Quinazolines and 1,4-Benzodiazepines. LIII.[1] Ring Expansion of Some Chloromethylpyrazolo[1,5-c]quinazolines and a 1,2,4-Benzothiadiazine 1,1-Dioxide

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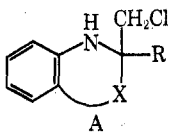
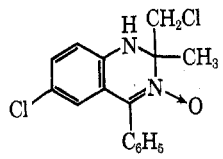
Reaction of the pyrazoloquinazoline **8** with potassium *tert*-butoxide gives the aziridine **10** which on treatment with base and methanol is transformed into the 1,4-benzodiazepine **11**. The dichloromethyl analog **7** undergoes a similar reaction to form **9**. The chloromethylbenzothiadiazine 1,1-dioxide **16** undergoes ring expansion in a different manner to form the 1,2,5-benzothiadiazepine **14**. This divergence is explained by the existence of two different types of anions.

Treatment of chloromethyl dihydro heterocycles of the general type A with base frequently gives rearrangement reactions in which the heterocyclic ring is expanded by incorporation into the ring of a methylene group derived from the chloromethyl group. However, whether this methylene group becomes attached to the nitrogen or to group X in A is not completely predictable. Specifically, reaction of the quinazoline **1** with



A

potassium *tert*-butoxide in tetrahydrofuran[2] gives mainly **2** while, under approximately the same conditions, reaction of the quinazolone **3** gives mainly **4**.[3] In the products **2** and **4**, the methyl group clearly tags the carbon atom which was in the 2 position of the starting material.



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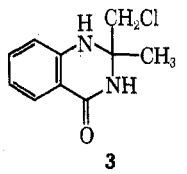

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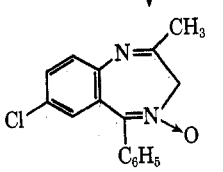
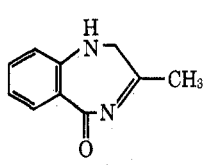
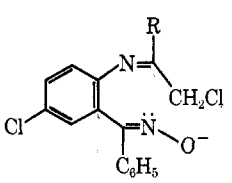


2



4

Previously, we discussed[2] both the effect of the solvent and the effect of the replacement of the methyl group by other groups, on the type of product obtained. We postulated two anions, *e.g.*, C, in which the charge is relatively concentrated on N-1, and B, in which the heterocyclic ring has been disrupted. Products related to **4** would be formed from an anion of type C, whereas products related to **2** would result from the cyclization of anion B. Products which can be considered to be derived from anion C are favored if R is a group which is less electron releasing than methyl, or if nonpolar solvents are used.[2]



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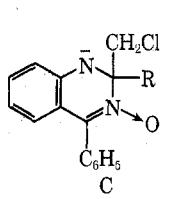


C

It appears from the structure of the products **2** and **4** that the end product is usually derived from the more stable of the anions analogous to B and C. That is, if the conjugate acid of B has the lower pK_a, products corresponding to **2** would be favored. However, if the tautomeric conjugate acid C has a lower pK_a, the anion analogous to C should predominate and products of type **4** would result.

Here we describe two additional heterocyclic systems which illustrate this hypothesis. The first system is exemplified by the pyrazolo[1,3-*c*]quinazolines **7** and **8** (Chart I). These compounds are readily prepared from the hydroxyquinoline **5**[4] and hydrazine[5] followed by condensation of the intermediate **6**[6] with the appropriate chloro ketone. Treatment of **8** with potassium *tert*-butoxide in tetrahydrofuran gave the aziridine **10**, whose structure was assigned on the basis of its nmr spectrum. Particularly, the unique appearance of two singlets at δ 1.85 and 2.73 ppm for the protons of the methylene group supports the assignment of an aziridine structure.[2] Reduction of **10** with lithium aluminum hydride disrupted the center rings to give an isopropyl derivative **12**. The structure of **12** is supported by spectral data. The nmr spectrum reveals clearly the attachment of the isopropyl chain to the aniline nitrogen. The proton of the aniline nitrogen appears as a broadened doublet (J = 7 Hz) at δ 7.8 ppm, the proton on the pyrazole nitrogen as a broad singlet at δ 12.7 ppm. In addition, the compound did not form a dye upon diazotization and coupling with β-naphthol. Treatment of **10** with sodium borohydride in methanol did not result in reduction, as expected, but led only to the methoxy derivative **11** containing a seven-membered ring as evidenced by its nmr spectrum (see Experimental Section) and hydrolysis. The same compound could also be obtained directly from **8** by the action of sodium methoxide in methanol. Hydrolysis of **11** with acid opened the seven-membered ring to give

(1) Part LII: A. Walser, G. Silverman, J. F. Blount, R. I. Fryer, and L. H. Sternbach, *J. Org. Chem.*, **36**, 1465 (1971).

