Thiazolo[3,4-*b*]indazole, a Ring-Fused Tetravalent Sulfur Thiazole System

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Deoxygenation of ethyl 4-(2-nitrophenyl)-2-phenylthiazole-5-carboxylate with $P(OEt)_3$ gave ethyl 3-phenylthiazolo[3,4-*b*]indazole-1-carboxylate, a fused thiazole derivative containing tetravalent sulfur. Cycloaddition of *N*-phenylmaleimide occurred across the thiocarbonyl ylide dipole giving a 1:1 cycloadduct together with the H_2S elimination product, *N*,4-diphenyl-1-ethoxycarbonylpyrido[1,2-*b*]indazole-2,3-dicarboximide. With dimethyl acetylenedicarboxylate, a 1:2 adduct was formed with addition occurring across the azomethine imine dipole. $P(OEt)_3$ deoxygenation of 4-(2-nitrophenyl)-2-phenylthiazole gave, however, 3-phenylthiazolo[5,4-*b*]indole, the same product being obtained by thermolysis or photolysis of the corresponding azide.

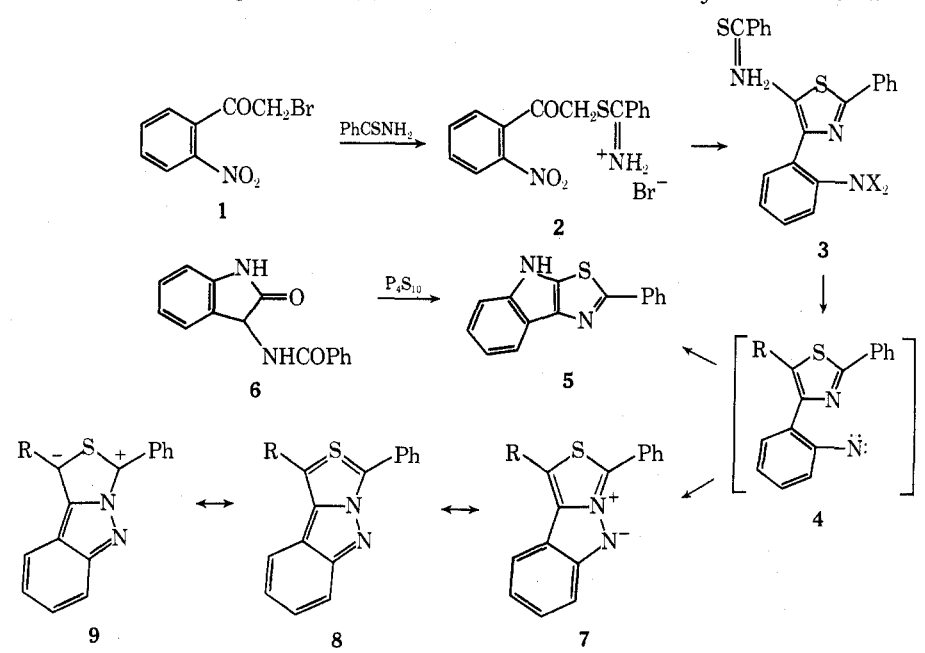
Fused thiophenes containing tetravalent sulfur are of considerable practical and theoretical interest,[2] and recent examples have included the furan,[3] pyrrole,[3,4] and pyrazole[5] ring systems fused to a thiophene nucleus, all of which proved versatile substrates in cycloaddition reactions. Our interests in mesoionic derivatives of the thiazole system,[6] which also may be considered to have some contribution from a canonical form involving a tetravalent sulfur atom, suggested the synthesis of a fused thiazole derivative that would incorporate a tetravalent sulfur atom. Such a system would require fusion at the 3,4 positions and contain a bridgehead nitrogen atom, offering interesting possibilities for the development of ylidic characteristics within the fused ring system. This would provide a new type of "tetravalent sulfur" ring system[7] in addition to the thiabenzenes[8] and 6a-thiathiophthenes[8a,9] for evaluating the importance of dipolar structures or of tetravalent sulfur species to the resonance hybrid.

The usual synthetic routes to the tetravalent sulfur systems[2,4,6] are precluded by the presence of the trigonal nitrogen atom which, however, does provide a basic center susceptible to electrophilic attack. A nitrene cyclization reaction appeared to offer the most direct, feasible route, such intramolecular nitrene cyclizations onto a trigonal nitrogen atom having been utilized in the synthesis of several polyazapentalene derivatives.[10]

The most readily available system would be 3-phenylthiazolo[3,4-*b*]indazole (**7**, R = H) which should be prepared by triethyl phosphite deoxygenation[11] of 4-(2-nitrophenyl)-2-phenylthiazole (**3**, R = H; X = O), this precursor being obtained from 2-bromo-2′-nitroacetophenone (**1**) and thiobenzamide. The isolation of the intermediate **2** in this sequence is worthy of note, as such intermediates have rarely been isolated in the reaction of α-halo ketones with thioamides.[12]

