$-172°$ in absolute chloroform) in 5 ml. of benzene was diluted to 50.0 ml. with absolute methanol. The mutarotation of the resulting solution in circular degrees, observed polarimetrically in a 1-dm. tube at 20°, was as follows: (α_D), $-13.85°$ (2.16 minutes), $-4.01°$ (26.5 minutes), $-2.19°$ (40.5 minutes), $-1.49°$ (49.5 minutes), $-0.94°$ (69 minutes), $-0.47°$ (3 hours), $-1.21°$ (20.8 hours) and $-1.56°$ (45 hours). The reaction mixture was concentrated *in vacuo* (25°) to a sirup which was diluted with 25 ml. of benzene and then reconcentrated. As a parallel experiment had shown that partial deacetylation had taken place, the residue was reacetylated with pyridine and acetic anhydride. The resulting product, from its solution in a mixture of 5 ml. of ether and 10 ml. of pentane, deposited 95 mg. (2.2%) of prismatic needles melting at 148–151°. After recrystallization from ether–pentane and from methanol this substance melted at 151–152° and rotated $+44°$ in chloroform (c, 0.55). Fischer, Bergmann and Rabe[8] reported a melting point of 151–152° and a rotation in acetylene tetrachloride of $+45.7°$ for methyl β-L-rhamnopyranoside triacetate. On concentration and seeding, the original mother liquor yielded 1.80 g. (41.6%) of crude methyl α-L-rhamnopyranoside triacetate melting at 81–87°. After purification, pure methyl α-L-rhamnopyranoside triacetate, melting at 88–89° either alone or in admixture with authentic material, was obtained. Fischer, Bergmann and Rabe[8] reported a melting point of 86–87° for this substance.

Summary

Tribenzoyl-α-L-rhamnopyranosyl bromide has been obtained in crystalline form and found to react with methanol in the absence of an acid acceptor to give methyl α-L-rhamnopyranoside tribenzoate in high yield.

The reaction of triacetyl-α-L-rhamnopyranosyl bromide with methanol in the absence of an acid acceptor leads to partial deacetylation; reacetylation of the product gave a relatively large yield of methyl α-L-rhamnopyranoside triacetate and a small yield of its anomer.

Tribenzoyl-α-L-rhamnopyranosyl chloride and the corresponding iodide have been obtained in crystalline form.

Partial benzoylation of α-L-rhamnose hydrate has given a small quantity of a crystalline L-rhamnose dibenzoate and substantial yields of a crystalline L-rhamnose tribenzoate. This latter compound appears to be different from the crystalline 2,3,4-tribenzoyl-L-rhamnose prepared by the partial hydrolysis of tribenzoyl-α-L-rhamnopyranosyl bromide.

The reaction of tribenzoyl-α-L-rhamnopyranosyl bromide with methanol in the presence of quinoline has given 3,4-dibenzoyl-β-L-rhamnopyranose methyl 1,2-orthobenzoate in crystalline form.

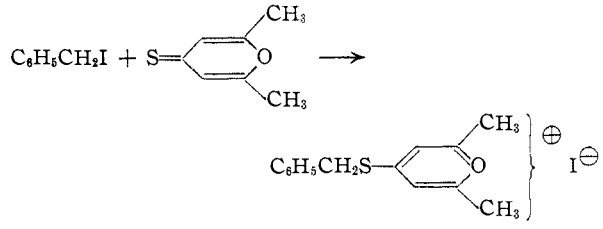
BETHESDA, MARYLAND RECEIVED JUNE 21, 1950

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Preparation of Substituted Mercaptopyrylium Salts[1]

BY L. CARROLL KING, FRANCIS J. OZOG AND JAMES MOFFAT

Hantzsch[2] reported that 2,6-dimethyl-4-thiopyrone could be alkylated with methyl sulfate. This type of reaction has been examined in some detail, and it has been demonstrated that a variety of reactive alkylating agents on treatment with 2,6-dimethyl-4-thiopyrone give the corresponding mercaptopyrylium salt. Using benzyl iodide as an example, the reaction can be formulated as



The reaction gave crystalline products with a number of alkyl iodides, with phenacyl type bromides, and with benzyl *p*-bromobenzenesulfonate. The data for crystalline reaction products obtained in this study are listed in Table I. With alkyl chlorides or bromides the reaction was very slow, or the products were oils. Chloroacetone and chloromethyl ether reacted with 2,6-dimethyl-4-thiopyrone to give oily products. These were not further characterized. *p*-Nitrobenzyl chloride gave only 15% of salt after reacting for one month in benzene solution. The product obtained when 2,6-dimethyl-4-thiopyrone reacted with 2,4,6-trimethylphenacyl bromide was a black powder unstable at room temperature. The following compounds did not react with 2,6-dimethyl-4-thiopyrone: 2-phenyl-2-iodoethanol, 1-phenyl-2-bromo ethanol, benzyl chloride, triphenylchloromethane and 2-bromo-1,2,3,4-tetrahydro-1-phenanthrone.