(2) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Amer. Chem., Soc.*, **89**, 332 (1967).

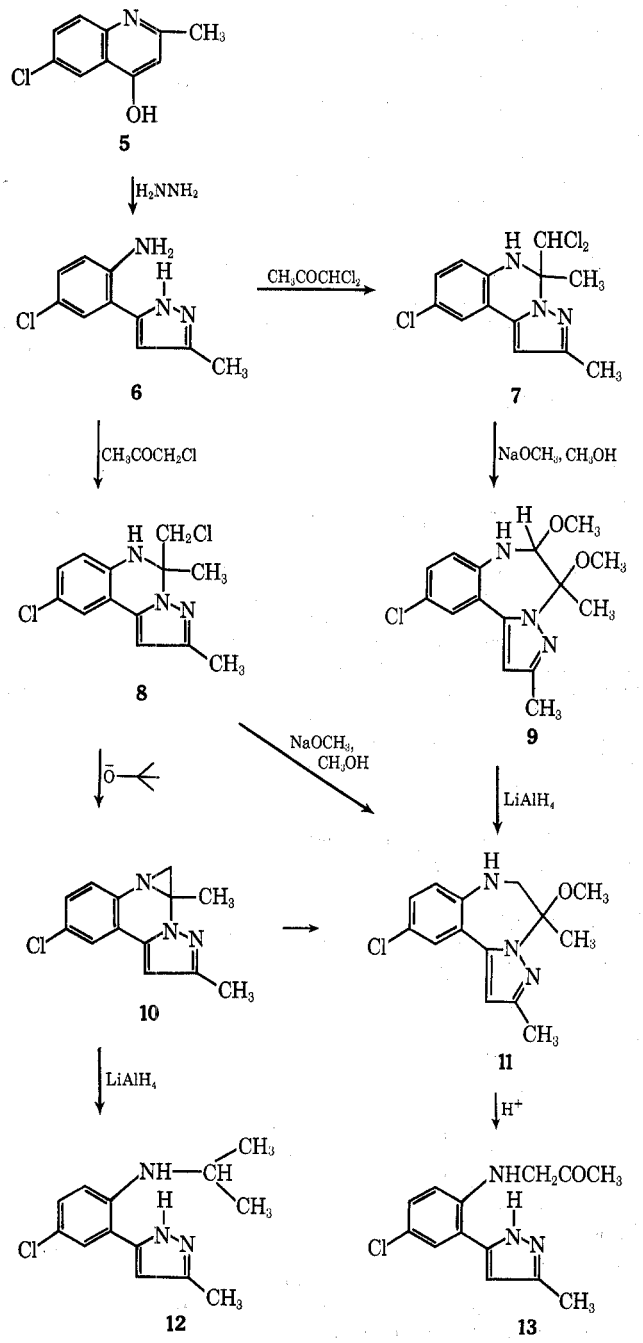
(3) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 777 (1971).

(4) C. R. Hauser and G. A. Reynolds, *J. Amer. Chem. Soc.*, **70**, 2402 (1948).

(5) G. Alberti, *Gazz. Chim. Ital.*, **87**, 772 (1957).

(6) G. DeStevens, A. Halamandaris, M. Bernier, and H. M. Blatter, *J. Org. Chem.*, **28**, 1336 (1963).

CHART I



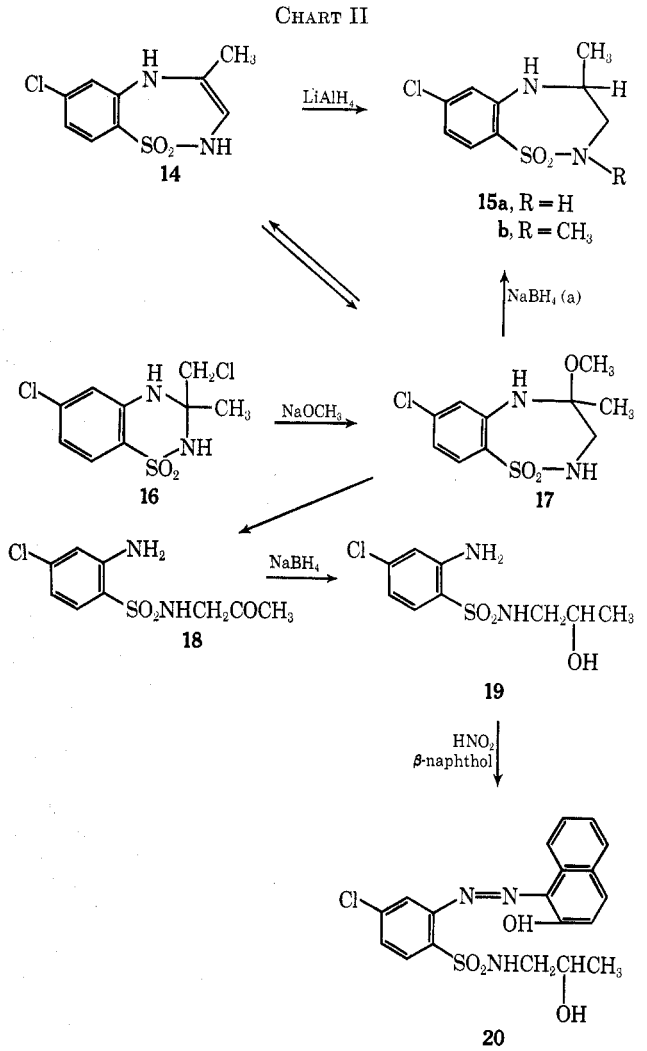
the acetonyl derivative **13**. The attachment of the acetonyl group to the anilino nitrogen was again evident from the nmr spectrum. The proton of the pyrazole nitrogen appears at δ 12.72 ppm, the proton of the aniline nitrogen as a triplet (J = 5 Hz) at δ 8.27. Similarly, reaction of the dichloromethyl derivative **7** with sodium methoxide in methanol gave the dimethoxy derivative **9**, again with ring expansion. Reduction of **9** with lithium aluminum hydride resulted in the formation of **11**, thus confirming the presence of the seven-membered ring.[7]

