Ring Tautomerism of o-Mercaptohydrocinnamonitriles. 2-Amino-4*H*-1-benzothiopyrans[1a,b]

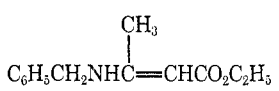
GARDNER W. STACY,* DAVID L. ECK,[1c] AND THOMAS E. WOLLNER[1d]

Department of Chemistry, Washington State University, Pullman, Washington 99163

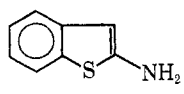
Received March 24, 1970

The formation of the thiochromenes, ethyl 2-amino-4*H*-1-benzothiopyran-3-carboxylate (**5c**) and 2-amino-4*H*-1-benzothiopyran-3-carbonitrile (**6c**), enamine ring tautomers of the substituted *o*-mercaptohydrocinnamonitriles, **5a** and **6a**, respectively, is described. Corresponding failure in the preparation of the parent *o*-mercaptohydrocinnamonitrile (**4a**) or either of its ring tautomers (**4b**, **4c**) from *o*-(benzylthio)hydrocinnamonitrile (**17**) is also reported. This latter failure, as well as thiochromene formation, is rationalized on the basis of the relative stability of exocyclic and endocyclic double bonds in six-membered rings. The preparation of the nitriles (**22a,b**) used in the formation of **5c** and **6c**, respectively, is also reported, as are two approaches (Scheme I) to *o*-(benzylthio)hydrocinnamonitrile (**17**), which was required for the attempted synthesis of the system **4**. In the latter case, the undesired formation of 2,3-dihydrobenzo[*b*]thiophene (**12**) from 2-(*o*-benzylthio)phenethyl alcohol (**9**) is described and compared with the recently discovered heterocyclization of *cis*-γ-benzylthiocrotononitrile to 2-aminothiophene (process **20**).

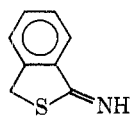
Imine–enamine tautomerism in various systems has been under investigation in recent years,[2] and generally the enamine predominates. For example, Dudek and Volpp[2a] demonstrated an enamine structure for ethyl β-benzylaminocrotonate (**1**). Systems exist, however, where the imine becomes tautomerically significant as a result of appropriate structural modifications. The 2-nitrogen substituted benzothiophenes illustrate this concept. Although the benzo[*b*]thiophene **2** has the expected 2-enamine structure,[3] the corresponding dihydrobenzo[*c*]thiophene **3** has an imino group in the 2 position.[4] This imino tautomer **3a** is favored because the alternative enamine would require the less stable *o*-quinoidal ring system (**3b**).



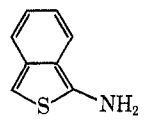
1



2

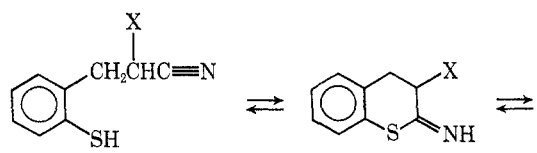


3a



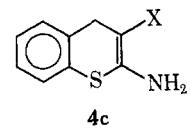
3b

We now wished to shift our attention from the five-membered ring of benzothiophenes to the six-membered ring of thiochromans **4–6b** and thiochromenes **4–6c**. Here a question to be answered was how readily would ring tautomerism, involving nitrile and thiol groups, occur? Because of the correlative work of Brown,[5] who observed that the formation or retention of an exocyclic double bond in a six-membered ring does not occur so readily as for a five-membered ring, we speculated that, in system **4**, the chain tautomer, *o*-mercaptohydrocinnamonitrile (**4a**), would prevail. However, it seemed plausible that location of an appropriate substituent (*e.g.*, X = $CO_2C_2H_5$ or CN) on the α carbon atom would result in ring tautomerism. This would follow because the carbon–nitrogen exocyclic double bond would be isomerized into the stable endocyclic position as a result of conjugation with the substituent X (**5c**, **6c**).



4a, X = H
5a, X = $CO_2C_2H_5$
6a, X = CN

4b



4c

All of these arguments have proven to be accurate. First, experiments to form **4b** or **4c** from *o*-(benzylthio)-hydrocinnamonitrile (**17**)[6] were unsuccessful, as indicated by recovery of starting material. Since the five-membered ring systems, 2,3-dihydro-3,3-dimethyl-2-iminobenzo[*b*]thiophene and 2-aminobenzo[*b*]thiophene (**2**), formed instantly in quantitative yields under the same conditions, these differences are significant and reflect the difficulty in the formation of an exocyclic double bond in a six-membered ring. A further attempt to remove the benzyl group of **17**, involving anhydrous aluminum bromide, which previously had been found to be a useful reagent for this purpose,[7] also failed. Although the chain tautomer of this system, *o*-mercaptohydrocinnamonitrile (**4a**), might eventually have been obtained, experimentation was discontinued in favor of work on the substituted *o*-mercaptohydrocinnamonitriles (**5a**, **6a**).

