Experimental Section

The liquid N-oxides were purified by vacuum distillation prior to use, and the melting points of the picrates matched those reported in the literature. The melting points of the solid N-oxides and their picrates were in agreement with literature values except in the following cases: 4-benzylpyridine N-oxide (I), mp 105–107° (lit.[10] mp 151°); the picrate of 4-picoline N-oxide (IV), mp 154° (lit.[11] mp 159–160°).

General Procedure for Exchange Reactions.—An equimolar mixture of the N-oxide (*ca.* 5 g) and base in deuterium oxide (15 ml) was refluxed for the appropriate amount of time. After the reflux period, the mixture was extracted with chloroform (200–300 ml) and the extract was dried over anhydrous sodium sulfate. After removal of the drying agent, the chloroform and organic base when present were removed by flash evaporation. The N-oxides so recovered were placed in a vacuum desiccator for drying, since most of the N-oxides are hygroscopic. Most of the deuterated N-oxides were of sufficient purity to be directly submitted for nmr analysis.[12] All recovered N-oxides had melting points which matched the literature values for the undeuterated analogs (or were slightly higher). The ir spectra exhibited a weak C–D stretch at 4.3–4.4 μ with variation of the O–H out-of-plane region at 11–15 μ. Yields of the recovered deuterated pyridine N-oxides averaged 87%.

Registry No.—I, 7259-53-2; II, 20531-86-6.

(10) A. R. Hands and A. R. Katritzky, *J. Chem. Soc.*, 1754 (1958). We were never able to duplicate the reported melting point for this compound. *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.51; H, 5.99. Analysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are uncorrected.

(11) V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954).

(12) All nmr spectra were obtained through the courtesy of Dr. Vincent J. Traynelis, West Virginia University, Morgantown, W. Va., to whom we wish to express our gratitude.

Preparation and Ring Opening of 1,2,3,4-Tetrahydro-2-oxopyrimido-[2,1-*b*]benzothiazol-5-ium Chloride[1]

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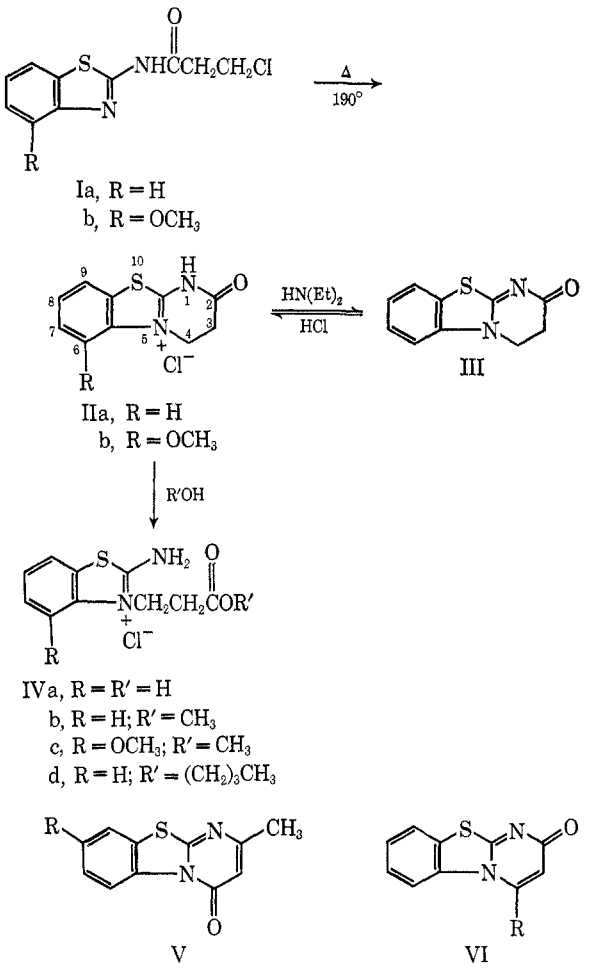
The synthesis of 1,2,3,4-tetrahydro-2-oxopyrimido-[2,1-*b*]benzothiazol-5-ium chloride (IIa) by fusion of 2-(3-chloropropionylamino)benzothiazole (Ia) has been recently reported.[3] These studies were carried out in the course of our investigations with 3-aminoisoquinoline and the 1,3-diazatricyclic ring system, such as VII, which could be similarly prepared by fusion of 3-chloro-N-(isoquinolin-3-yl)propionamide. We now wish to report the details of the synthesis and spectral characteristics of the benzothiazolium salts (II) and the observed facile ring-opening reaction which occurs when II is treated with water or alcohol to form the novel amino acids IV.

