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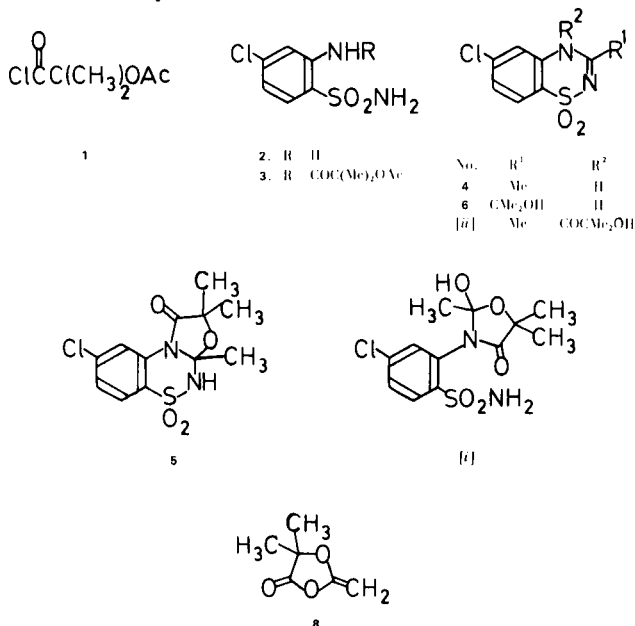
Acylation of 2-amino-4-chlorobenzenesulfonamide by 2-acetoxyisobutyryl chloride under acidic conditions unexpectedly gave 6-chloro-3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide and 8-chloro-2,2,3a-trimethyl-3a,4-dihydrooxazolo[2,3-*b*] [1,2,4]benzothiadiazin-1-one 5,5-dioxide, the skeletons of which incorporate the carbon atom of the acetoxy carbonyl group of the acid chloride.

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One standard preparation of 3-substituted 4*H*-1,2,4-benzothiadiazine 1,1-dioxides calls for acylation of 2-aminobenzenesulfonamides with acid chlorides, and results after cyclization in incorporation of the carbonyl carbon of the acid chloride into the 3-position of the heterocycle (1,2). When, however, the acid chloride contains an extra carbonyl group, as does 2-acetoxyisobutyryl chloride (1), I have found that the carbon atom of the latter carbonyl group instead may be incorporated into the 3-position of a benzothiadiazine dioxide, if the conditions of acylation and cyclization are acidic.

Acylation of 2-amino-4-chlorobenzenesulfonamide (2) with 1 in hot benzene unexpectedly gave a mixture from which three products were obtained in low yields; one product was the desired amide (3) and one was the known benzothiadiazine dioxide 4. The third product, m.p. 262-263°, had a novel tricyclic structure. Its elemental composition was established by microanalysis and mass spectrometry as C₁₂H₁₃ClN₂O₄S. The signals of three methyl groups were apparent in its ¹H- and ¹³C-nmr spectra, and its infrared spectrum displayed an absorption characteristic of a 5-membered lactam. These facts suggested that the compound of m.p. 262-263° was 5, and this structural assignment was confirmed by saponification of it to 4.

When compound 2 was treated with 1 in hot benzene



containing pyridine, the yield of 5 was increased, but when triethyl amine was used instead, little or no reaction of 2 occurred (tlc) (3). In contrast, compound 1 in pyridine at 5° changed 2 to 3 in good yield, and concentrated ammonium hydroxide uneventfully cyclized and saponified 3 to 6.

To learn whether 3 might have been an intermediate in the formation of 4 and 5, compound 3 was treated with toluenesulfonic acid, and yielded 5; compound 4 and several unidentified products were detected in the reaction mixture (tlc). Compound 5 may result from closure of 3 to [i] and elimination of water from it; reversed Michael reaction of 5 to [ii] followed by acid-catalysed hydrolysis of the latter may account for formation of 4.

EXPERIMENTAL (4)

2-Acetoxyisobutyryl Chloride (1).

This compound was prepared by modifying a known method (5). Acetyl chloride (0.72 ml.) was added to a mixture of 2-hydroxyisobutyric acid (25 g.) and acetic acid (12 ml.). The mixture was heated at 55° for 2 hours, and acetic acid was distilled at reduced pressure from it. Thionyl chloride (21 ml.) was added to the residue, and the solution was heated over 45 minutes at 110°. It was then cooled and distilled to give 33.3 g. (84%) of the desired 1, b.p. 59-61° at 7 mm (lit. (5)), b.p. 60-65° at 9 mm.

Reaction of 2 with 1 in Benzene.