(7) The preferential reduction of the methoxy group in position 2 is in good agreement with the structures assigned to **9** and **11**. An analogous case is the lability of a similarly situated carbinolamine ether in anthramycin methyl ether described by Leimgruber and coworkers [W. Leimgruber, V. Stefanović, F. Schenker, A. Karr, and J. Berger, *J. Amer. Chem. Soc.*, **87**, 5791 (1965); W. Leimgruber, A. D. Batcho, and F. Schenker, *ibid.*, **87**, 5703 (1965)]. The factor responsible for the preferential elimination of the 2-methoxy group is probably the presence of an NH group, since in compound **22** of ref 3 where two methoxy groups are adjacent to an NH group both are removed with lithium aluminum hydride.

In compounds **7** and **8** it is, therefore, the nitrogen in position 1 which is alkylated by the chloromethyl or dichloromethyl group, respectively, rather than the one at position 3 of the quinazoline ring. This suggests that the intermediates are of the C type.

The second system is exemplified by the 2*H*-1,2,4-benzothiadiazine 1,1-dioxide **16** (Chart II). The

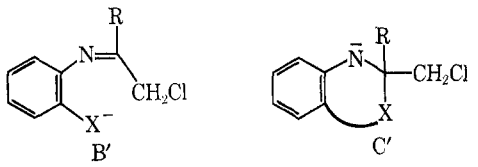
CHART II



starting material **16** was prepared from 2-amino-4-chlorobenzenesulfonamide and chloroacetone with azeotropic removal of the water formed in the reaction. Treatment of this compound with sodium methoxide in methanol gave **17**, which on heating with benzene yielded **14**. Compound **14** could be reconverted into **17** by repeated recrystallization from methanol. These compounds were characterized by their nmr spectra and interrelated by reduction to **15a**. Hydrolysis of **17** gave the open acetonyl derivative **18**. Reduction of **18** with lithium aluminum hydride gave **19**, which was diazotized and coupled with β-naphthol to give the dye **20**. This reaction demonstrates the presence of a primary aromatic amino group in **18** and consequently the position of the methyl group in **17**. Therefore in this compound it is not the anilino nitrogen but the sulfonamido nitrogen which is alkylated by the chloromethyl group.

Discussion

The divergent structures of the products obtained in the two systems discussed above can again be explained on the basis of the existence of two anions, which are ring–chain tautomers, represented in general form by anions B′ and C′. The pyrazolo compounds shown in Chart I are formed from anion C′ (X = 3-methyl-5-pyrazolyl) and the ring-expansion products of the type obtained in the sulfonamide series in Chart II are de-



rived from anion B′ (X = $-SO_2NH_2$). However, we cannot exclude the possibility that the sulfonamides do not fit into this general scheme, since the formation of the anion C′ might not be the first step in this case.[8]

Considerable additional work will be needed in order to fully elucidate the effects of the various factors which might influence the course of this ring enlargement.

Experimental Section[9]

5-(2-Amino-5-chlorophenyl)-3-methylpyrazole (6).—A mixture of 50 g of 6-chloro-4-hydroxy-2-methylquinoline, 27.1 g of hydrazine dihydrochloride, 66 ml of hydrazine, and 150 ml of ethylene glycol was heated in an oil bath at 200° for 3 hr. The reaction mixture was then cooled and diluted with 300 ml of water to precipitate 40.5 g of product, mp 123–127°. Recrystallization from ethyl acetate–hexane gave colorless needles: mp 134–136°; uv max 217 mμ (ε 25,000), 230 (24,000), 259 (10,000), and 325 (5000).