Deoxygenation of aromatic nitro compounds with triethyl phosphite commonly affords products expected from the corresponding nitrenes, although the exact nature of the intermediate is still uncertain.[13] Two products could be anticipated from **4** (R = H), the heteroaromatic betaine **7** (R = H) formed by coordination of the unshared electron pair on nitrogen with the nitrene, or 2-phenylthiazolo[5,4-*b*]indole (**5**), the result of electrophilic attack of the nitrene on the unsubstituted 5-thiazole position. At the time of initiating this work, there were no examples in the literature of C–N bond formation competing with N–N bond formation, but recently, however, several such examples have been reported.[14]

When **3** (R = H; X = O) was heated under reflux in xylene with $P(OEt)_3$ only one product was isolated. Analytical and spectral data (*Experimental Section*) readily established its structure as 2-phenylthiazolo[5,4-*b*]indole (**5**), especially the ν_{NH} ($CHCl_3$) 3460 cm^{-1}. This ring system has been described previously[15] as its 2-methyl derivative but no spectral characteristics were reported and the present structural assignment was confirmed by an alternative synthesis[15] from 2-aminooxindole via 3-benzamidooxindole (**6**) and P_4S_{10}. The intermediacy of the nitrene **4** (R = H) appears likely because of the ready isolation of **5** upon thermolysis or photolysis of 4-(2-azidophenyl)-2-phenylthiazole (**3**, R = H; X = N), obtained from **3** (R = H; X = O) by reduction followed by diazotization and treatment with sodi-



um azide. The azide 3 (R = H; X = N), characterized by its infrared absorption at 2130 cm^{-1} and an $M^{\cdot+}$ 278, had an interesting mass spectrum. The most abundant ion was $[M - N_2]^{\cdot+}$, *m/e* 250, and the remainder of the fragmentation pattern was in accord with the electron-impact induced loss of nitrogen to give 2-phenylthiazolo[5,4-*b*]indole (**5**). The generation of nitrenes from azides under electron impact is well documented.[16]

The preference for C–H bond insertion over N–N bond formation may be the result of thermodynamic control with the possibility that the N–N bond is made preferentially under kinetic control. The imminium imine thus formed could conceivably redissociate to the nitrene which then reacts to form the observed product, nitrene formation by dissociation of $=N^+-N^-$– being known for some time.[17]

Introduction of a 5 substituent into the thiazole nucleus resulted in reaction of the intermediate nitrene at the thiazole nitrogen atom, a not unexpected result as attack at the 5 position of the thiazole nucleus would generate a tetrahedral center. The choice of a blocking group for the 5 position was somewhat restricted as a methyl group might lead to the corresponding pyridine derivative or product of methyl group migration,[18] and our attempts to prepare the 5-phenyl substituted product was unsuccessful.

Ethyl 4-(2-nitrophenyl)-2-phenylthiazole-5-carboxylate (**3**, R = COOEt; X = O) was prepared by a reaction sequence from ethyl 2′-nitrobenzoylacetate involving bromination and subsequent reaction with thiobenzamide. 3,5-Diphenyl-1,2,4-thiadiazole and sulfur were also formed along with **3** (R = COOEt; X = O) and, as these two products are also observed from the oxidation of thiobenzamide with a variety of reagents,[19] it appears that the nitro group in either the bromo compound or **3** (R = COOEt; X = O) may act as an oxidizing agent. As the yield of the thiazole was substantially increased by the use of a large excess of thiobenzamide, it appears that the bromo ketone was the more likely oxidant.

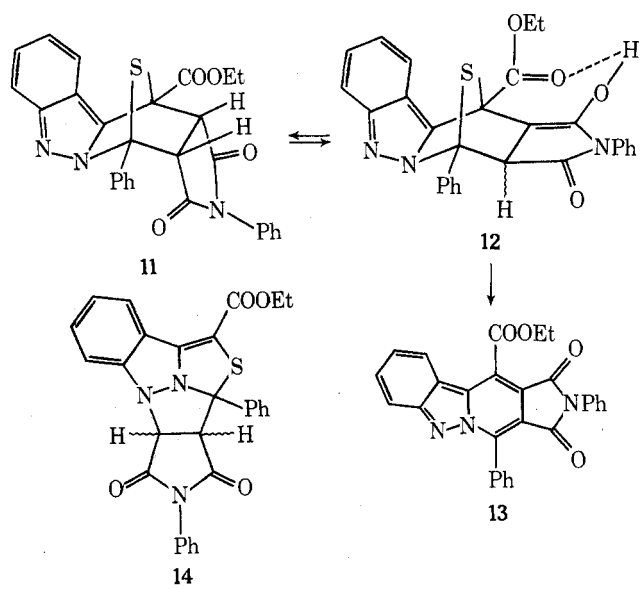
Triethyl phosphite deoxygenation of **3** (R = COOEt; X = O) resulted in the isolation of two products, the major one (24%) being obtained as maroon needles with an intense violet color in solution (λ_{max} 542 nm). This product has been identified as ethyl 3-phenylthiazolo[3,4-*b*]indazole-1-carboxylate (**7**, R = COOEt). Analytical and mass spectral data established the molecular formula as $C_{18}H_{14}N_2O_2S$, the latter also showing a doubly charged ion at *m/e* 161 (5%) often associated with tetravalent sulfur and other aromatic systems.[4,5,20]

