Acknowledgments.—This work was supported by a grant from the Research Corporation. The authors are also grateful to Mr. Robert Keown for the preparation of some of the 8-quinolinols used.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

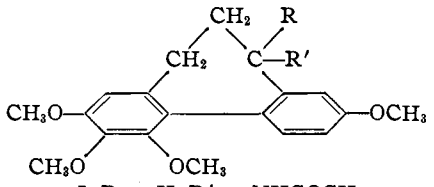
Syntheses in the Thiochromanone Field[1]

BY D. S. TARBELL, H. P. HIRSCHLER AND T. J. HALL

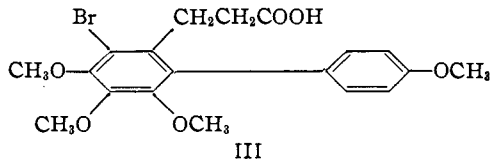
RECEIVED AUGUST 13, 1952

The synthesis of 5-phenyl-8-methoxythiochromanone by the hydrogen fluoride cyclization of β-carboxyethyl 4-methoxy-3-xenyl sulfide is described. The latter has been prepared by the addition of the appropriate thiophenol to methyl acrylate, or, more conveniently, by the action of diazotized 3-amino-4-methoxybiphenyl on β-mercaptopropionic acid in an acetate buffer. Study of the cleavage of the thiochromanone ring to form a vinyl ketone group, either in the above compound or in 5,6-benzothiochromanone and the corresponding sulfone, indicates that it is not a synthetically useful reaction.

The experiments described in this paper were undertaken to explore a possible route for the synthesis of N-acetylcolchinol methyl ether (I), an important degradation product of colchicine.[2] Previously, attempts to prepare the ketone II as a precursor of I by cyclization of the biphenylpropionic acid III had failed, because the bromine atom in III, put in as a blocking group, migrated during the Friedel–Crafts cyclization, and a 5-ring ketone resulted,[3] instead of the desired 7-ring ketone II.

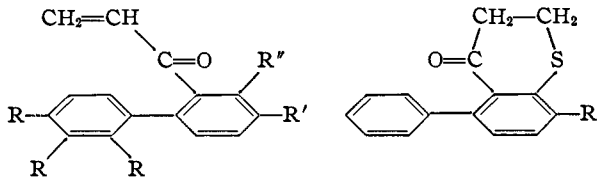


I, R = H, R′ = NHCOCH₃
II, R = R′ = =O



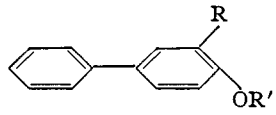
III

The object of the present work was to prepare a biphenyl with a three carbon chain containing a carbonyl group (potential or actual), and another functional group which would allow cyclization in the reverse direction from that attempted in III. For this purpose, the vinyl xenyl ketone IV, or the β-hydroxy- or β-haloethyl ketone derived from it, appeared suitable for study. It seemed that IV could be prepared by a basic cleavage[4] of the thiochromanone ring in V, followed by methylation. The $-SCH_3$ group in IV would be valuable as a blocking group to prevent cyclization to an indanone, and it could be easily removed later in the synthesis by Raney nickel desulfuration.[5] Although the thiochromanone V was synthesized, it was not possible to convert it to the vinyl ketone IV, and hence the over-all synthesis was unsuccessful



IV, R = H, R′ = OCH_3, R″ = SCH_3 V, R = OCH_3

The thiochromanone V was obtained by cyclization of the mercaptopropionic acid derivative VI with anhydrous hydrogen fluoride[6]; the mercaptopropionic acid was prepared as follows. 3-Phenyl-



VI, R = SCH_2CH_2COOH, R′ = CH_3
VII, R = $N{=}NC_6H_5$, R′ = H
VIII, R = $N{=}NC_6H_5$, R′ = CH_3
IX, R = NH_2, R′ = CH_3
X, R = SH, R′ = CH_3

XI, R = $SCH_2CH_2COOCH_3$, R′ = CH_3

azo-4-hydroxybiphenyl (VII) was methylated with an excess of alkali and methyl sulfate to form the methoxy compound VIII, and the azo group was reductively cleaved with hydrogen and platinum, yielding 3-amino-4-methoxybiphenyl (IX). The latter was also prepared by catalytic reduction of 3-nitro-4-methoxybiphenyl,[7] but the synthesis through the phenylazo compound was much more satisfactory. The amino group was converted to the thiophenol X through the xanthate procedure, and the thiophenol added smoothly to methyl acrylate in the presence of piperidine, giving the mercaptopropionic ester XI. This ester could not

(1) Aided by a grant from the National Institutes of Health.

