# Synthesis of Holomycin and Derivatives[1]

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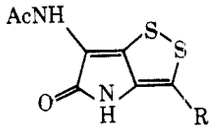
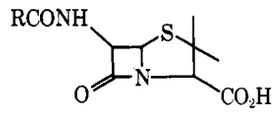
Holomycin, 6-acetamido-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (**1a**), and the 3-carboxylated derivative (**1b**) have been prepared by a ten-stage synthesis designed around two key reactions. Cyclization of 5-methoxalylamino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-1,3-dithiin (**6**) by base gave 7-hydroxy-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (**7**) containing the required pyrrolinone ring. A contraction of the dithioketal 7-*p*-methoxybenzylamino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (**9**) afforded the cyclic enol disulfide 6-*p*-methoxybenzylamino-3-methoxycarbonyl-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (**10a**). Further elaboration led to holomycin (**1a**) and the carboxy derivative **1b**.

The structure of the antibiotic holomycin (**1a**)[2] bears a formal resemblance to that of the penicillins **2**. Both substances are bicyclic lactams incorporating a sulfur heteroatom and have an acylamine side chain. We have devised a synthesis



**1a**, R = H, holomycin
b, R = $CO_2H$



**2**, penicillins

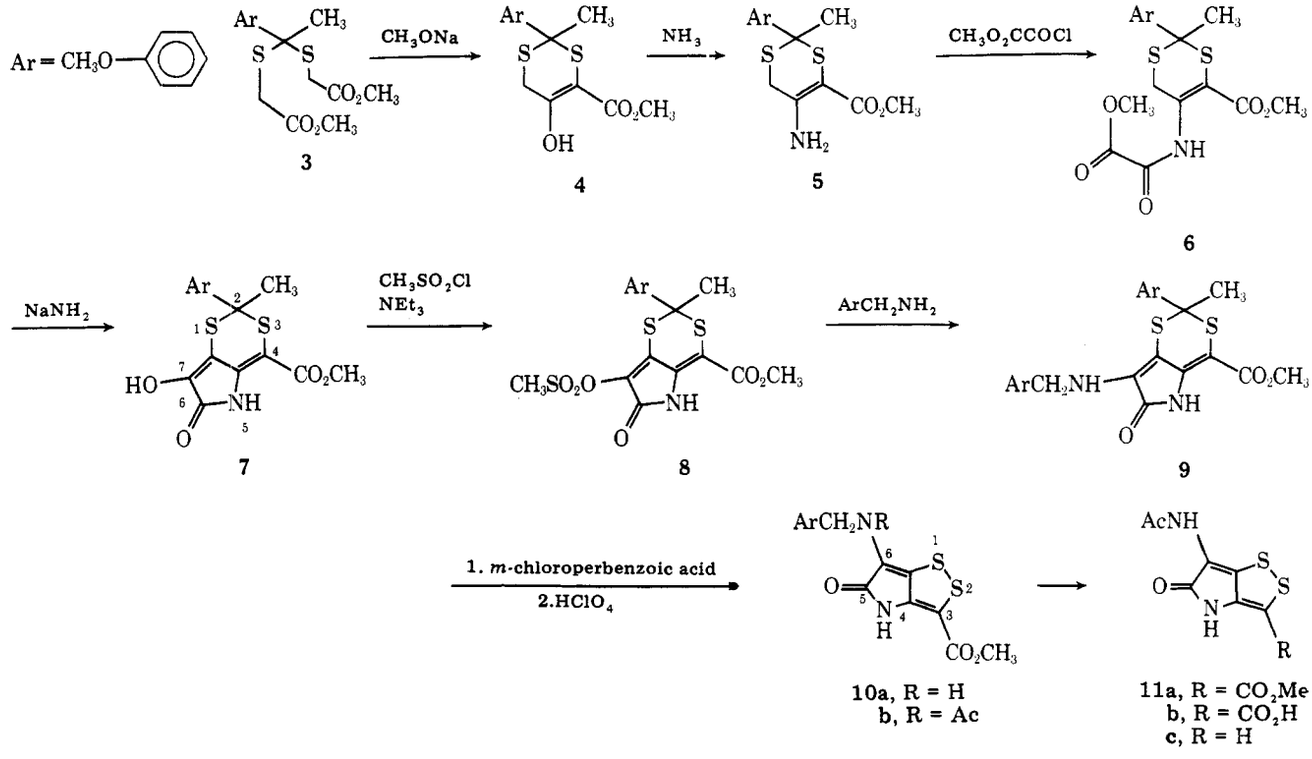
of the carboxyl substituted derivative **1b** of holomycin, a substance in which this analogy is advanced one step further, and have prepared holomycin itself by decarboxylation.

