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Thiazolo[3·2-*a*]benzimidazoles[1]

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Received June 5, 1967

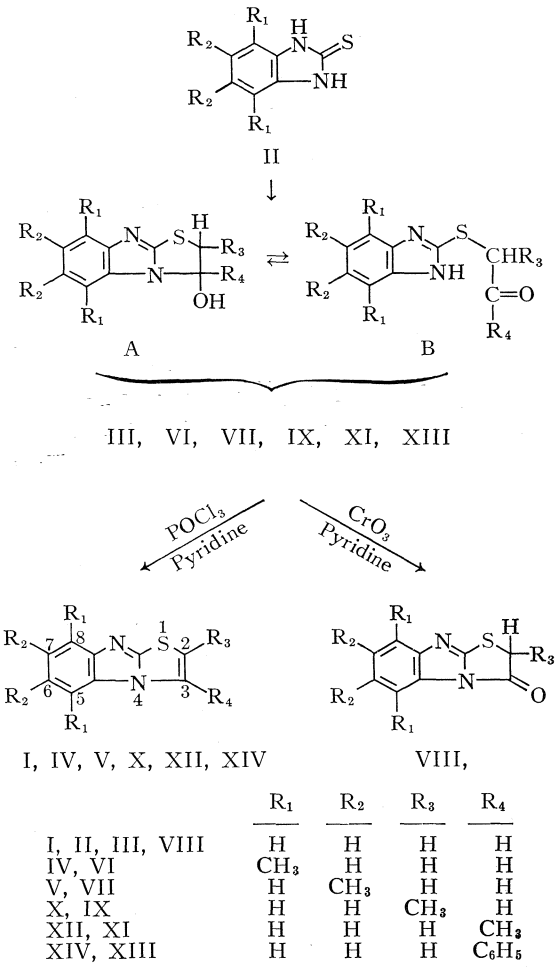
Thiazolo[3·2-*a*]benzimidazole (I) and several of its derivatives were synthesized by annelation of the thiazole ring to a benzimidazole. The intermediate 3-hydroxy-2,3-dihydrothiazolo[3·2-*a*] benzimidazoles were identified and the 3-position of the hydroxyl group was established by oxidation to 3-(2*H*)-thiazolo[3·2-*a*]benzimidazolone. Tautomerism of the 3-hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazoles was also investigated.

3-Hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazole and the corresponding 3-methyl compound were found to undergo nitrogen acetylation and rearrangement under acetylating conditions.

Canadian Journal of Chemistry. Volume **45**, 2903 (1967)

The synthesis of thiazolo[3·2-*a*]benzimidazole (I), a benzo derivative of imidazo-[2·1-*b*]thiazole has not been reported in the literature. Various derivatives of I had been prepared from 2-benzimidazolinethione and α-haloketones (1–4); however, the direction of this reaction had not been definitely established. The synthesis of 6- or 7-hydroxythiazolo[3·2-*a*]benzimidazoles has been described in a patent (5); our attempts to repeat this work were unsuccessful.

The objective of this work was to synthesize thiazolo[3·2-*a*]benzimidazole (I) and some of its alkyl derivatives and to investigate the reaction of 2-benzimidazolinethione (II) with various α-halocarbonyl compounds. Condensation of II with chloroacetaldehyde in 2-butanone (Reaction Scheme 1) gave a hydroxy compound which was tentatively identified as 3-hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazole (III). Dehydration of III with phosphorus oxychloride in pyridine gave the parent compound of the series, thiazolo-[3·2-*a*]benzimidazole (I). The infrared spectrum of III showed broad bands between 3 050 and 2 650 cm^{-1} for the hydrogen-bonded H—O stretching vibration and a strong band at 1 040 cm^{-1} for the C—OH stretch of the alcohol. The nuclear magnetic resonance (n.m.r.) spectrum (Fig. 1) showed an AMX pattern of three quartets at δ 6.62, 4.52, and 3.72 for the three protons of the thiazolidine ring.



	R_1	R_2	R_3	R_4
I, II, III, VIII	H	H	H	H
IV, VI	CH_3	H	H	H
V, VII	H	CH_3	H	H
X, IX	H	H	CH_3	H
XII, XI	H	H	H	CH_3
XIV, XIII	H	H	H	C_6H_5

REACTION SCHEME 1.

[1]This work received financial assistance from the National Research Council of Canada, Ottawa and was taken from a portion of the Ph.D. Thesis of A. E. Alper.

[2]Holder of the National Research Council of Canada studentship 1964–1965 and 1965–1966.

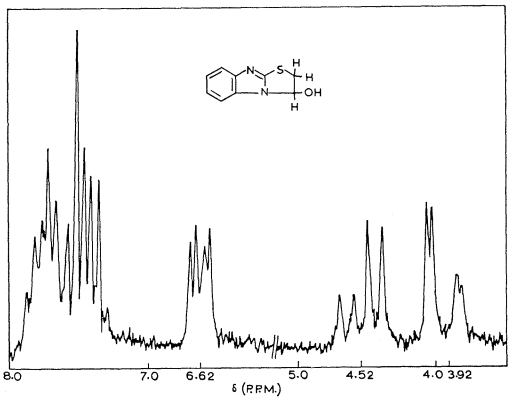


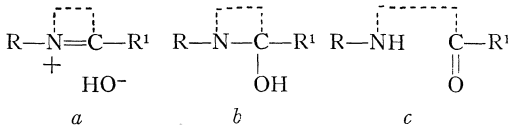
FIG. 1. The proton n.m.r. spectrum of 3-hydroxy-2,3-dihydrothiazolo[3.2-*a*]benzimidazole (III) in dimethylsulfoxide-d_6 solution at 60 Mcycles.

Similarly, 5,8-dimethylthiazolo[3·2-*a*]-benzimidazole (V) and 6,7-dimethylthiazolo[3·2-*a*]benzimidazole (V) were synthesized from 4,7-dimethyl-2-benzimidazolinethione and 5,6-dimethyl-2-benzimidazolinethione (6), respectively. The previously unknown 4,7-dimethyl-2-benzimidazolinethione was prepared by condensation of 2,3-diaminio-*p*-xylene (7) with potassium ethyl xanthate.

3-Hydroxy-2,3-dihydrothiazolo[3·2-*a*]-benzimidazole (III) was shown to have the hydroxyl group at C-3 by relating it to the known 3-(2*H*)-thiazolo[3·2-*a*]benzimidazolone (VIII) (8). Oxidation of III with chromium trioxide in pyridine gave a ketone identical in all respects with VIII.