(2) While this work was in progress, the synthesis of *dl*-I was reported by H. Rapoport, A. R. Williams and M. E. Cisney, THIS JOURNAL, **72**, 3324 (1950); **73**, 1414 (1951), while the *l*-form of I, obtainable by degradation of colchicine, was synthesized by J. W. Cook, *et al.*, *Chem. and Ind.*, 650 (1950); *J. Chem. Soc.*, 1397 (1951).

(3) H. R. Frank, P. E. Fanta and D. S. Tarbell, THIS JOURNAL, **70**, 2314 (1948); H. T. Huang, D. S. Tarbell and H. R. V. Arnstein, *ibid.*, **70**, 4181 (1948); N. Barton, J. W. Cook and J. D. Loudon, *J. Chem. Soc.*, 1079 (1949).

(4) *Cf.* (a) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 6, 24 (1951); (b) B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(5) The projected synthesis is somewhat similar to the method for the formation of indanones by cyclization of Mannich bases of aryl alkyl ketones described by J. H. Burckhalter and R. C. Fuson, *ibid.*, **70**, 4184 (1948).

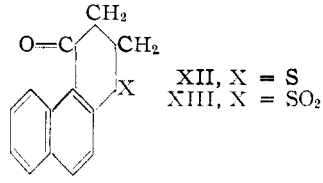
(6) Numerous other methods of cyclization, including stannic chloride or aluminum chloride and the acid chloride, the inverse Friedel–Crafts procedure (W. S. Johnson and H. W. Glenn, *ibid.*, **71**, 1092 (1949)), polyphosphoric acid (H. R. Snyder and F. X. Werber, *ibid.*, **72**, 2962, 2965 (1950)), fluosulfonic acid (W. Baker, *et al.*, *J. Chem. Soc.*, 1376 (1951)), and others, were unsuccessful.

(7) F. Bell and J. Kenyon, *ibid.*, 3047 (1926).

be hydrolyzed in base, because the thiophenol addition to the acrylate was reversed by base; the hydrolysis to the acid VI was, however, carried out quantitatively by allowing the ester to stand at room temperature for several days in aqueous acetone with hydrochloric acid.

In later work, it was found that the synthesis of VI could be very materially shortened by treating the diazonium compound from 3-amino-4-methoxybiphenyl with β-mercaptopropionic acid; nitrogen was evolved smoothly, and VI was obtained directly in 35–40% yield.

Attempted cleavage of the thiochromanone V and the more accessible 5,6-benzothiochromanone (XII) and its sulfone (XIII) to the vinyl ketone by numerous methods, such as formation of the sulfonium sulfate and subsequent cleavage with alkali,[8]



XII, X = S
XIII, X = SO_2

addition of heavy metal salts to promote the formation of sulfonium compounds[9] and basic cleavage,[10] were all unsuccessful. In almost all cases, conditions drastic enough to form the vinyl ketone appeared to cause it to polymerize.[11]

Experimental[12]

3-Phenylazo-4-hydroxybiphenyl (VII) was prepared in 97% crude yield by coupling diazotized aniline with 4-hydroxybiphenyl at 0°; a sample recrystallized twice from ethanol melted at 127.5°; the reported[7] value is 129°.

3-Phenylazo-4-methoxybiphenyl (VIII).—To 20 g. of 3-phenylazo-4-hydroxybiphenyl in 1.5 l. of alcohol was added 5 g. of potassium hydroxide pellets, which caused the solution to turn deep red. Methyl sulfate was then added, in 5-cc. portions, and the solution was heated until it showed an acid reaction. After a total of 70 cc. of methyl sulfate had been added, with the intermittent addition of more potassium hydroxide to keep the solution basic, as shown by the red color, the solution remained orange, even after addition of more alkali. A red precipitate settled out as the reaction proceeded. The alcohol was distilled off and was replaced by a mixture of 1 l. of water and 100 cc. of dilute ammonium hydroxide. After standing 2 hr. the precipitate was collected, washed with water, and recrystallized from ethyl acetate. Bright red needles (15 g., 71%) of m.p. 136.5–137.5° were obtained.