Anal. Calcd for $C_{10}H_{10}ClN_3$: C, 57.84; H, 4.85. Found: C, 57.73; H, 4.87.

9-Chloro-5-dichloromethyl-5,6-dihydro-2,5-dimethylpyrazolo[1,5-*c*]quinazoline (7).—A mixture of 70.6 g of 5-(2-amino-5-chlorophenyl)-3-methylpyrazole, 70.6 ml of 1,1-dichloro-2-propanone, and 1.7 l. of benzene was heated under reflux for 18 hr. The water which separated was collected in a Dean–Stark trap. The reaction mixture was then cooled, treated with charcoal, filtered, and concentrated to dryness *in vacuo*. The residue was crystallized from petroleum ether to give 94.3 g of crude product, mp 112–119°. Recrystallization from hexane gave colorless needles: mp 120–123°; uv max 230 mμ (ε 26,000), 243 (26,000), 271 (7600), and 343 (5700).

Anal. Calcd for $C_{13}H_{12}Cl_3N_3$: C, 49.31; H, 3.82. Found: C, 48.93; H, 3.80.

9-Chloro-5-chloromethyl-5,6-dihydro-2,5-dimethylpyrazolo[1,5-*c*]quinazoline (8).—A mixture of 20.45 g of **6**, 20.45 ml of chloroacetone, and 500 ml of benzene was heated under reflux for 5 hr. The water which separated was collected in a Dean–Stark trap. The reaction mixture was then cooled and the benzene layer decanted from the tars and concentrated *in vacuo*. Crystallization of the residue from petroleum ether gave 22.9 g of crude product, mp 111–115°. Recrystallization from hexane gave colorless prisms: mp 121–124°; uv max 230 mμ (ε 24,000), 243 (23,000), 273 (7500), and 345 (5000).

Anal. Calcd for $C_{13}H_{13}Cl_2N_3$: C, 55.35; H, 4.64. Found: C, 55.06; H, 4.76.

10-Chloro-6,7-dihydro-5,6-dimethoxy-2,5-dimethyl-5*H*-pyrazolo[1,5-*d*][1,4]benzodiazepine (9).—To a solution of 6.33 g of **7** dissolved in 100 ml of methanol cooled in an ice bath was added 2.16 g of sodium methoxide. The reaction mixture was then stirred overnight at room temperature. The precipitated solids were filtered and the filtrate was concentrated *in vacuo*. The residue was crystallized from hexane to give 5.3 g of crude product, mp 130–140°. Recrystallization from ether–hexane gave 4.1 g of white needles, mp 135–140°. Further recrystallization from ether–hexane gave colorless prisms: mp 144–147°; ir 3450 cm^{-1}; uv max 228 mμ (ε 22,000), 233 (21,000), 265 (13,000), and 335 (6800); nmr (DMSO) δ 2.00 (s, 3, $-CH_3$), 2.25 (s, 3, $-CH_3$), 2.91 (s, 3, $-OCH_3$), 3.20 (2, 3, $-OCH_3$), 4.59 ppm (d, 1, J = 6 Hz, –NHCH), 6.63 (s, 1, C_1 H), 6.95 (d, 1, J = 9 Hz, C_8 H), 7.2 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2 Hz, C_9 H), 7.63 (d, 1, J = 2 Hz, C_{11} H), 7.66 (d, 1, J = 6 Hz, NH).

Anal. Calcd for $C_{15}H_{18}ClN_3O_2$: C, 58.53; H, 5.89. Found: C, 58.43; H, 5.86.

10-Chloro-5,6-dihydro-2,5-dimethylazirino[α]pyrazolo[1,5-*c*]quinazoline (10).—To a solution of 12 g of **8** in 100 ml of tetrahydrofuran was added 1.7 g of potassium *tert*-butoxide and the mixture was stirred at room temperature for 3 hr. It was then filtered through Celite and concentrated *in vacuo*. The residue was crystallized from petroleum ether to give 2.3 g of crude product, mp 109–111°. Recrystallization from petroleum ether gave colorless prisms: mp 107–109°; uv max 235 mμ (ε 25,000), 270 (sh) (11,000), 320 (2500), and 343 (2400); nmr (DMSO) δ 1.85 (s, 4, CCH_3 and NCH), 2.25 (s, 3, $=CCH_3$), 2.73 (s, 1, NCH), 6.61 (s, 1), 7.3 (m, 2), and 7.7 ppm (m, 1).

Anal. Calcd for $C_{13}H_{12}ClN_3$: C, 63.54; H, 4.92. Found: C, 63.34; H, 5.19.