Compounds of structure V have been prepared by Antaki and Petrov[4] by heating 2-aminobenzothiazoles with β-aminocrotonic ester. Schrader[5] indicated that



acylacetamidobenzothiazoles could be dehydrated to VI, but no details were given and the structure remains uncertain.

We have found that 1,2,3,4-tetrahydro-2-oxopyrimido[2,1-*b*]benzothiazol-5-ium chloride (IIa) can be readily prepared by fusion of 2-(3-chloropropionylamino)benzothiazole (Ia) at 190°. Treatment of the quaternary halide IIa with anhydrous diethylamine resulted in the isolation of a halogen-free compound, which was assigned structure III. Tsatsas and Costakis[6] isolated III as a side product by treatment of equimolar quantities of 2-aminobenzothiazole and β-chloropropionyl chloride in alkaline medium. We could readily convert III into II with chloroform saturated with hydrogen chloride. The spectra (nmr and uv) and the elemental analyses of II and III confirm the proposed structures and agree with the structure for III as previously suggested.[6] These authors[6] claimed that the insolubility of their compound III kept them from obtaining an nmr spectrum. We had no difficulty in obtaining an nmr spectrum of this compound in deuteriochloroform.

In attempting to obtain nmr spectra of IIa in deuterium oxide solution, however, we found that a mixture of IIa and the ring-opened amino acid IVa was obtained. Spectral evidence indicated that, after the solution had stood at room temperature for 12 hr, the hydrolysis had gone to completion and pure IVa

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(2) To whom inquiries should be addressed: Department of Medicinal Chemistry, College of Pharmacy, Northeastern University, Boston, Mass. 02115.

(3) J. L. Neumeyer and K. K. Weinhardt, *Chem. Commun.*, 1423 (1968).

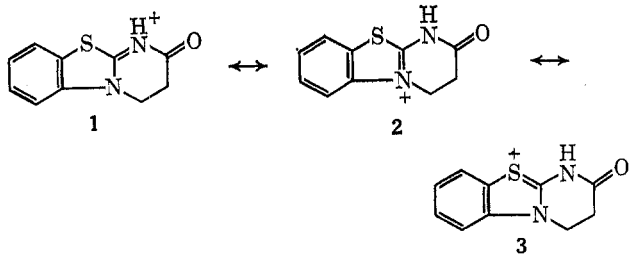
(4) H. Antaki and V. Petrov, *J. Chem. Soc.*, 551 (1951).

(5) G. Schrader, German Patent 603,623 (1937); Friedländer's Fortschritte der Teerfarbenfabrikation und verwandter Industriezweige, Vol. 21, Julius Springer, Berlin, 1937, p 317.

(6) G. Tsatsas and E. Costakis, *Chem. Commun.*, 991 (1967).

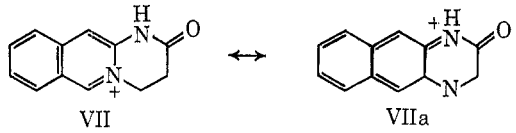
was obtained. It was not possible to obtain an nmr spectrum of either IIa or IIb owing to their insolubility in organic solvents and their rapid hydrolysis in water. The hydrolysis of IIa on a preparative scale with water, methanol, and 1-butanol resulted in the isolation of the corresponding acid IVa, or esters IVb and IVd, respectively, the structures of which were confirmed on the basis of spectral evidence (nmr, ir, and uv) and elemental analysis.