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.15; H, 5.60. Found: C, 79.26; H, 5.61.

3-Amino-4-methoxybiphenyl (IX).—3-Phenylazo-4-methoxybiphenyl (10 g.) was reduced with hydrogen and platinum at 60° in 125 cc. of absolute alcohol, using a Parr shaker. The catalyst was removed by filtration and water was added to precipitate the desired amine and leave the aniline in solution. The precipitate was allowed to stand overnight, and was then collected, giving an almost quantitative yield of the product, which, after recrystallization from alcohol or hexane, melted at 80–81°. This material gave no depression on mixed m.p. with the product obtained by catalytic reduction of 3-nitro-4-methoxybiphenyl.[7]

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58. Found: C, 78.69; H, 6.61.

The **acetyl derivative** of the amine melted at 186.7–187.5°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.68; H, 6.22. Found: C, 74.47; H, 6.10.

3-Mercapto-4-methoxybiphenyl (X).—3-Amino-4-methoxybiphenyl (15.9 g.) was converted to the hydrochloride by passing hydrogen chloride into an ether solution of the amine. The finely divided salt was suspended in 200 cc. of water containing 9.6 cc. of concd. hydrochloric acid, and a solution of 5.8 g. of sodium nitrite in 50 cc. of water was added at 0°. The diazonium solution, kept at 0°, was added with stirring to an aqueous solution of 14 g. of potassium ethyl xanthate at 40°. The thiocarbonate ester, a dark oil, was taken up in ether and the solution was washed with 100 cc. of 10% sodium hydroxide, and then with water until neutral. The ether solution was dried with calcium chloride, the solvent was evaporated, and the residual ester was saponified by refluxing for 8 hr. with a mixture of 400 cc. of alcohol, 100 cc. of benzene and 16 g. of potassium hydroxide. After this time, most of the organic solvents were allowed to boil away and 400 cc. of water was added to the residue. The mixture was extracted with ether and the extracts were discarded; the aqueous solution was acidified with concd. sulfuric acid, and the precipitated oil, which soon crystallized, was collected and washed with water. The product could be purified by vacuum distillation or sublimation; a sample distilled at 170–175° (1 mm.), melted at 60–62°. Two crystallizations from methanol raised the m.p. to 64–65°.

Anal. Calcd. for $C_{13}H_{12}OS$: C, 72.19; H, 5.60. Found: C, 71.90; H, 5.60.

The **disulfide** was prepared by oxidation of X with iodine in chloroform solution, and was obtained, after several crystallizations from chloroform–petroleum ether, as greenish-yellow plates, m.p. 168.5–169°.

Anal. Calcd. for $C_{26}H_{22}O_2S_2$: C, 72.53; H, 5.15. Found: C, 72.88; H, 5.12.

β-Carbomethoxyethyl 4-Methoxyl-3-xenyl Sulfide (XI).—A mixture of 4 g. of 3-mercapto-4-methoxybiphenyl, 6 g. of freshly distilled methyl acrylate and 5 drops of piperidine in 16 cc. of benzene was warmed below its boiling point on the steam-bath for 6 hr. It was cooled, the volatile material was removed *in vacuo*, and the residue was crystallized from methanol three times, melting at 62.5–63.5°. Recovery of additional product from the mother liquors gave a total yield of 4.2 g. (75%) of pure material; some of the disulfide was also isolated. A mixed m.p. with the mercapto compound showed a marked depression.

Anal. Calcd. for $C_{17}H_{18}O_3S$: C, 67.53; H, 5.99. Found: C, 67.89; H, 6.28.

β-Carboxyethyl 4-Methoxy-3-xenyl Sulfide (VI). A. By Hydrolysis of the Ester XI.—3-Mercapto-4-methoxybiphenyl (1.33 g.) dissolved in 25 cc. of acetone and 8 cc. of 20% aqueous hydrochloric acid, was allowed to stand at room temperature for several days. The solution was then diluted with water, extracted with ether, and the ether extract was washed several times with water. The ether solution was then extracted with 10% sodium carbonate, until acidification of the extracts with hydrochloric acid no longer yielded a precipitate. The acid was obtained as small white plates, m.p. 137–139°. On recrystallizations from dilute ethanol it formed white needles which weighed 1.2 g. (97%), and melted at 138.5–139°.

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.65; H, 5.59. Found: C, 66.92; H, 5.66.

