highly reactive aromatic ring. The isoindole **3b** could only be obtained as a by-product in the synthesis of **2b**. It showed an nmr spectrum similar to **3a** but was contaminated with about 10% **2b**. When **3a** was prepared by the reduction of **1a** it too was contaminated with **2a**. However, both crude samples gave pure pyrazino[2,1-*a*]isoindoles (**5**) with acetone.

The structures of **5a** and **b** were evident from the nmr spectrum in that a one-proton singlet in the aromatic region was absent. Their ultraviolet spectrum was similar to that of 1-phenylisoindole[3] and their infrared spectra were consistent with an isoindole structure.[4] These rearrangements may be rationalized by the mechanism outlined in Scheme II (p. 249).

Experimental Section

Lithium Aluminum Hydride Reductions. 1-(*p*-Chlorophenyl)-2,2,3,4,5,6-hexahydro-2,5-benzodiazocine (2b) and 2-(2-Aminoethyl)-1-(*p*-chlorophenyl)isoindole (3b).—Reduction of **1b** (100 g) was carried out with lithium aluminum hydride in ether according to the literature procedure.[1] There was obtained 43.9 g of **2b**, mp 106–108°, and 7.0 g of solid, mp 95–105°. The mother liquors were then distilled to give 30.2 g (32%) of an oil, bp 185–190° (0.1 mm). The nmr spectrum indicated that this was mostly **3b** contaminated by about 10% of **2a**. It was used directly to prepare **5b**.

1-Phenyl-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (2a) and 2-(2-Aminoethyl)-1-phenylisoindole (3a).—The above procedure was repeated with **1a** and there was obtained 44.3 g of **2a**, mp 126–128°, and 25.5 g of crude **3a**, bp 145–150° (0.2 mm). It could not be crystallized and was used directly to prepare **5a**.

Potassium Amide Ring Contractions. 2-(2-Aminoethyl)-1,3-dihydro-1-phenylisoindole (4).—The benzodiazocine **2a** (30.0 g) was added to a 500-ml solution of potassium amide in liquid ammonia prepared from 12.0 g of potassium metal and 0.1 g of ferric nitrate. The red solution was stirred for 4 hr at reflux temperature, the ammonia was evaporated, and ether was added. The ether layer was distilled after drying to give 24.0 g (80%) of a liquid, bp 148–151° (0.2 mm), mp 47–51° (lit.[2] mp 53°); dihydrochloride mp 213–216° (*i*-PrOH), lit.[2] mp 215–220°). The nmr spectrum matched that given in the literature[2] and showed the absence of starting material.

2-(2-Aminoethyl)-1-phenylisoindole (3a).—The benzodiazocine **2b** (22.6 g) was treated with potassium amide in liquid ammonia as in the foregoing procedure. There was obtained 14.4 g (64%) of an oil, bp 180–185° (0.2 mm), which did not crystallize. It gave a positive Ehrlich test[3] (*p*-dimethylaminobenzaldehyde and acetic acid) and was converted into a tar with hydrochloric acid: nmr spectrum ($CDCl_3$), δ 0.86 (s, 2, NH_2), 3.49 (t, 2, J = 6 Hz, CH_2), 4.21 (t, 2, J = 6 Hz, CH_2), 6.8–7.1 (m, 2), 7.22 (s, 1), and 7.3–7.9 ppm (m, 7).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32, H, 6.82; N, 11.85. Found: C, 81.37; H, 6.70; N, 11.82; Cl, 0.00.

Cyclizations with Acetone. 1,1-Dimethyl-6-phenyl-1,2,3,4-tetrahydropyrazino[2,1-*a*]isoindole (5a).—2-(2-Aminoethyl)-1-phenylisoindole (6.20 g) was dissolved in 25 ml of acetone. Heat was evolved and crystals formed. The mixture was cooled and filtered to give 4.70 g (65%) of **5a**: mp 146–148°; nmr ($CDCl_3$), δ 1.52 (s, 1, NH), 1.85 (s, 6, $(CH_3)_2$), 3.15 (m, 2, CH_2), 4.11 (m, 2, CH_2), 6.8–7.1 (m, 2) and 7.3–7.9 ppm (m, 7); uv_{max} (dioxane) 365 mμ (log ϵ 3.59), 335 (3.44). The reported[3] ultraviolet maxima for 1-phenylisoindole are 357 mμ (log ϵ 3.10), 325 (2.99).

