept for two hours at room temperature, then gently heated on the water-bath for a further hour, and thionyl chloride in excess was removed *in vacuo*. To the ice-cooled solution of the crude γ-(4-methylmercaptophenyl)butyryl chloride in 400 ml. of dry thiophene-free benzene, 135 g. of powdered aluminum chloride was stirred in in small portions. The mixture was kept overnight at room temperature, then poured on to ice; the benzene layer was washed throughly with 5% aqueous sodium hydroxide, then with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. Yield, 30 g. of the ketone (III) in the form of a thick, pale yellow oil, b.p. 202–205°/18 mm.

Anal. Calc'd for $C_{11}H_{12}OS$:C, 68.7; H, 6.2.

Found: C, 68.5; H, 6.3.

The *semicarbazone* crystallized from ethanol in fine colorless glistening prisms, melting at 215°.

4-(Methylmercaptophenylbutyryl)benzene (IV). The higher-boiling fractions from the preparation of the foregoing ketone consisted mainly of the ketone (IV), which had b.p. 250–260°/18 mm., and crystallized from benzene-ligroin in fine colorless needles melting at 70° (yield, 60 g.).

Anal. Calc'd for $C_{17}H_{18}OS$: C, 75.5; H, 6.6.

Found: C, 75.2; H, 6.5.

2'-Methylmercapto-3,4-dihydro-1,2-benzocarbazole (Va). A mixture of 2 g. of ketone (III), 2.2 g. of phenylhydrazine hydrochloride, and 3 g. of sodium acetate, was refluxed with 40 ml. of ethanol for one hour. After cooling, water was added, and the precipitate of the crude phenylhydrazone was washed with water, and dissolved in 20 ml. of a saturated solution of hydrogen chloride in acetic acid. After five minutes' heating on a water-bath, the mixture was poured into water, and the precipitate washed with water, dried, and crystallized from ligroin. Colorless needles m.p. 98°, extremely soluble in ethanol and benzene, and giving a yellow coloration with sulfuric acid and a violet *picrate*. The yield was 2 g.

Anal. Calc'd for $C_{17}H_{15}NS$: N, 5.2. Found: N, 5.0.

2'-Methylmercapto-1,2-benzocarbazole (Vb). A mixture of 1 g. of the foregoing dihydro compound, 1.2 g. of chloranil, and 25 ml. of dry xylene was gently refluxed for two hours. After cooling, the tetrachlorohydroquinone was filtered off and washed with a little xylene; the filtrate was shaken with 10% aqueous sodium hydroxide and then with water, and dried over calcium chloride. After evaporation of the solvent *in vacuo*, the solid residue was twice recrystallized from benzene; colorless prisms were obtained (0.8 g.), m.p. 149°, which gave an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{13}NS$: N, 5.0. Found: N, 5.3.

2'-Methylmercapto-6-methyl-3,4-dihydro-1,2-benzocarbazole (VIa). Prepared as usual from 2 g. of ketone (III), 2 g. of *p*-tolylhydrazine hydrochloride, and 3 g. of sodium acetate in ethanol; crystallized from benzene in fine colorless prisms (2 g.), m.p. 145°, which gave a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{17}NS$: N, 5.0. Found: N, 4.8.

2'-Methylmercapto-6-methyl-1,2-benzocarbazole (VIb). Crystallized from benzene in glinting colorless needles, m.p. 189°, which gave an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{15}NS$: N, 5.0. Found: N, 5.0.

2'-Methylmercapto-3,4-dihydro-1,2,7,8-dibenzocarbazole (VIIa). Prepared from 2 g. of ketone (III), 3 g. of α-naphthylhydrazine hydrochloride, and 4 g. of sodium acetate; crystallized from ligroin in fine yellowish needles, m.p. 138°, which gave an orange coloration with sulfuric acid. The yield was 1.5 g. The *picrate* was violet.

Anal. Calc'd for $C_{21}H_{17}NS$: N, 4.4. Found: N, 4.2.

2'-Methylmercapto-1,2,7,8-dibenzocarbazole (VIIb). Crystallized from benzene in microscopic yellowish needles, m.p. 154°, which gave an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NS$: N, 4.4. Found: N, 4.2.