Our synthetic scheme was designed around two key reactions, formation of the pyrrolinone ring by cyclization of the methoxalylamine **6** to **7** and contraction of the dithioketal **9** to disulfide **10a** following the general method developed by Kishi and co-workers.[3] Previous syntheses[4a-c] of holomycin have relied upon the oxidation of dithiols to create the disulfide ring and have not been adaptable to the preparation of nuclear substituted holomycins.

The dithioketal **3** was prepared from *p*-methoxyacetophenone and methythioglycolate and cyclized in a Dieckmann reaction to the keto ester **4**. Replacement of the enolic hydroxyl group by the amino function proceeded readily on treatment with ammonia, forming the enamine **5** which was acylated by methoxalyl chloride. The resulting methoxamide **6** was cyclized by sodium amide yielding the pyrrolinone **7**.

Difficulties were encountered in the elaboration of the enolic hydroxyl group of **7**. Direct replacement by the amino group did not occur on treatment with ammonia. The methanesulfonate **8** could, however, be induced to react with higher amines. For example, reaction with *p*-methoxybenzylamine gave the amine **9** in 12% yield, together with the products of attack of the amine at the sulfur atom of the methanesulfonyl group, *N*-methanesulfonyl-*p*-methoxybenzylamine and the enol **7**.

Treatment of the dithioketal **9** with *m*-chloroperbenzoic acid followed by perchloric acid gave the required disulfide **10a**. The remaining nontrivial step in the synthesis consisted of the cleavage of the *N*-*p*-methoxybenzyl group. This was accomplished by treatment of the acetylated amine **10b** with anhydrous hydrofluoric acid and anisole[5] affording 3-carbomethoxyholomycin (**11a**). Hydrolysis with base gave the desired 3-carboxyholomycin (**11b**). Holomycin **11c** was obtained in a single step from the methyl ester **11a** by cleavage and concomitant decarboxylation with lithium iodide in pyridine,




**3** **4** **5** **6** **7** **8** **9**

**10a**, R = H
**b**, R = Ac

**11a**, R = $CO_2Me$
**b**, R = $CO_2H$
**c**, R = H

a reaction presumably requiring isomerization of the double bond $\alpha,\beta$ to the carboxyl group to the $\beta,\gamma$ position. Thermal decarboxylation of carboxyholomycin at the melting point (202 °C) also gave holomycin.

The 3-carboxyholomycin **11b** inhibited *Staphylococcus aureus* at 50 μg/mL. The minimum inhibitory concentration of holomycin has been quoted as 100 μg/mL.[2] The acid **11b** was, however, considerably less active than holomycin against other organisms.

## Experimental Section

Melting points were determined with a Mel-Temp apparatus and are corrected. NMR spectra were recorded with Varian A-60, HA-100, and Brucker WH-90 spectrometers using $Me_4Si$ as an internal standard. Mass spectra were obtained with a Varian MAT CH-7 spectrometer.

