Intramolecular Cyclizations Leading to Bridgehead Bicyclics. 3. 5,5-Diphenyl-2-thiohydantoin Derivatives

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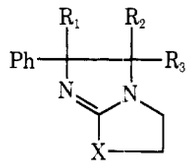
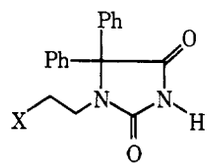
Reaction of 5,5-diphenyl-2-thiohydantoin with 1-bromo-2-chloroethane generated two isomeric imidazo-[2,1-*b*]thiazole derivatives through intramolecular S,N-dialkylation. Chemical, NMR, and mass spectral analyses of the isomeric reaction products confirmed the structures proposed. One of the bicyclic isomers was reduced to an analogue of levamisole.

An earlier investigation of hydantoin alkylating agents as potential central nervous system antitumor agents in this laboratory showed that bicyclic derivatives such as **1a** and **1b**





1a, X = O; R_1 = Ph; R_2 + R_3 = O
b, X = O; R_1 = Ph; R_2 = R_3 = H
c, X = S; R_1 = H; R_2 = R_3 = H
d, X = S; R_1 = Ph; R_2 = R_3 = H
e, X = S; R_1 = Ph; R_2 = H; R_3 = OH

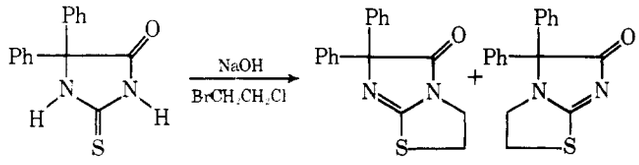
2a, X = SH
b, X = H

were obtainable through an intramolecular alkylation reaction.[2] Levamisole (**1c**), a sulfur-containing analogue of these compounds, is of current clinical interest due to its properties as a general immunostimulant.[3] It, therefore, became of interest to determine whether a similar type intramolecular alkylation would occur when the oxygen atom in the 2 position of the hydantoin ring was replaced by sulfur. If successful, this reaction would yield the basic ring system of levamisole.

Our initial approach to the attempted production of **4** utilized a synthetic pathway similar to that employed for the preparation of **1a**. 2-Bromoethanol was reacted with the sodium salt of **3** in an attempt to produce a hydroxyethyl derivative. While N-3 alkylation was expected, S-alkylation was also a possibility.[4] Although many sets of experimental conditions were employed, the reaction of **3** with 2-chloroethanol, 2-bromoethanol, or 2-bromoethanol tetrahydropyranyl ether produced unreacted **3** or its hydrolysis product 5,5-diphenylhydantoin (DPH).

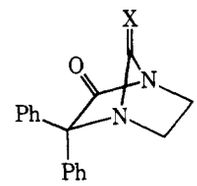
In contrast to the resistance to alkylation found with the 2-haloethanols, 1-bromo-2-chloroethane reacted with the sodium salt of **3** to give a mixture of two products (Scheme I)

Scheme I

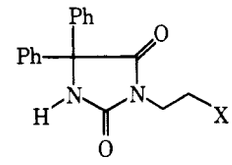


3 **4** **5**

whose elemental compositions and NMR spectra suggested structures **4**, **5**, or **6a**. While it had been possible to differentiate between **1a** and **6b** on the basis of the large difference in the chemical shifts of the two sets of methylene protons[2] in the NMR spectrum of **1a**, it was not possible to do this for **6a** vs. **4** and **5**. The lower electronegativity of sulfur relative to oxygen resulted only in an unseparated multiplet for the four



6a, X = S
b, X = O



7a, X = SH
b, X = H
c, X = Br
d, X = $[SC(NH_2)_2]^+Br^-$

added methylene protons of the two isomeric products. Acid hydrolysis of **6a** would be expected to yield a non-sulfur-containing piperazine derivative by elimination of the thiocarbonyl bridge. Acid hydrolysis of the two isomeric materials gave products which contained sulfur and gave correct elemental analytical values for **2a** or **7a**. The structures of these compounds were assigned by degradation and synthesis experiments.