2'-Methylmercapto-3,4-dihydro-1,2,5,6-dibenzocarbazole (VIIIa). Prepared from 2 g. of ketone (III), 3 g. of β-naphthylhydrazine hydrochloride, and 4 g. of sodium acetate; crystallized from benzene in microscopic colorless needles (2.2 g.), m.p. 169°, which gave an orange-yellow coloration with sulfuric acid, and a violet *picrate*.

Anal. Calc'd for $C_{21}H_{17}NS$: N, 4.4. Found: N, 4.4.

2'-Methylmercapto-1,2,5,6-dibenzocarbazole (VIIIb). Crystallized from benzene in glinting colorless leaflets, m.p. 180°, which gave a brown coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NS$: N, 4.4. Found: N, 4.2.

3'-Methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (IX). A mixture of 1.9 g. of ketone (III), 1.8 g. of isatin, and a solution of potassium hydroxide (1.8 g.) in water (2 ml.) and ethanol (12 ml.) was refluxed for 18 hours; after dilution with water, and removal of neutral impurities by ether-extraction, the aqueous layer was slightly acidified with acetic acid. The yellow precipitate (3 g.) obtained was recrystallized from methanol, yielding glinting yellow needles which softened at *circa* 160° and liquefied at 219°.

Anal. Calc'd for $C_{19}H_{15}NO_2S$: N, 4.3; Neut. equiv., 321.
Found: N, 4.0; Neut. equiv., 319.

7-Methyl-3'-methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (X). From 1.9 g. of ketone (III), 2 g. of 5-methylisatin, and 1.8 g. of potassium hydroxide, 3.5 g. of the acid (X) was obtained, crystallizing from methanol in microscopic yellow needles which softened at *circa* 150° and liquefied at 212°.

Anal. Calc'd for $C_{20}H_{17}NOS$: N, 4.1; Neut. equiv., 335.
Found: N, 4.0; Neut. equiv., 331.

7-Bromo-3'-methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (XI). Obtained in 90% yield from 1.9 g. of ketone (III), 2.5 g. of 5-bromoisatin, and 1.8 g. of potassium hydroxide; crystallized from ethanol in microscopic bright yellow needles melting at 231°.

Anal. Calc'd for $C_{19}H_{14}BrNOS$: N, 3.5; Neut. equiv., 400.
Found: N, 3.4; Neut. equiv., 402.

Dry distillation of the foregoing acid *in vacuo* yielded *7-bromo-3'-methylmercapto-1,2-dihydro-3,4-benzacridine* (XII), which formed from ethanol silky pale yellow needles, m.p. 108°, which gave a yellow coloration with sulfuric acid. Its *picrate* formed lustrous orange leaflets, m.p. 245°, from ethanol.

Anal. Calc'd for $C_{18}H_{14}BrNS$: N, 3.9; Br, 22.4.
Found: N, 3.7; Br, 22.0.

2-Phenyl-3-[β-(p-methylmercaptophenyl)ethyl]cinchoninic acid (XIII). From 1.2 g. of ketone (IV), 0.8 g. of isatin, and 1 g. of potassium hydroxide in 10 ml. of ethanol after 18 hours was obtained the acid (XIII) in 50% yield. It crystallized from ethanol in fine yellow prisms, m.p. 232° (decomp.).

Anal. Calc'd for $C_{25}H_{21}NO_2S$: N, 3.5; Neut. equiv., 395.
Found: N, 3.2; Neut. equiv., 390.

From 1.2 g. of the same ketone, 1 g. of 5-bromoisatin, and 1 g. of potassium hydroxide, 1.3 g. of *7-bromo-2-phenyl-3-[β-(p-methylmercaptophenyl)ethyl]cinchoninic acid* (XIV) was similarly obtained. It formed from acetic acid deep yellow prisms, m.p. 260° with decomposition.

Anal. Calc'd for $C_{25}H_{20}BrNO_2S$: N, 2.9; Neut. equiv., 474.
Found: N, 2.6; Neut. equiv., 470.

SUMMARY

1. The preparation of 7-methylmercapto-1-tetralone is described.

2. The use of the foregoing ketone for the synthesis of sulfur-containing carbazole and acridine derivatives is reported.

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