The unusual ease of the ring opening of II with nucleophiles can be explained by the activating influence of the neighboring quaternary nitrogen and the unbonded pair of electrons on the sulfur atom, which contribute to a resonance stabilization of the positive charge on the amide nitrogen and on the bridgehead nitrogen (**1** ↔ **2** ↔ **3**). This would result in the amide carbonyl being more electrophilic, facilitating hydrolysis.



1 **2** **3**

The stability of the pyrimido[2,3,-*b*]isoquinoline[3] (VII) under such mild hydrolytic conditions can be thus rationalized. The positive charge of the quaternary salt is largely localized on the isoquinoline nitrogen. A resonance form having the positive charge on the amide nitrogen, such as in VIIa, would require a less energetically favorable quinoid-type arrangement.



VII VIIa

Experimental Section[7]

1,2,3,4-Tetrahydro-6-methoxy-2-oxopyrimido[2,1-*b*]benzothiazol-5-ium Chloride (IIb).—A mixture of 4.6 g (0.0255 mol) of 2-amino-4-methoxybenzothiazole and 1.2 g of 56% sodium hydride in oil was stirred in 200 ml of refluxing benzene for 6 hr. The mixture was then cooled to 5° and 3.8 g (0.030 mol) of 3-chloropropionyl chloride in 10 ml of benzene was added at once. The mixture was stirred at ice-bath temperature for 0.5 hr and at room temperature for 3 days. Treatment with 50 ml of water, collection of the off-white solid on a Büchner funnel and air drying gave 2.69 g of Ib, mp 150–152° (resolidification). The 3-chloropropionamide Ib was not identified as such, but cyclized to IIb by heating to 190°. No recrystallizing solvent for the crude product could be found and it was purified by trituration with hot dioxane to yield 2.44 g (35%) of product IIb: mp 273°;[8] uv λ_{max}^{EtOH} 262 mμ (ε 8800) and 305 (15,200); ir (KBr) 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{11}ClN_2O_2S$: C, 48.80; H, 4.09; Cl, 13.10; N, 10.35; S, 11.84. Found: C, 48.87; H, 4.02; Cl, 13.04; N, 10.38; S, 11.85.

(7) All melting points were recorded on a Thomas–Hoover melting point apparatus unless otherwise specified and were uncorrected; the microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The infrared spectra were recorded on a Perkin-Elmer Model 521 grating spectrophotometer; the nmr spectra were determined on a Varian A-60 spectrophotometer with tetramethylsilane as the internal standard; uv spectra were recorded with a Beckman Model DK-1A.

(8) The melting point was determined on a Du Pont Model 900 Thermo Analyzer.

1,2,3,4-Tetrahydro-2-oxypyrimido[2,1-*b*]benzothiazol-5-ium Chloride (IIa).—2-(3-Chloropropionylamido)benzothiazole[3,6] (Ia, 16.0 g, 0.066 mol) was divided into portions of 2–3 g. Each portion was packed tightly into a large test tube which was then immersed for *ca.* 15 min in a 190° hot oil bath. The resulting orange solid was powdered and treated with 250 ml of water. The insoluble impurities were removed by filtration. The filtrate was divided into a 200-ml and a 50-ml aliquot. The 200-ml aliquot was lyophilized. The remaining yellow solid was carefully triturated with ethanol, which dissolved the hydrolysis product IVa and gave 10.5 g (82%) of IIa: mp 279° dec; uv λ_{max}^{EtOH} 251 mμ (ε 9200) and 301 (19,800); ir (KBr) 1740 cm^{-1} (C=O).

An nmr spectrum in D_2O solution showed the presence of large amounts of IVa, as a result of hydrolysis of IIa in the nmr solvent. The following assignment was made for IIa: δ 3.37 (triplet, $-COCH_2-$), 4.82 (triplet, $=\overset{+}{N}CH_2-$), and 7.3–8.17 (multiplet, aromatic H). The methylene protons were shifted in the acid IVa to δ 2.98 as a triplet ($-COCH_2-$) and to δ 4.45 as a triplet ($=\overset{+}{N}CH_2$).