**1,1-Bis(methoxycarbonylmethylthio)ethyl-*p*-methoxybenzene (3).** A mixture of *p*-methoxyacetophenone (23 g, 153 mmol), methyl thioglycolate (32.5 g, 307 mmol), and *p*-toluenesulfonic acid (1.2 g, 7 mmol) in benzene (400 mL) was heated under reflux with separation of water formed by a Dean-Stark trap. After 40 h separation of water was complete and the cooled deep red solution was washed with saturated $NaHCO_3$ solution and with water. Evaporation of the solvent and chromatography of the residue (alumina, 50% hexane in $Et_2O$) gave the thioketal **3** as an oil (22.5 g, 43%): NMR ($CDCl_3$, 60 MHz) δ 1.98 (s, 3, $CH_3$), 3.33 (s, 4, $CH_2$), 3.61 (s, 6, $CO_2CH_3$), 3.71 (s, 3, $OCH_3$), 6.85 (d, 2, $J$ = 9 Hz, ArH), 7.76 (d, 2, $J$ = 9 Hz, ArH). A sample was distilled at 150 °C (0.1 mm) for elemental analysis.

Anal. Calcd for $C_{15}H_{20}O_5S_2$: C, 52.31; H, 5.85; S, 18.62. Found: C, 51.90; H, 5.68; S, 18.68.

**5-Hydroxy-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-1,3-dithiin (4).** A solution of the thioketal **3** (16.34 g, 47.5 mmol) in ether (50 mL) was added to a solution of sodium methoxide (from 1.1 g, 47.5 mmol, of sodium) in methanol (25 mL) at 0 °C under a nitrogen atmosphere. Stirring was continued for 7 h at 0 °C and for a further 40 h at about 25 °C. The mixture was acidified with dilute HCl and the products were extracted into ether. The ether was washed with saturated $NaHCO_3$ and then was extracted by NaOH solution (4%, 100 mL). The aqueous layer was acidified with dilute HCl and extracted with ether. After washing with water and saturated NaCl solution, the ether was dried over $MgSO_4$ and the solvent removed giving the keto ester **4** as an oil (10.85 g, 73%): NMR ($CDCl_3$, 60 MHz) δ 2.01 (s, 3, $CH_3$), 3.45 (s, 2, $SCH_2$), 3.78 (s, 6, $OCH_3$, $CO_2CH_3$), 6.84 (d, 2, $J$ = 9 Hz, ArH), 7.64 (d, 2, $J$ = 9 Hz, ArH). The *p*-nitrobenzoyl derivative, mp 191–192 °C from tetrahydrofuran, was prepared for characterization.

Anal. Calcd for $C_{21}H_{19}NO_7S_2$: C, 54.65; H, 4.15; N, 3.04; S, 13.90. Found: C, 54.55; H, 4.04; N, 3.06; S, 13.82.

**5-Amino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-1,3-dithiin (5).** Ammonia was passed into a solution of the keto ester **4** (10.8 g, 34.6 mmol) in benzene (120 mL) and the solution heated to 80 °C. The cooled mixture was evaporated to dryness in vacuo giving a mixture of **4** and **5** in a ratio of ca. 3:1 (TLC, silica gel, 50% EtOAc–hexane). Repetition of the process five times increased the ratio of product to about 90%. Evaporation and crystallization of the residue from acetone gave the enamine **5** (7.1 g, 66%): mp 132–133 °C; NMR ($Me_2SO$-$d_6$, 100 MHz) δ 1.85 (s, 3, $CH_3$), 3.44, 3.70, 3.83 (2 doublets, incompletely resolved, $SCH_2$) 3.56 (s, 3, $CO_2CH_3$), 3.74 (s, 3, $OCH_3$), 6.85 (d, 2, $J$ = 9 Hz, ArH), 7.56 (d, 2, $J$ = 9 Hz, ArH), 8.2 (br s, 2, $NH_2$).

Anal. Calcd for $C_{14}H_{17}NO_3S_2$: C, 54.00; H, 5.50; N, 4.50; S, 20.59. Found: C, 53.90; H, 5.50; N, 4.49; S, 20.54.

