Degradative Ring Opening of Pyrido and Pyrazino 3-Benzenesulfonyloxyuracils and Their Conversion to Condensed Pyrazolones and Triazolones (1)

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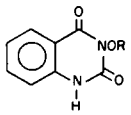
Ring opening, followed by an immediate Lossen rearrangement, of 3-benzenesulfonyloxypyrido[3,2-*d*, 3,4-*d* and 4,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones with sodium methoxide in methanol furnished good yields of the methyl esters of 3-[2-(methoxycarbonyl)hydrazino]-2-, 3-[2-(methoxycarbonylhydrazino]-4- and 4-[2-(methoxycarbonyl)hydrazino]-3-pyridinecarboxylic acids, respectively. These hydrazino esters were cyclized to the corresponding pyridopyrazolones. However, the reaction of 3-benzenesulfonyloxypyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione with sodium methoxide produced 8-methoxycarbonyl-*s*-triazolo[4,5-*a*]pyridin-3(2*H*)one. In similar fashion, sodium methoxide converted 3-benzenesulfonyloxylumazine to 8-methoxycarbonyl-*s*-triazolo[4,3-*a*]pyrazin-3(2*H*)one.

Three different kinds of reactions have been observed when 3-benzenesulfonyloxy-2,4-quinazolinedione (1, R = $C_6H_5SO_2$) was exposed to various basic reagents (2). These could be rationalized in terms of nucleophilic attack on the S atom of the sulfonate group, neutralization of the acidic NH proton or addition to the CO group at position 4.



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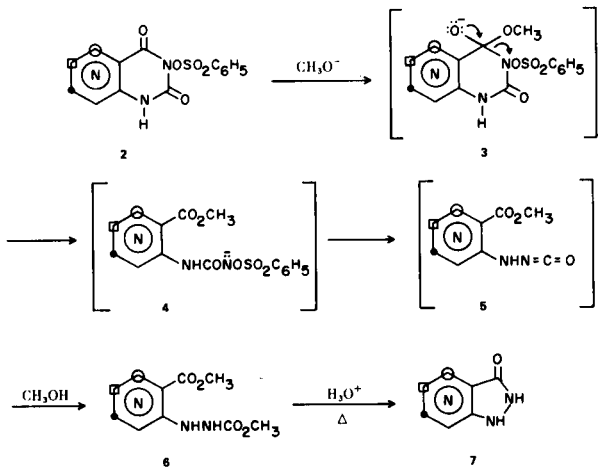
Examples of these types of reactions are quoted. Dilute hot aqueous sodium hydroxide hydrolyzed the sulfonate to the *N*-hydroxy derivative (**1**, R = H), while alkoxide or hydride ions degraded it to benzimidazolone. An exception to this general reaction with alkoxide ions was noted when sodium methoxide in methanol rearranged the benzenesulfonate of **1** to *o*-$C_6H_4(CO_2CH_3)NHNHCO_2CH_3$ in 45% yield (2). This hydrazino ester cyclized to 3-indazolone in a subsequent hydrolytic step (2). An investigation of the latter type of reactions using the pyrido and pyrazino analogs of **1** with sodium methoxide is reported now.

The Pyridouracil System.

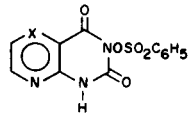
The four pyrido analogs of **1** (R = H or $C_6H_5SO_2$) have been synthesized and characterized previously (3). Three of those isomers are conveniently represented by **2**, where the encircled, boxed or dotted corners in that structure



represents, each, a pyridine nitrogen atom. The fourth isomers is best shown by **8a**. The first three isomers of **2** behave quite analogously to the quinazoline counterpart, **1**, insofar that they produced hydrazino esters, **6**, when treated with sodium methoxide in boiling methanol. The yields from **2** to **6** were excellent (74-89%) and none of the corresponding *N*-hydroxy compounds could be detected. It would appear that the electron-attracting sp^2-hybridized ring nitrogen atom imparts additional electrophilic character to the carbonyl carbon at position 4 in **2**, which manifests itself in a more facile reaction at that center. The suggested mechanism (2) involves attack by the nucleophile at C-4 to give **3**, which opens to the anion **4**. The latter undergoes a Lossen rearrangement to the isocyanate in **5**.