Since the direction of the condensation reaction between 2-benzimidazolinethione (II) and α-halocarbonyl compounds was established, thiazolo[3·2-*a*]benzimidazoles substituted on the thiazole ring were prepared. Condensation of II with α-bromopropionaldehyde diethyl acetal (9) gave 3-hydroxy-2-methyl-2,3-dihydrothiazolo[3·2-*a*]benzimidazole (IX) which on dehydration with phosphorus oxychloride in pyridine yielded 2-methylthiazolo[3·2*a*]benzimidazole (X). Similarly, II and chloroacetone gave 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3·2-*a*]benzimidazole (XI) which on treatment with dilute acid produced 3-methylthiazolo[3·2-*a*]benzimidazole (XII). The preparation of 3-phenylthiazolo[3·2-*a*]benzimidazole (XIV) involved two steps; first, the reaction of 2-benzimidazolinethione and bromoacetophenone gave α-(2-benzimidazolylthio)acetophenone (XIII); second, on treatment with concentrated hydrobromic acid, XIII underwent cyclodehydration to form 3-phenylthiazolo[3·2-*a*]benzimidazole (XIV).

The 3-hydroxy-2,3-dihydrothiazolo[3·2-*a*] benzimidazoles (III, VI, VII, IX, XI, and XIII) are potentially tautomeric carbinolamines. Their actual structure depends on the substituents of the thiazolidine ring. Three structures are possible for tautomeric systems of this type; however, all three have never been shown to exist simultaneously (10).



Infrared and n.m.r. spectral data were useful in studying this tautomerism. Ultraviolet spectra were of no help because the spectra of the 2-substituted benzimidazoles were identical with those of the 2,3-dihydrothiazolo[3·2-*a*]benzimidazoles. The 3-hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazoles unsubstituted on the thiazolidine ring (III, VI, and VII) as well as the 2-methyl compound (IX) exist only as the cyclic carbinolamines both in solution and in the solid state. The evidence for their structure in solution is based only on n.m.r. data because the solubilities of III, VI, VII, and IX did not permit study of their infrared spectra in solution. Other tautomers of these compounds may therefore be present in amounts less than 5%.

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3·2-*a*]benzimidazole (XI) has the cyclic structure in the solid state; however, in solution XI is a mixture of the carbinolamine and aminoketone tautomers XIA and XIB, respectively. The n.m.r. spectrum of 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3·2-*a*]benzimidazole (XI) (Fig. 2) shows that XIA and XIB are present in a ratio of 1:2. Two protons in the CH_2 group of B are equivalent as indicated by a single band at δ 4.35. The quartet at δ 3.94 is an AB pattern for the two nonequivalent protons

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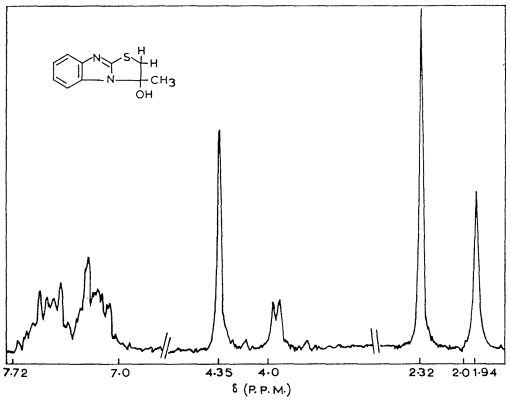

FIG. 2. The proton n.m.r. spectrum of 3-hydroxy-3-methyl-2,3-dihydrothiazolo [3·2-*a*] benzimidazole (XI) in dimethylsulfoxide-d_6 solution at 60 Mcycles.

of A. The chemical shift ($\nu_0\delta$ = 8.8 c.p.s.) and coupling constant (J = 11.5 c.p.s.) were calculated in the usual manner (11). Other details of the n.m.r. spectrum of XI are given in the experimental part. D'Amico *et al.* (3) had reported the synthesis of (2-benzimidozolylthio)-2-propanone (a sample of which was identical with XI); however, they gave no evidence for its tautomerism with the carbinolamine form. α-(2-Benzimidazolylthio)acetophenone (XIII) exists only as the open-chain aminoketone both in the solid state and in solution.

The chemical reactions of the 3-hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazoles also indicate their tautomeric nature. Acetylation of III and IX with acetic anhydride at room temperature gave the *O*-acetyl derivatives. The infrared spectra of these esters show carbonyl absorption at 1 750 cm^{-1}. Also, refluxing III and IX in ethanol containing hydrochloric acid gave corresponding 3-ethoxy compounds. Treatment of XI and XIII with acetic anhydride at room temperature gave their *N*-acetyl derivatives. The infrared spectra of both *N*-acetates showed a strong band at 1 715 cm^{-1} for the C=O stretch of the amide.

When XI and III were treated with acetic anhydride in pyridine at higher temperatures different products were obtained. Heating XI in acetic anhydride and pyridine for 3 h gave a white solid, XVI, m.p. 164–165°, (Reaction Scheme 2). D'Amico (3) had reported that this reaction gave the (2-benzimidazolylthio)-1-propen-2-ol acetate (XV, an enol acetate). In the imidazo[2·1-*b*]thiazole series, Ochiai (14) had found that the similar compound 2-acetylthio-5-methyl-4-carbethoxyimidazole when heated in acetic anhydride formed a 2-acetylimidazo[2·1-*b*]thiazole.

XVI was identified as 2-acetyl-3-methylthiazolo[3·2-*a*]benzimidazole. The infrared spectrum showed strong absorption at 1 646 cm^{-1} for the C=O stretch of conjugated ketone and 1 483 cm^{-1} for the thiazolo[3·2-*a*]benzimidazole system. In the n.m.r. spectrum, in addition to the complex pattern for the benzenoid protons, only two singlets appeared at δ 2.95 and 2.47, assigned to the methyl group at C-3 and the methyl protons of the acetyl group, respectively. Also, a satisfactory analysis for $C_{12}H_{10}N_2OS$ was obtained. The product formed a 2,4-dinitrophenylhydrazone and gave a positive iodoform test indicating that it was a methyl ketone. Finally, this ketone was identical (infrared spectrum and mixture melting point) with an authentic sample of 2-acetyl-3-methylthiazolo[3·2-*a*]-benzimidazole prepared from II by condensation with 3-chloro-2,4-pentanedione (15) followed by dehydration of the resulting 3-(2-benzimidazolylthio)-2,4-pentanedione (XVII) with dilute hydrochloric acid (Reaction Scheme 2). This product corresponds with that obtained by Ochiai (14) in the imidazo[2·1-*b*]thiazole series.

The mechanism for the formation of XVI from 3-hydroxy-3-methyl-2,3-dihydrothiazolo[3·2-*a*]benzimidazole XI is outlined in Reaction Scheme 2 and involves acetylation of the keto form of XI followed by intramolecular condensation. The carbinolamine formed is the cyclic tautomer of 3-(2-benzimidazolylthio)-2,4-pentanedione (XVII), which undergoes cyclodehydration to give 2-acetyl-3-methyl-thiazolo-[3·2-*a*]benzimidazole (XVI).

