795. *Synthesis of Benzimidazol-2-ylalkanethiols and Some Derivatives.*

By Edward S. Milner, jun., Stuart Snyder, and Madeleine M. Joullié.

The preparation of some new 2-substituted benzimidazoles is described.

Since 2-mercaptobenzimidazoles have been reported to have physiological activity and also practical application as antioxidants, interest in benzimidazol-2-ylalkanethiols has also grown as evidenced by a recent publication which describes the preparation of some derivatives of 2-mercaptomethylbenzimidazole.[1] We have prepared some derivatives of benzimidazol-2-yl-methanethiol and 1- and 2-benzimidazole-2′-ylethanethiol. Although benzimidazol-2-ylmethanethiol is not a new compound [2,3] we have obtained better yields of this product by preparing it from its more stable hydrochloride. Benzimidazol-2-yl-alkanethiols are better stored as hydrochlorides. Oxidation of the thiols with hydrogen peroxide led to the corresponding sulphonic acids. An interesting reaction occurred when the preparation of the corresponding sulphonamide was attempted by treating 2-benzimidazol-2′-ylethanesulphonic acid first with thionyl chloride and then with concentrated ammonia. The only product isolated was 2,2′-(sulphonyldiethylene)bisbenzimidazole, whose structure was proved by an independent synthesis involving the preparation and oxidation of 2,2′-(thiodiethylene)bisbenzimidazole.

New 2-substituted benzimidazoles.

				Analysis							
				Calc. (%)				Found (%)			
2-Substituent	Formula	Yield (%)	M. p.	C	H	N	S	C	H	N	S
$CH_2(SH),HCl$ [a]	$C_8H_9ClN_2S$	97	218—223° (decomp.)	47·9	4·5	14·0	16·0	48·0	4·3	14·0	15·8
$CH_2·CH_2·SH$	$C_9H_{10}N_2S$	95	209—210	60·6	5·65	15·7	18·0	60·4	5·5	15·9	18·1
$CHMe·SH$	$C_9H_{10}N_2S$	87	202—204	60·6	5·65	15·7	18·0	60·8	5·5	15·5	17·9
$CH_2·SO_3H$	$C_8H_8N_2O_3S$	50	>330	45·3	3·8	13·2	15·1	45·15	3·9	13·4	15·1
$CH_2·CH_2·SO_3H,H_2O$	$C_9H_{12}N_2O_4S$	—	—	44·2	4·95	11·5	13·1	44·0	4·7	11·3	13·5
$CH_2·CH_2·S·CH_2·CO_2H$	$C_{11}H_{12}N_2O_2S$	36	155—160	55·9	5·1	11·9	13·55	55·9	5·3	11·7	13·4
$CH_2·Ph$	$C_{14}H_{12}N_2S$	60	135—136	70·0	5·0	11·7	13·3	69·8	5·0	11·5	13·2
$CH_2·S·CH_2Ph$ [b]	$C_{15}H_{14}N_2S$	88	140—142	70·8	5·55	11·0	12·6	71·0	5·6	11·1	12·45
$CH_2·S·CH_2Ph$ [c]	$C_{22}H_{20}N_2S$	35	136·5—137·5	76·7	5·85	8·1	9·3	76·4	5·9	8·4	9·15
$-CH_2·S·C_6H_4·NH_2$-*p*, 2HCl [d]	$C_{14}H_{15}Cl_2N_3S$	71	273	51·2	4·6	12·8	9·8	51·15	4·7	12·8	10·0
$-CH_2·S·C_6H_4NHAc$-*p*	$C_{16}H_{15}N_3OS$	80	239—240	64·6	5·1	14·1	10·8	64·5	4·9	13·9	10·6
$-CH_2·SO_2·CH_2Ph$	$C_{15}H_{14}N_2O_2S$	78	212—214	62·9	4·9	9·8	11·2	62·7	5·15	9·7	11·4

[a] Calculated Cl: 17·7. Found: 17·8%. [b] Lit.,[1] m. p. 141—142°. [c] *N*-Benzyl substituted. [d] Calculated Cl: 21·6. Found: 21·5%.

The reaction of benzimidazol-2-ylmethanethiol with alkyl or aralkyl halides is reported to yield sulphides. Under our conditions the reaction of this compound with benzyl chloride also led to *N*-substitution. For this reason the reaction of *o*-phenylenediamine with the desired acid was preferred as a method of preparing sulphides.