The final product is formed when methanol adds to the isocyanate to produce **6**. The identity of each of three isomeric pyridines, **6**, was established by elemental analysis, their ir, proton magnetic resonance (pmr) and mass spectra. In their pmr spectra, each of the three isomers, **6**, exhibited two singlets due to the ester methyl groups, between δ 3.7 and 4.0, and two signals indicative of two exchangeable protons (NH) and a pattern typical of the particular disubstituted pyridine. Base-catalyzed, followed by acid-catalyzed hydrolysis of **6** afforded the cyclized pyridopyrazolone, **7**. One of the three isomers, **7**, is known and was identical to the one in the literature (4).

This pattern for the conversion of **2** to **6** (or **7**) was changed when the fourth isomer, **8a**, was treated with sodium methoxide in methanol. It created a molecule whose pmr spectrum revealed just one singlet attributable to a methyl ester group and whose molecular ion differed to those from **6** by one mole of methanol.



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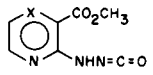

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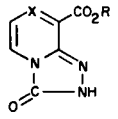

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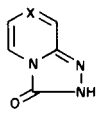

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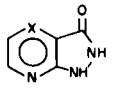

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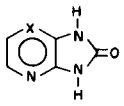

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For the above structure, a, X = CH, b, X = N; except for **10**: a, X = CH, R = CH_3; b, X = CH, R = H; c, X = N, R = CH_3; d, X = N, R = H.

Plausible structures for this mono ester are the *N*-methoxycarbonyl derivatives of either the pyridopyrazolone, **12a**, or the pyridoimidazolone, **13a**. A methyl ester in the pyridotriazolone system, **10a**, represented also a real possibility. Proof for **10a** was provided when hydrolysis of **10a** yielded the stable acid, **10b**. This meant that the CO_2CH_3 could not be attached to one of the 5-membered ring nitrogen atoms of either **12** or **13**, since the resultant carbamic acid would be expected to decarboxylate spontaneously. However, the acid, **10b**, lost carbon dioxide extremely reluctantly at 400° to give **11a**, which was identical to a sample made according to literature directions (5).

The formation of **10a** is feasible if methoxide ion attacks the 4-carbonyl group of **8a**. However, if the isocyanate so generated, **9a**, cyclizes on the pyridine ring nitrogen atom instead of adding methanol. The physical data of **11a** certainly is quite different from that of the two known isomeric structures, **12a** (6) and **13a** (7).

3-Benzenesulfonyloxylumazine.

The reaction of this sulfonate, **8b**, (8) with sodium methoxide provided a bright yellow solid (85%) whose pmr spectrum clearly showed a methyl singlet and an AB quartet in the aromatic region (8). With an ester carbonyl band at 1745 cm^{-1} and the base peak in its mass spectrum at m/e 194, it was evident that a methyl ester belonging to a condensed pyrazinoazolone was formed. Base-catalyzed hydrolysis produced a stable acid. This observation once more rules out a carbamic acid type which would have been formed if an *N*-(methyl esters) based on **12b** or **13b** was hydrolyzed. Thus, **10c**, becomes the logical choice for the structure of the new ester, and **10d**, that for the corresponding acid. Decarboxylation occured when **10d** was sublimed, *in vacuo*, at 180°. The more facile loss of carbon dioxide of **10d**, compared to **10b**, is understandable in terms of the attachment of the acid group at a carbon atom α to the ring/nitrogen atom in **10d** and β in **10b**. The pyrazinotriazolone, **11b**, formed after decarboxylation, possessed different physical properties to those of the two isomers **12b** (9) and **13b** (7), both of which were prepared for comparison. The structure of **11b** was confirmed by its pmr spectrum which clearly showed three aromatic protons with the expected spin-spin coupling constants, while **12b** and **13b** only possess two aromatic protons. Both show singlets at δ 7.05 and 7.93, respectively, in dimethyl sulfoxide solution. The uv spectrum of **11b** is characteristic and resembled that reported for several known C-methyl analogs (10,11).

The formation of **10c** again involved cyclization, this time of the intermediate isocyanate ester, **9b**. Attempts to synthesize **11b** was considered. Pyrido and pyrazino triazolones of types **11a** and **11b** have been described. Their synthesis usually involved treatment of the corresponding pyridyl- or pyrazinylhydrazine with either phosgene (11), ethyl chloroformate (5) or urea (5). All attempts to apply any of these methods to the reaction of hydrazinopyrazine to form **11b** were unsuccessful.