Treatment of XI with acetic anhydride at room temperature gave the *N*-acetyl derivative (XVIII). Heating XVIII in pyridine gave 3-(2-benzimidazolylthio)2,4-pentanedione (XVII) identical (infrared spectrum and mixture melting point) with

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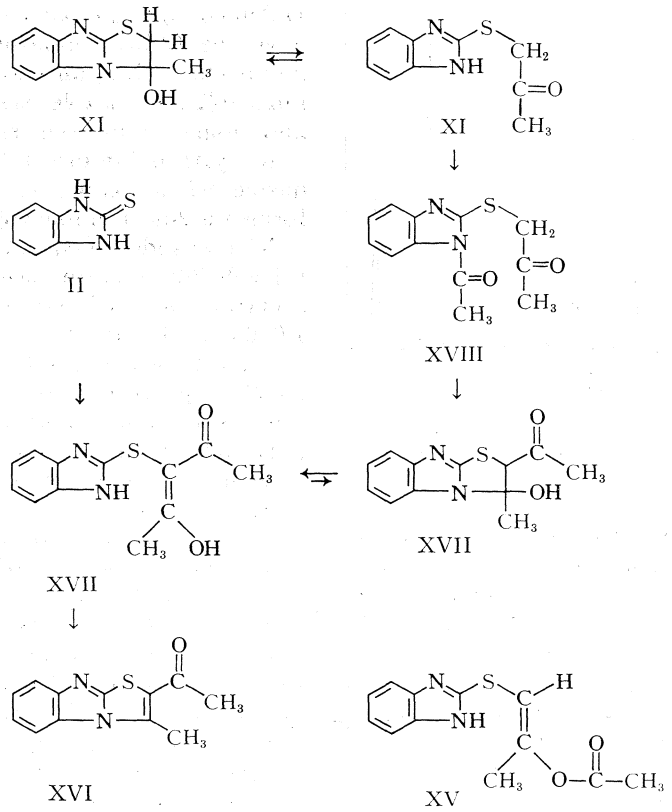

REACTION SCHEME 2.

an authentic sample. With acetic anhydride and pyridine, XVII underwent cyclodehydration to give (XVI).

No evidence was obtained for the ring–chain tautomerism of 3-hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazole (III). Refluxing III in acetic anhydride and pyridine, however, gave 2-acetylthiazolo-[3·2-*a*]benzimidazole (XX, Reaction Scheme 3). The ketone, XX, was characterized by its infrared spectrum which showed carbonyl absorption at 1 660 cm^{-1} for a conjugated ketone and a strong band 1 483 cm^{-1} for the thiazolo[3·2-*a*]benzimidazole system. The n.m.r. spectrum of XX in $CDCl_3$ had a singlet at δ 9.33 for H-3, a complex multiplet between δ 8.0 and 7.1 for the four benzenoid protons, and a singlet at δ 2.45 for the methyl group.

The formation of 2-acetylthiazolo[3·2-*a*]-benzimidazole (XX) from III most likely occurred with cleavage of the C—N bond and intramolecular condensation in an analogous manner to the reaction of XI. This was not unexpected as Gaylord (16, 17) had shown that stable carbinolamines of this type, e.g. 1-hydroxy-methyl-1*H*-benzotriazole, can be cleaved under similar conditions to form *N*-acylated products. By this mechanism, however, either 3-methylthiazolo[3·2-*a*]benzimidazole-2-aldehyde (XXI), or 2-acetylthiazolo[3·2-*a*]-benzimidazole (XX), or both may result.

In addition to the above spectral data, the aldehyde structure was excluded by sodium borohydride reduction of the product. The alcohol obtained was different from an authentic sample of 2-hydroxy-methyl-3-methylthiazolo[3·2-*a*]benzimidazole (XXII), the expected reduction product of the aldehyde (XXI). 2-Hydroxy-methyl-3-methylthiazolo[3·2-*a*]benzimidazole was synthesized by reduction of 2-carbethoxy-3-methylthiazolo[3·2-*a*]benzimidazole (XXIII) (3) with sodium borohydride (18).

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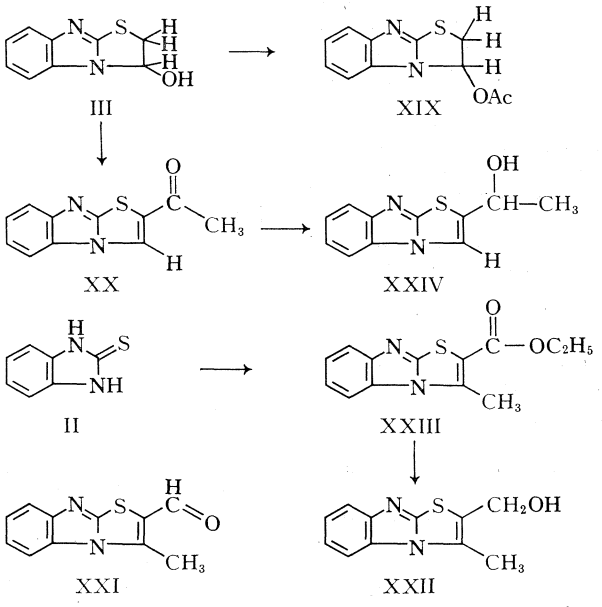

REACTION SCHEME 3.

The alcohol, obtained from sodium borohydride reduction of the acetylation product, was identified as 2-(1-hydroxyethyl)-thiazolo[3·2-*a*]benzimidazole (XXIV). The infrared spectrum of XXIV showed broad absorption at 3 228 cm^{-1} and a strong band at 1 079 cm^{-1} for the C—O stretch of a secondary alcohol. The n.m.r. spectrum (in $CDCl_3$) had a complex multiplet between δ 7.9 and 7.0 for the five aromatic protons, a quartet at δ 5.0 for the proton α to the hydroxyl group and a doublet at δ 1.59 for the methyl protons. The splitting of the signal for the methyl group indicated that this alcohol was the 1-hydroxyethyl compound.

In another approach to the synthesis of thiazolo[3·2-*a*]benzimidazole (I), 5,6,7,8-tetrahydrothiazolo[3·2-*a*]benzimidazole (XXV) was prepared from 2-aminothiazole and 2-chlorocyclohexanone (12). This is analogous to the condensation of 2-aminopyridine with 2-chlorocyclohexanone to give 6,7,8,9-tetrahydropyrido[1·2-*a*]benzimidazole. The latter can be dehydrogenated to pyrido[1·2-*a*]benzimidazole (13). Attempted dehydrogenation of XXV, however, resulted in either desulfurization or decomposition.

EXPERIMENTAL

Melting points were determined in sealed capillary tubes on a Gallenkamp apparatus and are corrected. Elemental analyses were carried out by C. Daessle, Montreal, and A. Bernhardt, Mülheim, Germany. Infrared spectra were determined, unless otherwise indicated, in potassium bromide pellets on a Perkin–Elmer model 521 grating spectrophotometer. Ultraviolet spectra were measured on a Perkin–Elmer model 350 spectrophotometer using absolute ethanol as solvent. Nuclear magnetic resonance spectra were determined on a Varian HR-60 or A-60 spectrometer and tetramethylsilane (0 p.p.m.) was used as an internal standard.