10-Chloro-6,7-dihydro-5-methoxy-2,5-dimethyl-5*H*-pyrazolo-[1,5-*d*][1,4]benzodiazepine (11). A. From 8.—To a solution of 28.2 g of **8** in 500 ml of methanol was added 21.6 g of sodium methoxide and the mixture was stirred at room temperature overnight. It was then neutralized with methanolic hydrogen chloride, filtered, and concentrated to dryness *in vacuo*. The residue was crystallized from ether–hexane to give 30.3 g of crude product, mp 127–132°. Recrystallization from 2-propanol–water and then from cyclohexane gave colorless prisms: mp 128–131°; ir 3450 cm^{-1}; uv max 230 (ε 19,000), 245 (19,500), 270 (11,000) and 340 (5600); nmr (DMSO) δ 1.82 (s, 3, $-CH_3$), 2.21 (s, 3, $-CCH_3$), 3.02 (s, 3, $-OCH_3$), 3.41 (m, → AB on exchange, 2, $-NHCH_2$), 6.6 (m, 2, C_1 H and NH), 6.87 (d, 1, J = 9 Hz, C_8 H), 7.13 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2 Hz, C_9 H), 7.68 (d, 1, J = 2 Hz, C_{11} H).

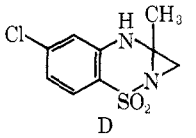
Anal. Calcd for $C_{14}H_{16}ClN_3O$: C, 60.54; H, 5.81. Found: C, 60.35; H, 5.81.

B. From 10.—To a solution of 4 g of **10** in 175 ml of methanol cooled in an ice bath was added 4 g of sodium borohydride and the reaction mixture was stored in a refrigerator for 2 days. It was then neutralized with saturated sodium bicarbonate solution, concentrated *in vacuo*, and diluted with water. The mixture was extracted with methylene chloride in three portions. The methylene chloride extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from hexane to give 3.5 g of crude **11**, mp 100–120°. Recrystallization from 2-propanol gave white prisms, mp 124–128°. The infrared spectrum was superimposable with that obtained from material described in the previous experiment.

C. From 9.—A solution of 3.1 g (10 mmol) of **9** in 30 ml of dry tetrahydrofuran was added to a solution of 0.84 g (22 mmol) of lithium aluminum hydride in 270 ml of tetrahydrofuran, and the mixture was stirred and heated under reflux for 3 hr. The reaction mixture was cooled, treated with ethyl acetate and water to destroy excess lithium aluminum hydride, and extracted with methylene chloride in four portions. The extracts were dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was crystallized from hexane to give 1 g of **11**, mp 125–130°, identified by mixture melting point and infrared spectrum.

5-[2-(Isopropylamino)-5-chlorophenyl]-3-methylpyrazole (12).—To a suspension of 1 g of lithium aluminum hydride in 100 ml of ether was added a solution of 4.9 g of **10** in 100 ml of ether. The reaction mixture was then stirred for 24 hr at room temperature and cooled on ice, and the excess lithium aluminum hydride

(8) As suggested by the referees, the intermediacy of a compound of type D in this sequence of reactions leading to **17** cannot be excluded. In that case the cyclic sulfonamido nitrogen would undergo alkylation.



D

(9) Melting points were determined on a Thomas–Hoover capillary melting point apparatus. Nmr spectra were obtained on a Varian A-60 instrument. Petroleum ether refers to a fraction of bp 40–60°. Alumina refers to Woelm grade I. The ir spectra were determined in chloroform unless otherwise specified. The ultraviolet spectra were taken in 2-propanol.

was decomposed by addition of 30 ml of ethyl acetate followed by 50 ml of 10% sodium bicarbonate solution. The reaction mixture was then filtered through Celite and separated, and the organic phase was dried over sodium sulfate. It was then concentrated *in vacuo* and the residue was crystallized from hexane to give 4 g of crude product, mp 125–133°. Recrystallization from ethanol–water gave colorless needles: mp 131–135°; ir 3450 cm^{-1}; uv max 225 mμ (ε 19,400), 235 (21,000) 270 (9500), and 340 (4500); nmr ($CDCl_3$) δ 1.15 [d, 6, J = 6 Hz, $-CH(CH_3)_2$], 2.02 (s, 3, $-CH_3$), and 3.6 ppm [m, 1, $-CH(CH_3)_2$], 6.54 (s, 1, C_4 H), 6.67 (d, 1, J = 9 Hz, C_3 H), 7.1 (q, 1, J_{AB} = 9, J_{AX} = 2 Hz, C_4, H), 7.51 (d, 1, J = 2 Hz, C_6, H), 7.8 (d, 1, J = 7 Hz, NHCH), 12.7 (broad s, 1, NH pyrazole).

Anal. Calcd for $C_{13}H_{16}ClN_3$: C, 62.51; H, 6.37. Found: C, 62.63; H, 6.45.