The synthesis of *o*-(benzylthio)hydrocinnamonitrile (**17**), the key precursor in the experiments just outlined,

* To whom correspondence should be addressed.

(1) (a) Presented as part of the Organic Chemistry Program at the 24th Annual Northwest Regional Meeting of the American Chemical Society, Salt Lake City, Utah, June 12, 1969. (b) For preceding paper VIII on Tautomerism, see D. L. Eck and G. W. Stacy, *J. Hetercycl. Chem.*, **6**, 147 (1969). (c) Dow Research Assistant, summer 1966; National Science Foundation Summer Fellow, 1967. (d) National Science Foundation Summer Fellow, 1963; National Science Foundation Cooperative Fellow, 1963–1964.

(2) (a) G. O. Dudek and G. P. Volpp, *J. Amer. Chem. Soc.*, **85**, 2697 (1963); (b) J. Dabrowski and J. Terpinski, *Tetrahedron Lett.*, **49**, 1363 (1965); (c) H. Bredereck, G. Simchen, R. Wahl, and F. E. Effenberger, *Chem. Ber.*, **101**, 512 (1968); (d) H. Ahlbrecht, *Tetrahedron Lett.*, **42**, 4421 (1968).

(3) G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *J. Org. Chem.*, **30**, 4074 (1965).

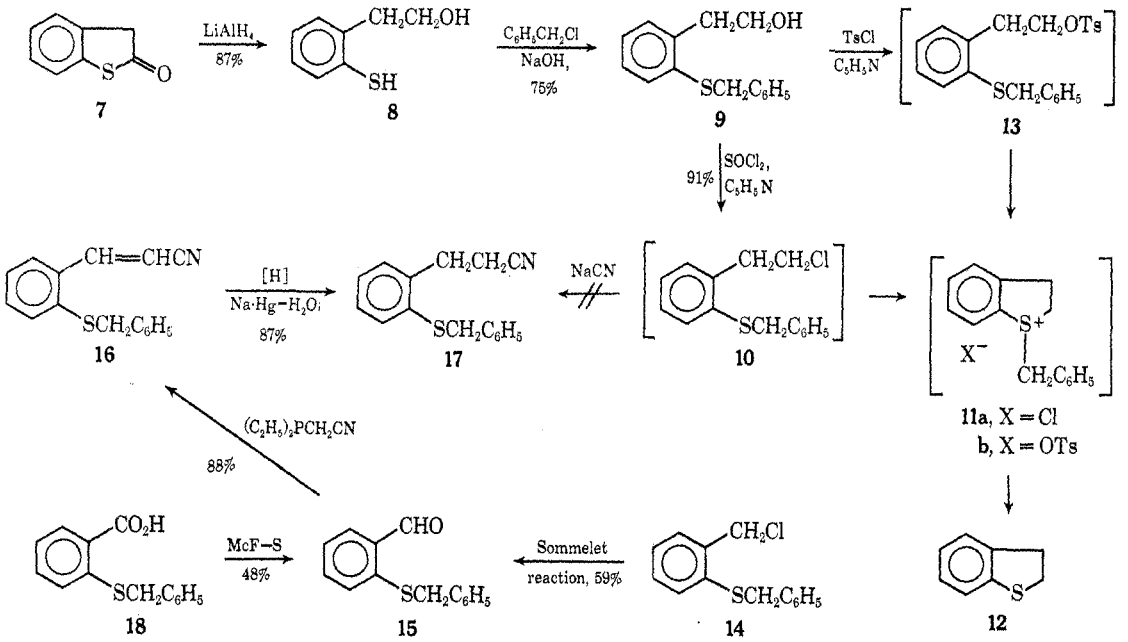
(4) (a) A. W. Day and S. Gabriel, *Ber.*, **23**, 2478 (1890); (b) G. W. Stacy, A. J. Papa, F. W. Villaescusa, and S. C. Ray, *J. Org. Chem.*, **29**, 607 (1964).

(5) H. C. Brown, *ibid.*, **22**, 439 (1957).

(6) This was an attempted application of our new method of forming tautomeric mercaptonitriles: G. W. Stacy and D. L. Eck, *Tetrahedron Lett.*, 5201 (1967); also see ref 1b.

(7) G. W. Stacy and T. E. Wollner, *J. Org. Chem.*, **32**, 3082 (1967).