The major isomer was shown to be **5** by hydrolysis to **2a** and Raney nickel desulfuration of **2a** to the known[5] 1-ethyl-5,5-diphenylhydantoin (**2b**). An identical sample of **2b** was prepared independently from DPH using the general aminomethylation method of Orazi and Corral.[6,7]

Hydrolysis of the minor isomer **4** to the mercaptoethyl derivative **7a** followed by Raney nickel reduction gave 3-ethyl-5,5-diphenylhydantoin (**7b**), a known compound,[8] which was independently synthesized by alkylation of DPH.[8]

Protons attached to the ring nitrogens at the 1 and 3 positions in the hydantoin ring are distinguished by characteristic chemical shifts. In deuteriochloroform, N-1 and N-3 protons absorb at ca. δ 6.7 and 9.3, respectively.[9] The NH absorptions of **7a** (δ 7.0), **7c** (δ 7.6), **2a** (δ 9.4), and **2b** (δ 8.9) are consistent with this general observation. The NH absorption for **7b** in deuteriodimethyl sulfoxide (δ 9.6) is consistent with the literature values for hydantoin protons in that solvent (N-1, δ 9.3; N-3, δ 11.1). All of these protons were exchangeable with deuterium oxide.

The reduction of the hydantoin amide carbonyl by several hydride reducing agents has been reported.[2,10] Based on that work, the most appropriate reagent for the production of the levamisole analogue **1d** from **4** appeared to be sodium bis(2-methoxyethoxy)aluminum hydride. Only partial reduction was achieved with this reagent, however, with the alcohol, **1e**, being produced. This alcohol was successfully reduced to the desired compound, **1d**, by conversion to an iodide with methyltriphenoxyphosphonium iodide and reduction with sodium cyanoborohydride.[11]

Discussion

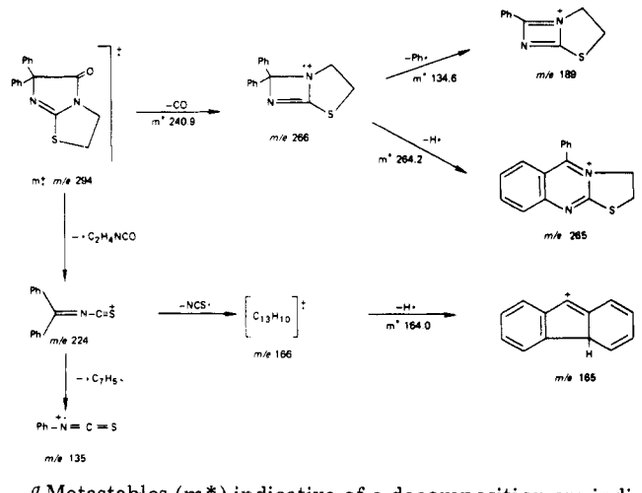
Polish workers,[12,13] using almost identical reaction conditions, claimed that **4** was produced in 70% yield from the reaction of 1,2-dibromoethane with **3**. They did not mention **5**,

the compound found here to be the major isomer. Repetition of their exact experimental conditions gave the same mixture of **4** and **5** described above. The Polish workers' proof of structure rested on elemental analyses, several infrared spectra, and an independent synthesis of **7a** using **7c** and **7d** as intermediates. We repeated their synthesis of **7a** and in several cases obtained products with different melting points. Since in most instances the melting point was the only item given for comparison,[12] we further characterized the compounds mass spectrometrically.

Molecular ions of high to moderate abundance were present for all the compounds examined (see Experimental Section). Mass spectrometry also offered a rapid and facile method for determining the type and position of nitrogen substitution in this series since fragmentation of these compounds was analogous to that of 1- and 3-methyl 5,5-disubstituted hydantoins.[14] The 3-substituted hydantoins (e.g., **7b** and **7c**) exhibited a more facile loss of carbon monoxide (M − 28) and HCO (M − 29) from their molecular ions than did the corresponding 1-alkylhydantoins (e.g., **2b**). Since the N-3 position of the hydantoin ring appeared to be involved in extrusion of isocyanic acid (HNCO, 43 amu) from the molecular ion,[14] substitution there was also evident from ions corresponding to the loss of a substituted isocyanate but not HNCO. Hydantoins **7b** and **7c** showed strong peaks at *m/e* 209 to indicate the loss of RNCO, while the analogous ion in **2b** (*m/e* 237, base peak) corresponded to loss of HNCO.