5-[5-Chloro-2-(2-oxopropylamino)phenyl]-3-methylpyrazole (13).—A mixture of 4 g of **11** and 80 ml of hydrochloric acid was heated on the steam bath for 5 min. The reaction mixture was then neutralized with saturated sodium bicarbonate solution and the precipitated solid was collected. The aqueous phase was extracted with methylene chloride in four portions. The methylene chloride extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate to give 1.8 g of crude product, mp 175–178°. Recrystallization from benzene gave white needles: mp 175–177°; ir (KBr) 3270 and 1710 cm^{-1}; uv max 220 mμ (ε 23,000), 233 (24,000), 263 (13,000), and 335 (5500); nmr (DMSO) 2.17 (s, 3, CH_3), 2.32 (s, 3, CH_3), 4.16 (d, 2, J = 5 Hz, $NHCH_2$–), 6.45 (s, 1, C_4 H), 6.48 (d, 1, J = 9 Hz, C_3, H) 7.08 (q, 1, J_{AB} = 9 Hz, J_{AX} = 2 Hz, C_4, H), 7.48 (d, 1, J = 2 Hz, C_6, H), 8.27 (t, 1, J = 5 Hz, $NHCH_2$), 12.73 (broad s, 1, NH pyrazole).

Anal. Calcd for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35. Found: C, 59.53; H, 5.27.

7-Chloro-2,5-dihydro-4-methyl-1,2,5-benzothiadiazepine 1,1-Dioxide (14).—A solution of 5.6 g (0.02 mol) of **17** in a mixture of 20 ml of tetrahydrofuran and 75 ml of benzene was boiled for 30 min and then concentrated to one-third volume. The hot solution was diluted with an equal volume of hexane and chilled on ice; the solids were collected to give 4.5 g (92% yield) of the crude product, mp 165–167°. Recrystallization from tetrahydrofuran–hexane gave colorless needles: mp 175–178°; uv max 220 mμ (ε 19,500) and 285 (6100); nmr (DMSO) δ 1.83 (s, 3, $-CH_3$), 4.96 (s, 1 =CH), 8.17 (s, 1, NH), and 8.54 ppm (s, 1, NH).

Anal. Calcd for $C_9H_9ClN_2O_2S$: C, 44.17; H, 3.71. Found: C, 44.30; H, 4.31.

Five recrystallizations of 1 g of **14** from methanol gave 0.1 g of **17**, mp 133–136°.

7-Chloro-2,3,4,5-tetrahydro-4-methyl-1,2,5-benzothiadiazepine 1,1-Dioxide (15a). A. By Reduction with Lithium Aluminum Hydride of 14.—To a suspension of 1.5 g (40 mmol) of lithium aluminum hydride in 150 ml of dry ether was added 4.9 g (0.02 mol) of **14**, and the mixture was stirred and heated under reflux for 2.5 hr. It was then cooled and the excess lithium aluminum hydride was decomposed by the addition of ethyl acetate and water. The reaction mixture was then filtered through Celite and the filter was washed with tetrahydrofuran. The aqueous phase was separated and extracted with ether. The combined organic extracts were dried over sodium sulfate and concentrated to dryness *in vacuo* to give 2.5 g of crude product, mp 190–195° dec. Recrystallization from 2-propanol gave colorless prisms: mp 221–225° dec; uv max 220 mμ (ε 31,000), 257 (8400), and 309 (2700).

Anal. Calcd for $C_9H_{11}ClN_2O_2S$: C, 43.81; H, 4.49. Found: C, 43.82; H, 4.41.

B. By Reduction of 17 with Sodium Borohydride.—To a solution of 50 g of **17** in 1 l. of dry 1,2-dimethoxyethane was added 10 g of sodium borohydride and the mixture was stirred under reflux for 18 hr. The reaction mixture was then cooled and the excess borohydride was decomposed with acetic acid and water. It was then diluted with water and extracted with methylene chloride in four portions. The organic extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from hexane to give 33.5 g (67%) of crude product, mp 208–221° dec.

7-Chloro-2,3,4,5-tetrahydro-2,4-dimethyl-1,2,5-benzothiadiazepine 1,1-Dioxide (15b).—A solution of 5 g (20 mmol) of **15a** in 250 ml of 1,2-dimethoxyethane was stirred and heated under reflux for 30 min with 1.2 g (25 mmol) of a 50% dispersion of sodium hydride in mineral oil. To the cooled reaction mixture was then added 3.5 g (25 mmol) of methyl iodide dropwise with stirring. The reaction mixture was then stirred under reflux for 1 hr, filtered, and concentrated to dryness *in vacuo*. The residue was then dissolved in tetrahydrofuran and filtered through alumina using more tetrahydrofuran to wash the alumina. The eluates were concentrated to dryness *in vacuo*, and the residue was crystallized from ether to give 3.5 g of crude product, mp 140–150°. Recrystallization from 2-propanol gave off-white prisms: mp 148–150°; ir (KBr) 3380 cm^{-1}; uv max 220 mμ (ε 29,000), 258 (8900), and 310 (3100); nmr ($CDCl_3$) δ 1.3 (d, 3, J = 6 Hz, CH_3), 2.86 (s, 3, NCH_3), and 4.28 ppm (s, 1, NH).