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.64; H, 7.24; N, 10.12. Found: C, 82.70; H, 7.20; N, 10.05.

1,1-Dimethyl-6-(*p*-chlorophenyl)-1,2,3,4-tetrahydropyrazino-[2.1-*a*]isoindole (5b).—The crude chloro analog **3b** (6.70 g) was treated as above giving 5.10 g (66%) of **5b**, mp 169–173°. Spectral properties were similar to **5a**.

Anal. Calcd for $C_{19}H_{19}ClN_2$; C, 73.45; H, 6.12; N, 9.02. Found: C, 73.52; H, 6.22; N, 9.09.

(4) We are indebted to Dr. Lwowski for sending us examples of infrared spectra of isoindoles. Both his and our isoindoles showed broad bands of medium intensity at 1680 cm^{-1}.

Registry No.—**2a**, 3045-09-8; **2b**, 13827-78-6; **3a**, 18039-62-8; **3b**, 18039-63-9; **5a**, 18039-64-0; **5b**, 18039-65-1.

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Nuclear Magnetic Resonance Spectra of Some 1,4-Thiazine 1,1-Dioxides and Their Anions

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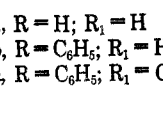
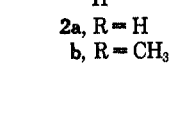
In contrast to extensive investigations of 1,4-benzothiazines, and particularly phenothiazines, very little work has been done on the simple derivatives of the 1,4-thiazine ring system. The parent compound of this series was described by Barkenbus and Landis.[1] In view of its failure to yield a sulfonamide by the Hinsberg method, it was assigned structure **1a**. Fujii[2] reported the synthesis of 3,5-diphenyl-1,4-thiazine by the condensation of phenacyl sulfide with ammonia. We have shown[3] that this derivative is correctly represented by structure **1b**, in conformity with the structure proposed for the parent compound. Cyclization of substituted β,β'-diketo sulfides with ammonia afforded analogous 1,4-thiazine derivatives, including compound **1c**.[4] By contrast, the condensation of phenacyl sulfone and its symmetrical dimethyl derivative with ammonia was reported to give thiazines **2a** and **2b**, respectively.[3,5] The change in position of the double bond with the state of oxidation of the sulfur has been proposed in view of the appearance of an N–H absorption band in the infrared spectrum of **2a**.[3] The structure assignments of **2a** and **2b** have now been confirmed and their anions have been studied by nmr.



1a, R = H; R_1 = H
b, R = C_6H_5; R_1 = H
c, R = C_6H_5; R_1 = CH_3



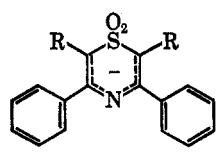
2a, R = H
b, R = CH_3

Measured in dimethyl sulfoxide-d_6, the nmr spectrum of **2a** showed a multiplet at δ 7.47–7.88 (aromatic protons) and a singlet at 6.36 (α-sulfonyl protons) in the ratio of 5:1. The downfield shift of the aromatic protons relative to benzene (which appears at δ 7.38 in DMSO-d_6) is probably due to the strong inductive effect

(1) C. Barkenbus and P. S. Landis, *J. Amer. Chem. Soc.*, **70**, 684 (1948).
(2) K. Fujii, *J. Pharm. Soc. Jap.*, **77**, 359 (1957).
(3) C. R. Johnson and I. Sataty, *J. Med. Chem.*, **10**, 501 (1967).
(4) D. Sica, C. Santacroce, and R. A. Nicolaus, *Gazz. Chim. Ital.*, **98**, 17 (1968).
(5) (a) V. Baliah and T. Rangarajan, *J. Org. Chem.*, **26**, 970 (1961); (b) G. Pagani and S. Maiorana, *Chim. Ind.* (Milan), **49**, 1194 (1967).

of the sulfonyl group. The intervening olefinic linkage is not expected to attenuate this effect very much.[6]