SCHEME I

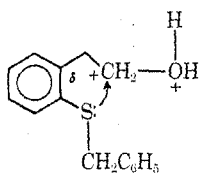


is presented in Scheme I. Problems were involved in the sequence explored, and some unanticipated results were uncovered. Because of the availability of benzo[*b*]thiophen-2(3*H*)-one (**7**) by oxidation of 2-benzo[*b*]thienyllithium,[8] we were attracted to the prospective series leading from **7** to benzyl *o*-(2-chloroethyl)-phenyl sulfide (**10**) and then to *o*-(benzylthio)hydrocinnamonitrile (**17**). This approach depended on the facile reduction of the thiolactone **7** to *o*-mercaptophenethyl alcohol (**8**) by lithium aluminum hydride in 87% yield. In the next step, selective alkylation of sulfur in the presence of the hydroxyl group of **8** with benzyl chloride under alkaline conditions to give **9** proved no problem. However, treatment of **9** with thionyl chloride did not give the intermediate chloride **10**, but instead 2,3-dihydrobenzo[*b*]thiophene (**12**) in 91% yield. Benzyl chloride also was isolated from the reaction mixture in 80% yield. The same products were also obtained employing alternative conditions, such as phosphorus pentachloride in carbon tetrachloride or concentrated hydrochloric acid. An attempt to prepare tosylate **13** was no more successful; 2,3-dihydrobenzo[*b*]thiophene (**12**) again was formed.

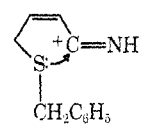
Such cyclization probably occurs through a cyclic sulfonium intermediate **11** by interaction of sulfur with electron-deficient carbon (process **19**). Of related interest is the *S*-methyl series;[9] unlike our *S*-benzyl series, here *o*-methylthiophenethyl alcohol reacts with hydrochloric acid to yield a chloride. However, the fact that the ortho isomer reacts 620 times more rapidly than the para isomer is consistent with a cyclic sulfonium intermediate. Indeed, a substance claimed to be a chloroplatinate salt of the sulfonium chloride was isolated.

The postulate of a sulfonium intermediate is supported further by the high yields of benzyl chloride obtained in the several experiments studied. Comparable observations were made relevant to the formation of perhydrobenzofurans under similar conditions.[10] The special role of the five-membered cyclic sulfonium intermediate also becomes more apparent when one considers the usual difficulty in cleavage of benzyl sulfides.[11]

Finally, it should be noted that our recently discovered heterocyclization of benzylthionitriles[1b] follows a parallel course and a similar high yield when a five-membered ring is involved. In the conversion of **9** to **12**, an electron deficiency is created on the hydroxyl-bearing carbon atom by protonation, as in the case of hydrochloric acid, or by combination, as with tosyl chloride. The electron-deficient carbon atom then interacts with nucleophilic sulfur in the cyclization process (**19**). In the parallel reaction of *cis*-γ-benzylthiocrotonitrile,[1b] the carbon atom of the nitrile group becomes electron deficient by virtue of protonation of the nitrogen atom and then interacts with electron-dense sulfur (process **20**).



19



20

The synthesis of **17** was eventually accomplished through a sequence involving a Wittig-type reaction[12] with *o*-(benzylthio)benzaldehyde (**15**) followed by reduction of cinnamonitrile **16** with sodium amalgam, both processes taking place in high yield. The prerequisite aldehyde **15** was prepared most conveniently by the Sommelet reaction; the McFadyen and Stevens method was less satisfactory for this purpose.

(8) G. van Zyl, D. C. DeJongh, V. L. Heasley, and J. W. van Dyke, *J. Org. Chem.*, **26**, 4942 (1961).

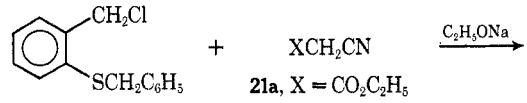
(9) G. M. Bennett and M. M. Hafez, *J. Chem. Soc.*, 652 (1941).

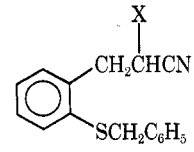
(10) (a) S. E. Cantor and D. S. Tarbell, *J. Amer. Chem. Soc.*, **86**, 2902 (1964); (b) G. R. Gray, F. C. Hartman, and R. Baker, *J. Org. Chem.*, **30**, 2020 (1965).

(11) D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951).

(12) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

We next investigated our premise that introduction of an appropriate substituent (*e.g.*, **5** and **6**) would promote ring tautomerism through conjugation. The required nitriles (**22a,b**) were prepared by alkylation of ethyl cyanoacetate (**21a**) or malononitrile (**21b**), respectively, by benzyl α-chloro-*o*-tolyl sulfide (**14**). These intermediates (**22a,b**) then were heterocyclized by the action of aluminum bromide in benzene followed by hydrolysis to produce the desired thiochromenes (**5c**, **6c**).