Anal. Calcd for $C_{10}H_{13}ClN_2O_2S$: C, 46.06; H, 5.03. Found: C, 45.97; H, 5.10.

6-Chloro-3-chloromethyl-3,4-dihydro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (16).—A mixture of 206.6 g (1 mol) of 2-amino-4-chlorobenzenesulfonamide, 118.5 ml (1.5 mol) of chloroacetone, 1 g of *p*-toluenesulfonic acid, and 3 l. of toluene was stirred and heated under reflux for 2.5 hr. The water which separated was collected in a Dean–Stark trap. The reaction mixture was then filtered and the insoluble material was discarded. To the filtrate was added 1 l. of hexane and after standing overnight 252.5 g (89%) of crude product, mp 160–163°, was collected. Recrystallization from ethanol–water with charcoal gave colorless prisms: mp 171–173°; uv max 216 mμ (ε 36,000), 253 (12,500), and 315 (3500).

Anal. Calcd for $C_9H_{10}Cl_2N_2O_2S$: C, 38.45; H, 3.58. Found: C, 38.25; H, 3.71.

7-Chloro-2,3,4,5-tetrahydro-4-methoxy-4-methyl-1,2,5-benzol thiadiazepine 1,1-Dioxide (17).—To a stirred solution of 28.1 g (0.1 mol) of **16** in 150 ml of methanol, prechilled to an internatemperature of 10°, was added 6.0 g (0.11 mol) of sodium methoxide. The solution was stirred at 10° for 15 min and then at room temperature overnight. The precipitated solid was filtered off and discarded. The filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from 100 ml of ether to give 14.4 g (52%) of crude **17**, mp 130–134°. Recrystallization from methanol gave colorless prisms: mp 134–137°; uv max 220 mμ (ε 36,000), 250 (8300), and 300 (2800); nmr (DMSO) δ 1.43 (s, 3, $-CCH_3$), 3.03 (s, 3, $-OCH_3$), and 3.3 ppm (m, 3, NH and CH_2).

Anal. Calcd for $C_{10}H_{13}ClN_2O_3S$: C, 43.40; H, 4.37. Found: C, 43.72; H, 4.91.

***N*-Acetonyl-2-amino-4-chlorobenzenesulfonamide (18).**—A solution of 15 g of **17** in 500 ml of tetrahydrofuran and 120 ml of water was allowed to stand for 3 days at room temperature in an open beaker while the tetrahydrofuran evaporated slowly. The solid which separated was collected and washed with water to give 11 g of crude **18**, mp 115–119°. Recrystallization from tetrahydrofuran–hexane gave colorless plates: mp 116–118°; ir (KBr) 3450, 3360, 3340, and 1730 cm^{-1}; uv max 217 mμ (ε 36,600), 250 (9200), and 315 (4500); nmr (DMSO) δ 2.07 (s, 3, $-CH_3$), 3.73 (d, 2, J = 6 Hz, $-CH_2$), and 7.86 ppm (t, 1, J = 6 Hz, –NH–).

Anal. Calcd for $C_9H_{11}ClN_2O_3S$: C, 41.15; H, 4.22. Found: C, 41.07; H, 4.38.

2-Amino-4-chloro-*N*-(2-hydroxypropyl)benzenesulfonamide (19).—To a solution of 5 g of **18** in 200 ml of methanol cooled in an ice bath was added 5 g of sodium borohydride and the mixture was stored in a refrigerator overnight. It was then diluted to 2 l. with ice, neutralized with glacial acetic acid, and extracted with methylene chloride in five portions. The organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give 5.5 g of residue, which was crystallized from ethyl acetate–petroleum ether to give 3.5 g of crude product, mp 91–97°. Recrystallization from benzene gave colorless prisms, mp 103–105°.

Anal. Calcd for $C_9H_{13}ClN_2O_3S$: C, 40.83; H, 4.95; N, 10.58. Found: C, 40.80; H, 5.22; N, 10.72.

***N*-(2-Hydroxypropyl)-4-chloro-2-(2-hydroxy-1-naphthyl)azobenzenesulfonamide (20).**—A solution of 1 g of **19** in 3 ml of concentrated HCl was diluted with 5 ml of water and treated with several drops of a solution of 1 g of sodium nitrite in 5 ml of water until the mixture gave a positive starch iodide test. This solution was then added to a solution of 0.1 g of β-naphthol in 2 ml of 10% aqueous sodium hydroxide in 5 ml of water. The orange solids which precipitated on standing were collected and recrystallized twice from ethanol to give 0.1 g of orange-red needles, mp 233–236°.