EXPERIMENTAL

All melting points are uncorrected and were determined in capillary tubes on a Thomas Hoover Unimelt up to 300° and over 300° on a Mel-Temp melting point apparatus. Nitrogen analyses were determined by means of a Coleman Nitrogen Analyzer and those for other elements by Micro-Tech Labs, Skokie, Illinois. Ir spectra were obtained on a Perkin-Elmer 337 recording infrared spectrophotometer. Pmr spectra were recorded by means of a Varian A-60 spectrometer in ppm (δ), downfield from TMS. Uv spectra were determined on a Beckman DK-1L recording spectrophotometer. Mass spectra were obtained by Mr. Richard Dvorak at

70 eV using a Hitachi Perkin-Elmer RMU-6D single focusing mass spectrometer. Usually, ions with 5% of base peak or more are recorded starting from m/e 39. Thin layer chromatographs (tlc) were developed over 15 minutes on 7.2 cm slides coated with silica gel and a fluorescent indicator (Eastmen Chromagram Sheet 6060) using either ethyl acetate of methanol. Spots were detected by UV light.

The potential tautomerism of the cyclic "ones" *vs* "ols" is recognized and for the sake of uniformity, structures **7**, **10-14**, are named as "ones". Ir absorption bands in the 1600-1800 cm^{-1} region are listed, but do not necessarily denote heteroaromatic ring carbonyl stretching frequencies. No specific assignments are made.

Methyl 4-[2-(Methoxycarbonyl)hydrazino]nicotinate, Method A.

To a stirred suspension of 3-benzenesulfonyloxypyrido[4,3-*d*]-pyrimidine-2,4-(1*H*,3*H*)dione (3.2 g., 0.01 mole) in boiling methanol (150 ml.) was added sodium methoxide solution [0.23 g. of sodium (0.01 g-atom) in 68 ml. of methanol]dropwise over 0.5 hour. Solvents were removed, *in vacuo* (rotary flash evaporator, at 20-30 Torr). The residue was triturated with water (40 ml.) and the product (1.66 g., 74%) was deposited after the mixture was kept at 5° for several hours. It melted at 175-176° and recrystallized from water did not improve this m.p.; ir (Nujol): 3345, 3200 (NH), 1740, 1705 cm^{-1} (CO); pmr (deuteriochloroform): δ 3.70, 3.94 (s, CH_3's); 7.05 (d, H-5, $J_{5,6}$ = 5.0 Hz); 8.55-8.75 (m, H-6); 8.90-9.23 (m, H-2), 9.45, 9.73 (s, br, NH's); mass spectrum (70 eV) m/e (relative intensity): 226 (12), 225 (100), 194 (11), 193 (55), 161 (8), 150 (11), 149 (71), 148 (11), 135 (12), 134 (48), 121 (6), 120 (11), 109 (6), 107 (6), 106 (64), 105 (11), 93 (14), 92 (15), 79 (8), 78 (46), 77 (9), 59 (96), 53 (9), 52 (11), 51 (33), 50 (12).

Anal. Calcd. for $C_9H_{11}N_3O_4$: N, 18.66. Found: N, 18.70.

1*H*-Pyrazolo[4,3-*c*]pyridin-3(2*H*)one. Method B.

A solution of the above hydrazino ester (0.2 g.) in 5% sodium hydroxide solution (3 ml.) was boiled under reflux (1.5 hours). The *p*H was adjusted to > 1 with concentrated hydrochloric acid, and boiling continued (20 minutes). The cooled solution was treated with sodium carbonate until the *p*H was 5. After 18 hours at 5°, the solid was collected (0.12 g., 100%) m.p. 290° dec., lit. (4) m.p. 292-294°; its uv spectrum was identical to the one reported in the literature (4); ir (Nujol); 1630 cm^{-1}; pmr (DMSO): δ 8.65 (s, H-4); 7.66 (d, H-6), 6.98 (d, H-7), $J_{6,7}$ = 7.8 Hz; mass spectrum (70 eV) m/e (relative intensity): 136 (8), 135 (100), 106 (13), 79 (7), 78 (17), 76 (7), 53 (13), 51 (12), 50 (11).