Anal. Calcd for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; Cl, 14.73; N, 11.64; S, 13.32. Found: C, 50.05; H, 3.84; Cl, 14.52; N, 11.51; S, 13.52.

3,4-Dihydro-2H-pyrimido[2,1-*b*]benzothiazol-2-one (III).—A suspension of 2.0 g (0.0083 mol) of the quaternary salt IIa in 25 ml of anhydrous diethylamine was stirred at room temperature for 15 min. The insoluble residue was collected on a Buchner funnel, washed with small amounts of ethanol, and recrystallized from 25 ml of ethanol to give 0.9 g (53%) of pure III: mp 218–219.5° (lit.[6] mp 214–217°); uv λ_{max}^{EtOH} 308 mμ (ε 28,000); ir (KBr) 1655 cm^{-1}. The following assignment was made for III in $CDCl_3$: δ 7.04–7.7 (multiplet, aromatic H), 4.23 (triplet, $-\overset{|}{N}CH_2-$), and 2.84 (triplet, $-COCH_2-$).

Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.82; H, 3.95; N, 13.72; S, 15.68. Found: C, 59.08; H, 3.88; N, 13.84; N, 15.36.

A small amount of III was reconverted into its hydrochloride salt IIa by treatment of a cold chloroform solution with anhydrous hydrogen chloride.

2-Amino-3-(2-carboxyethyl)benzothiazolium Chloride (IVa).—The 50-ml aliquot from the foregoing step (preparation of IIa) was warmed on a steam bath for 2 hr and the water was removed *in vacuo* to yield 3.5 g of crude amino acid IVa, mp 163–167° dec. Two recrystallizations from ethanol gave pure IVa: mp 169–170° dec; uv λ_{max}^{EtOH} 253 mμ (ε 10,300), 277 (9600), and 285 (10,400).

Anal. Calcd for $C_{10}H_{11}ClN_2O_2S$: C, 46.42; H, 4.29; Cl, 13.70; N, 10.83; S, 12.37. Found: C, 46.65; H, 4.39; Cl, 13.51; N, 10.64; S, 12.13.

2-Amino-3-[2-(methoxycarbonyl)ethyl]benzothiazolium Chloride (IVb).—A solution of IIa [obtained by the fusion of 3 g (0.0125 mol) of Ia] in 50 ml of methanol was heated at reflux for 15 hr and cooled. Addition of 100 ml of ether caused the separation of an oil that solidified slowly. Recrystallization from dioxane–methanol and from tetrahydrofuran–acetonitrile gave 1.0 g (34%) of IVb: mp 154–157° dec; uv λ_{max}^{EtOH} 259 mμ (ε 8200), 286 (sh), 292 (4000), and 298 (sh); ir (KBr) 1740 cm^{-1} (C=O). A nmr spectrum in D_2O solution was recorded: δ 7.3–7.95 (multiplet, aromatic H), 4.6 (triplet, $=\overset{+}{N}CH_2$), 3.07 [triplet, $CH_2(C=O)O-$], 3.88 (singlet, $O=COCH_3$).

Anal. Calcd for $C_{11}H_{13}ClN_2O_2S$: C, 48.44; H, 4.80; N, 10.27. Found: C, 48.22; H, 4.61; N, 10.19.

2-Amino-3-[2-(*n*-butoxycarbonyl)ethyl]benzothiazolium Chloride (IVd).—Using conditions similar to those described above for the methyl ester IVb, 1.5 g (0.0063 mol) of the quaternary salt IIa in 10 ml of 1-butanol was stirred for 20 hr at 90°. Treatment of the cooled solution with 10 ml of ether yielded 1.68 g (85%) of IVd, mp 170–171° (acetonitrile). The following assignment was made for the nmr spectrum (DMSO-d_6 solution): δ 7.2–8.05 (multiplet, aromatic H), 4.69 (triplet, $\overset{+}{N}CH_2$), 2.91 [triplet, $-CH_2(C=O)O-$], 10.3 (board, exchanges with D_2O, NH_2), 3.99 (triplet, $O=COCH_2-$), 1.0–1.8 (multiplet, $O=CO-CH_2CH_2CH_3$), and 0.83 (triplet, CH_3).