Benzimidazol-2-ylthioglycollic acid is reported to cyclize to thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one. The assigned structure was based on infrared and analytical data only. It was of interest to determine whether a similar cyclization could be obtained from (2-benzimidazol-2-ylethylthio)acetic acid. This compound was prepared [3] from benzimidazol-2-ylethanethiol and chloroacetic acid; although the analytical data were good the compound melted over a range of five degrees. No evidence could be obtained

[1] Fedorov, Mamedov, and Zelinskii, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1962, **9**, 1626.
[2] Hughes and Lions, *J. Proc. Roy. Soc. N.S. Wales*, 1938, **71**, 209.
[3] Misra, *J. Org. Chem.*, 1958, **23**, 897.

for exclusive sulphur or nitrogen alkylation. Cyclization of this product was accomplished, but two structures are possible; one would have a tertiary amide linkage and the other a thioester group. 2*H*-*m*-Thiazino[3,2-*a*]benzimidazol-4(3*H*)one is reported to have an absorption band at 1675 cm.$^{-1}$ in chloroform.[3] The infred spectrum of our compound showed a band at 1695 cm.$^{-1}$. However, thioester groups also absorb in the 1690 cm.$^{-1}$ region and the infrared evidence is not conclusive.

In an attempt to obtain other thio-derivatives which might cyclize easily 2-chloroethylbenzimidazole was treated with thiourea. Although the dihydrochloride of 1-2-2′-benzimidazolylethyl)isothiourea was obtained the corresponding free base could not be isolated or cyclized. The infrared spectrum of the salt showed a strong band in the 1640 cm.$^{-1}$ region typical of isothioureas. It is noteworthy that a similar compound could not be isolated from the reaction of 2-chloromethylbenzimidazole and thiourea, a bis-benzimidazol-2-ylmethyl disulphide being formed instead.[3]

It was thought that the reaction of 1,2-dichloroethane and 2-benzimidazole-2-yl-ethanethiol might yield a cyclic product. However, the product was either 1,1′- or 2,2′-[ethylenebis(thiomethylene)]bisbenzimidazole; the high melting point and the infrared spectrum seem to favour the latter. The analytical data and melting points of some of the compounds prepared are shown in the Table.

Experimental

All melting points are uncorrected. The melting point of several of these compounds is quite dependent on the rate of heating. A rate of 1°/min. was used for most determinations.

Preparation of Benzimidazol-2-ylalkanethiols.—All compounds were prepared by a modified Phillips reaction. The modifications involved a longer refluxing period (20 hr. or more) and heating the solutions with charcoal for the last 2 hr. Benzimidazol-2-ylmethanethiol was isolated as its hydrochloride by reducing the volume of the solution and saturating it with hydrogen chloride; the hydrochloride was recrystallized from ethanol–ether. The preparation of 2-benzimidazol-2′-ylethanethiol will be described as an example. *o*-Phenylenediamine (54·07 g.; 0·5 mole) and β-mercaptopropionic acid (63·65 g.; 0·6 mole) were refluxed in 6N-hydrochloric acid for 64 hr. Charcoal was added and the solution refluxed for another hour and set aside overnight. The charcoal was removed by filtration, and the solution cooled to 0° and neutralized with ammonia solution. The precipitate was crystallized from aqueous ethanol. The infrared spectra of these thiols show a very weak absorption band in the 2600—2550 cm.$^{-1}$ region.

Preparation of Sulphides.—All the sulphides were prepared by a similar modified Phillips reaction from the appropriate acid. *o*-Phenylenediamine dihydrochloride (18·11 g.; 0·1 mole) was dissolved in 4N-hydrochloric acid (250 ml.) and refluxed with benzylmercaptoacetic acid (27·34 g.; 0·15 mole) for 48 hr. The oil produced was separated, dissolved in 95% ethanol, and decolourized with charcoal. The charcoal was removed by filtration, the solution cooled to −10° and neutralized slowly with ammonia solution with vigorous stirring. The product was recrystallized from aqueous ethanol. 4′-Benzimidazol-2-ylmethylthioaniline could only be isolated as its hydrochloride. Acetylation of this compound was carried out by first dissolving the dihydrochloride (6·83 g., 0·02 mole) in water (60 ml.), adding charcoal, and heating the solution to 50°. The charcoal was removed by filtration and acetic anhydride (5 ml.; 0·05 mole) added at 60°. A sodium acetate solution (4·10 g., 0·05 mole; in 40 ml. of water) was added immediately and on cooling the product formed. The acetylated compound was crystallized from benzene–ethanol. The infrared spectrum of this compound showed bands at 1665 and 1565 cm.$^{-1}$, typical of the secondary amide linkage.

Preparation of Sulphones.—The sulphides can be oxidized easily to the corresponding sulphones. The preparation of 2-benzylsulphonylmethylbenzimidazole will exemplify the general procedure. 2-(Benzylmercaptomethyl)benzimidazole (6·3 g., 0·025 mole) was dissolved in acetic acid (150 ml.) and treated with 0·1 mole of 30% hydrogen peroxide. The mixture was heated for 2 hr. on a water-bath. The acetic acid was removed under reduced pressure and the residue recrystallized from aqueous ethanol. The infrared spectrum of this sulphone showed bands at 1300 and 1110 cm.$^{-1}$, typical of the sulphone grouping.