3-Hydroxy-2,3-dihydrothiazolo[3·2-a]benzimidazole (III)

2-Benzimidazolinethione (II) (1.5 g, 0.01 mole) was suspended in 30 ml of 2-butanone[3] and 1.9 ml of a 40–45% solution of chloroacetaldehyde in water was added. The mixture was refluxed for 4 h, cooled, and filtered to give 2.2 g (quantitative yield) of 2-hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazole hydrochloride, m.p. (decomp.) 178–180°. Two recrystallizations from ethanol gave an analytical sample, m.p. (decomp.) 180–180.5°.

Anal. Calcd. for $C_9H_9N_2OSCl$: C, 47.44; H, 3.92; N, 12.26. Found: C, 47.68; H, 3.95; N, 12.14.

The crude hydrochloride (1.1 g) was dissolved in water and filtered to remove any unreacted 2-benzimidazolinethione. The filtrate was made basic

[3]2-Butanone was used as a solvent for these reactions because alcohols gave a mixture of the hydroxy compound and its corresponding ether.

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with sodium bicarbonate to give 0.93 g of III which did not melt but decomposed gradually between 180 and 205°. Repeated recrystallizations from tetrahydrofuran did not give a substance having a sharp melting point.

The spectral characteristics of III were as follows: ν_{max} 3 200–2 600 (bonded OH), 1 040 (C—OH), and 742 cm^{-1} (C—H of *o*-disubstituted benzene ring); δ (DMSO-d_6 after exchange with trifluoroacetic acid was used. 7.9–7.3 (four-proton, complex multiplet, aromatic protons), 6.62 (one-proton quartet, J = 12.0 and J = 6.0 c.p.s., the proton at C-2 is *cis* to the OH at C-3), and 3.92 (one-proton quartet, J = 12.0 and J = 2.1 c.p.s., the proton at C-2 is *trans* to the OH at C-3).

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found for III: C, 56.18; H, 4.22; N, 14.48.

3-Acetoxy-2,3-dihydrothiazolo[3·2-a]benzimidazole (XIX)

A solution containing 1 g (0.0052 mole) of 3-hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazole (III) in 30 ml of acetic anhydride was allowed to stand at room temperature overnight. The reaction mixture was added to 150 ml of water and was neutralized with sodium bicarbonate. The resulting precipitate was filtered off and dried to give 1.1 g (92%) of 3-acetoxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazole, m.p. 94–96°. Crystallization from hexane gave colorless needles, m.p. 102–103°; ν($CHCl_3$) 1 750 cm^{-1} (C=O acetate); ν(KBr) 1 732, 1 239, and 1 019 cm^{-1} (acetate); δ($CDCl_3$) 7.7–7.0 (five-proton multiplet, benzenoid protons and the proton α to the acetoxy group), 4.29 (one-proton quartet, J = 13.5 and J = 5.0 c.p.s., the proton at C-2 *trans* to the acetoxy group), 3.70 (one-proton doublet, J = 13.5 c.p.s., the proton at C-2 *cis* to the acetoxy group), and 2.05 (three-proton singlet, methyl group).

Anal. Calcd. for: $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found for XIX: C, 56.52; H, 4.50; N, 11.86.

Thiazolo[3·2-a]benzimidazole (I)

Phosphorus oxychloride (6 ml) was added dropwise to a stirred solution of 1.9 g (0.01 mole) of III in 40 ml of dry pyridine over a 45 min period. The stirring was continued for 1 h. Ice was added cautiously and the mixture was poured into 200 ml of water. Ether extraction (3 × 350 ml) gave 1.5 g of I, m.p. 130–135°. Treatment with charcoal and three recrystallizations from hexane yielded 1.3 g (77%) of I, m.p. 135.5–136.5°; λ_{max} 282 (log ϵ 2.89), 273 (2.99), 247 (3.16), 241 (3.19), and 214 mμ (3.47); ν_{max} 1 459 (strong), 740, and 726 cm^{-1} (four adjacent benzenoid hydrogens, see Fig. 3); δ($CDCl_3$) 7.83–7.0 (complex multiplet, four-proton benzenoid protons), 7.6 (one-proton doublet, J = 4.7 c.p.s., H-3) and 6.7 (one-proton doublet, J = 4.7 c.p.s., H-2, see Fig. 4).

Anal. Calcd. for $C_9H_6N_2S$: C, 62.04; H, 3.47; N, 16.09. Found for I: C, 61.84; H, 3.59; N, 16.24.

Oxidation of III with Chromium Trioxide

Chromium trioxide (1.5 g) was dissolved in 20 ml of pyridine (10). 3-Hydroxy-2,3-dihydrothiazolo[3·2-*a*] benzimidazole (III) (0.95 g, 0.005 mole) was added

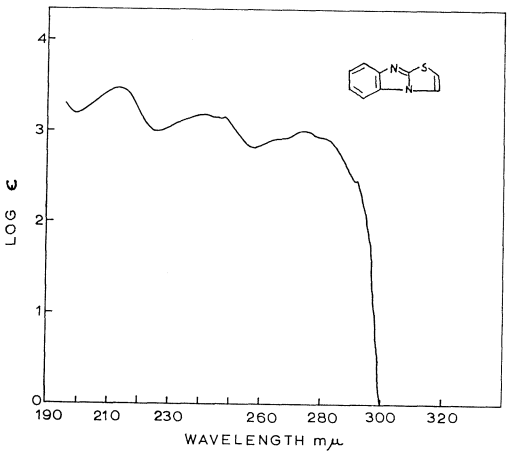

FIG. 3. The ultraviolet spectrum of thiazolo[3·2-*a*] benzimidazole (I) in ethanol.

and the mixture was stirred for 15 min. The resulting red-orange solution was allowed to stand at room temperature for 22 h. The reaction mixture was added to 200 ml of water and continuously extracted with chloroform for 48 h. The extract was concentrated to approximately 15 ml and filtered to give 0.6 g (63%) unreacted III (undepressed melting point and identical infrared spectrum). The filtrate was evaporated to dryness to obtain 0.33 g (24%) of VIII, yellow needles, m.p. 177–179° (lit. (8) m.p. 177–179°); ν_{max} 1 742 (C=O of a fused γ-lactone) and 760 cm^{-1} (C—H of an 1,2-disubstituted benzene ring); δ ($CDCl_3$) 8.0–7.0 (four-proton complex multiplet, benzenoid protons) and 4.5 (two-proton singlet, S—CH_2—).

4,7-Dimethyl-2-benzimidazolinethione

A mixture of 2,3-diamino-*p*-xylene (7) (6.8 g, 0.05 mole), potassium hydroxide (2.8 g, 0.05 mole) and carbon disulfide (10 ml) was refluxed in 50 ml of ethanol and 10 ml of water for 3 h. During the course of the reaction hydrogen sulfide was evolved and a solid precipitated. The reaction mixture was diluted with 30 ml of water and acidified with 10–20 ml of a 1:2 acetic acid – water solution to give 7.2 g (81%) of product, colorless platelets (ethanol) which did not melt below 350°; ν_{max} 3 300–2 600 (broad bonded N—H), 1 154 (intense, C=S), and 793 cm^{-1} (C—H, two adjacent benzenoid hydrogens); δ(DMSO-d_6) 12.54 (broad, NH_2— protons) and 6.70 (two-proton benzenoid protons, 2.30 (two, six-proton methyl groups).