The infrared carbonyl absorption in **7** (R = COOEt) occurred at 1690 cm^{-1}, 15 cm^{-1} lower than that in its precursor **3** (R = COOEt; X = O), indicating that the negative charge is delocalized over the ester group to some extent. This is commonly observed with heteroaromatic betaines with analogous substitution patterns, such as in 4-acetylsydnone[21a] and in *anhydro*-2,3-diphenyl-5-ethoxycarbonyl-4-hydroxythiazolium hydroxide.[21b]

This ring system was found to undergo cycloaddition reactions and, from the several possible ylide structures in the molecule, *N*-phenylmaleimide was found to add across the thiocarbonyl ylide dipole **9**. Such an addition is consistent with that observed previously in other tetravalent sulfur systems[4,5] and in this case reaction occurred in 17 hr in refluxing xylene. Two products were isolated from the reaction. The first, obtained in 65% yield, proved to be a 1:1 adduct whose spectral characteristics indicated that it was the enol **12** of the anticipated product **11**, with ν_{CO} 1705, 1760 cm^{-1} accompanying a ν_{OH} 3265 cm^{-1}. The NMR spectrum, in addition to the ester absorptions at δ 1.20 and 4.21, showed only a singlet bridgehead methine proton at δ 5.63, aromatic protons as two multiplets at δ 6.99–7.63 and 7.86–8.22, and a D_2O-exchangeable broad proton at δ 12.50 attributed to the enolic OH group.

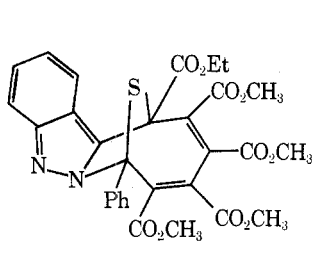
The enolization of the carbonyl group of an imidic cycloadduct has not previously been observed. Models indicate the possibility of stabilizing the enol group through hydrogen bonding with the bridgehead ester function, although this would involve a seven-membered ring system. Unfortunately, approximately the same favorable bond angles and lengths attend intramolecular hydrogen bonding from the cycloadduct regardless of whether the bridgehead proton is cis or trans with respect to the epithio bridge, precluding any assignment of stereochemistry to the cycloadduct. Nonequivalence of the methylene protons is indicated by the methylene resonances which appeared as a complex pattern and may be a consequence of this hydrogen bonding.[22]

The second product (29%) had a molecular composition corresponding to the loss of hydrogen sulfide from the primary cycloadduct **12**. Assigned structure **13**, it was formed in increased yields at the expense of **12** by increasing the reaction time, and **12** was also converted into **13** by refluxing in xylene or by treatment with methanolic sodium methoxide. Analogous loss of H_2S under these conditions is well established for related bridged-sulfur cycloadducts.[4,22] Formation of the tricyclic derivative **13** by loss of H_2S from the initial 1:1 adduct can only be rationalized in terms of structure **12** for the initial cycloadduct, alternative modes of cycloaddition, such as represented by **14**, requiring extensive skeletal rearrangements to accommodate such a loss.



It was anticipated that dimethyl acetylenedicarboxylate would also undergo cycloaddition with **7** (R = COOEt) to give, after extrusion of sulfur from the initial cycloadduct, a pyrido[1,2-*b*]indazole derivative analogous to **13**. Instead a 2:1 adduct was obtained (82%), the most plausible structure for which being the epithiodihydroazocinoindazole **15** or the dihydrothiazolodihydrodiazepinoindazole **16**, representing an addition of two molecules of dimethyl acetylenedicarboxylate across the thiocarbonyl ylide or the azomethine imine ylide of **7** (R = COOEt), respectively. Although analytical and spectral data clearly establish the formation of a 2:1 adduct, the latter are not sufficiently definitive to allow an unambiguous assignment of structure to be made. However, the ^{13}C pulsed FT spectrum[23] of the adduct provides evidence that lends strong support to structure **16**. Apart from the ester groups, structure **15** differs principally from structure **16** in that the former contains two sp^3

carbon atoms at the termini of the epithio bridge whereas the latter has only one sp^3 carbon atom at the original 2 position of the thiazole nucleus. An absorption at 114 ppm and the complete absence of an absorption between 61.62 and 127.49 ppm are consistent with structure **16.**



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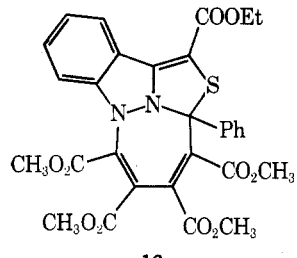