Preparation of Sulphonic Acids.—The sulphonic acids are best prepared by an oxidation

method similar to the one used for preparing the sulphones. Benzimidazol-2-methanethiol hydrochloride (10·03 g.; 0·05 mole) was suspended in acetic acid (250 ml.), 30% hydrogen peroxide (0·20 mole) was added, and the mixture was heated on a steam-bath for 3 hr. After removal of impurities by filtration, the solution was concentrated under reduced pressure. The product was crystallized from acetic acid. The infrared spectrum of this compound showed strong bands at 1266—1170 and 1040—1010 cm.$^{-1}$, typical of a sulphonic acid. Benzimidazol-2′-ylethanesulphonic acid was extremely hygroscopic. Although no infrared spectrum of this compound was obtained, the compound gave a positive sulphonic acid test.[4]

Preparation of 2,2′-(*Sulphonyldiethylene*)*bisbenzimidazole.*—2-Benzimidazol-2′-ylethanesulphonic acid (25·1 g., 0·11 mole) was refluxed with thionyl chloride (100 ml.). The excess of thionyl chloride was removed under reduced pressure and the reddish brown residue was treated with concentrated ammonia solution to yield a brown precipitate which was dissolved partially in hot dilute hydrochloric acid. The mixture was filtered and the solution cooled and neutralized with ammonia solution. The solid formed was crystallized from aqueous ethanol; yield 15%, m. p. 205—207° (decomp.). The infrared spectrum of this product showed bands at 1330 and 1115 cm.$^{-1}$, typical of a sulphone grouping (Found: C, 61·05; H, 5·4; N, 16·1; S, 9·08. Calc. for $C_{18}H_{18}N_4O_2S$: C, 60·9; H, 5·1; N, 15·8; S, 9·05%). To confirm the structure, this compound was prepared by an unequivocal synthesis from 2,2′-(thiodiethylene)bisbenzimidazole, prepared by the method of Wang and Joullié.[5] This compound was oxidized as described for the preparation of sulphones. The product (27%) had m. p. and mixed m. p. 204—206° (decomp.) (from aqueous ethanol) (Found: C, 60·8; H, 5·3; N, 15·6; S, 9·2. Calc. for $C_{18}H_{18}N_4O_2S$: C, 61·0; H, 5·1; N, 15·8; S, 9·05%). The infrared spectra of the two compounds were essentially identical.

Preparation of (2-*Benzimidazol-2′-ylethylthio*)*acetic Acid.*—This compound was prepared from 2-benzimidazol-2′-ylethanethiol and chloroacetic acid according to the procedure used for preparing β-benzimidazol-2-ylthiopropionic acid from 2-mercaptobenzimidazole.[3]

Cyclization of (2-2-*Benzimidazol-2′-ylethylthio*)*acetic Acid.*—Attempts were made to cyclize this product with acetic anhydride and pyridine according to the directions of Misra.[3] Finally the cyclization was accomplished in refluxing acetic anhydride only. The product was crystallized from aqueous ethanol to give a solid (28%) m. p. 157—158° (Found: C, 60·6; H, 4·5; N, 12·7; S, 14·8. Calc. for $C_{11}H_{10}N_2OS$: C, 60·5; H, 4·6; N, 12·8; S, 14·7%). The infrared spectrum of this product showed a strong carbonyl band at 1695 cm.$^{-1}$.

Reaction of Benzimidazol-2-ylmethanethiol with Benzyl Chloride.—Although this reaction has been reported to yield only the thiobenzylated product if potassium hydroxide is used,[1] when benzimidazole-2′-methanethiol was treated with various amounts of benzyl chloride in sodium hydroxide solution benzylation always occurred both on sulphur and nitrogen.

Reaction of Benzimidazol-2-ylmethanethiol with 1,2-*Dichloroethane.*—Benzimidazol-2-ylmethanethiol (4·9 g.; 0·03 mole) was treated with 1,2-dichloroethane (3·0 g., 0·03 mole) and the mixture heated for 1 hr. and then set aside for 2 days. The solution was neutralized with ammonia solution. The product (50%) had m. p. 245—247° (Found: C, 60·9; H, 5·2; N, 15·8; S, 18·2. Calc. for $C_{18}H_{18}N_4S_2$: C, 61·0; H, 5·1; N, 15·8; S, 18·1%).

Reaction of 2-*Chloroethylbenzimidazole with Thiourea.*—Thiourea (3·0 g., 0·039 mole) was dissolved in hot ethanol (60 ml.) and treated with 2-chloroethylbenzimidazole (7·2 g., 0·028 mole). The mixture was refluxed for 2½ hr. The precipitate was crystallized from ethanol–ether, and the product (36%) then had m. p. 239—242° (decomp.) (Found: C, 41·05; H, 4·8; N, 19·1; S, 10·6. Calc. for $C_{10}H_{14}Cl_2N_4S$: C, 40·95; H, 4·8; N, 19·1; S, 10·9%). The infrared spectrum of this compound showed a strong broad carbonyl band at 1620—1640 cm.$^{-1}$; such an absorption could be typical of an isourea grouping.

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UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA 4, PENNSYLVANIA, U.S.A. [*Received, October 10th,* 1963.]

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