**5-Methoxalylamino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-1,3-dithiin (6).** Methoxalyl chloride (15 g, 122 mmol) was added to a stirred suspension of the enamine **5** (5.63 g, 18.1 mmol) in ether (300 mL). After 30 min a small amount of insoluble material was removed by filtration and the solution allowed to stand for 24 h during which time yellow crystals were deposited. Filtration gave **6** (3.7 g), and cooling of the mother liquors gave a further crop (0.9 g, total yield 64%): mp 116–117 °C; NMR ($CDCl_3$, 60 MHz) δ 2.00 (s, 3, $CH_3$), 3.77 (s, 3, $CO_2CH_3$), 3.81 (s, 3, $OCH_3$), 3.92 (s, 3, $CO_2CH_3$), 4.07 (part of incompletely resolved doublet, SCH), 4.54 (d, 1, $J$ = 15 Hz, SCH), 6.83 (d, 2, $J$ = 8.5 Hz, ArH), 7.58 (d, 2, $J$ = 8.5 Hz, ArH), 12.5 (s, 1, NH).

Anal. Calcd for $C_{17}H_{19}NO_6S_2$: C, 51.38; H, 4.82; N, 3.52; S, 16.13. Found: C, 51.14; H, 4.96; N, 3.27; S, 16.04.

**7-Hydroxy-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (7).** A solution of the ester **6** (5.0 g, 12.6 mmol) in THF (50 mL) was added to a stirred suspension of $NaNH_2$ (1.0 g, 25.6 mmol) in THF (50 mL) under nitrogen. The mixture was heated under reflux for 4 h and then cooled and most of the solvent removed in vacuo. After acidification with dilute HCl the products were extracted into $CHCl_3$ which was then washed with water. Concentration of the solution and filtration yielded yellow crystals of **7** (3.21 g, 70%): mp 257–259 °C dec; NMR ($CDCl_3$, 60 MHz) δ 1.99 (s, 3, $CH_3$), 3.78 (s, 3, $CO_2CH_3$), 3.83 (s, 3, $OCH_3$), 6.83 (d, 2, $J$ = 8.5 Hz, ArH), 7.58 (d, 2, $J$ = 8.5 Hz, ArH), 8.58 (br, 1, OH), 12.2 (br, 1, NH).

Anal. Calcd for $C_{16}H_{15}NO_5S_2$: C, 52.59; H, 4.14; N, 3.83; S, 17.55. Found: C, 52.62; H, 4.09; N, 3.79; S, 17.35.

**7-Methanesulfonyloxy-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (8).** A stirred suspension of the enol **7** (2.0 g, 5.5 mmol) in dichloromethane (50 mL) was treated with triethylamine (1.56 mL, 11.3 mmol) followed by methanesulfonyl chloride (0.54 mL, 7.0 mmol). The mixture was then diluted with chloroform and washed with water, with dilute HCl, and finally with brine. After drying ($Na_2SO_4$), the solution was concentrated in vacuo to about 15 mL affording yellow crystals of **8** (1.65 g, 68%), mp 235 °C.

Anal. Calcd for $C_{17}H_{17}NO_7S_3$: C, 46.04; H, 3.86; N, 3.16; S, 21.69. Found: C, 45.94; H, 3.88; N, 3.12; S, 21.64.

**Reaction of the Enol 7 with Ammonia.** Dry $NH_3$ was passed into a solution of the enol **7** (1.01 g, 2.76 mmol) in benzene (15 mL) for 2 h. Analysis by TLC indicated that a large number of compounds were produced. No pure products could be isolated. A similar result was obtained using $NH_4OAc$ in ethanol under reflux.