Anal. Calcd. for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.71. Found: C, 60.72; H, 5.79; N, 15.76.

5,8-Dimethyl-3-hydroxy-2,3-dihydrothiazolo[3·2-a]-benzimidazole (VI)

4,7-Dimethyl-2-benzimidazolinethione was treated with chloroacetaldehyde as described above for the preparation of III, to give 4.9 g (88.9%) of VI; m.p. (decomp.) 191.5–193.5° (crystallized twice from tetrahydrofuran); ν_{max} 3 200–2 600 (broad,

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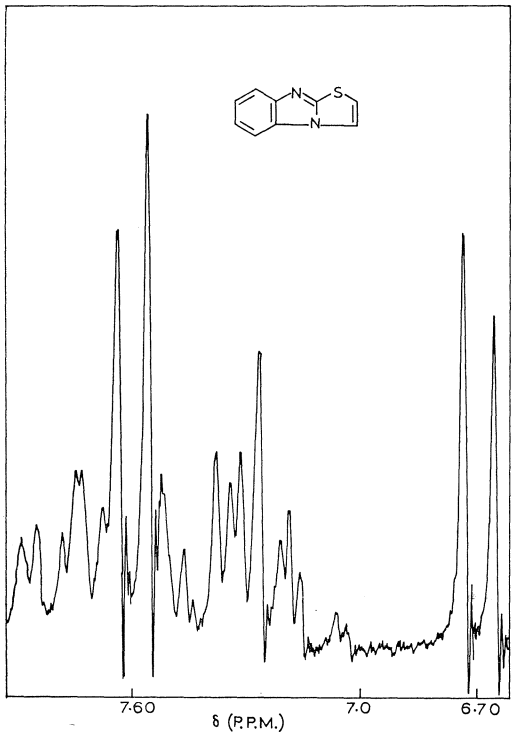

FIG. 4. The proton n.m.r. spectrum of thiazolo-[3·2-*a*]benzimidazole (I) in chloroform-*d* solution at 60 Mcycles.

bonded OH), 1 049 (C—OH), and 810 cm^{-1} (C—H, two adjacent benzenoid protons; δ(DMSO-d_6 after exchange in trifluoroacetic acid) 6.80 (two-proton singlet, benzenoid protons), 6.32 (one-proton quartet, J = 5.0 and J = 1.5 c.p.s., CH—OH), 4.25 (one-proton quartet, J = 11.9 and J = 5.0 c.p.s.; the proton at C-2 is *cis* to OH at C-3), 3.65 (one-proton quartet, poorly resolved, J = 11.9 c.p.s. and J = 1 c.p.s.; the proton at C-2 is *trans* to OH at C-3), 2.53, and 2.42 (three-protons each, two singlet methyl groups).

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found for VI: C, 59.85; H, 5.38; N, 12.57.

5,8-Dimethylthiazolo[3·2-a]benzimidazole (IV)

The dehydration of 3.3 g (0.015 mole) of VI was carried out as described for III to give 2.8 g (93%) of IV, m.p. 134–135° (colorless platelets from hexane); λ_{max} 277 (log ε 4.04), 241 (4.16), and 221 mμ (4.57); ν_{max} 1 471 (strong), 808, and 841 cm^{-1} (C—H, two adjacent benzenoid hydrogens); δ($CDCl_3$) 7.70 (one-proton doublet, J = 4.8 c.p.s., N—CH=), 6.92 (two-proton quartet with an AB pattern, $\nu_0\delta_{AB}$ = 11.1 c.p.s., J_{AB} = 7.5 c.p.s., benzenoid protons), 6.68 (one-proton doublet J = 4.8 c.p.s., S—CH=), 2.64, and 2.55 (three-protons each, two singlet methyl groups).

Anal. Calcd. for $C_{11}H_{10}N_2S$: C, 65.31; H, 4.98; N, 13.85. Found for IV: C, 65.29; H, 5.09; N, 13.77.

6,7-Dimethyl-3-hydroxy-2,3-dihydrothiazolo[3·2-a]-benzimidazole (VII)

Condensation of 4.0 g (0.022) mole) of 5,6-dimethyl-2-benzimidazolinethione (6) with chloroacetaldehyde was carried out under the conditions described for the preparation of III to give 4.3 g (88%) of VII, m.p. (decomp.) 185–202° (crystallized twice from tetrahydrofuran); ν_{max} 3 200–2 600 (broad, bonded OH), 1 046, 1 054 (C—OH), 845 cm^{-1} (C—H of 1,2,4,5-tetrasubstituted benzene ring); δ(DMSO-d_6 after exchange in trifluoroacetic acid) 7.50, 7.43 (one-proton each, two singlets, benzenoid protons), 6.30, (one-proton quartet, J = 2.3 and J = 5.9 c.p.s., CHOH), 4.24 (one-proton quartet, J = 12.0 and J = 5.9 c.p.s. the proton at C-2 is *cis* to OH at C-3), 3.64 (one-proton quartet, J = 12.0 and J = 2.3 c.p.s., the proton at C-2 is *trans* to OH at C-3), and 2.28 (six-proton singlet, two methyl groups).

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found for VII: C, 60.10; H, 5.59; N, 12.67.

6,7-Dimethylthiazolo[3·2-a]benzimidazole (V)

This compound was obtained by dehydration of 6,7-dimethyl-3-hydroxy-2,3-dihydrothiazolo[3·2-*a*] benzimidazole (VII) (0.8 g, 0.004 mole) as described in the preparation of I. The yield of V was 0.62 g (78%), (colorless platelets from benzene after treatment with charcoal), m.p. 164–165°; λ_{max} 277 (log ε 4.05), 245 (4.28), and 215 mμ (4.59); ν_{max} 1 462 (strong) and 840 cm^{-1} (C—H of a 1,2,4,5-tetra-substituted benzene ring); δ($CDCl_3$) 7.52 and 7.26 (one-proton each, two singlets, benzenoid protons), 7.46 (one-proton doublet, J = 4.6 c.p.s., N—CH=), 6.63 (one-proton doublet, J = 4.6 c.p.s., S—HC=) and 2.3 (six-proton singlet, two methyl groups).

Anal. Calcd. for $C_{11}H_{10}N_2S$: C, 65.31; H, 4.98; N, 13.85. Found for V: C, 65.22; H, 5.10; N, 13.77.