In the presence of strong bases, **2a** loses the 4 proton and gives a stable anion (**3a**). For the purpose of this study, the anion was generated directly in the nmr tube by adding a slight excess of potassium *t*-butoxide to a DMSO-d_6 solution of **2a**. The *t*-butyl group resonates at a much higher field and does not interfere. The nmr spectrum of **3a** showed a multiplet at δ 7.88–8.13 (aromatic *ortho* protons), a multiplet at 7.26–7.51 (*meta* and *para* protons), and a singlet at 5.91 (α-sulfonyl protons). The singlet lost intensity gradually and disappeared altogether after 1 day as a result of D–H exchange with the solvent. Peak intensities were therefore measured for an analogous sample prepared in ordinary DMSO and found to be exactly in the ratio of 2:3:1. No change was observed in the spectrum after heating the DMSO solution of **3a** over steam for 22 hr. With addition of acetic acid, the nmr signals of **2a** were restored.



3a, R = H
b, R = CH_3

The downfield shift of the *ortho* protons, in spite of the negative charge, apparently results from strong deshielding by induced ring currents. While conformational preference has not been established for **2a**, the anion is expected to be largely planar. In addition to maximum overlap of atomic orbitals, such conformation would minimize electrostatic repulsions between the partial negative charges of the oxygens and the negative charge of the anion. The interatomic current induced in the thiazine ring by the external magnetic field would be more intense in this system than in the neutral and probably puckered molecule of **2a**. Because of their close proximity, the *ortho* protons are deshielded by the thiazine current, in addition to deshielding by the current induced in the benzene ring itself. The opposite shielding by the increased electron density on the carbon atoms to which they are bound is weaker, producing a net deshielding for these protons and a downfield shift of *ca.* 0.3 ppm. The *meta*, and particularly the *para*, protons are little affected by the current induced in the thiazine ring. Under the influence of the higher charge density, they shift upfield by about 0.3 ppm. By comparison, the nmr spectrum of benzoic acid in DMSO-d_6 showed multiplets at δ 7.97–8.20 (*ortho* protons) and 7.47–7.73 (*meta* and *para* protons). After addition of potassium *t*-butoxide and formation of benzoate anion, the two multiplets shifted upfield by 0.18 and 0.13 ppm, respectively.

The α-sulfonyl protons are more strongly shielded by the high charge density on the thiazine ring than they are deshielded by the currents which are induced in this ring and in the phenyl groups. Accordingly, they experience an upfield shift of 0.45 ppm. This is considerably less than the upfield shift of nearly 1.85 ppm which has been attributed to the negative charge of cyclopentadienide anion.[7]

The nmr spectrum of thiazine **2b** was measured likewise in DMSO-d_6. It showed singlets at δ 7.48 (aromatic protons) and 1.91 (methyl protons) in the proper ratio of 5:3. Anion **3b**, prepared similarly to **3a**, gave a multiplet at δ 7.18–7.47 and a singlet at 2.00 in the same ratio. Very slight decrease in the relative intensity of the methyl signal was observed after 2 days. Because of the destabilizing effect of the methyl groups, the negative charge in **3b** is delocalized into the aromatic rings more than it is in **3a**. The current induced in the thiazine ring, which is proportional to the square of the charge, would be correspondingly weaker. Furthermore, the steric hindrance to coplanarity of the thiazine and benzene rings is greatly increased in **3b**. The twist angle in the most probable conformation of 2-methylbiphenyl has been estimated at about 59°, compared with the values of 20–30° quoted for biphenyl itself.[8] Thus, all the aromatic protons of **3b** shift upfield, but not to the same extent. The downfield shift of the methyl protons (by 0.09 ppm) is considerably smaller than the shift calculated on the basis of ring currents for the corresponding protons in toluene (*ca.* 0.8 ppm).[9] In addition to shielding by the negative charge, the methyl protons might also be affected by the shielding zone of the adjacent phenyl group. The shielding effect on methyl of a perpendicular *o*-phenyl group has been estimated at about 0.22 ppm.[10]

The pronounced stability of the 4H-1,4-thiazine 1,1-dioxide structure is demonstrated by the full recovery of **2a** and **2b** after reflux for 2 weeks with triethylamine. Under similar conditions, Δ^2-dihydrothiopyran 1,1-dioxide irreversibly isomerized to the Δ^3 isomer.[11] The preference of the 4 H isomer is these thiazines is a complete reversal of the consistent preference of the alternate 2 H isomer is thiopyran 1,1-dioxides.[12] On the other hand, there is good agreement between the structure of thiazines **1a–c** and the usual structure of thiopyrans. Cyclic delocalization of electrons, in the manner proposed by Price and Parasaran,[13] is certainly an attractive explanation for the preference of the 1,3-diene arrangement in the sulfides. However, the limited data available concerning the conformation, bond distances, and bond angles of thiopyrans[14] suggests that cyclic conjugation of this type does not occur to an appreciable extent.