Spectroscopic evidence for the 2-aminothiochromene structural assignment was conclusive. For example, the infrared spectrum of ethyl 2-amino-4*H*-1-benzothiopyran-3-carboxylate (**5c**) had two strong bands in the N—H stretch region at 3470 and 3310 cm^{-1}; the spectrum showed no evidence for absorption bands in the C≡N and C=N regions which would be required by the tautomers **5a** and **5b**, respectively. There was a strong ester carbonyl band at 1650 cm^{-1}. The nmr spectrum provided additional evidence with five areas of absorption at δ 7.1–7.3, 6.4, 4.0–4.3 (q), 3.5, and 1.2–1.4 (t) with an area ratio of 4:2:2:2:3. The two-proton peak at 6.4 corresponds to the amino function, while the peak at 3.5 can be assigned to the methylene group in the 4 position. The stability of the enamine structures **5c** and **6c** relative to the imino structure agrees with Dudek's[2b] findings for β-benzylaminocrotonate and Brown's[5] observations on exocyclic double bonds. It is also in keeping with observed reluctance of nitrogen to form a double bond when alternative single bond formation is possible.[13]

Experimental Section

All melting points are corrected while boiling points at reduced pressures are uncorrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn. The infrared spectra were determined on Beckman IR-5 and IR-8 spectrophotometers and assignments were based on data cited by Bellamy,[14] if not otherwise stated. The spectra of liquids were run as neat films with sodium chloride optics. Nmr spectra were determined by a Varian A-60 spectrometer using carbon tetrachloride or deuterated chloroform as the solvent and tetramethylsilane as the internal standard. The chemical shift in parts per million is followed in parentheses by the splitting pattern: cm = complex multiplet, q = quartet, d = doublet, singlets being otherwise assumed, and the number of protons found by integration follows. Routine work-up of experimental procedures unless otherwise stated involves extraction with ethyl ether, washing the combined extracts with sodium chloride solution, drying over anhydrous magnesium sulfate, and finally removal of the ether to give a distillable or crystallizable residue.

o-Mercaptophenethyl Alcohol (8).—To a stirred suspension of 1.90 g (0.05 mol) of lithium aluminum hydride in 100 ml of anhydrous ether under nitrogen was added dropwise a solution of 3.60 g (0.024 mol) of benzo[*b*]thiophene-2(3*H*)-one (**7**)[15] in 75 ml of anhydrous ether over a period of 20 min. The mixture was stirred at room temperature for 4 hr, and then 40 ml of water was added carefully with cooling to decompose excess lithium aluminum hydride, after which was added dropwise 125 ml of 10% sulfuric acid with continued cooling. The phases were separated, and the aqueous phase was extracted with ether (two 100-ml portions). After work-up, the viscous residue was vacuum distilled to yield 3.20 g (87%): bp 93–96° (0.08 mm); $n^{25}D$ 1.5959; ir 3360 (OH), 2562 cm^{-1} (SH).

Anal. Calcd for $C_8H_{10}OS$: C, 62.30; H, 6.54; S, 20.79. Found: C, 62.36; H, 6.70; S, 20.86.

o-(Benzylthio)phenethyl Alcohol (9).—A solution of 2.60 g (0.017 mol) of **8** in 2 ml of 95% ethanol was added dropwise to a stirred solution of 0.80 g (0.02 mol) of sodium hydroxide in 10 ml of 95% ethanol to which 1 ml of water was added (nitrogen). The solution was stirred 0.5 hr at room temperature and then 2.28 g (0.018 mol) of benzyl chloride was added dropwise. The mixture was stirred and refluxed for 6 hr and then filtered. The ethanol was removed under reduced pressure, and the residue taken up in 50 ml of ether. After work-up, distillation of the viscous liquid yielded 2.10 g (75%): bp 147–151° (0.05 mm); $n^{25}D$ 1.6146; ir 3360 cm^{-1} (OH).

Anal. Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60; S, 13.12. Found: C, 73.89; H, 6.66; S, 13.28.

Formation of 2,3-Dihydrobenzo[*b*]thiophene (12) from 9.—To a solution of 3.00 g (0.0123 mol) of **9** in 3 ml of dry pyridine was added dropwise with cooling (under nitrogen) 1.60 g (0.0134 mol) of thionyl chloride. After the addition, the mixture was stirred at 65° for 12 hr, and then 50 ml of cold water was added and the mixture was extracted with chloroform (three 30-ml portions). After work-up, the residue was fractionally distilled yielding two main fractions: an 80% yield of benzyl chloride [bp 80–83° (16 mm), ir identical with that of an authentic sample]; and 1.50 g (90%) of 2,3-dihydrobenzo[*b*]thiophene (**12**) [bp 108–110° (16 mm), $n^{25}D$ 1.6184].

Anal. Calcd for C_8H_8S: C, 70.54; H, 5.92; S, 23.54. Found: C, 70.23; H, 5.72; S, 23.27.