**7-*p*-Methoxybenzylamino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (9).** A solution of the mesylate **8** (2.0 g, 4.5 mmol) and *p*-methoxybenzylamine (5.25 g, 38.3 mmol) in tetrahydrofuran was heated under reflux for 15 h. The cooled solution was evaporated to dryness and triturated with ethyl acetate. Filtration gave a residue of the enol **7** (1.01 g, 2.76 mmol). The filtrate was concentrated and triturated with carbon tetrachloride giving white crystals of *N*-methanesulfonyl-*p*-methoxybenzylamine (560 mg, 2.60 mmol): mp 95–96 °C; NMR ($CDCl_3$, 60 MHz) δ 2.80 (s, 3, $SO_2CH_3$), 3.79 (s, 3, $OCH_3$), 4.24 (d, 2, $J$ = 5.5 Hz, $NCH_2$), 4.92 (br s, 1, NH), 6.88 (d, 2, $J$ = 8.5 Hz, ArH), 7.29 (d, 2, $J$ = 8.5 Hz, ArH). The filtrate was purified by TLC (silica gel, hexane–EtOAc, 1:1) and the product crystallized from acetone–hexane affording the amine **9** as red crystals (0.26 g, 12%): mp 157–159 °C; NMR ($CDCl_3$, 60 MHz) δ 1.99 (s, 3, $CH_3$), 3.80 (s, 9, $OCH_3$ and $CO_2CH_3$), 4.55 (d, 2, $CH_2N$), 5.22 (br t, 1, NH), 6.87 (d, 4, $J$ = 8.5 Hz, ArH), 7.22 (d, 2, $J$ = 8.5 Hz, ArH), 7.65 (d, 2, $J$ = 8.5 Hz, ArH), 9.43 (s, 1, NH).

Anal. Calcd for $C_{24}H_{24}N_2O_5S_2$: C, 59.50; H, 4.99; N, 5.78; S, 13.21. Found: C, 59.45; H, 5.17; N, 5.80; S, 12.91.

**6-*p*-Methoxybenzylamino-3-methoxycarbonyl-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (10a).** A solution of the dithiin **9** (98 mg, 0.20 mmol) and *m*-chloroperbenzoic acid (50 mg, 0.29 mmol) in $CH_2Cl_2$ was kept at room temperature for 30 min. The solution was washed successively with solutions of $Na_2SO_3$, $NaHCO_3$, and NaCl. The solvent was removed in vacuo and $CH_2Cl_2$ (15 mL) and 70% $HClO_4$ (40 mg) in tetrahydrofuran (2 mL) added. After standing for 48 h the solution was washed by $NaHCO_3$ solution and the solvent removed in vacuo. Purification by TLC (silica gel, EtOAc–hexane, 1:1) and crystallization from acetone gave the dithiole **10a** (52 mg, 74%) as brown crystals: mp 169–170 °C; NMR ($CDCl_3$, 60 MHz) δ 3.80 (s, 3, $CO_2CH_3$), 3.86 (s, 3, $OCH_3$), 4.47 (br, 2, $NCH_2Ar$), 4.5–4.8 (br, 1, NH), 6.92 (d, 2, $J$ = 8.5 Hz, ArH), 7.30 (d, 2, $J$ = 8.5 Hz, ArH), 8.7 (br, 1, NH); MS $m/e$ 350 ($M^+$).

Anal. Calcd for $C_{15}H_{14}N_2O_4S_2$: C, 51.42; H, 4.03; N, 7.99. Found: C, 51.16; H, 4.15; N, 7.90.