3-Hydroxy-2-methyl-2,3-dihydrothiazolo[3·2-a] benzimidazole (IX)

α-Bromopropionaldehyde diethyl acetal (9) (2.1 g, 0.01 mole) was gently refluxed with 1 ml of 20% hydrochloric acid for 30 min. The mixture was added to 20 ml of 2-butanone and treated with sodium bicarbonate until the evolution of gas had stopped. The mixture was filtered and 0.8 g (0.004 mole) of II was added. The reaction was carried out in the usual manner to give 0.82 g (quantitative yield) of IX, m.p. 201–203° (tetrahydrofuran); ν_{max} 3 200–2 600 (bonded O—H), 1 039 (C—OH), and 750 cm^{-1} (C—H of disubstituted benzene ring); δ(DMSO-d_6 after exchange with trifluoroacetic acid) 7.6–6.9 (four-proton complex multiplet, benzenoid protons of both isomers), 5.98 (doublet, J = 5.2 c.p.s., C*H*OH of *cis* isomer), 5.82 (doublet, J = 2.0 c.p.s., C*H*OH of *trans* isomer), 4.65 (multiplet, C*H*CH_3 of *cis* isomer), 4.12 (octet, C*H*CH_3 of *trans* isomer), and 1.4 (three-proton doublet, J = 7.0 c.p.s., CH_3 protons of both isomers).

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found for IX: C, 58.38; H, 5.02; N, 13.47.

This product is actually a mixture of the *cis* and *trans* alcohols in the ratio 4:5 as shown by n.m.r.

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(Attempted separation of the isomers by thin-layer chromatography was unsuccessful).

A solution containing 0.5 g (0.0024 mole) of IX in 10 ml of acetic anhydride was allowed to stand at room temperature overnight. The reaction mixture was added to 300 ml of water and was neutralized with sodium bicarbonate. Ether extraction (3 × 50 ml) gave 0.56 g (95%) of 3-acetoxy-2-methyl-2,3-dihydrothiazolo-[3·2-*a*]benzimidazole as a colorless oil; ν_{max} (KBr) 1 748 cm^{-1} (C=O, ester); $\delta(CDCl_3)$ 7.8–7.1 (multiplet, benzenoid protons of both isomers), 7.0 (doublet, J = 7.0 c.p.s., C*H*OAc of *cis* isomer), 6.75 (singlet, C*H*OAc of *trans* isomer), 4.78 (octet, proton at C-2 in *cis* isomer), 4.20 (quartet, proton at C-2 in *trans* isomer), 2.1 (singlet, OOCCH_3 for both isomers) 1.69, and 1.63 (two doublets, J = 7.0 c.p.s., CH_3 of both isomers).

On distillation *in vacuo* (174° at 3 mm Hg) this acetate gave X.

2-Methylthiazolo[3·2-a]benzimidazole (X)

The dehydration of 0.82 g (0.004 mole) of IX was carried out as described for III to give 0.7 g (93%) of X; m.p. 156–158°. Crystallization from hexane raised the melting point to 158–159°; λ_{max} 275 (log ϵ 4.12), 286 (3.95), 248 (4.40), 242 (4.36), and 215 mμ (4.63); ν_{max} 1 461 cm^{-1} (strong); $\delta(CDCl_3)$ 7.9–7.15 (four-proton complex multiplet, benzenoid protons), 7.3 (one-proton quartet, J = 1.5 c.p.s., N—CH=), and 2.40 (three-proton doublet, J = 1.5 c.p.s., CH_3).

Anal. Calcd. for $C_{10}H_8N_2S$: C, 63.79; H, 4.27; N, 14.88. Found for X: C, 63.62; H, 4.42; N, 14.7.

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3·2-a]-benzimidazole (XI)

(a) In 2-Butanone

Condensation of 1.5 g (0.001 mole) of 2-benzimidazolinethione (II) with 0.93 g (0.01 mole) of chloroacetone was carried out under the conditions described for the preparation of III to obtain 2.0 g (97%) of XI, m.p. 111–112° (diethyl ether); ν_{max} (KBr) 3 200–2 600 (bonded OH), 1 085 cm^{-1} (C—OH, tertiary alcohol); ν_{max} ($CHCl_3$) 3 650 (sharp, free OH), 3 554 (broad, bonded OH), 3 448 (sharp, free NH), 3 250 (broad, bonded NH), and 1 715 cm^{-1} (C=O of keto tautomer); δ(DMSO-d_6) after exchange with trifluoroacetic acid) 7.72–6.95 (four-proton complex multiplet, benzenoid protons of tautomers XIA and XIB), 4.35 (singlet, CH_2 of XIB), 3.94 (quartet, AB pattern, J_{AB} = 11.5 c.p.s., $\nu_0\delta_{AB}$ = 8.8 c.p.s., CH_2 of XIA), 2.32 (singlet, CH_3 of XIB), and 1.94 (singlet, CH_3 of XIA).

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found for XI: C, 58.42; H, 5.05; N, 13.44.

(b) In Ethanolic Potassium Hydroxide

2-Benzimidazolinethione (1.5 g 0.01 mole) in 85% ethanolic potassium hydroxide was treated with chloroacetone according to the procedure of D'Amico *et al.* (3). A white powder (1.7 g) was obtained which was identical (infared spectrum and mixture melting point) with an authentic sample of IX and with a sample of D'Amico's product.[4] (m.p. 112–113° from ethanol).

[4]We are grateful to Dr. J. J. D'Amico for a sample of his product.

3-Methylthiazolo[3·2-a]benzimidazole (XII)

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3·2-*a*]-benzimidazole (IX) (0.6 g, 0.003 mole) was refluxed with 70 ml of 4% hydrochloric acid for 15 h. The reaction mixture was diluted with 110 ml of water and made basic with sodium bicarbonate, to give 0.55 g (quantitative yield) of XII, m.p. 160–161° (hexane) (lit. m.p. 165–166° (3)); λ_{max} 277 (log ϵ 4.15), 288 (sharp), 245.5 (4.40), 238.5 (4.40), and 213 mμ (4.58); ν_{max} 1 463 cm^{-1} (strong); $\delta(CDCl_3)$ 7.9–7.0 (four-proton complex multiplet, benzenoid protons), 6.11 (one-proton quartet, J = 1.5 c.p.s., S—CH=), and 2.59 (three-proton doublet, J = 1.5 c.p.s., CH_3).

α-(2-Benzimidazolylthio)acetophenone (XIII)

2-Benzimidazlinethione (II) (0.37 g, 0.0025 mole) and bromoacetophenone (0.50 g 0.0025 mole) were suspended in 40 ml of 2-butanone and the mixture was refluxed for 4 h. The reaction mixture was cooled and filtered to produce 0.85 g (quantitative yield) of (2-benzimidazolylthio)acetophenone hydrobromide, m.p. 205–207°. The hydrobromide (0.6 g, 0.00175 mole) was suspended without further purification in 10 ml of ethanol and the mixture heated to reflux. Freshly distilled triethylamine was added dropwise until all the salt had dissolved. The solution was refluxed for 10 min and poured into 100 ml of water. A precipitate of XIII (0.45 g) formed, colorless needles, m.p. 165.5–167.5° (benzene); ν_{max} (KBr) 3 100–2 600 (broad, hydrogen-bonded NH), 1 690 (C=O, aryl ketone), 739 (C—H, 1,2-disubstituted benzene ring), and 750 cm^{-1} (C—H, phenyl group); ν_{max} ($CHCl_3$) 3 458 (free NH), 3 250 (bonded NH), and 1 683 cm^{-1} (C=O); δ (DMSO-d_6) 8.2–7.0 (nine-proton complex multiplet, benzenoid protons), 5.06 (two-proton singlet, S—CH_2), and 4.6 (one-proton singlet, N—H).