In repeating these preparations numerous times, it was found advantageous not to isolate the mercapto compound X or the acrylate addition product XI. Instead, the crude mercapto compound was treated with zinc–acetic acid to reduce any disulfide present, the product was treated with methyl acrylate, and the ester XI was hydrolyzed without isolation.

B. From Diazotized 3-Amino-4-methoxybiphenyl and β-Mercaptopropionic Acid.—The amine hydrochloride of X (5 g., prepared as above) was diazotized and excess ni-

(8) *Cf.* F. Arndt and J. Pusch, *Ber.*, **58**, 1652 (1925).

(9) F. Kehrmann and G. A. Sava, *ibid.*, **45**, 2895 (1912); K. A. Hofmann and K. Ott, *ibid.*, **40**, 4930 (1907); T. P. Hilditch and S. Smiles, *J. Chem. Soc.*, **91**, 1394 (1907); K. Krollpfeiffer, H. Hartman and F. Schmidt, *Ann.*, **563**, 15 (1949).

(10) *Cf.* F. C. Bordwell, W. H. McKellin and D. Babcock, THIS JOURNAL, **73**, 5566 (1951).

(11) In two cases, a crystalline compound whose analysis and infrared spectrum indicated it to be the desired vinyl ketone IV was isolated, but the results were not reproducible.

(12) Analyses by Micro-Tech Laboratories, Mrs. G. Sauvage and Miss Claire King.

trous acid removed with urea. The diazonium solution was then buffered at a *p*H of about 6 by the addition of 50 g. of sodium acetate and 15 cc. of glacial acetic acid in 50 cc. of water.[13] The diazonium solution was then added dropwise with stirring at 0° during a 2-hr. period to a solution of 4 g. of β-mercaptopropionic acid and 10 g. of sodium acetate in 50 cc. of water. There was an immediate formation of a yellow-white solid and an evolution of gas during the addition. The best method of working up the product was to collect it and recrystallize it once from aqueous alcohol. The product was then allowed to stand in aqueous acetone with some concd. hydrochloric acid for 3 days at room temperature, following the hydrolysis procedure described above for the ester XI. The solution was extracted with ether, the extracts were washed with sodium carbonate, and the desired acid VI was obtained by acidification of the carbonate solution; it weighed 4.7 g. (36%) and melted at 135–137°. The ether extract yielded an appreciable amount of neutral crystalline material, m.p. 82–82.5°, shown to be 4-methoxybiphenyl by a mixed m.p.

5-Phenyl-8-methoxythiochromanone (V).—The only way found for the cyclization of VI to V was the following. The acid VI (1 g.) was treated in a platinum dish with 20–30 g. of anhydrous hydrogen fluoride. The dish was placed in a paraffin-coated desiccator over calcium chloride and allowed to stand overnight. The viscous oil in the dish was dissolved in benzene, with warming on a steam-bath, and was extracted with sodium carbonate; the residue in the dish was also extracted by sodium carbonate; usually about 0.6 g. of the starting acid VI was recovered by acidification of the carbonate extracts. The benzene solution was washed with water, dried, and chromatographed on alumina, using dry benzene as the eluent. The benzene yielded a dark oil, from which was obtained crystalline material, which, after two crystallizations from methanol, weighed 0.2 g. (50%, based on unrecovered starting material) and melted at 124–125°.

(13) The reaction did not take place in an unbuffered solution of low *p*H; *cf.* D. S. Tarbell, E. G. Lindstrom, *et al.*, THIS JOURNAL, **70**, 1381 (1948).

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 71.02; H, 5.43.

The dinitrophenylhydrazine melted, after two recrystallizations from chloroform–ethanol, at 253–256°.

Anal. Calcd. for $C_{22}H_{18}N_4O_5S$: C, 58.65; H, 4.02. Found: C, 58.70; H, 4.39.

β-(2-Naphthyl)-mercaptopropionic Acid.—This compound was not obtained by the action of diazotized β-naphthylamine on β-mercaptopropionic acid, using either an acetate buffer or an acid solution; tar and naphthalene were the products. It was readily prepared by heating 4 g. of β-thionaphthol with 10 g. of methyl acrylate and a few drops of piperidine for 6 hr. The volatile material was then removed *in vacuo*, the residue was dissolved in acetone, concd. hydrochloric acid was added until a precipitate appeared, and additional acetone was added to clear the solution. After standing for 4 days, the mixture was worked up as described above, and 4.5 g. (77%) of the desired acid was obtained, m.p. 102–103°, after crystallization from benzene.[14]

5,6-Benzothiochromanone (XII).[14]—This compound was prepared in 60% yield by the cyclization with anhydrous hydrogen fluoride, by essentially the procedure described above for V. The same yield was obtained by the use of sulfuric acid (as in ref. 14) but the product from the hydrogen fluoride was easier to work up.