**6-Acetamido-3-methoxycarbonyl-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (11a).** The amine **10a** (48 mg, 0.14 mmol) was heated under reflux in dry benzene (4 mL) and acetic anhydride (2 mL) for 8 h. Evaporation in vacuo gave the amide **10b** which was not purified. A mixture of **10b** (50 mg, 0.13 mmol) and anisole (80 mg, 0.74 mmol) was stirred with anhydrous HF (10 mL) for 20 h. Evaporation gave a dark red residue which was purified by TLC (silica gel, $CHCl_3$–MeOH, 14:1) and recrystallized from tetrahydrofuran affording 3-carbomethoxyholomycin **11a** (30 mg, 86% from **10a**) as a red powder: mp 259–262 °C dec; NMR ($Me_2SO$-$d_6$, 90 MHz) δ 2.16 (s, 3, $CH_3CO$), 3.94 (s, 3, $CO_2CH_3$), 10.16 (br s exchanged by $D_2O$, 1, NH), 11.05 (br s exchanged by $D_2O$, 1, NH); UV max (MeOH) 223 (sh), 257, 336, 448 nm (log ε 3.96, 3.75, 3.54, 3.79); MS (70 eV) $m/e$ (rel intensity) 272 ($M^+$, 38), 230 (100), 198 (26), 170 (24), 142 (14).

Anal. Calcd for $C_9H_8N_2O_4S_2$: C, 39.70; H, 2.96; N, 10.29. Found: C, 39.39; H, 2.80; N, 10.35.

**6-Acetamido-3-carboxy-5-oxo-4,5-dihydro-1,2-dithiolo-[4,3-*b*]pyrrole (11b).** A solution of KOH (25 mg, 0.45 mmol) in methanol (0.5 mL) was added to the ester **11a** (8.7 mg, 0.032 mmol) in tetrahydrofuran (5 mL). After 7 h at room temperature crystals of the sodium salt of **11b** were separated by filtration and washed by tetrahydrofuran. A solution of this salt in water (0.3 mL) was acidified with excess 2 N HCl and the precipitated **11b** filtered and washed with water. Drying in vacuo and crystallization from tetrahydrofuran gave the acid **11b** as solvated orange crystals (4.1 mg, 50%): mp 201–202 °C (TLC of material recovered from the melting point determination showed the presence of holomycin formed by thermal decarboxylation); MS (70 eV) *m/e* (rel intensity) 214 ($M^+ - CO_2$, 40), 172 ($M^+ - CO_2 - CH_2CO$, 81), 44 ($CO_2$, 100).

Anal. Calcd for $C_8H_6N_2O_4S_2 \cdot \frac{2}{3}(C_4H_8O)$: C, 41.82; H, 3.73; N, 9.15. Found: C, 41.54; H, 3.87; N, 8.96.

**6-Acetamido-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (Holomycin, 11c).** A mixture of the ester **11a** (10 mg, 0.037 mmol) and anhydrous LiI (70 mg, 0.52 mmol) in pyridine (2 mL) was heated on a steam bath for 35 h. Dilute HCl was added and the products extracted into ethyl acetate which was then washed with dilute HCl and brine. After drying ($MgSO_4$) the solvent was removed in vacuo and the residue purified by TLC (silica gel, ethyl acetate–hexane–acetic acid, 1:1:0.04) yielding holomycin (**11c**) as an orange powder (3.5 mg, 44%), mp 265–270 °C dec. A sample sublimed at 200 °C (0.4 mm) had mp 271–274 °C dec, not depressed by admixture with an authentic sample of mp 270–273 °C[6] (lit.[2,4b] 264–271 °C dec); UV max ($CH_3OH$) 230 (sh), 246 (sh), 299, 386 nm (log $\epsilon$ 3.48, 3.37, 3.11, 3.54); IR (KBr) 1660, 1635, 1595, 1545 $cm^{-1}$; MS (70 eV) *m/e* (rel intensity) 214 ($M^+$, 19), 172 (50), 43 (100). The physical data are consistent with the literature values.[2,4b]

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**Registry No.**—**3**, 62698-38-8; **4**, 62698-39-9; 4 *p*-nitrobenzoyl derivative, 62698-37-7; **5**, 62698-40-2; **6**, 62698-41-3; **7**, 62698-42-4; **8**, 62698-43-5; **9**, 62698-44-6; **10a**, 62698-45-7; **10b**, 62698-46-8; **11a**, 62698-47-9; **11b** Na salt, 62698-48-0; **11b**, 62698-49-1; **11c**, 488-04-0; *p*-methoxyacetophenone, 100-06-1; methyl thioglycolate, 2365-48-2; methoxalyl chloride, 5781-53-3; methanesulfonyl chloride, 124-63-0; *p*-methoxybenzylamine, 2393-23-9; *N*-methanesulfonyl-*p*-methoxybenzylamine, 42060-31-1.