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found for XIII: C, 67.23; H, 4.51; N, 10.25.

N-Acetate of XIII

A solution containing 0.5 g of XIII was allowed to stand at room temperature overnight. The reaction mixture was filtered to give 0.49 g [2-(1-acetyl)-benzimidazolylthio]acetophenone, m.p. 168–172°. Two recrystallizations from benzene – petroleum ether (b.p. 60–80°) gave colorless needles, m.p. 167–168°; ν_{max} ($CHCl_3$) 1 683 (C=O, aryl ketone), and 1 716 cm^{-1} (C=O, amide); δ_{max} ($CDCl_3$–DMSO-d_6) 8.2–7.1 (nine-proton complex multiplet, benzenoid protons), 4.85 (two-proton singlet, —CH_2—S—), and 2.81 (three-proton singlet, CH_3C=O).

Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.78; H, 4.55; N, 9.03. Found: C, 65.67; H, 4.49; N, 9.25.

3-Phenylthiazolo[3·2-a]benzimidazole (XIV)

α - (2 - Benzimidazolylthio)acetophenone (XIII) (1.0 g, 0.0038 mole) was refluxed with 30 ml of fuming hydrobromic acid for 3.5 h. The reaction mixture was added to 400 ml of water and filtered to give 0.34 g of 2-benzimidazolinethione (II). The filtrate was made basic with potassium bicarbonate and the resulting precipitate filtered and dried to

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give 0.5 g of a white solid. Two recrystallizations from ethanol gave 0.4 g (43%) of XIV, m.p. 140–142°; λ_{max} 283 (log ϵ 4.01), 268 (4.10), 248 (4.10) and 235 mμ (426); ν_{max} 1 479 cm^{-1} (strong); δ($CDCl_3$) 8.1–7.0 (four-proton complex multiplet), 7.5 (five-proton singlet, benzenoid protons), and 6.6 (one-proton singlet, S—CH=).

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found for XIV: C, 72.17; H, 4.17; N, 11.16.

5,6,7,8-Tetrahydrothiazolo[3·2-a]benzimidazole (XXV)

2-Aminothiazole (10 g, 0.10 mole) and 2-chlorocyclohexanone (12) (12 g, 0.10 mole) were fused together in the absence of solvent and refluxed for 15 min. The resulting dark mass was taken up in 500 ml of water and extracted with ether (3 × 50 ml) to remove any unreacted 2-chlorocyclohexanone. The aqueous solution was made basic with a 10% sodium hydroxide solution and then extracted with chloroform (3 × 100 ml) to give a yellow oil. From the distillation of the oil at 146° at 12 mm Hg, 3.7 g of a colorless liquid was obtained which slowly crystallized, m.p. 61–65°. Three recrystallizations from petroleum ether (b.p. 30–60°) provided 2.8 g of XXV, m.p. 72–73°; λ_{max} 260 (log ϵ 3.98) and 213 mμ (4.35); δ (CCl_4) 7.12 (one-proton doublet, J = 4.8 c.p.s., N—CH=), 6.56 (one-proton doublet, J = 4.8 c.p.s., S—CH=), 2.43 (four-proton singlet, CH_2 at C-5 and C-8), and 1.75 (four-proton singlet, CH_2 at C-6 and C-7).

Anal. Calcd. for $C_9H_{10}N_2S$: C, 60.63; H, 5.65; N, 15.71. Found for XXV: C, 60.64; H, 5.56; N, 15.56.

2-Acetyl-3-methylthiazolo[3·2-a]benzimidazole (XVI)

(a) From 2-Benzimidazolinethione (II)

A mixture of 2-benzimidazolinethione (1.5 g, 0.01 mole) and 3-chloro-2,4-pentanedione (15) (1.4 g, 0.01 mole) was refluxed for 4 h in 2-butanone. The reaction mixture was cooled. The resulting precipitate was filtered off, dried *in vacuo* and suspended in water. The water suspension was made basic with sodium bicarbonate and gave 2.1 g of a white solid. Crystallization from ethanol gave 2.0 g (90%) of 3-(2-benzimidazolylthio)-2,4-pentanedione XVII, m.p. 178–179° (lit. (3) m.p. 185–186°). This product (0.3 g) was refluxed in 50 ml of 5% hydrochloric acid for 3 h. The reaction mixture was added to 500 ml of water and made basic with sodium bicarbonate. The resulting solid was filtered off and dried to give 0.25 g of XVI, colorless crystals, m.p. 163–165° (ethanol); ν_{max} 1 646 (C=O, conjugated ketone), 1 483 (thiazolo[3·2-*a*]benzimidazole system), 756, and 740 cm^{-1} (*o*-disubstituted benzene); δ ($CDCl_3$) 7.8–7.0 (four-proton multiplet, benzenoid protons), 2.95 (three-proton singlet, CH_3 at C-3), and 2.47 (three-proton singlet —CO—CH_3); λ_{max} (EtOH) 273 (log ϵ = 4.64) and 213 mμ (4.62).

(b) From 3-hydroxy-3-methyl-2,3-dihydrothiazolo [3·2-a]benzimidazole (XI)

A solution of XI (4.0 g, 0.019 mole) in 100 ml of pyridine and 50 ml of acetic anhydride was heated at 100° for 3 h. The reaction mixture was added to 350 ml of water. The resulting precipitate was filtered off and dried to give 4.1 g (95%) of colorless needles, m.p. 162–165°. Two recrystallizations from benzene gave an analytical sample, m.p. 164–165°. Mixture melting point with an authentic sample of 2-acetyl-3-methylthiazolo [3·2-*a*]benzimidazole was 163–165°.

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.62; H, 4.37; N, 12.17. Found for XVI: C, 62.33; H, 4.35; N, 12.28.

[2-(1-Acetyl)benzimidazolylthio]propan-2-one (XVIII)

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3·2-*a*]-benzimidazole, XI, (0.6 g, 0.0028 mole) was allowed to stand overnight at room temperature in 20 ml of actic anhydride. The reaction mixture was added to 250 ml of water. The resulting precipitate was filtered off and dried to give 0.72 g (quantitative yield) of XVIII, m.p. 115.5–118°. Crystallization from hexane raised the melting point to 121–122°; ν_{max} 1 707 cm^{-1} (C=O of amide and ketone overlapping); δ($CDCl_3$) 7.7–7.1 (four-proton complex multiplet, benzenoid protons), 4.1 (two-proton singlet —S—CH_2—), 2.75 (three-proton singlet, N—C—CH_3), 2.40 (three-proton singlet, CH_2–CO—CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.28. Found for XVIII: C, 58.24; H, 5.02; N, 11.42.