Methyl 3-[2-(Methoxycarbonyl)hydrazino]isonicotinate.

Using an identical procedure on 3-benzenesulfonyloxypyrido-[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)dione, as described in Method A, this *product* (1.83 g., 81%) was collected and crystallized from water, m.p. 130.5-132°, ir (Nujol): 3380, 3090 (NH), 1725, 1700 (CO) cm^{-1}; pmr (deuteriochloroform): δ 3.78, 3.94 (s, CH_3's) 7.65 (d, H-5), $J_{5,6}$ = 5.0 Hz, 8.12 (d, H-6), 8.54 (s, H-2), 7.44, 8.71 (s, br, NH's); mass spectrum (70 eV) m/e (relative intensity): 226 (11) 225 (100), 193 (30), 161 (11), 150 (8), 149 (55), 135 (11), 134 (66), 109 (6), 106 (24), 105 (7), 92 (10), 91 (10), 78 (57), 59 (72), 51 (28).

Anal. Calcd. for $C_9H_{11}N_3O_4$: N, 18.66. Found: N, 18.95.

1*H*-Pyrazolo[3,4-*c*]pyridin-3(2*H*)one.

Using Method B, the above hydrazino ester (0.5 g.) was cyclized. After boiling in the acid milieu, the solution was evaporated. in *vacuo*. Addition of 15 ml. of water produced the hydrochloride of the title compound (0.33 g: 87%) m.p. 328° dec. It can be sublimed at 210° (0.01 Torr); ir (Nujol): 1630, 1560 cm^{-1}; pmr (DMSO-d_6): δ 6.75, 7.60 (s, br, either OH or NH, both are exchangeable); 8.61 (d, H-4, $J_{4,5}$ = 7.0 Hz); 8.83 (d, H-5), 9.80 (s, H-7).

Anal. Calcd. for $C_6H_6ClN_3O$: N, 24.49. Found: N, 24.44.

The free base was obtained by dissolving the hydrochloride salt (0.2 g.) in the minimal amount of hot water (1 ml.). The solution was filtered and the *p*H adjusted with sodium acetate to 5. It was kept at 5° for 18 hours to afford yellow crystals, (0.1 g., 61%), m.p. 280°; ir (Nujol): no strong absorption above 1600 cm^{-1}; mass spectrum (70 eV) m/e (relative intensity): 136 (8), 135 (100), 106 (8), 80 (16), 79 (7), 78 (14), 65 (11), 64 (9), 53 (26), 52 (18), 51 (17), 50 (17), 44 (5), 38 (16), 37 (6).

Anal. Calcd. for $C_6H_5N_3O$: N, 31.10. Found: N, 30.90.

1*H*-Pyrazolo[4,3-*b*]pyridin-3(2*H*)one Hydrate.

The reaction of sodium methoxide with 3-benzenesulfonyloxy-pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione, was conducted as described in Method A. The residue, after evaporation of solvents, was extracted with chloroform, and this extract concentrated to produce a red oil (0.5 g, 89%) which refused to crystallize. Its pmr spectrum (deuteriochloroform): δ 3.76, 4.00 (s, CH_3's); 7.33-7.50 (m, H-4, H-5); 8.19 (dd, H-6, $J_{5,6}$ = 5.0, $J_{4,6}$ = 1.6 Hz); 7.94, 9.10 (s, br, NH's) and mass spectrum (70 eV) m/e (relative intensity): 225 (5), 193 (7), 79 (13), 78 (100), 77 (18), 52 (16), 51 (15), 39 (9), showed the compound to be pure. Attempts to purify deepened the color of the product and it (0.4 g.) was cyclized by Method B. After the acid reflux, the solution was cooled, and the *p*H adjusted to 2 by the addition of solid potassium carbonate. The yellow precipitate (0.23 g., 85%) melted at 200°; ir (Nujol): 3350 (NH), 1590 cm^{-1}; pmr (DMSO): δ 7.70 (dd, H-6); 8.34 (dd, H-7); 8.70 (dd, H-5); $J_{5,6}$ = 5.0, $J_{5,7}$ = 1.1, $J_{6,7}$ = 8.8 Hz; mass spectrum (70 eV) m/e (relative intensity): 136 (10), 135 (100), 80 (19), 79 (10), 78 (26), 65 (10), 53 (14), 52 (17), 51 (10), 50 (7), 38 (16), 36 (52).