A mixture of 2 (6) (10.0 g., 0.0482 mole), 1 (8.75 g., 0.0530 mole) and benzene (250 ml.) was heated under reflux 2 hours, cooled and evaporated to dryness. Trituration of the residue with ethyl acetate caused crystallization and the mixture was filtered to give 1.58 g. (10%) of 5, m.p. 238-240°, pure to tlc. Crystallization from dimethylformamide-water gave the analytical sample, m.p. 261.5-263.0° dec.; ir: λ max 2.96, 5.87 μ; uv: λ max 245 (log ε = 3.98) nm; ¹H-nmr: δ 8.00 and 7.97 (2H, overlapping doublets of H₉ (J_m = 2 Hz) and H₆ (J_o = 9 Hz)), 7.64 (H₇, q, J_m = 2 Hz, J_o = 9 Hz), 2.9-3.9 (br, NH), 1.68 (s, 3a-Me), 1.58 (s) and 1.56 (s) (6H, C(Me)₂) ppm; ¹³C-nmr: δ 172.3 (C₁); 138.0, 132.5 and 131.1 (C_{5a}, C₈ and C_{9a}); 127.8, 125.5 and 124.8 (C₆, C₇ and C₉); 100.2 (C_{3a}); 80.1 (C₂); 27.8 (C_{3a}-CH₃); 25.7 and 24.8 (2C₂-CH₃) ppm; ms: m/e 316 (M⁺).

Anal. Calcd. for C₁₂H₁₃ClN₂O₄S: C, 45.50; H, 4.14; Cl, 11.19; N, 8.84; S, 10.12. Found: C, 45.12; H, 4.23; Cl, 11.02; N, 9.06; S, 10.16.

The yield of 5 was raised to 18% by adding one equivalent of pyridine to the reaction mixture.

The residue (about 15 g.) was a mixture of four other products (tlc). Several crystallizations and chromatographies were needed to separate pure samples of the two major components 4 (545 mg., 5%, m.p. 278-280°) (lit (6), m.p. 267-277°), identified by compari-

son of its ir spectrum to that of an authentic sample) and **3** (1.76 g., 11%, m.p. 169-172°).

Saponification of **5** to **4**.

A solution of **5** (318 mg., 1.00 mmole) in 5 ml. of 1 *N* sodium hydroxide was heated at 90° for 2 hours, cooled, acidified, and filtered. The precipitate was washed with water and was dried to give 201 mg. (87%) of **4**, m.p. 277-280° (lit. (**6**), m.p. 276-277°), identified by ir, uv, and mass spectra; the nmr spectrum of the 277-280° material was identical to that of an authentic sample.

2-(2-Acetoxyisobutyryl)amido-4-chlorobenzenesulfonamide (**3**).

A solution of 2-amino-4-chlorobenzenesulfonamide (**2**) 5.00 g., 0.0242 mole, 2-acetoxyisobutyryl chloride (**1**) (4.85 g., 0.0260 mole) and pyridine (25 ml.) was kept at 5° for 13 days. It was poured over ice and water, and the precipitate was collected, washed with water and was dried to give 6.68 g. (83%) of **3**, m.p. 168.0-170.0°. Recrystallization from hexane-ethyl acetate gave the analytical sample, m.p. 168.5-170.0°; ir: λ max 3.03, 3.16, 3.28, 5.80, 5.95 μ ; ¹H-nmr: δ 10.5-10.1 (br s, NH, ex), 8.38 (d, H₃, J_M = 2 Hz), 7.88 (d, H₆, J_O = 9 Hz), 7.19 (q, H₅, J_M = 2 Hz, J_O = 9 Hz), 7.08-6.75 (br s, NH₂), 2.14 (s, 3H, OCOMe), 1.67 (s, 5H, CMe₂) ppm; uv: λ max 250 (log ϵ = 4.14), 286 (log ϵ = 3.36) nm; ms: m/e 334 (M⁺).

Anal. Calcd. for C₁₂H₁₅ClN₂O₅S: C, 43.05; H, 4.52; Cl, 10.59; N, 8.37; S, 9.58. Found: C, 43.28; H, 4.68; Cl, 10.60; N, 8.58; S, 9.66.

6-Chloro-3-(2-hydroxy-2-propyl)-4H-1,2,4-benzothiadiazine 1,1-Dioxide (**6**).

A mixture of **3** (303 mg., 1.21 mmoles) and concentrated ammonium hydroxide (10 ml.) was heated 2 hours on a steam bath, cooled in ice, and filtered to give 75 mg. of the desired **6**. The filtrate was acidified with concentrated hydrochloric acid, and the precipitate was collected, washed with water and dried to give a further 106 mg. of **6**; the ir spectra of the two lots (combined yield of 74%, m.p. 241-146°) were identical. Crystallization from acetone-hexane gave the analytical sample, m.p. 249-250°; ir: λ max 2.92, 3.08, 6.29 μ ; uv: λ max 267 (log ϵ = 3.88) nm; ¹H-nmr: δ 11.7 (br s, NH, ex), 7.98 and 7.90 (overlapping doublets of H₅ (J_M = 2 Hz) and H₈ (J_O = 8.5 Hz)), 7.52 (q, H₇, J_M = 2 Hz, J_O = 8.5 Hz), 6.2 (br s, OH, ex), 1.48 (s, 2Me) ppm; ms: m/e 275 (M⁺).