Experimental Section

Nmr spectra were recorded on a Varian A 56/60 spectrometer with a sweep width of 500 Hz and with tetramethylsilane as an internal standard. The 1,4-thiazine 1,1-dioxides were prepared in boiling acetic acid as previously described.[3] 2,2′-Thiobispropiophenone S,S-dioxide is conveniently prepared by oxidation

(6) W. A. Waters, *J. Chem. Soc.*, 1551 (1933).

(7) G. Fraenkel, R. E. Carter, A. McLachlan, and J. H. Richards, *J. Amer. Chem. Soc.*, **82**, 5846 (1960).

(8) H. Suzuki, "Electronic Absorption Spectra and Geometry of Organic Molecules," Academic Press, New York, N. Y., 1967, p 282.

(9) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(10) T. H. Regan and J. B. Miller, *J. Org. Chem.*, **32**, 592 (1967).

(11) E. A. Fehnel, *J. Amer. Chem. Soc.*, **74**, 1569 (1952).

(12) (a) W. E. Truce, D. J. Abraham, and P. S. Radhakrishnamurti, *Tetrahedron Lett.*, 1051 (1963); (b) G. Pagani, *Gazz. Chim. Ital.*, **97**, 1518 (1967); (c) E. Molenaar and J. Strating, *Rec. Trav. Chim. Pays-Bas*, **86**, 1047 (1967); (d) L. Skattebøl, B. Boulette, and S. Solomon, *J. Org. Chem.*, **33**, 548 (1968).

(13) T. Parasaran and C. C. Price, *ibid.*, **29**, 946 (1964).

(14) M.-U. Haque and C. N. Caughlan, *ibid.*, **32**, 3017 (1967).

of the corresponding sulfide with *m*-chloroperbenzoic acid according to the usual procedure. Infrared spectra were measured in Nujol mulls with a Perkin-Elmer Model 337 spectrophotometer. The spectrum of thiazine **2a** showed major bands at 3258, 1630, 1516, 1242 (vs), 1104 (vs), and 709 cm^{-1}. The spectrum of thiazine **2b** had major bands at 3270, 3230, 1635, 1523, 1230 (vs), 1156, 1088 (vs), 761, 726, and 698 cm^{-1}.

Registry No.—**2a**, 14953-99-2; **2b**, 14954-06-4; **3a**, 12310-21-3; **3b**, 12310-20-2.

Acknowledgment.—The author is grateful to Professor C. R. Johnson, Wayne State University, under whose direction he prepared the compounds; and to the University of Calgary where the spectra were determined. He also thanks the Department of Chemistry and Graduate School of Southern Illinois University for permitting him to complete this study.

Reaction of Diethyl Bromomalonate with Sodium Diethyl Phosphite[1]

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The reaction of diethyl bromomalonate (**1**) and sodium diethyl phosphite (**2**) in ether has been reported to yield tetraethyl 1,1,2,2-ethanetetracarboxylate (**3**).[2] As part of a study of the reactions of **1** with

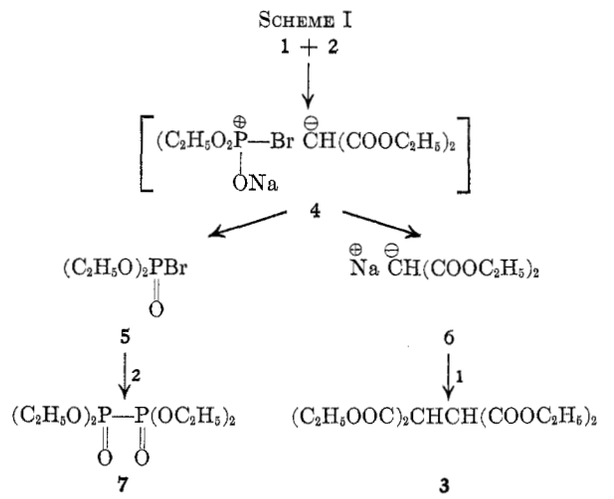
$$\underset{\mathbf{1}}{BrCH(COOC_2H_5)_2} + \underset{\mathbf{2}}{(C_2H_5O)_2PONa} \longrightarrow \underset{\mathbf{3}}{(C_2H_5OOC)_2CHCH(COOC_2H_5)_2}$$