Anal. Calcd. for $C_6H_5N_3O \cdot H_2O$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.44; H, 4.83; N, 27.75.

8-Methoxycarbonyl-*s*-triazolo[4,3-*a*]pyridin-3(2*H*)one, **10a**.

The reaction of **8a** under conditions of Method A, furnished a residue, which was washed with water (30 ml., twice) to produce **10a** (1.5 g., 78%) m.p. 266-268°, which was recrystallized from water (72% recovery) m.p. 272.5-274°; ir (Nujol): 3200 (NH), 1700 cm^{-1} (CO); pmr (DMSO): δ 3.92 (s, CH_3); 6.72 (t, H-6); 8.05 (dd, H-7); 8.20 (dd, H-5); $J_{5,6}$ = $J_{6,7}$ = 7.0; $J_{5,7}$ = 1.2 Hz; mass spectrum (70 eV) m/e (relative intensity): 194 (10), 193 (100), 162 (23), 136 (6), 135 (65), 134 (7), 106 (14), 91 (8), 77 (35), 76 (23), 75 (10), 64 (6), 51 (8), 39 (6).

Anal. Calcd. for $C_8H_7N_3O_3$: N, 21.75. Found: N, 21.61.

8-Carboxy-*s*-triazolo[4,3-*a*]pyridin-3(2H)one, **10b**.

A solution of **10a** (0.5 g.) in 15 ml. 5% sodium hydroxide was boiled under reflux for 2 hours. On acidification with 5 ml. of concentrated hydrochloric acid, the acid crystallized after 1 hour at 5° (0.4 g., 86%), m.p. 345° dec; ir (Nujol): 1745, 1690 (C=O) cm^{-1}; mass spectrum (70 eV) m/e (relative intensity): 180 (9), 179 (100), 163 (5), 147 (21), 136 (7), 135 (97), 119 (7), 107 (6) 106 (8), 105 (13), 94 (10), 93 (9), 92 (9), 91 (12), 80 (15), 79 (40), 78 (34), 77 (18), 76 (10), 67 (7), 66 (17), 65 (18), 64 (19), 63 (7), 40 (18), 39 (30), 38 (26), 37 (21).

Anal. Calcd. for $C_7H_5N_3O_3$: N, 23.46. Found: N, 23.40.

Decarboxylation of **10b** was achieved by inserting a test-tube (1 cm diameter) containing 20 mg. of **10b** into a preheated sand bath

at 400° for 2 minutes. The crystals which condensed on the upper wall of the test tube were collected, m.p. 224-225° [lit. (5) m.p. 225-226°]. Their ir spectrum and tlc's were identical with those of a sample synthesized by the literature method (5). The mass spectra of the two samples were also identical (12).

8-Methoxycarbonyl-*s*-triazolo[4,3-*a*]pyrazin-3(2*H*)one, (**10c**).

When **8b** (3.2 g.) was reacted with sodium ethoxide, Method A, **10c** crystallized on cooling the methanol solution. It was filtered, washed with a small amount of water and dried. It weighed 1.66 g. (85%), m.p. 261-263° dec., ir (Nujol): 3190 (NH), 1745, 1720 (CO) cm^{-1}; pmr (DMSO): δ 4.03 (s, CH_3), 7.65 (d, H-5, $J_{5,6}$ = 5.0 Hz), 8.10 (d, H-6); mass spectrum (70 eV) m/e (relative intensity): 195 (5), 194 (100), 163 (7), 136 (36), 135 (10), 108 (7), 92 (6), 80 (57), 79 (9), 78 (7), 59 (16), 53 (14), 52 (14), 51 (7), 42 (7), 40 (19), UV max in ethanol, nm (log ε) 237 (4.26), 267 sh (3.44). The analytical sample was recrystallized from water, m.p. 264°.

Anal. Calcd. for $C_7H_6N_4O_3$: C, 43.31; H, 3.12; N, 28.86. Found: C, 43.56; H, 3.18; N, 28.50.

8-Carboxy-*s*-triazolo[4,3-*a*]pyrazin-3(2*H*)one, hydrate (**10d**).