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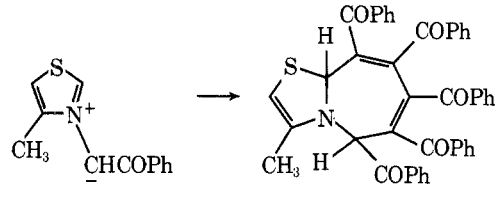
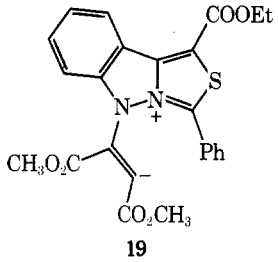
Formation of a 2:1 adduct has also been observed[24] with the thiazolium *N*-ylide **17,** in this case the thiazolo[3,2-*a*]azepine derivative **18** being obtained. An intermediate



17 **18**



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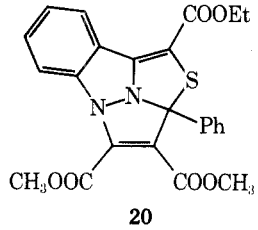
such as **19** would be anticipated in the formation of **16,** this 1,4-dipole undergoing condensation with another molecule of dimethyl acetylenedicarboxylate giving what is essentially a 1,7-dipole that undergoes ring closure to the observed product. Introduction of nitrogen atoms into the nucleus of other tetravalent sulfur systems considerably reduces the rate of cycloaddition of dipolarophiles[25] and in this case ring closure of **19** to form the 1:1 adduct **20** is less



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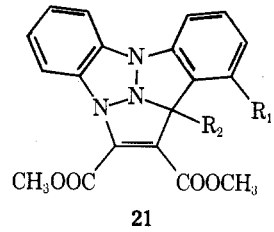

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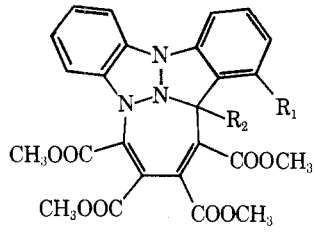

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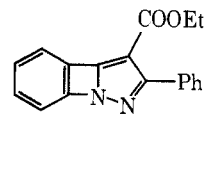

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favored than condensation with a second molecule of dipolarophile owing to the steric compression required for the fusion of three five-membered rings in a 1:1 adduct. However, the atoms at the points of ring fusion are apparently important in this respect as both a 1:1 adduct **21** and 2:1 adduct **22** are formed in the reaction of a dibenzotriazapentalene with dimethyl acetylenedicarboxylate.[26]

A second product isolated from the deoxygenation of **3** (R = COOEt; X = O) (5%) was shown to have a molecular formula $C_{18}H_{14}N_2O_2$, corresponding to the loss of sulfur from **7** (R = COOEt). Its formation by this route seems unlikely in view of our inability to convert **7** (R = COOEt) into this product on refluxing with triethyl phosphite in xylene. The ester ν_{CO} at 1750 cm^{-1} is 45 cm^{-1} higher than that found in its precursor **3** (R = COOEt; X = O) and 60 cm^{-1} higher than in the tetravalent sulfur system **7** (R = COOEt), indicating reduced electron delocalization over this group. A diazabiphenylene structure, e.g., **23,** seems unlikely since the aromatic multiplets of this product are found between δ 7.21 and 8.42, whereas the chemical shifts of the protons in biphenylene are reported[27] to be considerably upfield at δ 6.7 and 6.6 owing to the lack of effective bond delocalization.

Several improvements in the method of formation of the intermediates for the preparation of **3** (R = H, COOEt) are reported in the Experimental Section. Particularly interesting is the preparation of ethyl 2′-nitrobenzoylacetate from the reaction of 2-nitrobenzoyl chloride with the magnesium enolate of ethyl *tert*-butylmalonate. Heating the acyl malonate with β-napthalenesulfonic acid resulted in a 93% yield of pure product (>95%).

Experimental Section[28]

2′-Nitroacetophenone. This was prepared essentially according to the procedure of Reynolds and Hauser[29] with the following modification. The 150 ml of Et_2O added to the original magnesium ethoxide mixture was replaced by a mixture of 65 ml of anhydrous Et_2O and 85 ml of dry THF. The addition of 2-nitrobenzoyl chloride then resulted in the formation of a soluble magnesium malonate complex which was readily hydrolyzed by dropwise addition of the specified amount of dilute H_2SO_4. Following hydrolysis and decarboxylation of the acylmalonate intermediate, 2′-nitroacetophenone was obtained in 91–93% yield.

4-(2-Nitrophenyl)-2-phenylthiazole (3, R = H; X = O). A solution of thiobenzamide (27.4 g, 0.2 mol) and 2-bromo-2′-nitroacetophenone[30] (24.3 g, 0.1 mol) in 95% EtOH (150 ml) was refluxed for 1 hr. On cooling colorless needles, 25.4 g (90%), mp 97.5–99°, were obtained. Crystallization from MeOH afforded colorless needles: mp 98–99°; ir (KBr) 1530, 1360 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 7.26–8.11 (m, 10, aromatic); $M^{\cdot+}$ *m/e* 282 (19), 121 (100).

Anal. Calcd for $C_{15}H_{10}N_2O_2S$: C, 63.85; H, 3.57; N, 9.92. Found: C, 63.84; H, 3.56; N, 10.03.