Similar results were obtained by using other reagents: phosphorus pentachloride in carbon tetrachloride gave 47% **12** and 50% benzyl chloride, concentrated hydrochloric acid gave 72% **12** and 68% benzyl chloride, and tosyl chloride–pyridine gave 69% **12**.

The sulfone of 2,3-dihydrobenzo[*b*]thiophene (12) was prepared by oxidation with 30% hydrogen peroxide in glacial acetic acid to give a 79% yield of product, mp 91–92.5° (lit.[16] mp 91.5–92°).

Anal. Calcd for $C_8H_8SO_2$: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.19; H, 4.71; S, 18.82.

o-(Benzylthio)benzaldehyde (15) from Benzyl α-Chloro-*o*-tolyl Sulfide (14) by the Sommelet Reaction.—A solution of 12.42 g (0.05 mol) of benzyl α-chloro-*o*-tolyl sulfide[3] and 9.11 g (0.065 mol) of hexamethylenetetramine in 150 ml of chloroform was heated under reflux for 2 hr with 100 ml of 20% hydrochloric acid. The mixture was cooled and extracted with ether (three 100-ml portions). Work-up yielded 6.75 g (59%) of pale yellow solid, mp 69–74°. This material could be employed without further purification in the preparation of **16**. A sample was recrystallized twice from absolute ethanol to yield colorless needles: mp 75–76°; ir ($CHCl_3$) 2700 (aldehyde C–H), 1690 cm^{-1} (C=O); nmr (CCl_4) δ 10.14 (1, CHO), 7.22–7.05 (cm, 9, benzene rings), 3.93 (2, CH_2).

Anal. Calcd for $C_{14}H_{12}OS$: C, 73.60; H, 5.31; S, 14.04. Found: C, 73.70; H, 5.18; S, 13.94.

A **2,4-dinitrophenylhydrazone** recrystallized from ethyl acetate–ethanol gave orange needles, mp 199–200°.

Anal. Calcd for $C_{20}H_{16}N_4O_4S$: C, 58.95; H, 3.72; N, 13.75. Found: C, 58.73; H, 3.81; N, 13.68.

o-Benzylthiobenzaldehyde (15) from o-(Benzylthio)benzoic Acid (18) by the McFadyen and Stevens Method.—A mixture of 34.0 g (0.08 mol) of crude 1-(*o*-benzylthiobenzoyl)-2-*p*-tolysulfonylhydrazide (see below) in 250 ml of freshly distilled ethylene glycol was heated to 160°, and then 18 g (0.80 mol) of

(13) (a) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956); (b) K. L. Morgan, *ibid.*, 1461 (1952).

(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958.

(15) Prepared in 30% yield by oxidation of benzo[*b*]thienyllithium in the presence of an alkyl Grignard reagent (ref 8).

(16) R. Fricke and G. Spilker, *Ber.*, **58**, 1589 (1952).

anhydrous sodium carbonate was added. The mixture was heated until evolution of gas ceased (2–3 min). The soluion was cooled slightly and then diluted with 2 l. of hot water. Work-up of the mixture produced a red oil which crystallized on standing, mp 67–71°. If the oil was distilled under reduced pressure, it gave a yellow liquid which readily crystallized: bp 144–150° (0.08 mm); mp 69–71°. The infrared absorption spectrum of this substance was identical with that of a sample prepared by the Sommelet reaction.

1-(*o*-Benzylthiobenzoyl)-2-*p*-tolylsulfonylhydrazide.—To a stirred solution of 19.0 g (0.072 mol) of *o*-(benzylthio)benzhydrazide[17] in 225 ml of dry pyridine, was slowly added 15.5 g (0.082 mol) of *p*-toluenesulfonyl chloride, while the temperature was maintained below 10°. The mixture was allowed to warm to room temperature and stirred for 3 hr, after which it was then heated at 75° for 1 hr. The hot mixture was poured into a mixture of 350 ml of hydrochloric acid and 500 g of ice. The yellow precipitate which formed was collected, washed several times with ether, and dried to yield 38.0 g of pale yellow crystals, mp 146–172°. A sample of the material (2.0 g) was recrystallized three times from a mixture of heptane–ethyl acetate to yield 1.0 g of colorless plates, mp 145.5–146°.

Anal. Calcd for $C_{21}H_{20}N_2O_3S$: C, 61.13; H, 4.89; S, 15.55. Found: C, 60.92; H, 4.89; S, 15.43.