The reaction can be carried out in benzene, ether or acetone as solvent. The yields obtained in the various solvents were comparable, but the reaction proceeded much more rapidly in acetone.

The crystalline mercaptopyrylium salts obtained in this study could not be crystallized from alcohol or water.[3] They were readily purified by washing with acetone or benzene, and analytical samples were obtained by dissolving the salt in nitromethane and precipitating with ether.

The assignment of the substituted mercaptopyrylium salt structure to the products of the reaction is based on the method of formation, and is supported in each case by analytical data. Further substantiation comes from the reactions of some of the salts to give compounds previously obtained by other methods. Thus, 2,6-dimethyl-4-methylmercaptopyrylium iodide on treatment with ammonium hydroxide gave the known[4] 4-methylmercapto-2,6-lutidine, and 2,6-dimethyl-4-benzylmercaptopyrylium iodide was converted to 4-benzylmercapto-2,6-lutidine by ammonium hydroxide[5] and to 2,6-dimethyl-4-benzylmercapto-

(1) This work was partially supported by a grant-in-aid from the National Cancer Institute.

(2) Hantzsch, *Ber.*, **52**, 1535 (1919).

(3) They appear to react with hydroxylated solvents. This observation is similar to that noted for 4-methoxy-2,6-dimethylpyrylium salts by Baeyer, *Ber.*, **43**, 2337 (1910).

(4) Marckwald, Klemm and Trabert, *ibid.*, **33**, 1562 (1900).

(5) Anker and Cook, *J. Chem. Soc.*, 117 (1946).

TABLE I

Alkylating agent	Reacn. time,[a] hr.	Pyrylium salt: Yield, %	M. p.,[b] °C., dec.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Iodine[c] Calcd.	Iodine[c] Found
Methyl iodide[d]	1	Quant.	176–177	$C_8H_{11}IOS$	34.05	34.33	3.93	4.07	45.0	44.5
Methylene iodide	5	57	184–185	$C_{15}H_{18}I_2O_2S_2$	32.86	32.31	3.31	3.36		
Ethyl iodoacetate[e]	1	82	128–129	$C_{11}H_{15}IO_3S$	37.30	37.38	4.27	4.31	35.8	34.8
Allyl iodide[f,g]	1	93	106–107	$C_{10}H_{13}IOS$	38.97	39.01	4.25	4.28	41.2	39.5
Benzyl iodide[h]	0.5	95	156–158	$C_{14}H_{15}IOS$	46.93	46.11	4.22	4.84	35.4	35.5
p-Nitrobenzyl iodide[e]	2	84	124–125	$C_{14}H_{14}INO_3S$	41.70	41.94	3.50	3.60	31.5	30.9
Cinnamyl bromide[i]	120[j]	83	157–159	$C_{16}H_{17}BrOS$	56.97	57.02	5.08	5.23		
Phenacyl bromide[k,l]	1	Quant.	190	$C_{15}H_{15}BrO_2S$	53.10	53.31	4.46	4.47		
o-Nitrophenacyl bromide[m]	1	91	171–172	$C_{15}H_{14}BrNO_4S$	46.89	46.22	3.67	4.23		
p-Methylmercaptophenacyl bromide	1	94	183–184	$C_{16}H_{17}BrO_2S_2$	49.87	48.82	4.45	4.76		
2-Bromoacetylphenanthrene[n]	1	93	227–228	$C_{23}H_{19}BrO_2S$	62.87	63.06	4.36	4.65		
Benzyl *p*-bromobenzenesulfonate	1	81	114–115	$C_{20}H_{19}BrO_4S_2$	51.39	51.63	4.10	4.09		