When the ethanol solution was warmed gently, a precipitate of the open-chain intermediate **2** was frequently obtained as colorless needles (90%), ir (KBr) 2200–2700 (immonium), 1800 cm^{-1} (CO). This was converted into **3** quantitatively by shaking with a mixture of water, ether, and NEt_3.

Deoxygenation of 4-(2-Nitrophenyl)-2-phenylthiazole (3, R = H; X = O). The thiazole (1.1 g, 0.0029 mol), $P(OEt)_3$ (2 ml, freshly distilled from sodium), and xylene (7 ml) were refluxed under N_2 for 84 hr. The volatile components were removed in vacuo and the residual brown oil chromatographed (silica gel, 60 g, eluted with benzene) to afford, after crystallization from benzene, 2-phenylthiazolo[5,4-*b*]indole (**5**) as pale-yellow, fine, irregular prisms: mp 235–236°; 0.4 g (41%); ir ($CHCl_3$) 3460 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 7.20–8.19 (m, 9, aromatic), 3.48 (br s, exchanged with D_2O, 1, NH); $M^{\cdot+}$ *m/e* 250 (100).

Anal. Calcd for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found: C, 72.20; H, 3.96; N, 11.06.

3-Benzamido-2-oxindole (6). To a solution of 3-aminooxindole hydrochloride[31] (1.73 g, 0.0094 mol) and Et_3N (30 ml) in $CHCl_3$ (70 ml) was added with stirring a solution of benzoyl chloride (1.32 g, 0.0094 mol) in $CHCl_3$ (15 ml). After 5 min the reaction mixture became pasty, and after 30 min it was filtered and washed with $CHCl_3$ to afford a white solid which crystallized from absolute EtOH as fine, colorless, matted needles: 2.25 g (95%); mp 250.5–251.5°; ir (KBr) 3300 (NH), 1730 cm^{-1} (CO); $M^{\cdot+}$ *m/e* 252 (27), 105 (100).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.07; H, 4.82; N, 11.09.

Reaction of 3-Benzamido-2-oxindole with Phosphorus Pentasulfide. A mixture of the above amide (1.26 g, 0.005 mol) and P_4S_{10} (1.11 g, 0.0025 mol) in pyridine (60 ml) was refluxed for 2 hr, reduced in volume to 20 ml by distillation, and poured into ice–water containing dilute NaOH. Upon filtration a cream-colored solid was obtained which crystallized from absolute EtOH as pale-yellow needles: 0.75 g (60%); mp 236–237°; identical[32] in all respects with 2-phenylthiazolo[5,4-*b*]indole (**5**) obtained by deoxygenation of the corresponding nitro compound (**3**, R = H; X = O).

4-(2-Aminophenyl)-2-phenylthiazole (3, R = X = H). A refluxing suspension of 4-(2-nitrophenyl)-2-phenylthiazole (11.3 g, 0.04 mol) and iron powder (76.8 g, 0.136 g-atom) in EtOH (500 ml) was treated dropwise with stirring over 1.5 hr with a solution of concentrated HCl (24 ml) in EtOH (200 ml). Reflux was continued for an additional 1 hr, at the end of which time the reaction mixture was filtered, neutralized with aqueous KOH, concentrated by evaporation, and extracted with $CHCl_3$. The organic layer was filtered to remove iron salts and evaporated to afford a tan solid which crystallized from EtOH as light tan plates, 5.8 g (54%). Work-up of the mother liquors afforded an additional 1.0 g (67% total yield). The combined products were recrystallized from MeOH, affording pale yellow plates: mp 121.5–122.5°; ir (KBr) 3450, 3325 cm^{-1} (NH); NMR ($CDCl_3$) δ 6.51–7.97 (m, 10, aromatic), 5.36 (br s exchanged with D_2O, 2, NH_2); $M^{\cdot+}$ *m/e* 252 (100).

Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.38; H, 4.80; N, 11.11. Found: C, 71.37; H, 4.87; N, 11.02.

4-(2-Azidophenyl)-2-phenylthiazole (3, R = H; X = N). A suspension of 4-(2-aminophenyl)-2-phenylthiazole (2.02 g, 0.008 mol) in concentrated HCl (7 ml) at 0° was treated with a solution of sodium nitrite (0.55 g, 0.008 mol) in H_2O (30 ml). After standing for 1.5 hr at 0°, sodium azide (0.52 g, 0.008 mol) in H_2O (60 ml) was added to the reaction mixture which was stirred for 8 hr at room temperature, at the end of which time the originally bright yellow color had been discharged to leave a white solid which was filtered, washed with H_2O, taken up in acetone, filtered, and evaporated to dryness. Crystallization from MeOH afforded colorless, fine matted needles: 1.1 g (50%); mp 104.5–105° (gas evolution); ir (KBr) 2130 cm^{-1} (N_3); NMR ($CDCl_3$) δ 7.09–7.98 (m, 10, aromatic); $M^{\cdot+}$ *m/e* 278 (16), 250 (100).

Anal. Calcd for $C_{15}H_{10}N_4S$: C, 64.84; H, 3.57; N, 20.12. Found: C, 64.73; H, 3.62; N, 20.13.