Anal. Calcd for $C_{19}H_{18}ClN_3O_4S$: C, 54.34; H, 4.32; N, 10.01; S, 7.63. Found: C, 54.46; H, 4.22; N, 9.83; S, 7.94.

Registry No.—**6**, 30855-63-1; **7**, 30855-64-2; **8**, 30855-65-3; **9**, 30855-66-4; **10**, 30855-67-5; **11**, 30855-68-6; **12**, 30855-69-7; **13**, 30855-70-0; **14**, 30855-71-1; **15a**, 30855-72-2; **15b**, 30855-73-3; **16**, 30855-74-4; **17**, 30855-75-5; **18**, 30855-76-6; **19**, 30855-77-7; **20**, 30855-78-8.

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Pyrazolotriazines from Condensation of Nitro with Amino Groups

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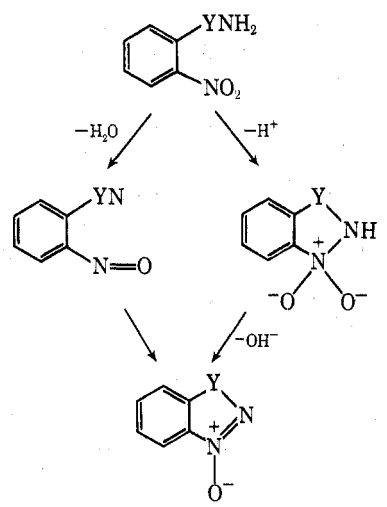
The *o*-nitrophenylhydrazones and 2,4-dinitrophenylhydrazones of α-cyanophenylacetaldehyde and its *p*-chloro and *p*-methoxy derivatives were isomerized to the corresponding 1-*o*-nitroaryl-5-aminopyrazoles. These were converted to 3-arylpyrazolo[5,1-*c*]benzo-1,2,4-triazine 5-oxides with potassium hydroxide. The expected interference if a nitroso nitrene intermediate were involved could not be detected. The 3-phenyl and 3-*p*-methoxyphenyl analogs were deoxygenated to the corresponding 3-arylpyrazolobenzotriazines by catalytic hydrogenation. 3-Phenylpyrazolo[5,1-*c*]benzo-1,2,4-triazine was also prepared by cyclization of the diazonium salt of 5-amino-1,4-diphenylpyrazole.

Various heterocyclic structures having a cyclic azoxy group can be prepared by base-catalyzed reaction of nitro and primary amino groups in the same molecule.[3] The mechanism has been assumed to be nucleophilic attack by the amino group on the nitro nitrogen, analogous to the aldol condensation,[3,4] but the assumption has never been questioned and the mechanism has never been investigated. A plausible alternative mechanism is internal oxidation of the amino group by the nitro group, with expulsion of water and formation of a nitroso nitrene as an intermediate (eq 1). Oxidation of



(1)

Y = bridge of 1 or 2 atoms

amino groups to give products that might have arisen from a nitrene has been reported,[5] and there is precedent for reaction of a nitrene with a nitroso group in the recent report that *o*-azido-*o'*-nitrosobiphenyl is converted to benzocinnoline oxide by heat.[6] The fact that this product is also formed by the base-catalyzed cyclization of *o*-nitro-*o'*-aminobiphenyl[7] is suggestive (eq 1, Y = *o*-C_6H_4).

We had in our hands a way to test whether the cyclization of nitro and amino groups to form an azoxy function involves a nitrene intermediate. The test is based on the fact that reactions that should produce 5-nitrenopyrazoles in fact produce the isomeric fragmentation products, azoacrylonitriles.[8] A 1-*o*-nitrophenyl-5-aminopyrazole, therefore, should produce some fragmentation product when exposed to cyclizing conditions, if it passes through a nitrene stage (Scheme I). This would be a significant limitation on the synthetic use of this cyclization.

A group of 1-(*o*-nitrophenyl)-5-aminopyrazoles were prepared by treating arylcyanoacetaldehydes (I) with 2-nitro- or 2,4-dinitrophenylhydrazine. When carried out in benzene without any added catalyst but with continuous removal of water, the reaction generally yielded the corresponding hydrazones II, which were readily cyclized by exposure to acid to form the isomeric 5-aminopyrazoles (Table I). The uncyclized hydrazones more or less readily assumed a red tint on long exposure in solution to air. The parent compound, α-cyanophenylacetaldehyde phenylhydrazone, eventually produced small amounts of α-phenyl-β-phenylazoacrylonitrile; deliberate oxidation with permanganate gave this product in 95.4% yield.

The 1-(*o*-nitrophenyl)-5-aminopyrazoles were warmed with potassium hydroxide in aqueous pyridine and were thereby converted to orange-red, crystalline products. No infrared absorption could be detected in the region for C≡N stretching, although their color while somewhat light was not inconsistent with the highly conjugated arylazoacrylonitrile structure. These substances, which were obtained pure in very high yields

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