Besides an abundant molecular ion at *m/e* 294, the mass spectrum of the minor bicyclic isomer, **4**, possessed diagnostic ions at *m/e* 266, 265, 224, 189, 165, and 135. The rearranged ion responsible for the base peak at *m/e* 265 resulted from successive losses of carbon monoxide and a hydrogen radical in a manner analogous to that observed[2] for the corresponding oxygen analogue **1a**. Scheme II shows the postulated formation and structure of these important ions. The major bicyclic isomer, **5**, like the analogous 1-substituted diphenylhydantoins, did not extrude the elements of CO and HCO as readily as **4** or the corresponding 3-substituted hydantoins. The molecular ion of **5** produced the base peak and, although the fragmentation pattern was similar to that of **4**, distinct differences existed in the relative abundances of the major ions, reflecting the structural isomerism.

Scheme II. Postulated Fragmentation Pathway and Ion Structures for 4[a]



[a] Metastables (m*) indicative of a decomposition are indicated if observed.

The fragmentation pattern of the levamisole analogue **1d** was quite similar to that reported for the parent compound.[15] Unlike levamisole, phenyl disubstitution on the same carbon atom was also indicated by ions at *m/e* 166 and 165.

Experimental Section[16]

2,3,5,6-Tetrahydro-6,6-diphenylimidazo[2,1-*b*]thiazole (1d). Methyltriphenoxyphosphonium iodide (1.55 g, 3.4 mmol) and **1e** (0.50 g, 1.7 mmol) were stirred at room temperature for 2 h in dry hexamethylphosphoric triamide (5 mL). When sodium cyanoborohydride (0.43 g, 6.8 mmol) was added to the solution, the color of the reaction mixture changed from brown to colorless. After heating for 2 h at 70 °C, the solution was cooled, diluted with chloroform, and extracted with ten 10-mL portions of 10% HCl solution. The HCl extracts were made basic with 10% aqueous sodium hydroxide solution and this solution was extracted with chloroform. The solvent was evaporated and the residue dissolved in ether. The ether solution was washed several times with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a solid which was recrystallized from 70% ethanol to give 0.16 g (33%) of a NBP-negative white solid: mp 146–147.5 °C; IR 1585, 1570, 1270, 1200, 1180, 1165, 1090, 1055, 1015, 980, 855, 770, 745, 700, 660 cm^{-1}; NMR ($CDCl_3$) δ 3.4 (m, 4, CH_2CH_2), 3.80 (s, 2, CH_2), 7.3 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) 280 (M^+, 100), 279 (12), 224 (98), 203 (M − Ph, 84), 176 (59), 166 (11), 165 (40), 121 (20), 117 (10), 77 (14); IRI 2460.

Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.81; H, 5.76; N, 9.99; S, 11.43. Found: C, 72.66; H, 5.99; N, 10.12; S, 11.34.

2,3,5,6-Tetrahydro-6,6-diphenylimidazo[2,1-*b*]thiazol-5-ol (1e). A solution of **4** (0.40 g, 1.4 mmol) in dry THF (20 mL) was added dropwise to a stirred, room temperature solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (0.9 mL of 70% solution in benzene, 3 mmol) in dry THF (5 mL). The reaction mixture was refluxed for 1 h and water (5 mL) was added with ice-bath cooling. The solvents were evaporated in vacuo at room temperature and the residue extracted with several portions of chloroform. The combined extracts were washed with a saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a solid which was recrystallized from chloroform–benzene to give 0.24 g (59%) of a NBP-negative, white solid: mp 184.5–186.5 °C; IR 3200–3000, 1580, 1560, 1290, 1164, 1090, 1070, 985, 930, 825, 750, 695 cm^{-1}; NMR (Me_2SO-d_6) δ 3.2–3.6 (m, 4, CH_2CH_2), 5.55 (d, J = 7 Hz, 1, CHOH), 6.55 (d, J = 7 Hz, 1, OH), 7.1–7.6 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) 296 (M^+, 7) 279 (20), 278 (100), 224 (14), 165 (9), 147 (14), 139 (6), 103 (27), 77 (6).

Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.88; H, 5.45; N, 9.45; S, 10.82. Found: C, 68.98; H, 5.33; N, 9.34; S, 10.60.

1-(2-Mercaptoethyl)-5,5-diphenylhydantoin (2a). Compound **5** (2.3 g, 0.008 mol) was reacted with HCl and worked up as described above for the preparation of **7a** to give a 2.0 g (82%) of product with mp 190.5–191 °C after recrystallization from ethanol: IR 3150, 1770, 1710, 1325, 1290, 1250, 1220, 1175, 1142, 1105, 1075, 1025, 925, 775, 760, 718, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (t, 1, SH), 1.90 (m, 2, CH_2S), 3.5 (m, 2, CH_2N), 7.4 (s, 10, aromatic), 9.4 (b, 1, NH); mass spectrum *m/e* (rel intensity) 312 (M^+, 13), 265 ($M^+ - CH_2SH$, 42), 222 (9), 194 (8), 187 (12), 165 (12), 104 (11), 91 (100), 77 (14); IRI 2645.

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.17; N, 8.97; S, 10.26. Found: C, 65.36; H, 5.28; N, 8.86; S, 9.99.

1-Ethyl-5,5-diphenylhydantoin (2b). Method A. Compound **2a** (1.00 g, 0.003 mol) was reacted with Raney nickel as described in the preparation of **7b** to give 0.51 g (57%) of product, mp 183.5–184 °C. Recrystallization from 50% ethanol gave white crystals: mp 184.5—185 °C (lit.[5] mp 185–187 °C); IR 3150, 1760, 1720, 1700, 1415, 1340, 1280, 1210, 1130, 1050, 990, 885, 775, 760, 720, 700 cm^{-1}; NMR ($CDCl_3$) δ 0.60 (t, 3 CH_3), 3.40 (q, 2, ch_2), 7.35 (s, 10, aromatic), 8.90 (b, 1, NH); mass spectrum *m/e* (rel intensity) 280 (M^+, 21), 238 (17), 237 (M − HNCO, 100), 209 (30), 208 (87), 203 (M − Ph, 10), 194 (23), 165 (37), 132 (35), 104 (56), 91 (56), 77 (47); IRI 2310.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.71; H, 5.61; N, 9.89.

Method B. A 37% aqueous solution of formaldehyde (1.8 g, 0.022 mol) was added to a cooled, stirred suspension of DPH (5.04 g, 0.02 mol), morpholine (1.8 g, 0.02 mol), and methanol (20 mL). The suspension dissolved. After 2 h at room temperature, the solution was evaporated in vacuo. Benzene was added and evaporated several times to remove traces of residual water and the resulting high-viscosity oil was subjected to prolonged high-vacuum treatment. This oil was dissolved in dry DMF (30 ml) and sodium hydride in 50% mineral oil (0.5 g of NaH, 0.02 mol) was added with stirring. After hydrogen evolution had ceased, ethyl iodide (3.30 g, 0.02 mol) was added and the solution was stirred for 24 h. The solvent was removed, the residue was washed with hexane, and the residual hexane was removed in vacuo. The residue was stirred with 5% aqueous NaOH solution (100 mL) for 2 h. Insoluble material was filtered. Acidification with concentrated HCl gave the product which was recrystallized from 50%

aqueous ethanol to give 1.98 g (36%) of white crystals, mp 184–184.5 °C, identical with the product from method A.