Thermolysis of 4-(2-Azidophenyl)-2-phenylthiazole (3, R = H; X = N). A solution of 4-(2-azidophenyl)-2-phenylthiazole (0.10 g, 0.00036 mol) in decalin (7 ml) was refluxed for 28 hr and cooled, giving a deposit of 0.05 g (54%) of light-brown, irregular prisms, mp 231–234.5°, identical[32] in all respects with 2-phenylthiazolo[5,4-*b*]indazole (**5**) obtained by deoxygenation of the corresponding nitro compound **3** (R = H; X = O).

Photolysis of 4-(2-Azidophenyl)-2-phenylthiazole. A solution of the above azide (0.19 g, 0.00067 mol) in benzene (50 ml) was irradiated at 300 nm for 18 hr, some gas evolution being noted. The solvent was removed by evaporation to afford 0.16 g (94%) of light-brown, irregular prisms, mp 236.5–237.5°, identical[32] in all respects with 2-phenylthiazolo[5,4-*b*]indazole (**5**) obtained by deoxygenation of the corresponding nitro compound.

Ethyl 2′-Nitrobenzoylacetate. A three-neck 500-ml round-bottom flask was fitted with a mechanical stirrer, reflux condensor, drying tube, and dropping funnel, and charged with Mg turnings (5.4 g, 0.22 g-atom). To this was added CCl_4 (0.5 ml) and absolute EtOH (5 ml). The ensuing reaction was allowed to run for several minutes, and a solution of anhydrous Et_2O (70 ml) and dry THF (80 ml) was added slowly with stirring. Next a solution of ethyl *tert*-butylmalonate[33] (41.4 g, 0.22 mol) in absolute EtOH (20 ml) and Et_2O (25 ml) was added over the course of 30 min and the mixture refluxed for 4 hr. A solution of 2-nitrobenzoyl chloride[29] (37.0 g, 0.20 mol) in Et_2O (50 ml) was added dropwise with stirring, and the mixture was refluxed for 30 min and left at room temperature overnight. A solution of concentrated H_2SO_4 (25 ml) in H_2O (200 ml) was added, and after stirring for 2 hr, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 75 ml). The combined organic fractions were washed with H_2O (2 × 250 ml) and saturated NaCl (1 × 150 ml), dried (Na_2SO_4), and evaporated to afford 67.7 g of ethyl *tert*-butyl-2′-nitrobenzoylmalonate as a clear yellow oil.

A portion of this oil (17.0 g, 0.55 mol) was heated at 100° (0.1 mm) for 1.5 hr, at the end of which time the small amount of colorless liquid that had distilled was discarded. β-Naphthalenesulfonic acid (0.01 g) was added to the residual yellow oil and heating was resumed at 100° (0.05 mm) for 2 hr to effect decarboxylation. Distillation then afforded ethyl 2′-nitrobenzoylacetate as a pale yellow liquid, bp 170° (0.1 mm): 11.0 g (93% based upon crude nitrobenzoyl malonate, 93% based upon 2-nitrobenzoyl chloride); ir (neat) 1740, 1700 cm^{-1} (CO); NMR ($CDCl_3$) δ 7.48–8.29 (m, 4, aromatic), 4.14 (q, 2, ethyl CH_2), 3.95 (s, 2, CH_2), 1.28 (t, 3, CH_3).

Ethyl 2-Bromo-2′-nitrobenzoylacetate. A solution of Br_2 (3.5 g, 0.022 mol) in CCl_4 (5 ml) was added dropwise with stirring to ethyl 2′-nitrobenzoylacetate (4.74 g, 0.02 mol) in CCl_4 (10 ml). The red color of the Br_2 was discharged instantaneously. Stirring was continued overnight at room temperature, and the mixture was washed with saturated aqueous $NaHSO_3$, then saturated aqueous $NaHCO_3$. The aqueous washings were extracted with $CHCl_3$ and the combined organic extracts were washed with H_2O (2 × 15 ml) and saturated aqueous NaCl, dried (Na_2SO_4), and evaporated to a pale orange oil which was dissolved in hot MeOH and cooled to deposit colorless prisms: 4.5 g (71.3%); mp 66–67.5°; ir (KBr) 1730, 1720 cm^{-1} (CO); NMR ($CDCl_3$) δ 7.44–8.39 (m, 4, aromatic), 5.17 (s, 1, CH), 4.27 (q, 2, CH_2), 1.29 (t, 3, CH_3); $M^{\cdot+}$ *m/e* 318 (0.5), 316 (0.5), 150 (100).

Anal. Calcd for $C_{11}H_{10}BrNO_5$: C, 41.79; H, 3.18; N, 4.43. Found: C, 41.39; H, 3.27; N, 4.44.