Rearrangement of [2-(1-acetyl)benzimidazolylthio] propan-2-one in pyridine

A solution containing 50 mg XVIII (0.0002 mole) in 3 ml of pyridine was heated at 100° for 3 h. The reaction mixture was added to 100 ml of water. On standing the aqueous solution gave 45 mg of white precipitate, m.p. 176–177°. The mixture melting point of this product with 3-(2-benzimidazolylthio)-2,4-pentanedione (XVII) was 177–179°. The infrared spectra of the two compounds were identical.

Cyclodehydration of 3-(2-benzimidazolylthio)-2,4-pentanedione (XVII) with acetic anhydride in pyridine

A stirred solution containing 0.25 g (0.008 mole) of XVII in 2 ml of pyridine and 1 ml of acetic anhydride was heated at 100° for 3 h. The resulting precipitate was collected by filtration and dried to give 0.20 g of colorless crystals, m.p. 163–165°. A mixture melting point with 2-acetyl-3-methylthiazolo[3·2-*a*]benzimidazole was not depressed.

2-Acetylthiazolo[3·2-a]benzimidazole (XX)

3-Hydroxy-2,3-dihydrothiazolo[3·2-*a*]benzimidazole (III) (1.0 g, 0.005 mole) in 25 ml of acetic anhydride and 50 ml of pyridine was refluxed for 3 h. The reaction mixture was added to 800 ml of water and was made basic with dilute ammonium hydroxide. The resulting precipitate was collected by filtration and dried *in vacuo* to give 0.80 g (72%) of a pale-yellow solid, m.p. 226–228°. Crystallization from ethanol gave 2-acetylthiazolo[3·2-*a*]benzimidazole (XX), m.p. 227–228°; ν_{max} 1 660 (C=O, conjugated ketone) and 765 cm^{-1} (*o*-disubstituted benzene); δ(DMSO-d_6) 9.3 (one-proton singlet, H-3), 8.0–7.1 (four-proton complex multiplet, benzenoid protons), and 2.45 (three-proton singlet, CH_3CO—); λ_{max} (EtOH) 271 (log ϵ 4.62) and 212 mμ (4.67).

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Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.86. Found for XX: C, 61.09; H, 3.70; N, 13.07.

2-Carbethoxy-3- methylthiazolo[3·2-a]benzimidazole (XXIII)

2-Carbethoxy-3-methylthiazolo[3·2-*a*]benzimidazole (XXIII), m.p. 120–122° (lit. (3) m.p. 122–123°) was obtained (82%) from 2-benzimidazolinethione and ethyl chloroacetoacetate according to the procedure of D'Amico *et al.* (3); ν_{max} 1 711, 1 221, and 1 078 (carbethoxy group) and 738 cm^{-1} (*o*-disubstituted benzene); $\delta(CDCl_3)$ 7.9–7.0 (four-proton multiplet, benzenoid protons), 4.38 (two-proton quartet, J = 7.2 c.p.s., —O—CH_2—), and 3.0 (three-proton singlet, CH_3), and 1.4 (three-proton triplet, J = 7.2 c.p.s., —O—CH_2—CH_3); λ_{max} (EtOH) 266 (log ϵ 4.49) and 212 mμ (4.49).

2-Hydroxymethyl-3-methylthiazolo[3·2-a]benzimidazole (XXII)

A solution containing 1.6 g (0.04 mole) of sodium borohydride in 160 ml of ethanol was added all at once to 20 ml of ethanol containing 1.0 g (0.004 mole) of 2-carbethoxy-3-methylthiazolo[3·2-*a*]benzimidazole. After the initial exothermic reaction, the mixture was refluxed for 2 h and then poured into 900 ml of water. The solution was filtered to give 0.75 g of a white solid, m.p. 181–185°. Crystallization from ethanol and water gave 0.7 g of (XXII), m.p. 186–189°. Two further recrystallizations from dioxane gave an analytical sample, m.p. 194–195°; ν_{max} 3 300—3 000 (broad, O—H), 1 019 (C—OH, primary alcohol) and 734 cm^{-1} (*o*-disubstituted benzene); δ(DMSO-d_6) 7.9–7.0 (four-proton multiplet, benzenoid protons), 5.5 (one-proton, broad OH), 4.55 (two-proton singlet, CH_2), and 2.52 (three-proton singlet, CH_3).

Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.52; H, 4.62; N, 12.83. Found for XXII: C, 60.44; H, 4.67; N, 12.95.

2-(1-Hydroxyethyl)thiazolo[3·2-a]benzimidazole (XXIV)

A solution of 3.0 g (0.006 mole) of sodium borohydride in 200 ml of ethanol was added all at once to 200 ml of ethanol containing 1.2 g (0.005 mole) of 2-acetyl-thiazolo[3·2-*a*]benzimidazole (XX) and the reaction mixture was refluxed for 2 h. The ethanol solution was concentrated to approximately 50 ml and poured into 300 ml of water. The aqueous solution was extracted with chloroform (3 × 60 ml). The chloroform extract gave 1.1 g of colorless crystals, m.p. 112–114°. Crystallization from benzene gave XXIV, m.p. 116–118°; ν_{max} 3 228 (OH) and 1 079 cm^{-1} (C—OH, secondary alcohol); $\delta(CDCl_3)$ 7.9–7.0 (five-proton multiplet, benzenoid protons and H-3), 5.7 (one-proton broad singlet, OH), 5.0 (one-proton quartet, J = 6.5 c.p.s., C*H*OH), and 1.59 (three-proton doublet, J = 6.5 c.p.s., CHOH—CH_3). In addition, the n.m.r. spectrum showed signals at 4.15 and 1.2 p.p.m. for an unidentified impurity which did not disappear after several recrystallizations. Therefore, the elemental analysis was carried out on the acetate which was obtained in pure form.

2-(1-Acetoxyethyl)thiazolo[3·2-a]benzimidazole

2-(1-Hydroxyethyl)thiazolo[3·2-*a*]benzimidazole (XXIV) (0.22 g, 0.001 mole) was allowed to stand in 10 ml of acetic anhydride at room temperature for 24 h. The reaction mixture was added to 200 ml of water and the aqueous solution was made basic with sodium bicarbonate. Extraction with ether (3 × 50 ml) gave 0.2 g of a white solid. Purification by thin-layer chromatography (ether) gave 0.16 g of colorless crystals, m.p. 94–96°. Crystallization from hexane gave 2-(1-acetoxyethyl)thiazolo[3·2-*a*]benzimidazole, m.p. 104–105°; ν_{max} 1 734, 1 225, and 1 062 cm^{-1} (acetate); $\delta(CDCl_3)$ 7.9–7.1 (five-proton multiplet, benzenoid protons and H-3 as sharp singlet at 7.75), 6.13 (one-proton quartet, J = 6.5 c.p.s., —C*H*OAc), 2.08 (three-proton singlet, CH_3CO—), and 1.67 (three-proton doublet, J = 6.5 c.p.s., CHCH_3).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.99; H, 4.63; N, 10.76. Found: C, 60.07; H, 4.70; N, 10.88.

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