Anal. Calcd. for C₁₀H₁₁ClN₂O₃S: C, 43.72; H, 4.04; Cl, 12.91; N, 10.20; S, 11.67. Found: C, 43.98; H, 4.14; Cl, 12.87; N, 10.36; S, 11.50.

8-Chloro-2,2,3a-trimethyl-3a,4-dihydrooxazole[2,3-*b*] [1,2,4]benzothiadiazin-1-one 5,5-Dioxide (**5**).

A solution of **3** (500 mg.) and *p*-toluenesulfonic acid monohydrate (284 mg.) in benzene (15 ml.) was boiled under reflux for 3 hours under a Dean-Stark trap; a further 284 mg. of acid was added, and, after another 21 hours of reflux, the solution was cooled and evaporated to dryness. Trituration of the residue with ethyl acetate and filtration gave 170 mg. (36%) of the desired **5**, identified by comparison of its ir spectrum and R_f-value with those of an authentic sample. Examination of the filtrate residue by tlc showed that **5**, **4** and five other (unidentified) products were present.

Conversion of **1** to 2-Acetoxyisobutyric Acid Anhydride (**7**).

A solution of **1** (7.50 g., 0.0455 mole), triethyl amine (6.90 ml.), and ether (200 ml.) was boiled under reflux 18 hours, cooled,

and filtered. The filtrate was washed with water and brine, and was dried, filtered and evaporated. The residue was distilled to give 1.15 g. (18%) of anhydride **7**, b.p. 88-96° at 0.15 mm, which was identified spectroscopically; ir (dichloromethane): λ max 5.48, 5.76, 7.29d, 8.61, 9.56 μ ; ¹H-nmr (deuteriochloroform): δ 2.08 (6H, OCOMe), 1.58 (12H, CMe₂) ppm; ms: m/e 129 (M-C₆H₉O₄), 101 (129-128).

4,4-Dimethyl-2-methylene-1,3-dioxolan-5-one (**8**)

A solution of **1** (7.50 g., 0.0455 mole) and triethyl amine (6.90 ml., 0.0501 mole) in dichloromethane (100 ml., dried by passage through basic alumina) was boiled under reflux 2 hours, cooled, diluted with 150 ml. of 1:1 ether-hexane, filtered, and evaporated. The residue was distilled to give 2.15 g. (37%) of **8** as a colorless lachrymatory liquid, b.p. 32° at 15 mm; ir (dichloromethane): λ max 5.48, 5.91 (br), 8.49, 9.41, 9.95 μ ; ir (carbon disulfide): λ max 5.46, 5.83sh, 5.90 μ ; ¹H-nmr (deuteriochloroform): δ 3.68 (d, C(H_A)H_B, J_{AB} = 4.1 Hz), 3.60 (d, C(H_A)H_B, J_{AB} = 4.1 Hz), 1.55 (s, 6H) ppm; ¹³C-nmr (deuteriochloroform): δ 172.6 (C₅), 158.2 (C₂), 79.6 (CH₂), 61.4 (C₄), 23.7 (CH₃) ppm; ms: m/e 128 (M⁺), 100 (M-CO), 72 (100-CO), 58 (100-C₂H₂O). Perhaps, because of sensitivity to moisture, acceptable microanalytical values not obtained for this substance.

Acknowledgement.

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REFERENCES AND NOTES

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- (2) J. G. Topliss, L. M. Konzelman, and E. P. Shapiro, *J. Org. Chem.* **28**, 2595 (1963).
- (3) Compound **1**, however, was changed to the corresponding anhydride **7**, as judged by comparison of an ir spectrum of a sample of the reaction mixture of that of an authentic specimen of **7**. Anhydride **7** may arise from **1** by reaction of water with **8**. Under anhydrous conditions (see Experimental), triethylamine in dichloromethane converted **1** to **8**, but when **1** in ether was treated with triethyl amine and was then worked-up with water, anhydride **7** was obtained instead of **8**.
- (4) Melting points were determined on a Thomas-Hoover apparatus and, like boiling points, are uncorrected. Ir spectra were recorded on a Perkin-Elmer instruments, models 137 or 180, as potassium chloride discs or solutions as noted, respectively. Uv spectra were measured in methanol solution on a Cary 228 spectrophotometer. Mass spectra were determined on a Varian CH5 spectrometer. ¹H- and ¹³C-nmr spectra were recorded in d₆-DMSO (except as noted) on Varian A-60A or XL-100 instruments, and tetramethylsilane was used as an internal standard. E. Merck supplied F-254 silica gel plates, which after development were visualized in uv light and were stained with iodine vapor; ASTM silica gel for column chromatography was obtained from the same source. Basic alumina was obtained from Woelm.
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