A solution of **10c** (0.5 g.) in 25 ml. of 10% aqueous sodium carbonate was heated under reflux for 2 hours. After cooling, the *p*H was adjusted to 5 with acetic acid. The yellow precipitate turned out to be the sodium salt of **10d** (m.p. >500°). This solid was suspended in 5% hydrochloric acid (20 ml.), warming gently on the steam bath for 10 minutes with occasional swirling. The product, **10d**, (0.4 g., 78%) was collected, m.p. 242-244° (dec. darkens at 200°); ir (Nujol): 3480, 3150 (NH), 1710 (CO) cm^{-1}; pmr (DMSO): δ 7.64 (d, H-5, $J_{5,6}$ = 5.0 Hz), 8.44 (d, H-6) its mass spectrum showed the same pattern as the decarboxylated product, **11b**.

Anal. Calcd. for $C_6H_4N_4O_3H_2O$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.11; H, 2.97; N, 28.30.

s-Triazolo[4,3-*a*]pyrazin-3(2*H*)one (**11b**).

This compound was obtained quantitatively by subliming **10d** at 185° (0.01 Torr) m.p. 244-245° (dec. sintered at 190°); ir (Nujol): 1730 (CO) cm^{-1}; pmr (DMSO): δ 7.56 (d, H-5), 7.94 (dd, H-6), 8.91 (d, H-8), $J_{5,6}$ = 5.2, $J_{6,8}$ = 1.8 Hz: mass spectrum (70 eV) m/e (relative intensity): 137 (7), 136 (88), 80 (28), 79 (10), 66 (21), 53 (18), 52 (24), 51 (6), 44 (100). The ion, m/e 44, appears only if the inlet temperature is *ca.* 200° (13) and is completely absent when this temperature is reduced to 100°. Then m/e 136 becomes the base peak. UV max in ethanol, nm log ε) 223 (4.20), 260 (3.41), 350 (3.41).

Anal. Calcd. for $C_5H_4N_4O$: N, 41.61. Found: N, 41.25.

The base peak, m/e 44 in the mass spectrum of **11b** intrigued us, particularly since the mass spectrum of **10c** was devoid of this ion. In searching the literature, the mass spectra of the pyridine analogs based on **11a** did not produce a significant amount of an ion, m/e 44. Thus, it appeared that the ring system based on **11b** might exhibit m/e 44 characteristically. The mass spectrum of the 5,8-dimehtyl homolog of **11b** did show m/e 44 as the base peak. The possible structure of this ion ($O = C = NH_2^+$) and its origin in terms of structures based on **11b** is under investigation.

REFERENCES

(1) Presented at the 4th International Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 13, 1973; Reported in the Abstracts of the Meeting, p. 59.

(2) K. -Y. Tserng and L. Bauer, *J. Org. Chem.*, **38**, 3498 (1973).

(3) K. -Y. Tserng and L. Bauer, *J. Heterocyclic Chem.*, **9**, 1433 (1972).

(4) G. M. Badger and R. P. Rao, *Aust. J. Chem.*, **18**, 379 (1965).

(5) K. T. Potts and H. R. Burton, *J. Org. Chem.*, **31**, 251 (1966).

(6) G. M. Badger and R. P. Rao, *Aust. J. Chem.*, **18**, 1267, (1965).

(7) F. M. Hershenson, L. Bauer and K. F. King, *J. Org. Chem.*, **33**, 2543 (1968).

(8) L. Bauer, C. N. V. Nambury and F. M. Hershenson, *J. Heterocyclic Chem.*, **3**, 224 (1966); We acknowledge the early exploratory work by Drs. F. M. Hershenson and C. N. V. Nambury.

(9) E. C. Taylor, J. W. Barton and T. S. Osdene, *J. Am. Chem. Soc.*, **80**, 421 (1958).

(10) G. M. Badger, P. J. Nelson and K. T. Potts, *J. Org. Chem.*, **29**, 2542 (1964).

(11) S. E. Mallett and F. L. Rose, *J. Chem. Soc. C*, 2038 (1966).

(12) K. T. Potts, E. Brugel and U. P. Singh, *Org. Mass Spectrom.*, **5**, 1, (1971).

(13) K. T. Potts and E. Brugel, *ibid.*, **5**, 663 (1971).