Ethyl 4-(2-Nitrophenyl)-2-phenylthiazole-5-carboxylate (3, R = COOEt; X = O). Ethyl 2-bromo-2′-nitrobenzoylacetate (6.32 g, 0.020 mol) in benzene (20 ml) was added dropwise with stirring under N_2 in the dark to a refluxing solution of thiobenzamide (6.0 g, 0.043 mol) in benzene (50 ml). The reaction mixture rapidly turned brown, slowly changing to orange, and eventually fading to pale yellow. Reflux was continued for 1 hr after completion of the addition and stirring was continued at room temperature under N_2 in the dark overnight. Filtration afforded ca. 5.0 g of pale orange solid which was triturated with absolute EtOH to leave a colorless solid which crystallized from CH_3CN as colorless, irregular prisms turning orange, then red upon exposure to light: 2.0 g (28%); mp 196–197°; ir (KBr) 1705 cm^{-1} (CO); NMR ($CDCl_3$) δ 7.52–8.45 (m, 9, aromatic), 4.27 (q, 2, CH_2), 1.19 (t, 3, CH_3); $M^{\cdot+}$ *m/e* 354 (20), 122 (100).

Anal. Calcd for $C_{18}H_{14}N_2O_4S$: C, 61.00; H, 3.98; N, 7.90. Found: C, 60.89; H, 4.10; N, 8.04.

The combined benzene and EtOH washings were concentrated and heated with Et_2O. Filtration afforded a heterogeneous solid which was found to consist mostly of elemental sulfur (ca. 0.8 g). The Et_2O solution, upon cooling, deposited 3.1 g of 3,5-diphenyl-1,2,4-thiadiazole as pink needles, mp 82.5–87°. It crystallized from Et_2O as colorless needles, mp 89–91° (lit.[19] mp 91–92°), $M^{\cdot+}$ *m/e* 238 (100).

P(OEt)$_3$ Deoxygenation of Ethyl 4-(2-Nitrophenyl)-2-phenylthiazole-5-carboxylate (3, R = COOEt; X = O). The nitrophenylthiazole (1.06 g, 0.03 mol) and $P(OEt)_3$ (4 ml, freshly distilled from sodium) in dry xylene (25 ml) were refluxed for 32 hr under N_2. The volatile components were removed by distillation (100°, 0.1 mm) and the reddish residue was chromatographed (silica gel, 25 g, eluted with benzene–$CHCl_3$) to afford a first fraction that crystallized from hexane as colorless, matted needles or colorless plates: 0.042 g (5%); mp 143–144.5°; ir (KBr) 1750 cm^{-1} (CO); NMR ($CDCl_3$) δ 8.01–8.42 (m, 3, aromatic), 7.32–7.62 (m, 5, aromatic), 7.21–7.25 (d of d, 1, aromatic), 4.63 (q, 2, CH_2), 1.44 (t, 3, CH_3); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 290 (100), M − CH_3 275 (26), M − C_2H_5O 245 (7), M − $C_3H_4O_2$ 218 (73), 129 (13), 105 (42), 102 (14).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65; mol wt, 290.32. Found: C, 73.98; H, 4.92; N, 9.43; mol wt, 290.1055 (mass spectroscopy).

The second fraction from the column, ethyl 3-phenylthiazolo[3,4-*b*]indazole-1-carboxylate (**7**, R = COOEt), crystallized from CH_3CN as maroon needles: 0.29 g (24%); mp 168–169°; ir (KBr) 1690 cm^{-1} (CO); λ_{max} ($CHCl_3$) 542 nm (log ϵ 3.92), 375 sh (3.86), 363 (3.90), 322 br sh (4.35), 306 (4.39), 269 (4.23); NMR ($CDCl_3$) δ 8.44–8.79 (m, 3, aromatic), 7.45–7.78 (m, 5, aromatic), 7.08–7.22 (m, 1, aromatic), 4.54 (q, 2, CH_2), 1.53 (t, 3, CH_3); $M^{\cdot+}$ *m/e* 322 (100), 294 (58), 249 (10), 161 (5), 146 (13), 121 (24), 102 (12), 177 (11).

Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 66.87; H, 4.33; N, 8.85.

Reaction of Ethyl 3-Phenylthiazolo[3,4-*b*]indazole-1-carboxylate (7, R = COOEt) with *N*-Phenylmaleimide. The tetravalent thiazole (0.101 g, 0.00031 mol) and *N*-phenylmaleimide (0.150 g, 0.0087 mol) in xylene (15 ml) were refluxed under N_2 for 17 hr, and the resulting solution concentrated to ca. 6 ml. Upon cooling, 1,2,3,4-tetrahydro-*N*,4-diphenyl-1,4-epithio-1-ethoxycar-

bonylpyrido[1,2-*b*]indazole-2,3-dicarboximide (**12**) separated as colorless prisms, 0.038 g (24%). Preparative thin layer chromatography (silica gel, 5 × 0.5 mm, eluted with benzene–$CHCl_3$–EtOAc, 7:7:1) afforded an additional 0.064 g (42%, total yield 65%) which crystallized as colorless prisms from EtOH: mp 218.5–220° dec (gas evolution); ir (KBr) 3265 (enolic OH), 1760, 1705 cm^{-1} (CO); λ_{max} (MeOH) 347 nm (log ϵ 3.31), 298 sh (3.38), 287 (3.50), 230 sh (3.45), 207 (3.91); NMR ($CDCl_3$) δ 12.50 (br s exchanged with D_2O, 1, enolic OH), 7.86–8.22 (m, 3, aromatic), 6.99–7.62 (m, 11, aromatic), 5.63 (s, 1, CH), 4.21 (m, 2, CH_2), 1.20 (t, 3, CH_3); $M^{\cdot+}$ *m/e* 495 (11), 461 (100).