[a] In boiling acetone unless otherwise stated. [b] All melting points were observed on a Fisher–Johns melting point block, and represent the range where crystals become fluid. [c] Determined by conductometric titration with standard silver nitrate. [d] A two-molar excess of methyl iodide was used. [e] Finklestein, *Ber.*, **43**, 1531 (1910). [f] Letsinger and Traynham, THIS JOURNAL, **70**, 2818 (1948). [g] The salt was recrystallized from acetone. [h] Coleman and Hauser, THIS JOURNAL, **50**, 1196 (1928). The pyrylium iodide obtained was converted to the known perchlorate: see Experimental. [i] Claisen and Tietze, *Ber.*, **58**, 279 (1925). [j] The reaction was carried out in benzene at room temperature. [k] A yield of 93% was obtained in benzene after 175 hours at room temperature. [l] The pyrylium bromide obtained was converted to the perchlorate by treatment with aqueous sodium perchlorate; m. p. 200–201°. *Anal.* Calcd. for $C_{15}H_{15}ClO_6S$: C, 50.21; H, 4.21. Found: C, 49.90; H, 4.29. [m] Gevekoht, *Ann.*, **221**, 327 (1883). [n] Haworth and Mavin, *J. Chem. Soc.*, 1012 (1933).

pyrylium perchlorate by aqueous sodium perchlorate.[5]

Experimental

2,6-Dimethyl-4-pyrone.—Dehydroacetic acid, 280 g., and 800 ml. of concentrated hydrochloric acid were refluxed for one hour. The condenser was removed and the solution boiled for three hours. The cooled solution was saturated with potassium carbonate and extracted thoroughly with warm benzene. The benzene was concentrated until 350 ml. remained. On cooling, the product separated; yield 185 g. (90%). This product was used directly in the next step.[6]

2,6-Dimethyl-4-thiopyrone.—To 145 g. of 2,6-dimethyl-4-pyrone in 900 ml. of benzene, 240 g. of phosphorus pentasulfide was added with stirring. The mixture was heated on a steam-bath for one hour and filtered hot. The benzene was evaporated in a current of air, yielding 85 g. of crude product. To the residue in the reaction flask was added 1 liter of cold water and the mixture filtered after the reaction had ceased. The residue was treated with hot benzene, the benzene solution decolorized, and evaporated as before, yielding 56 g. of crude product for a total yield of 141 g. (86%). The product was recrystallized from isopropyl alcohol; m.p. 145°.[7]

Preparation of Alkylating Agents.—The preparation of benzyl *p*-bromobenzenesulfonate and *p*-methylmercaptophenacyl bromide is described below. All alkylating agents not commercially available were prepared according to procedures described in the literature. In all cases physical constants were in agreement with the data given in the literature.

***p*-Methylmercaptophenacyl Bromide.**—To a solution of 8.4 g. of *p*-methylmercaptoacetophenone[8] in 100 ml. of chloroform 7.8 g. of bromine was added dropwise. The solvent was removed, and the product crystallized from ethyl acetate–Skellysolve C after decolorizing with charcoal; yield 43%, m.p. 63–64°.

Anal. Calcd. for C_9H_9BrOS: C, 44.09; H, 3.70. Found: C, 44.46; H, 3.75.

Benzyl *p*-Bromobenzenesulfonate.—To a well-stirred solution of 10.8 g. (0.1 mole) of benzyl alcohol and 25.5 g. (0.1 mole) of *p*-bromobenzenesulfonyl chloride (freshly recrystallized from Skellysolve B) in 300 ml. of anhydrous ether at −5° was added 11.2 g. of finely powdered potassium hydroxide in 0.5-g. portions, keeping the temperature below 0°. The mixture was poured over ice-water, the ether layer separated, washed with potassium carbonate solution, and dried over anhydrous potassium carbonate. The ether was removed under vacuum yielding 28.6 g. (87%) of crude product. The ester was purified by precipitation from benzene solution with Skellysolve A, m.p. 59–60°.[9]

Anal. Calcd. for $C_{13}H_{11}BrO_3S$: C, 47.72; H, 3.39. Found: C, 47.89; H, 3.42.

Alkylation of 2,6-Dimethyl-4-thiopyrone.—All alkylations were carried out in a similar manner. The following examples will illustrate the procedure.