2,3-Dihydro-6,6-diphenylimidazo[2,1-*b*]thiazol-5(6*H*)-one (4) and 2,3-Dihydro-5,5-diphenylimidazo[2,1-*b*]thiazol-6(5*H*)-one (5). A solution of **3** (27.0 g, 0.1 mol), 1-bromo-2-chloroethane (14.5 g, 0.1 mol), and sodium hydroxide (4.4 g, 0.11 mol) in methanol (200 mL) was refluxed for 12 h. Some insoluble material was removed by filtration, the filtrate evaporated to dryness in vacuo, and the residue extracted with chloroform. This extract was washed first with 5% aqueous KOH solution, then H_2O and dried over anhydrous Na_2SO_4. Removal of the solvent gave 16.80 g of a crude solid which was a mixture of **4** and **5**. Two methods were used successfully to separate these compounds.

Method A. The first fraction which separated with C_6H_6 elution on alumina grade II contained **4** which was recrystallized from chloroform to give 2.04 g (6.2%) of white crystals: mp 201–203 °C (lit.[12] 202–203 °C); NBP negative; IR 1710, 1600, 1560, 1240, 1170, 1082, 1030, 1010, 922, 908, 810, 762, 755 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (m, 4, CH_2CH_2), 7.40 (m, 10, aromatic); UV (EtOH) λ_{max} 243 nm (ϵ 7760); mass spectrum *m/e* (rel intensity) 294 (M^+, 52), 266 (30), 265 (100), 224 (34), 189 (16), 165 (33), 135 (35), 104 (8), 77 (16); IRI 2605.

Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.41; H, 4.81; N, 9.53; S, 10.90. Found: C, 69.28; H, 4.92; N, 9.48; S, 10.50.

Elution of a second fraction with benzene gave **5** which was recrystallized from chloroform–ethyl acetate to give 11.01 g (33.2%) of white crystals: mp 180–182 °C; NBP negative; IR 1710, 1300, 1210, 1120, 1068, 1008, 970, 945, 930, 918, 906, 870, 850, 770, 765, 740, 718, 700 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (m, 4, CH_2CH_2), 7.30 (m, 10, aromatic); UV (EtOH) λ_{max} 263 nm (ϵ 6990), 241 (19 135); mass spectrum *m/e* (rel intensity) 294 (M^+, 100), 266 (36), 265 (33), 224 (15), 198 (16), 165 (44), 163 (32), 135 (62), 91 (10), 86 (17), 77 (23); IRI 2870.

Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.41; H, 4.81; N, 9.53; S, 10.90. Found: C, 69.63; H, 4.92; N, 9.51; S, 10.59.

When **5** was recrystallized from benzene, a complex containing 1 mol of benzene was formed, mp 105–108 °C.

Anal. Calcd for $C_{23}H_{20}N_2OS$: C, 74.16; H, 5.42; N, 7.52; S, 8.60. Found: C, 74.34; H, 5.41; N, 7.58; S, 8.90.

Method B. A crude mixture of **4** and **5** was dissolved in benzene and the solution cooled overnight. Compound **5** (as the benzene complex) separated and was collected by filtration. The filtrate was reduced by 30–50% and refrigerated and a second crop of **5** was collected (total yield of **5**, 42%). The resulting filtrate was evaporated to dryness and the residue dissolved in ethyl acetate. After standing overnight at room temperature, a 9.3% yield of **4** was produced.

3-(2-Mercaptoethyl)-5,5-diphenylhydantoin (7a). Method A. Compound **4** (0.50 g, 1.7 mmol) and 20% HCl (5 mL) in absolute ethanol (15 mL) were refluxed for 4 h. Removal of solvent in vacuo produced a white solid which was recrystallized from 95% ethanol to give 0.32 g (60%) of white needles, mp 145–149 °C, solidify and remelt 152–154 °C (lit.[12] 229–230 °C). Recrystallization from chloroform gave mp 152.5–154 °C; IR (EtOH recrystallization) 3200, 1760, 1700, 1138, 1110, 1030, 1000, 930, 910, 890, 875, 788, 757, 720, 696 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, 1, SH), 2.80 (m, 2, CH_2S), 3.75 (t, 2, CH_2N), 7.00 (s, 1 NH), 7.35 (s, 10, aromatic); mass spectrum *m/e* (rel intensity) 312 (M^+, 14), 253 (100), 209 (7), 208 (17), 181 (13), 180 (58), 165 (19), 104 (45), 91 (15), 77 (32); IRI 2590.