5,6-Benzothiochromanone Sulfone (XIII).—The thiochromanone (1 g.) was refluxed 1 hr. with 10 g. of 30% hydrogen peroxide in glacial acetic acid, and the excess peroxide was decomposed by addition of manganese dioxide. The solution was filtered, was diluted with water and the resulting precipitate was isolated. After three crystallizations from ethanol, 0.79 g. (69%) of sulfone, m.p. 150–151°, was obtained.

Anal. Calcd. for $C_{13}H_{10}O_3S$: C, 63.45; H, 4.06. Found: C, 63.57; H, 4.10.

(14) The m.p. reported for the acid (F. Krollpfeiffer and H. Schultze, *Ber.*, **56**, 1819 (1923)) prepared by the action of β-bromopropionic acid on β-thionaphthol, is 104–105°.

ROCHESTER, N. Y.

NOTES

Preparation of β-Hydroxydialkyl Peroxides

BY M. R. BARUSCH AND J. Q. PAYNE

RECEIVED DECEMBER 12, 1952

Three β-hydroxydialkyl peroxides were prepared by a reaction of *t*-butylhydroperoxide with epoxides. The compounds synthesized were β-hydroxyethyl-*t*-butyl peroxide, β-hydroxypropyl-*t*-butyl peroxide and β-hydroxyisobutyl-*t*-butyl peroxide. Yields obtained ranged from 33–43%. No effort was made to develop optimum conditions to improve these yields. 3,5-Dinitrobenzoates of two of the hydroxy peroxides were prepared. It seems likely that reactions of this type could be used as a general preparative method for β-hydroxydialkyl peroxides or hydroperoxides.

β-Hydroxyethyl-*t*-butyl Peroxide.—A 500-ml. round-bottom flask fitted with a mercury-sealed stirrer, dropping funnel, condenser and thermometer, was immersed in an ice–salt-bath. Forty-four grams (1.0 mole) of ethylene oxide and 150 ml. of ethyl ether were introduced. Maintaining the temperature below 3°, 15 ml. of 40% potassium hydroxide was added over a 30-minute period. Forty-seven grams (0.33 mole) of 63% *t*-butyl hydroperoxide obtained from the Union Bay State Company was added dropwise over a 1.5-hr. interval, maintaining the temperature below 5°. The mixture was allowed to come to room temperature and stirring continued for four hours. The aqueous layer was discarded. Light ends were removed from the organic phase by distillation at atmospheric pressure followed by vacuum distillation to 30° (20 mm.) head temperature. From the bottoms 14.6 g. (33% yield) of crude product was recovered, b.p. 35° at 35 mm. to 34° at 1.5 mm. Redistillation of this material produced 11.5 g. of product, b.p. 37–38° at 2 mm., $n^{20}D$ 1.4249, d^{20}_4 0.9561.

Anal.[1] Calcd. for $C_6H_{14}O_3$: C, 53.71; H, 10.51. Found: C, 53.79; H, 10.49.

The 3,5-dinitrobenzoate of this compound was prepared by the method of Malone and Reid.[2] The derivative was recrystallized several times from aqueous ethanol and finally from absolute ethanol. It had a melting point of 63–63.6°.

Anal. Calcd. for $C_{13}H_{16}O_8N_2$: C, 47.56; H, 4.91; N, 8.53. Found: C, 47.32; H, 4.99; N, 8.67.

β-Hydroxypropyl-*t*-butyl Peroxide.—In similar manner to the above, but in the absence of the ether, 39 g. (0.67 mole) of 1,2-propene oxide, 10 ml. of 40% potassium hydroxide and 24 g. (0.17 mole) of 63% *t*-butyl hydroperoxide were agitated. After the addition of the hydroperoxide was complete, the mixture was allowed to come to room temperature and then was heated to 40° for two hours. The

(1) Microanalyses were made by Microchemical Specialties, Berkeley, California.

(2) O. B. Malone and E. E. Reid, THIS JOURNAL, **51**, 3424 (1929).