Anal. Calcd for $C_{14}H_{19}ClN_2O_2S$: C, 53.41; H, 6.08; N, 8.90. Found: C, 53.45 H, 6.05; N, 8.94.

2-Amino-4-methoxy-3-[2-(methoxycarbonyl)ethyl]benzothiazolium Chloride (IVc).—A solution of 1 g (0.0037 mol) of

the methoxypyrimidobenzothiazolium chloride IIb in 20 ml of methanol was refluxed for 3 hr. The excess solvent was removed *in vacuo*. The solid residue was treated with 50 ml of boiling acetonitrile and the mixture was filtered to separate 0.46 g of solid insoluble in the acetonirile. After the filtrate had stood for 2 days, 0.26 g (26%) of IVc were collected, mp >125° (slow dec).

An additional 0.4 g (36%) of IVc was obtained when the acetonitrile-insoluble solid was dissolved in methanol and ether was added carefully. The following assignment was made for the nmr spectrum (DMSO-d_6 solution): δ 7.2–7.72 (multiplet, aromatic H), 9.91 (broad, exchanges, NH_3), 4.81 (triplet, $\overset{+}{N}CH_2$), 3.97 (singlet, $-OCH_3$), 3.67 (singlet, $O{=}COCH_3$), and 2.91 [triplet, $-CH_2(C{=}O)O-$].

Anal. Calcd for $C_{12}H_{15}ClN_2O_3S$: C, 47.61; H, 4.99; N, 9.25. Found: C, 47.73; H, 5.08; N, 9.22.

Registry No.—IIa, 21140-01-2; IIb, 23230-61-7; III, 17326-07-7; IVa, 23230-63-9; IVb, 23230-64-0; IVc, 23230-65-1; IVd, 23230-66-2.

Acknowledgment.—We wish to thank Dr. K. Stevenson and Professor R. E. Lyle for helpful discussions and Dr. P. L. Levins for the spectral data.

Transformation Products of 2-(2-Imidazolin-2-yl)benzophenone

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2-(2-Imidazolin-2-yl)benzophenone, which has been shown to exist in two tautomeric forms (**1** and **2**),[2] was treated with *p*-toluenesulfonic acid in refluxing xylene to give the dehydrated compound **3** (Scheme I). It was found that **3** underwent a slow oxidation with air in refluxing ethanol using platinum on carbon as a catalyst to give the ketoimidazo compound **5**. This compound, on reduction with sodium borohydride, gave the imidazolylbenzhydrol **4**, which on dehydration gave the original imidazoisoindole **3**. The known reaction of dimethylsulfoxonium methylide with ketones to give epoxides *via* methylene transfer[3] prompted us to treat both compounds **1** and **5** with this reagent. The synthesis of other small heterocyclic ring systems by the use of this reagent has recently received some attention in the literature.[4] As anticipated, methylene transfer took place. The intermediates (such as A) were not isolated but cyclized in the reaction medium to give the observed products. Thus compound **1** gave the imidazoisoquinoline **6**. The corresponding ketone **5** gave the expected unsaturated product **9**. Further dehydration of **9** in boron trifluoride etherate in acetic acid gave the fully saturated derivative **8**. This compound was also obtained from compound **6**, first by dehydration with thionyl chloride to give the intermediate **7**, followed by dehydrogenation in refluxing tetralin with palladium on carbon as a catalyst. The structure of compound **7** was readily confirmed by an independent synthesis from isocoumarone (**10**) by treatment with ethylenediamine in the presence of *p*-toluenesulfonic acid. Similarly, compound **8** could be prepared by the catalytic dehydrogenation of **12**. This, in turn, was prepared in one of three ways. Treatment of either the dihydroisocoumarone **11** or 3-methyl-3-phenylphthalide (**13**) or its isomer **16** with ethylenediamine in the presence of *p*-toluenesulfonic acid all gave compound **12**.