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.17; N, 8.97; S, 10.26. Found: C, 65.83; H, 5.36; N, 9.10; S, 10.02.

Method B. A solution of **7d** (4.35 g, 0.01 mol) and NaOH (1.00 g, 0.025 mol) in water (30 mL) was refluxed for 2 h. After cooling to room temperature, the solution was acidified with 10% sulfuric acid. The resulting solid was filtered, washed with water until the filtrates were neutral, and recrystallized from 95% ethanol to give 2.10 g (67%) of a white solid, mp 144–145 °C. The IR, NMR, mass spectral, and GC properties were identical with those of the material produced by method A.

3-Ethyl-5,5-diphenylhydantoin (7b). Method A. Raney nickel W-7 (prepared from 20 g of alloy) was stirred with **7a** (1.00 g, 0.003 mol) in absolute ethanol at room temperature for 12 h. The nickel was filtered washed with 3% NaOH solution. The filtrates and washings were combined and evaporated to dryness. The residue was added to water (50 mL), the mixture acidified with concentrated HCl, and the solution extracted with ethyl acetate. The extracts were washed three times with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a solid which was recrystallized from 50% aqueous ethanol to give 0.40 g (44%) of white crystals: mp 153.5–155 °C (lit.[8,10] 156 °C); IR 3250, 1760, 1680, 1480, 1415, 1340, 1015, 1007, 855, 795, 760, 715, 695 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, 3, CH_3), 3.4 (q, 2, CH_2), 7.35 (s, 10, aromatic) 9.56 (b, 1, NH); mass spectrum *m/e* (rel intensity) 280 (M^+, 42), 251 (19), 209 (M^+ – C_2H_5NCO, 51), 208 (23), 203 (M^+ – Ph, 15), 181 (27), 180 (100), 165 (18), 104 (48), 77 (33); IRI 2235.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.58; H, 5.61; N, 9.86.

Method B. Compound **7b**, prepared from DPH and ethyl iodide by the method of Hoffman,[8] gave white crystals, mp 156 °C (lit.[8] 156 °C). The IR, NMR, and mass spectrum for this material were the same as those produced from method A.

3-(2-Bromoethyl)-5,5-diphenylhydantoin (7c). A solution of DPH (25.2 g, 0.10 mol) and KOH (5.6 g, 0.10 mol) in 95% ethanol (300 mL) was added dropwise over a 6-h period to a stirred, refluxing solution of 1,2-dibromoethane (100 g, 0.53 mol) in 95% ethanol (200 mL). After reflux for an additional 9 h, the solvent was removed and the residue dissolved in ethyl acetate. This solution was washed first with 5% aqueous NaOH solution, then water, and finally was dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave a white solid which was contaminated with a small amount of dimeric (1,2-disubstituted ethane) product. Two recrystallizations from acetone gave 22.3 g (62%) of white crystals: mp 155.5–156 °C (lit.[13,17] 156–157 °C); IR 3200–3050, 1760, 1700, 1310, 1260, 1230, 1190, 1130, 1100, 1030, 1000, 985, 935, 890, 830, 775, 758, 700 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (m, 4, CH_2CH_2), 7.40 (s, 10, aromatic), 7.6 (b, 1, NH); mass spectrum *m/e* (rel intensity) 360 (M + 2, 20), 358 (M^+, 20), 329 (10), 209 (M – BrC_2H_4NCO, 69), 208 (19), 181 (25), 180 (100), 165 (20), 104 (53), 91 (21), 77 (37); IRI 2565.

Anal. Calcd for $C_{17}H_{15}N_2O_2Br$: C, 56.83; H, 4.22; N, 7.80; Br, 22.24. Found: C, 57.18, H, 4.30; N, 7.93; Br, 22.09.