## References and Notes

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(6) Kindly supplied by G. H. Büchi.

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# Nucleophilic Substitution Reactions on *N*-Nitropyrazoles[1]

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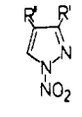
1,4-Dinitropyrazoles **1c–d** undergo "cine" substitution with secondary amines to give 3(5)-di-R-amino-4-nitropyrazoles. 1-Nitro-4-bromo- and 1,3-dinitropyrazoles **1a** and **1b** with cyclic secondary amines undergo displacement on the nitrogen of the *N*-nitro group to give the *N*-nitro amines.

The examples reported in the literature of aromatic nucleophilic substitution in azole rings[2] all follow, according to Miller,[3] an addition–elimination mechanism. In the case of halogeno pyrazoles the presence of strong electron-withdrawing groups appears to be required for the reaction to proceed as was recently confirmed by Alcalde et al.[4] Nevertheless, aromatic nucleophilic substitution in pyrazoles[2,5–7] has not been studied extensively and nothing systematic is known about the susceptibility or the point of attack in the ring and of its dependence on the activating effect of substituents in other positions in the ring.

To our knowledge, in all but one of the reported examples for pyrazoles, the activating group was at C-4 and the halogen displaced by nucleophiles was in either the 3(5) position for N-unsubstituted pyrazoles or C-5 for *N*-arylpyrazoles. The one exception reported by Coburn[8] is the reaction of 4-bromo-3,5-dinitro-1-methylpyrazole with amines to give the 4-amino derivatives, the nucleophilic substitution taking place in the 4 position and the two activating groups situated in positions 3 and 5.

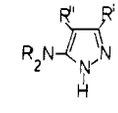
In continuation of our investigations of *N*-nitroazoles[1,9] we were interested in the reactivity toward nucleophiles of *N*-nitro-substituted pyrazoles. Therefore we investigated the reaction of some 3- and 4-substituted *N*-nitropyrazoles with secondary amines as nucleophiles.

Expecting nucleophilic substitution at the 4 position we refluxed 4-bromo-1-nitropyrazole (**1a**) with piperidine in



1a, R′ = H; R″ = Br
b, R′ = $NO_2$; R″ = H
c, R′ = H; R″ = $NO_2$
d, R′ = $CH_3$; R″ = $NO_2$

ethanol solution and in excess piperidine, respectively. However, the reaction products were a trace of 4-bromo-3(5)-piperidylpyrazole (**2a**), 4-bromopyrazole, and *N*-nitro-



2a, R′ = H; R″ = Br; $R_2N$ = piperidyl
b, R′ = H; R″ = $NO_2$; $R_2N$ = piperidyl
c, R′ = H; R″ = $NO_2$; $R_2N$ = morpholyl
d, R′ = H; R″ = $NO_2$; $R_2N$ = $(C_2H_5)_2N$
e, R′ = $CH_3$; R″ = $NO_2$; $R_2N$ = piperidyl
f, R′ = $CH_3$; R″ = $NO_2$; $R_2N$ = morpholyl

piperidine, the latter compound most likely originating from a nucleophilic displacement by piperidine on the nitrogen of the *N*-nitro group of **1a**. Assuming then that dinitropyrazoles might be even better molecules to undergo such a displacement reaction by considering that 3- or 4-nitropyrazole anions would be even better leaving groups than 4-bromopyrazole anion, we treated 1,3-dinitropyrazole (**1b**) and 1,4-dinitropyrazole (**1c**) with morpholine and with piperidine. The re-