(a) **2,6-Dimethyl-4-benzylmercaptopyrylium Iodide.**—A solution of 2.18 g. (0.01 mole) of benzyl iodide, 1.40 g. (0.01 mole) of 2,6-dimethyl-4-thiopyrone and 40 ml. of acetone was heated under reflux for one hour, cooled, and the acetone removed under vacuum.[10] The residue was washed twice with benzene, then with ether and dried; weight 3.40 g. (95%), m.p. 156–158° (dec.). An analytical sample was prepared by precipitating the salt from nitromethane solution with ether.

(b) **2,6-Dimethyl-4-cinnamylmercaptopyrylium Bromide.**—A solution of 3.04 g. (0.0154 mole) of cinnamyl bromide and 2.16 g. (0.0154 mole) of 2,6-dimethyl-4-thiopyrone in 200 ml. of benzene was allowed to stand at room temperature for 5 days, then filtered, the residue washed with benzene, and dried; weight 4.32 g. (83%), m.p. 157–159° (dec.).

4-Methylmercapto-2,6-lutidine.—To 10.0 g. of 2,6-dimethyl-4-methylmercaptopyrylium iodide in 10 cc. of water was added 30 ml. of 15% ammonium hydroxide solution containing 8 g. of ammonium carbonate. The mixture was heated on a steam-bath for 10 minutes, cooled and extracted with ether. The ether was removed and the base distilled *in vacuo;* yield, 4.60 g., b.p. 88–89° (2 mm.). A sample recrystallized from Skellysolve A in an ice-salt-bath melted at 51°.[11]

Anal. Calcd. for $C_8H_{11}NS$: C, 62.70; H, 7.24; N, 9.14. Found: C, 62.37; H, 7.26; N, 9.26.

Picrate: M.p. 171°. Calcd. for $C_{14}H_{14}N_4O_7S$: C, 43.98; H, 3.69; N, 14.66. Found: C, 44.16; H, 3.44; N, 14.65.

4-Benzylmercapto-2,6-lutidine.—This compound was prepared from 2,6-dimethyl-4-benzylmercaptopyrylium iodide; b.p. 166–172° (5 mm.), m.p. 56°.[12]

(6) This is a modification of the procedure of Arndt, Eistert, Scholz and Aron, *Ber.*, **69**, 2379 (1936), and is similar to the procedure used by Deshapande, *J. Ind. Chem. Soc.*, **9**, 304 (1932), for the preparation of 2,6-diethyl-4-pyrone. The yield of pyrone is better than in any previous report.

(7) This is a modification of the procedure of Hantzsch.[2]

(8) King, McWhirter and Roland, THIS JOURNAL, **70**, 239 (1948).

(9) All glassware used in this preparation was soaked in sodium hydroxide solution prior to use.

(10) When phenacyl halides were used as alkylating agents, the product was isolated by filtration.

(11) Marckwald[4] reports 51° for the base and 169° for the picrate.

(12) Anker and Cook[5] report the base as an oil; b. p. 260° (25 mm.), picrate, m. p. 171°.

Anal. Calcd. for $C_{14}H_{15}NS$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.31; H, 6.67; N, 6.25.

Picrate: M.p. 171°. Calcd. for $C_{20}H_{18}N_4O_7S$: C, 52.40; H, 3.96; N, 12.22. Found: C, 52.46; H, 3.79; N, 12.53.

2,6-Dimethyl-4-benzylmercaptopyrylium Perchlorate.—To a solution of 0.50 g. of 2,6-dimethyl-4-benzylmercaptopyrylium iodide in hot water were added 5 ml. of 70% aqueous sodium perchlorate. The product separated on cooling. It was recrystallized from methanol; yield 0.40 g. (87%), m.p. 145–146° (dec.).[13]

(13) Anker and Cook[3] report 146°.

Summary

1. 2,6-Dimethyl-4-thiopyrone reacts with active alkylating agents to give substituted mercaptopyrylium salts.

2. The structure of some of the pyrylium salts has been established by converting them to the corresponding lutidines of known structure.

EVANSTON, ILLINOIS RECEIVED JUNE 8, 1950

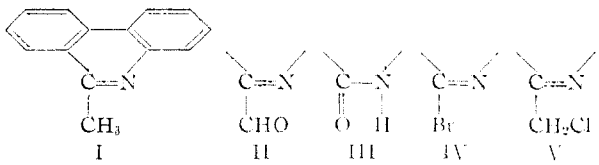
[CONTRIBUTION NO. 214 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

Studies in Phenanthridine Chemistry

BY JACOB FINKELSTEIN AND SEYMOUR M. LINDER

During an investigation into the structural relationship between Antergan and N-substituted dihydrophenanthridines,[1] which was also reported upon by Huttrer,[2] some phenanthridine derivatives were made for pharmacological and chemotherapeutic screening. The purpose of this paper is to record some observations on the application of standard reactions to phenanthridines.