3-[2-(Amidinothio)ethyl]-5,5-diphenylhydantoin Hydrobromide (7d). A solution of **7c** (3.59 g, 0.01 mol), thiourea (0.76 g, 0.01 mol), and 95% ethanol (10 mL) was heated to reflux. After 1 h the solution almost completely solidified. After heating for a total of 2 h, the resulting solid was filtered and recrystallized from 95% ethanol to give 2.83 g (65%) of product: mp 280–280.5 °C (lit.[12] mp 260–262 °C); IR 3400–3150, 1755, 1700, 1640, 1110, 970, 880, 760, 740, 728, 695 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}N_4BrO_2S$: C, 49.65; H, 4.41; N, 12.87; Br, 18.35; S, 7.36. Found: C, 49.18; H, 4.69; N, 12.81; Br. 18.24; S, 7.87.

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Registry No.—**1d**, 62476-40-8; **1e**, 62506-10-9; **2a**, 62476-41-9; **2b**, 54508-20-2; **3**, 21083-47-6; **4**, 42748-70-9; **5**, 62476-42-0; **7a**, 42748-71-0; **7b**, 39588-47-1; **7c**, 13272-33-8; **7d**, 42748-72-1; 1-bromo-2-chloroethane, 107-04-0; DPH, 57-41-0; 1,2-dibromoethane, 106-93-4; thiourea, 62-56-6.

References and Notes

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in the range 190–240 °C or temperature programmed from 200 to 280 °C at 4 °C/min. Isothermal retention indices (IRI)[18,19] were determined in the temperature range 180–240 °C. Electron impact mass spectra were obtained on a Du Pont 21-492B gas chromatograph–mass spectrometer system consisting of Varian 2740 gas chromatograph interfaced to the mass spectrometer via a single stage glass jet separator. All spectral data reported here were acquired from samples of the pure compound by direct probe insertion into the ion source. When mixtures did occur, the components were separated on a 1.83 m × 2 mm i.d. glass column packed with 3% Se-30 on 100/120 mesh Gas Chrom Q and operated under the conditions described above. Mass spectra were recorded for all peaks of interest. Exact masses and most probable elemental compositions of the major ions in **4**, **1d**, and levamisole (**1c**) were obtained from high-resolution mass spectra run on a JEOL JMS-01SG-2 mass spectrometer. Compounds were tested for alkylating ability with *p*-nitrobenzylpyridine (NBP) as previously described.[2]

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Chemistry of Cyclobutene-1,2-dicarbonitrile. 2. Cycloadducts

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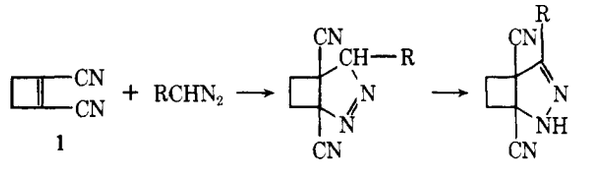
Cyclobutene-1,2-dicarbonitrile (1) undergoes [3 + 2] cycloaddition with diazomethane to give 2,3-diazabicyclo[3.2.0]hept-2-ene-1,5-dicarbonitrile (**2**) and with ethyl diazoacetate to give ethyl 3,4-diazabicyclo[3.2.0]hept-2-ene-2-carboxylate (**4**). Upon irradiation, 1 dimerizes to *anti*-tricyclo[4.2.0.0^{2,5}]octane-1,2,5,6-tetracarbonitrile (**7**). The preparation of acid, amide, and ester analogues of **7**, by dimerization and solvolytic processes, is described. In the presence of acrylonitrile, α-chloroacrylonitrile, 1-cyanovinyl acetate, dimethyl maleate, and furan, irradiation of 1 yields mixtures of **7** and bicyclo[2.2.0]hexane-1,2,4-tricarbonitrile (**15**), 2-chlorobicyclo[2.2.0]hexane-1,2,4-tricarbonitrile (**16**), 2-(1,2,4-tricyanobicyclo[2.2.0]hexyl) acetate (**17**), dimethyl 1,4-dicyanobicyclo[2.2.0]hexane-2,3-dicarboxylate (**18**), and 3-oxatricyclo[5.2.0.0^{2,6}]non-4-ene-1,7-dicarbonitrile (**19**), respectively. The adduct **18** undergoes a thermal stereospecific cycloreversion to give dimethyl 3,6-dicyano-2,6-octadiene-1,8-dioate (**21**). Spectral data suggesting similar cycloreversions for the other related adducts are noted.