Anal. Calcd for $C_{28}H_{21}N_3O_4S$: C, 67.86; H, 4.27; N, 8.48. Found: C, 67.45; H, 4.32; N, 8.52.

A second band consisting of *N*,4-diphenyl-1-ethoxycarbonylpyrido[1,2-*b*]indazole-2,3-dicarboximide (**13**) crystallized from EtOH as fine yellow, matted needles: 0.050 g (29%); mp 267–268°; ir (KBr) 1730, 1705 cm^{-1} (CO); λ_{max} (MeOH) 398 nm (log ϵ 3.87), 293 (4.35), 257 (3.99), 207 (4.26).

Anal. Calcd for $C_{28}H_{19}N_3O_4$: C, 72.87; H, 4.15; N, 9.11. Found: C, 72.72; H, 3.92; N, 9.16.

Base-Catalyzed Elimination of H_2S from *N*-Phenylmaleimide Adduct. To 1,2,3,4-tetrahydro-*N*,4-diphenyl-1,4-epithio-1-ethoxycarbonylpyrido[1,2-*b*]indazole-2,3-dicarboximide (**12**, 0.025 g, 0.00005 mol) in MeOH (3 ml) was added at room temperature methanolic sodium methoxide [prepared from sodium metal (0.02 g, 0.0087 g-atom) and MeOH (5 ml)]. An immediate dark reddish-brown color slowly faded to yellow, and after 30 min a yellow precipitate was collected by filtration. This material proved to be identical[32] with **13** obtained as described previously, 0.012 g (52%).

Thermolysis of *N*-Phenylmaleimide Adduct. 1,2,3,4-Tetrahydro-*N*,4-diphenyl-1,4-epithio-1-ethoxycarbonylpyrido[1,2-*b*]indazole-2,3-dicarboximide (**12**, 0.025 g, 0.00005 mol) in xylene (3 ml) was refluxed for 6 days. The solvent was removed by evaporation and the yellow residual solid crystallized from EtOH as fine, yellow, matted needles: 0.017 g (73%), identical[32] with **13** obtained as described previously.

Reaction of Ethyl 3-Phenylthiazolo[3,4-*b*]indazole-1-carboxylate (7, R = COOEt) with Dimethyl Acetylenedicarboxylate. The title thiazole (0.164 g, 0.0005 mol) and DMAD (0.25 g, 0.0018 mol) were refluxed in xylene (10 ml) under N_2 for 30 min. Volatile components were removed by distillation at 100° (0.1 mm), leaving a brown oil which was purified by preparative layer chromatography (silica gel, 4 × 0.75 mm, eluted with benzene–$CHCl_3$–EtOAc, 3:3:1) to give a pale yellow oil which was taken up in hot MeOH, cooled, and induced to crystallize by scratching. The 1:2 adduct **16** was obtained as colorless prisms: 0.252 g (82%); mp 112.5–113.5°; ir (KBr) 1730 cm^{-1} (CO); λ_{max} (MeOH) 265 nm sh (log ϵ 4.21), 225 (4.48); NMR ($CDCl_3$) δ 7.23–7.71 (m, 9, aromatic), 4.27 (q, 2, CH_2), 3.84 (s, 3, OCH_3), 3.80 (s, 6, OCH_3), 3.62 (s, 3, OCH_3), 1.05 (t, 3, CH_3); $M^{\cdot+}$ 606 (20), 533 (100).

Anal. Calcd for $C_{30}H_{26}N_2O_{10}S$: C, 59.40; H, 4.32; N, 4.62. Found: C, 59.10; H, 4.30; N, 4.59.

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Registry No.—**2**, 56929-93-2; **3** (R = H; X = O), 56929-94-3; **3** (R = H; X = H), 56929-95-4; **3** (R = H; X = N), 56929-96-5; **3** (R = COOEt; X = O), 56929-97-6; **5**, 56929-98-7; **6**, 56929-99-8; **7** (R = COOEt), 56930-00-8; **12**, 56960-33-9; **13**, 56930-01-9; **16**, 56930-02-0; thiobenzamide, 2227-79-4; 2-bromo-2′-nitroacetophenone, 6851-99-6; 3-aminooxindole hydrochloride, 43012-47-1; benzoyl chloride, 98-88-4; ethyl 2′-nitrobenzoylacetate, 52119-39-8; ethyl *tert*-butylmalonate 759-24-0; 2-nitrobenzoyl chloride 610-14-0; ethyl 2-bromo-2′-nitrobenzoylacetate, 56930-03-1; 3,5-diphenyl-1,2,4-thiadiazole, 4115-15-5; *N*-phenylmaleimide, 941-69-5; dimethyl acetylenedicarboxylate, 762-42-5.

References and Notes

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