The most readily obtainable phenanthridines, 6-methylphenanthridine and phenanthridone[3] were used as starting materials, and the derivatives synthesized may be classified into five groups: I prepared directly from 6-methylphenanthridine; II from 6-phenanthridinecarboxaldehyde; III from phenanthridone; IV from 6-bromophenanthridine; and V from 6-chloromethylphenanthridine.



I II III IV V

Since phenanthridine may be considered as a derivative of quinoline or isoquinoline, the 6-methyl group should be active and resemble quinaldine in the type of reactions it may undergo. We found that under the conditions of the Mannich reaction, 6-methylphenanthridine reacted with paraformaldehyde and dimethylamine hydrochloride, to give 6-(β-dimethylaminoethyl)-phenanthridine in good yield. Other secondary amines react similarly.

It was also found that a hydrogen of the methyl group of 6-methylphenanthridine is sufficiently active to undergo the Schmid-Karrer[4] modification of the Ziegler[5] reaction to form 6-chloromethylphenanthridine identical with that prepared by cyclizing chloroacetyl-*o*-aminodiphenyl as described by Morgan and Walls.[6] When 6-chloromethylphenanthridine reacted with isopropylamine, benzylamine, benzylisopropylamine, dimethylamine, piperidine and morpholine, the corresponding secondary and tertiary amines were obtained. It was also found that benzyl tertiary amines of this type could be obtained by benzylation of the secondary amines. However, another method was investigated without satisfactory results. Gilman, *et al.*,[7] showed that aryl halides react with lithium dialkylamides to yield the corresponding tertiary amines and, on occasion, may be preferred over the reaction of RX with a secondary amine. Horning and Bergstrom[8] also found that lithium dialkylamides react with aryl halides and, in addition, with *n*-butyl bromide, while the lower halides failed. When 6-chloromethylphenanthridine reacted with lithium benzylisopropylamide, only 1,2-di-(6-phenanthridyl)-ethane was isolated, indicating that the halogen is too reactive and undergoes a Wurtz type of reaction. A N-phenanthridylmethyl-*p*-toluenesulfonamide could not be prepared by treating 6-chloromethylphenanthridine and *p*-toluenesulfonamide. Instead, only the N,N-diphenanthridylmethyl-*p*-toluenesulfonamide was formed. When an N-substituted-*p*-toluenesulfonamide, as benzyl, was treated with 6-chloromethylphenanthridine, the expected alkylation reaction took place with the formation of N-benzyl-N-phenanthridylmethyl - *p* - toluenesulfonamide, a substance capable of further syntheses after removal of the benzyl group. Other reactions resulting in the replacement of the chlorine group of 6-chloromethylphenanthridine included the preparation of ethers such as, for example, 6-diethylaminoethoxymethylphenanthridine, and of phenanthridineacetonitrile, a versatile compound for further synthetic reactions.

Phenanthridone, being an amide, was N-alkylated by Graebe and Wander[9] by adding an alkyl halide to the potassium salt. The reaction is rather general and, under the same conditions with β-diethylaminoethyl chloride, the 5-(β-diethylaminoethyl)-phenanthridone was obtained.

Ritchie[10] was first to prepare 6-phenanthridinecarboxaldehyde and describe some of its properties. An important reaction which this compound undergoes is the reductive aldehyde–amine condensation. With both β-diethylaminoethylamine and β-ami-

(1) Finkelstein and Linder, THIS JOURNAL, **72**, 3282 (1950).

(2) Huttrer, *ibid.*, **71**, 4147 (1949).

(3) Numbered according to "The Ring Index" by Patterson and Capell.

(4) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(5) Ziegler, *et al.*, *Ann.*, **551**, 80 (1942).

(6) Morgan and Walls, *J. Chem. Soc.*, 2147 (1931).

(7) Gilman, *et al.*, THIS JOURNAL, **67**, 2106 (1945).

(8) Horning and Bergstrom, *ibid.*, **67**, 2110 (1945).

(9) Graebe and Wander, *Ann.*, **276**, 245 (1893).

(10) Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **78**, 134–186 (1945).