***o*-(Benzylthio)cinnamonitrile (16).**—While the temperature was maintained below 10°, 17.7 g (0.10 mol) of methylcyanodiethyl phosphate[18] was added dropwise to a stirred suspension of 2.40 g (0.10 mol) of sodium hydride in 50 ml of 1,2-dimethoxyethane (freshly dried over calcium hydride). The mixture then was stirred at room temperature until all the sodium hydride had dissolved (1 hr). A solution of 22.8 g (0.10 mol) of *o*-(benzylthio)-benzaldehyde (**15**) in 100 ml of 1,2-dimethoxyethane was then added dropwise while the temperature was kept below 0°. After the addition had been completed, the mixture was stirred at room temperature for 4 hr during which time a gummy precipitate formed; it was then poured into 1 l. of cold water. Work-up gave an orange oil which solidified on standing to give 22.3 g (88%) of a light brown mass, mp 64–73°. Although this material was satisfactory for subsequent use, an analytical sample was recrystallized twice from heptane to give colorless needles: mp 89–90°; ir (CCl_4) 2220 cm^{-1} (CN); nmr (CCl_4) δ 3.90 (2, CH_2), 5.41–5.70 (d, 1, CH), 7.52–7.81 (d, 1, CH), 7.09–7.77 (cm, 9, benzene rings).

Anal. Calcd for $C_{16}H_{13}NS$: C, 76.45; H, 5.22; S, 12.91. Found: C, 76.22; H, 5.44; S, 12.91.

***o*-(Benzylthio)hydrocinnamonitrile (17).**—A solution of 10.06 g (0.04 mol) of **16** in 300 ml of ethanol was poured into 100 ml of water to form a fine suspension. Then 200 g of 2% sodium amalgam was added, and the mixture was stirred at 45–50° for 3 hr. The mixture was poured into 500 ml of water and worked up in the usual way. The residual oil solidified on standing to give a pale yellow product, 10.05 g (98%), mp 48–53°. The solid was recrystallized from hexane to give 8.86 g (87%) of colorless needles, mp 53–55°. A sample was further recrystallized from hexane to give mp 54–55°; ir (CCl_4) 2260 cm^{-1} (CN); nmr (CCl_4) δ 2.14–2.38 (t, 2, CH_2), 2.47–2.98 (t, 2, CH_2), 3.94 (2, CH_2), 7.08–7.36 (cm, benzene rings).

Anal. Calcd for $C_{16}H_{15}NS$: C, 75.95; H, 5.93; S, 12.62. Found: C, 75.81; H, 6.07; 12.43.

Attempted Formation of the Tautomeric System 4. A. Treatment of 17 with Hydrogen Chloride.—A solution of 2.51 g (0.01 mol) of **17** in 40 ml of anhydrous ether was cooled to Dry Ice bath temperatures. The solution was saturated with anhydrous hydrogen chloride and then allowed to slowly warm to room temperature. After the mixture had stood for 3 days with occasional addition of hydrogen chloride, the ether was removed to give an oil, the infrared spectrum of which was the same as the unreacted starting material.

B. With Aluminum Bromide.—To a cooled solution of 8.00 g (0.03 mol) of anhydrous aluminum bromide in 20 ml of anhydrous benzene was added a solution of 5.06 g (0.02 mol) of **17** in 40 ml of anhydrous benzene. The mixture was then stirred for 30 hr at room temperature after which 75 ml of water was added dropwise, and the benzene layer was removed. The aqueous phase was extracted with ether (two 50-ml portions), and work-up produced 2.48 g of an intractable orange oil.

Ethyl *o*-(Benzylthio)-α-cyanohydrocinnamate (22a).—To a solution of 0.23 g (0.01 g atom) of sodium metal in 40 ml of absolute ethanol was added slowly 2.26 g (0.02 mol) of ethyl cyanoacetate (nitrogen). The resulting solution was stirred for 0.5 hr at room temperature and then 2.49 g (0.01 mol) of **14** was added dropwise. The mixture was refluxed for 2 hr and the sodium chloride removed by filtration. The ethanol was removed under reduced pressure, and the residue taken up in 50 ml of ether. Work-up gave a residue, which was molecularly distilled at 200° (0.05 mm) yielding 1.61 g (50%): $n^{25}D$ 1.5669; ir 2250 (C≡N), 1725 cm^{-1} (ester C=O).

Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 70.12; H, 5.89; S, 9.61. Found: C, 70.04; H, 6.01; S, 9.61.

This compound was also prepared by alkylation with sodium hydride in either dimethyl sulfoxide or dimethylformamide in crude yields of over 90%.

[*o*-(Benzylthio)benzyl]malononitrile (22b).—The same procedure was used as in the preparation of **22b** as for **22a** with the exception that malononitrile was substituted for ethyl cyanoacetate. After work-up the residue was molecularly distilled at 220° (0.05 mm) to produce 2.0 g (72%) of a yellow oil, ir 2260 cm^{-1} (C≡N).

Anal. Calcd for $C_{17}H_{14}N_2S$: C, 73.34; H, 5.07; S, 11.52. Found: C, 73.04; H, 5.15; S, 11.62.