Experimental Section[5]

5-Phenyl-5H-imidazo[2,1-*a*]isoindole (3). A. From Compound 1.—A mixture of 2.5 g (50 mmol) of **1**[2], 0.5 g of *p*-toluenesulfonic acid, and 250 ml of *m*-xylene was heated under reflux for 1 hr in a 500-ml flask equipped with a Dean–Stark trap and condenser. Xylene was removed under reduced pressure, 40 ml of 0.1 *N* sodium hydroxide was added, and the mixture was extracted with methylene chloride. The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to leave a pale pink solid. The solid was dissolved in 70 ml of hot ethyl acetate, treated with Norit, and filtered. The solution was concentrated to a volume of 40 ml, followed by the addition of 100 ml of petroleum ether and cooling. Filtration gave 8.9 g (76.7%) of **3** as a pale pink solid, mp 145–148° dec. Recrystallization twice from ethyl acetate–petroleum ether gave colorless prisms: mp 147–150° dec; uv max 224 mμ (inflection, ϵ 14,700), 280 (14,200), and 295 (inflection, 10,400); nmr ($CDCl_3$) δ 5.90 (singlet, 1 H) and multiplets centered at δ 7.20 (10 H) and 7.90 (1 H).

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.82; H, 4.85; N, 12.03.

B. From Compound 4.—A solution of 0.5 g (2 mmol) of **4** and 0.1 g of *p*-toluenesulfonic acid in 50 ml of xylene was heated at reflux for 46 hr, using a Dean–Stark trap to collect the water formed. Solvent was removed under reduced pressure, 20 ml of 0.1 *N* sodium hydroxide was added, and the mixture was extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate, and evaporated to leave a yellow oil which crystallized upon scratching. The solid was dissolved in 25 ml of hot ethyl acetate, treated with Norit, filtered, and concentrated to a volume of 5 ml. Petroleum ether (5 ml) was added and the solution was cooled. Filtration gave 250 mg (53.9%) of **2** as colorless crystals, mp (and mixture melting point with a sample prepared as in A above) 146–148°.

2-(2-Imidazolyl)benzophenone (5).—A mixture of 11.6 g (50 mmol) of **3**, 5.0 g of a 10% platinum on carbon catalyst, and 300 ml of ethanol was heated at reflux, with a gentle stream of air bubbling through the mixture, for 16 hr. The mixture was filtered and the filtrate was evaporated under reduced pressure to leave a pale yellow solid. Recrystallization from ethyl acetate gave 8.2 g (66.1%) of **5**, mp 155–158° dec. Recrystallization gave the analytical sample as colorless prisms: mp 158–160° dec; uv max 251 mμ (ϵ 20,200) and 315 (2350); ir ($CHCl_3$) 1658 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.20; H, 4.85; N, 11.25.

2-(2-Imidazolyl)benzhydrol (4).—A solution of 4.96 g (20 mmol) of **5** and 1.89 g (50 mmol) of sodium borohydride in 75 ml of ethanol was heated under reflux for 2 hr. Ethanol was removed under reduced pressure and 50 ml of water was added. The mixture was extracted with methylene chloride and the extracts were washed with water, dried over sodium sulfate, and evaporated to leave a pale yellow oil. The oil was crystallized

(1) To whom correspondence should be addressed.

(2) W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2874 (1968).

(3) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 867 (1962).

(4) See P. Bravo, G. Gaudiano, and A. Umani-Rochi, *Tetrahedron Lett.*, No. 9, 679 (1969), and references cited therein.

(5) All melting points were determined microscopically on a hot stage and are corrected. The uv spectra were determined in 2-propanol on a Cary Model 14 spectrophotometer, nmr spectra with a Varian A-60 instrument, and ir spectra on a Beckman IR-9 spectrophotometer. Petroleum ether refers to a fraction of bp 30–60°.