The strain present in the cyclobutene ring system allows cycloaddition processes to occur with cyclobutene-1,2-dicarbonitrile[1] (**1**) at conditions under which analogous cyclohexenes and cyclooctenes react only sluggishly or not at all.[2] Since results concerning the normal Diels–Alder reaction of **1** with conjugated dienes have been reported recently,[1] this paper will describe only our observations regarding the reactions of cyclobutene **1** with diazoalkanes to give [3 + 2] cycloadducts and with activated olefins to give [2 + 2] cycloadducts, the latter being a photoinitiated process.

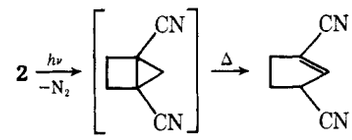
The reaction of diazomethane with **1** occurred readily at room temperature to give the known[3] adduct 2,3-diazabicyclo[3.2.0]hept-2-ene-1,5-dicarbonitrile (**2**). A similar reaction with ethyl diazoacetate gave ethyl 3,4-diaza-1,5-dicyanobicyclo[3.2.0]hept-2-ene-2-carboxylate (**4**), arising by a [1,3]



1 **2**, R = H; **3**, R = $CO_2C_2H_5$ **4**, R = $CO_2C_2H_5$

prototropic rearrangement of the initially formed adduct **3**. The evidence for the rearrangement to **4** included the presence of strong absorption bands for the NH and C=N groups, but none for the –N=N– group, in the infrared region (at ca. 3280, 1700, and 1560 cm^{-1}, respectively), and the lack of a resonance for the hydrogen α to an azo function (ca. δ 5.5) in the ^{1}H NMR spectrum. Energetically, the rearranged form **4** may be favored over **3** because of the conjugation introduced between the carbonyl and the imino groups.

Because of the favored hydrazone structure, **4** was photolytically and (relatively) thermally stable; at 175 °C for 24 h, there was no evolution of nitrogen, although only 20% of **4** was recovered. On the other hand, the adduct **2** was photolabile in the presence of a photosensitizer (acetone), undergoing a

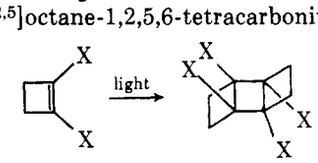


5 **6**

slow evolution of nitrogen. The major organic product isolated, by preparative VPC, was cyclopentene-1,3-dicarbonitrile (**6**), probably arising via thermolysis of initially formed bicyclo[2.1.0]pentane-1,3-dicarbonitrile (**5**). Although no comparisons were made, the dinitrile adduct **2** is apparently appreciably more stable than the related ester dimethyl 2,3-diazabicyclo[3.2.0]hept-2-ene-1,5-dicarboxylate,[3,4] since the latter ester reportedly[3] undergoes facile and rapid loss of nitrogen in the absence of a sensitizer, conditions under which the dinitrile **2** was remarkably stable (a 70% recovery after 72 h irradiation).

The cyclobutene **1** is a strong absorber of light at ca. 234 nm (ϵ_{max} 12 200 in acetonitrile).[2,5] This, coupled with the strain present in the cyclobutene ring system,[6] allows photoinitiated [2 + 2] cycloaddition of **1** with suitable olefins to occur.

Cyclobutene **1** undergoes self-dimerization[8] to yield *anti*-tricyclo[4.2.0.0^{2,5}]octane-1,2,5,6-tetracarbonitrile (**7**). We



1, X = CN; **8**, X = CO_2CH_3; **9**, X = CO_2H; **10**, X = $CONH_2$
7, X = CN; **11**, X = CO_2CH_3; **12**, X = CO_2H; **13**, X = $CONH_2$

studied this reaction, using both sunlight and a medium-pressure (unfiltered) mercury vapor lamp as light sources. In sunlight (in a quartz apparatus), the reaction was extremely slow, with a 20% conversion after several weeks; this process was not subject to photosensitization, since comparable con-