Ethyl 2-Amino-4*H*-1-benzothiopyran-3-carboxylate (5c).—To a cooled, stirred solution of 4.0 g (0.015 mol) of anhydrous aluminum bromide in 20 ml of dry benzene (nitrogen) was added a solution of 3.25 g (0.01 mol) of crude **22a** in 10 ml of dry benzene. During the addition, a very thick syrup formed causing irratic stirring; however, stirring was continued for 12 hr, and then the contents were poured into 150 ml of ice water. After the usual type of work-up, the residue was vacuum distilled yielding 1.0 g (43%) of a viscous oil which solidified on standing: bp 135–140° (0.08 mm); mp 59.5–61.5°. Recrystallization from pentane yielded 0.55 g (29%): mp 61–61.5°; ir (10% $CHCl_3$) 3470, 3310, (N—H), 1650 cm^{-1} (ester C=O); nmr ($CHCl_3$) δ 7.1–7.3 (cm, 4, benzene rings), 6.4 (2, NH_2), 4.0–4.3 (q, 2, CH_2), 3.5 (2, CH_2), 1.2–1.4 (t, 3, CH_3).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; S, 13.63. Found: C, 61.29; H, 5.74; S, 13.47.

Treatment of an ether solution of **5c** with dry hydrogen chloride resulted in the separation of **the hydrochloride of 5c**, mp 120–125° dec.

Anal. Calcd for $C_{12}H_{14}ClNO_2S$: C, 53.03; H, 5.19; Cl, 13.05. Found: C, 52.75; H, 5.16; Cl, 13.23.

2-Amino-4*H*-1-benzothiopyran-3-carbonitrile (6c).—To a cooled, stirred solution of 4.0 g (0.015 mol) of anhydrous aluminum bromide in 20 ml of anhydrous benzene was added dropwise (under nitrogen) a solution of 2.70 g (0.01 mol) of crude **22b** in 10 ml of anhydrous benzene. During the addition, two phases formed and the mixture became dark red. The mixture was stirred 13 hr at room temperature and then cooled while 100 ml of water was added. After the work-up, the residue was distilled, bp 180–188° (0.01 mm); the product solidified and was sublimed three times and then washed with pentane to yield 0.75 g (40%): mp 95–100° (a well-defined melting point could not be obtained since the compound sublimed from 90–100°); ir (10% $CHCl_3$) 3470, 3380 (N—H), 2180 cm^{-1} (C≡N); nmr ($CHCl_3$) δ 4.7 (2, NH_2), 3.4 (2, CH_2).

Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; S, 17.03. Found: C, 64.00; H, 4.34; S, 16.90.

Registry No.—**5c**, 25866-37-9; **5c** HCl, 25866-38-0; **6c**, 25907-84-0; **8**, 25866-39-1; **9**, 25866-40-4; **12**, 4565-32-6; **15**, 24852-71-9; **15** 2,4-DNP, 25907-86-2; **16**, 25866-42-6; **17**, 25866-43-7; **22a**, 25866-44-8; **22b**, 25866-45-9; 1-(*o*-benzylthiobenzoyl)-2-*p*-tolylsulfonylhydrazide, 25907-87-3.

(17) In this McFadyen and Stevens sequence some known intermediates were prepared. *o*-(Benzylthio)benzhydrazide was formed from ethyl *o*-(benzylthio)benzoate in 92% yield, mp 163–164° (lit. mp 164°). (a) F. Gialdi, R. Ponce, and A. Barruffini, *Farmaco, Ed. Sci.*, **15**, 856 (1960) [*Chem. Abstr.*, **55**, 21040 (1960)]. Ethyl *o*-(benzylthio)benzoate was prepared as colorless needles in 90% yield, mp 68.5–69° (lit. mp 68°). (b) W. J. Barry and I. L. Finer, *J. Chem. Soc.*, 138 (1954). Finally, the initial intermediate in the series, *o*-(benzylthio)benzoic acid (**18**), was obtained by alkylation of *o*-mercaptobenzoic acid (Aldrich) by benzyl chloride in quantitative yield, mp 188.5–189° (lit. mp 189°). (c) H. Apitzsch, *Ber.*, **46**, 3102 (1913).

(18) N. D. Dawson and A. Burger, *J. Amer. Chem. Soc.*, **74**, 5313 (1952).

Acknowledgment.—We wish to thank the Research Committee of Washington State University for partial support of this work, as well as the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant 2403-A1, 4.