nucleophilic agents, we have reinvestigated this reaction. The most apparent mode of formation of the tetraester (**3**) is a nucleophilic substitution reaction between **1** and malonate anion. This is supported by our observations which we wish to report here, together with additional features of the reaction. The sequence of reactions in Scheme I describes the transformation of **1** into **3**.

The first step is suggested by those reports on the reactions between tervalent phosphorus and bromo compounds in which attack on halogen is postulated.[3] Initial displacement on bromine has been proposed in the debromination of α-bromo ketones with triphenylphosphine in protic media.[4]

The addition of ethanol to the reaction of **1** with **2** in ether gave a smaller yield of tetraester **3**. The major products of the reaction were diethyl malonate (**8**) and triethyl phosphate (**9**). These were the only

SCHEME I



$$4 + C_2H_5OH \longrightarrow \underset{\mathbf{8}}{CH_2(COOC_2H_5)} + \underset{\mathbf{9}}{(C_2H_5O)_3PO}$$

products when the reaction was carried out in ethano as solvent; no **3** was observed.[5] The difference in behavior observed in some cases with chlorine derivatives, *e.g.*, diethyl chloromalonate does not react with **2** under these conditions,[2] lends further support for the first step. The difference may be attributed to the greater polarizability of bromine which makes reaction on halogen more favorable.

Additional evidence for the first step was found in reactions performed in the presence of benzyl bromide. In addition to **3**, diethyl benzylmalonate (**10**) was obtained, the latter resulting from the reaction of malonate anion with benzyl halide. Some diethyl benzylphos-

$$\underset{\mathbf{10}}{C_6H_5CH_2CH(COOC_2H_5)_2} \qquad \underset{\mathbf{11}}{(C_2H_5O)_2P(O)CH_2C_6H_5}$$

phonate (**11**) was also formed in these reactions. Moreover, when bromo ester **1** was added to a large excess of the phosphite (**2**), followed then by the addition of benzyl bromide, a large amount of **10** was found but none of the tetraester (**3**). Under these conditions it appeared that all of the bromo ester had been converted into the ion pair (**4**), thus preventing the formation of **3**. To exclude the possibility that the benzyl malonate (**10**) had actually arisen from the reaction of **1** with benzyl anion, the reaction of benzyl bromide with phosphite **2** was investigated. The formation of 1,2-diphenylethane would be expected if benzyl anion were generated. This compound, however, was not found. The principal product of the reaction was benzylphosphonate **11**.

In the original preparation of tetraester **3**, equimolar quantities of bromomalonate (**1**) and sodium diethyl phosphite (**2**) were employed.[2] On the basis of our initial view of the reaction, it was anticipated that 0.5 molar equiv of **2** would be sufficient, since it was necessary only for half of the bromo ester to be converted into malonate anion. Experiments, however, revealed that optimum yields of **3** were obtained when

(1) From the M.S. Thesis of D. J. T., 1968.

(2) A. E. Arbuzov and V. S. Abramov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 223 (1946).

(3) (a) B. Miller in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, pp 133–199; (b) R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965, pp 114–116, 141–160.

(4) I. J. Borowitz and R. Virkhaus, *J. Amer. Chem. Soc.*, **85**, 2183 (1963); P. A. Chopard, R. F. Hudson, and G. K. Klopman, *J. Chem. Soc.*, 1379 (1965); I. J. Borowitz, K. C. Kirby, Jr., and R. Virkhaus, *J. Org. Chem.*, **31**, 4031 (1966).

(5) We have attributed the dehalogenation of bromomalonate in ethanol to the action of sodium diethyl phosphite rather than to any diethyl phosphite formed from the sodium salt and alcohol. Debromination with diethyl phosphite occurs more slowly and incompletely (unpublished observations in this laboratory). There is also little reaction between bromomalonate and diethyl phosphite in ether.[1]