Peracid Oxidation of Ene–Lactams. A Synthesis of Macrocyclic Imides

JEHAN F. BAGLI AND HANS IMMER

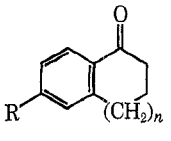
Department of Chemistry, Ayerst Research Laboratories, Montreal, Quebec, Canada

Received March 18, 1970

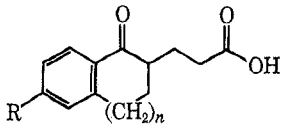
The substituted propionic acids **2a–c** prepared by conventional procedures were converted to the amides **3a–d**, which were ring closed in presence of *p*-toluenesulfonic acid to the unsaturated lactams **4a–d**. On peracid oxidation of **4a**, the ketone **5** was obtained. The oxidation of **4b–d** yielded with oxygen insertion the products **7a–c**. The structures of these compounds were proven by alkaline degradation. The mechanism of the peracid oxidation is discussed.

In our earlier work on the synthesis of medium-ring benzoic acid lactones,[1] we oxidized cyclic enol ethers with an excess of *m*-chloroperbenzoic acid. In some instances we observed a deviation from the normal reaction pathway leading to cyclic carbonates instead of the expected lactones. A mechanism for this insertion of an extra oxygen atom was proposed. The present paper deals with the peracid oxidation of ene–lactams which provides a synthetic approach to a novel class of macrocyclic imides.

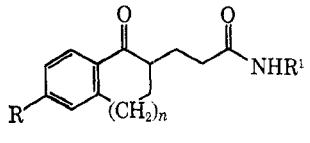
Ketones **1a–c** were converted into the corresponding formyl derivatives with ethyl formate in the usual manner. These compounds were reacted with ethyl acrylate in the presence of triethylamine to generate propionic acid esters which were transformed to the acids **2a–c**. These were converted to the amides **3a–d** which in turn were cyclized with *p*-toluenesulfonic acid in boiling toluene to yield the cyclic ene–lactams **4a–d**.



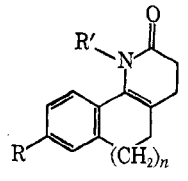
1a, R = H; $n = 2$
b, R = H; $n = 1$
c, R = OCH_3; $n = 1$



2a, R = H; $n = 2$
b, R = H; $n = 1$
c, R = OCH_3; $n = 1$

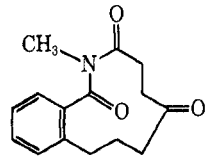


3a, R = H; $R^1 = CH_3$; $n = 2$
b, R = R^1 = H; $n = 1$
c, R = H; $R^1 = CH_3$; $n = 1$
d, R = OCH_3; $R^1 = CH_3$; $n = 1$

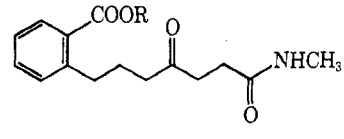


4a, R = H; $R^1 = CH_3$; $n = 2$
b, R = R^1 = H; $n = 1$
c, R = H; $R^1 = CH_3$; $n = 1$
d, R = OCH_3; $R^1 = CH_3$; $n = 1$

Oxidation of the ene–lactam **4a** with an excess of *m*-chloroperbenzoic acid led, in good yield, to a product whose analytical and spectral data corroborated with structure **5**. On alkaline treatment of this ketone, the benzoic acid **6a** was obtained, which was characterized as its methyl ester **6b**.

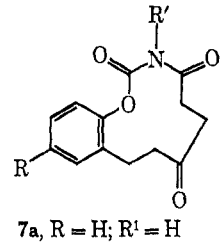


5



6a, R = H
b, R = CH_3

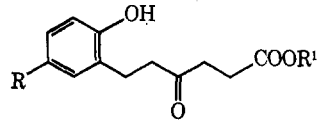
In contrast, the oxidation of the ene–lactam **4b** under the same conditions led to a compound containing an extra oxygen (molecular ion at *m/e* 247). Its elemental analysis confirmed the formula $C_{13}H_{13}NO_4$. The infrared, ultraviolet, and nmr spectra were in complete agreement with the assigned structure **7a**. Similar oxidation of the lactams **4c** and **d** led to the isolation of the macrocyclic imides **7b** and **c**, respectively.



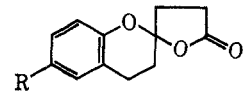
7a, R = H; R^1 = H
b, R = H; $R^1 = CH_3$
c, R = OCH_3; $R^1 = CH_3$

The structures of these compounds were proven by alkaline degradation.

Treatment of the ketones **7a** and **b** with aqueous methanolic sodium hydroxide yielded the phenolic acid **8a**. The compound **7c**, under identical conditions, led to **8b**.



8a, R = H; R^1 = H
b, R = OCH_3; R^1 = H
c, R = OCH_3; $R^1 = CH_3$



9a, R = H
b, R = OCH_3

(1) (a) H. Immer and J. F. Bagli, *J. Org. Chem.*, **33**, 2457 (1968); (b) J. F. Bagli and H. Immer, *Can. J. Chem.*, **46**, 3115 (1968).