was then added 500 mg (0.0015 mol) of **1b** and the mixture was heated on a steam bath for 0.5 hr with occasional shaking. The suspension was evaporated to dryness and the residue was extracted with $CHCl_3$ (3 × 20 ml) and ether (20 ml). The combined extract was evaporated to dryness and the oily residue was partitioned between water (20 ml) and petroleum ether (20 ml). The insoluble solid was collected, washed with water, and dried. It weighed 376 mg (87%), mp 103–105°, and was identical with compound **16** isolated from J.

The chloroform-insoluble residue was suspended in 10 ml of water and acidified with dilute HCl (1:1) to pH 2. After several hours, pure **2b** was collected and washed with acetone (310 mg 94%).

K. Sodium Isopropoxide in 2-Propanol.—This experiment was performed as described in E. The corresponding chloroform extract was evaporated to dryness. The residue was triturated with ether (3 × 30 ml). The ether-insoluble residue was triturated with water (10 ml) to give **16** (0.2 g). The ether extract was evaporated to 10 ml to obtain a second batch of **16** (0.4 g, combined yield was 21%).

The ether filtrate was evaporated to dryness and the residue was refluxed with 5% NaOH (6 ml) for 30 min to give **4a** (0.15 g, 10%) after acidification.

The chloroform-insoluble residue was dissolved in 20 ml of water and acidified by pH 2 to afford **2b** (0.86 g, 45%).

Registry No.—**1a**, 41120-14-3; **1b**, 41120-15-4; **2a**, 5329-43-1; **2b**, 37833-99-1; **2c**, 41120-18-7; **2d**, 41120-19-8; **3**, 41120-20-1; **4b**, 41120-21-2; **4c**, 41120-26-7; **5a**, 615-16-7; **5b**, 41120-23-4; **5c**, 41120-24-5; **16**, 41120-25-6.

Quinazolines and 1,4-Benzodiazepines. LIX.[1] Preparation of Pyrrolo[2,1-*c*]-1,4-benzodiazepines

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10-Substituted 7-chloro-5,10-dihydro-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines (**5**) were obtained from the corresponding 3-allylbenzodiazepine 4-oxides (**2**) with acetic anhydride. Oxidative cleavage of the pyrrole ring of **5h** gave the known compounds **6** and **9**. The pyrrolidinobenzodiazepine **11** was prepared by conventional reactions *via* the 3-(2-methoxycarbonylethyl)benzodiazepines **4** and **7**. Compound **4** was obtained by base catalyzed addition of methyl acrylate to the benzodiazepine **1a**. The 5-methyl analog of **5** was not accessible through the corresponding 3-allylbenzodiazepine 4-oxide (**14**) since the Polonovsky rearrangement led to compounds **15c–e** instead.

In the course of other studies connected with the synthesis of 3-substituted benzodiazepines,[2,3] a 3-allyl-1,4-benzodiazepine 4-oxide, compound **2a** (Scheme I), was also prepared. It was found that under Polonovsky conditions this compound was converted to the pyrrolo[2,1-*c*]benzodiazepine **5h**. The structure of the pyrrolobenzodiazepine was derived from the spectroscopic and analytical data and was further substantiated by chromic acid oxidation to the known benzodiazepine-2,3-dione **6**[4] and the quinazolinone **9**.[5] Treatment of **5h** with lithium aluminum hydride reduced the amide carbonyl and led to compound **8**. In the nmr spectrum the 11-methylene group of this compound appeared as an AB system with a coupling contant of 15 Hz.

Treatment of the *N*-methoxymethyl derivative **5k** (prepared from **2d**) with ethanolic hydrogen chloride did not result in the expected replacement of the methoxymethyl group by a proton[2] but only in the exchange of the methoxy group by ethoxy to yield compound **5m**.

A plausible mechanism for the conversion of the 3-allylbenzodiazepine to the pyrrolobenzodiazepine is depicted in Scheme II. The first step is no doubt the formation of the Polonovsky rearrangement product, the 3-acetoxy derivative A. Loss of the acetic acid would then yield the diene B. The intermediate diene B could then rearrange thermally *via* the aziridine C or with participation of acetate *via* D to the pyrrolobenzodiazepine **5h**. The transformation D → **5h** involves a 1,3-hydride shift while the thermal rearrangement of C may be formulated as a proton or a hydride shift. Evidence for the formation of a diene such as B was obtained by the isolation of the diene **3f** from the reaction of the dimethylallyl derivative **2c** with acetic anhydride. As anticipated, this particular diene did not convert to a pyrrolobenzodiazepine even under forcing conditions. In addition to being sterically less favorable, the transformation of this diene to the pyrrolobenzodiazepine would also require a methyl shift. The 3-crotylbenzodiazepine **2b** also underwent the conversion to the pyrrolobenzodiazepine **5i**, although in lower yield. The previously described 3-benzylbenzodiazepine **2e**[3] could not be transformed analogously to an indolobenzodiazepine. Instead a mixture of the two isomeric 3-benzylidenebenzodiazepines **3g** was obtained. The major component was readily isolated by crystallization and had been prepared earlier by condensation of 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one with benzaldehyde.[6] The minor component was isolated by chromatography. Based on the chemical shift difference of the benzylidene protons, we have assigned the configuration of phenyl trans to the carbonyl group to the major product.

The pyrrolidinobenzodiazepine **11** was prepared as outlined in Scheme I. Addition of methyl acrylate to **1a** yielded the ester **4**, which was reduced with zinc and acetic acid to afford **7**. Thermal cyclization of this δ-amino ester led to the pyrrolidone **10**. Reduction of both amide carbonyls with lithium aluminum

(1) Part LVIII: R. Y. Ning, L. H. Sternbach, W. Pool, and L. O. Randall, *J. Med. Chem.*, **16**, 879 (1973).

(2) A. Walser, G. Silverman, J. Blount, and R. Ian Fryer, *J. Org. Chem.*, **36**, 1465 (1971).

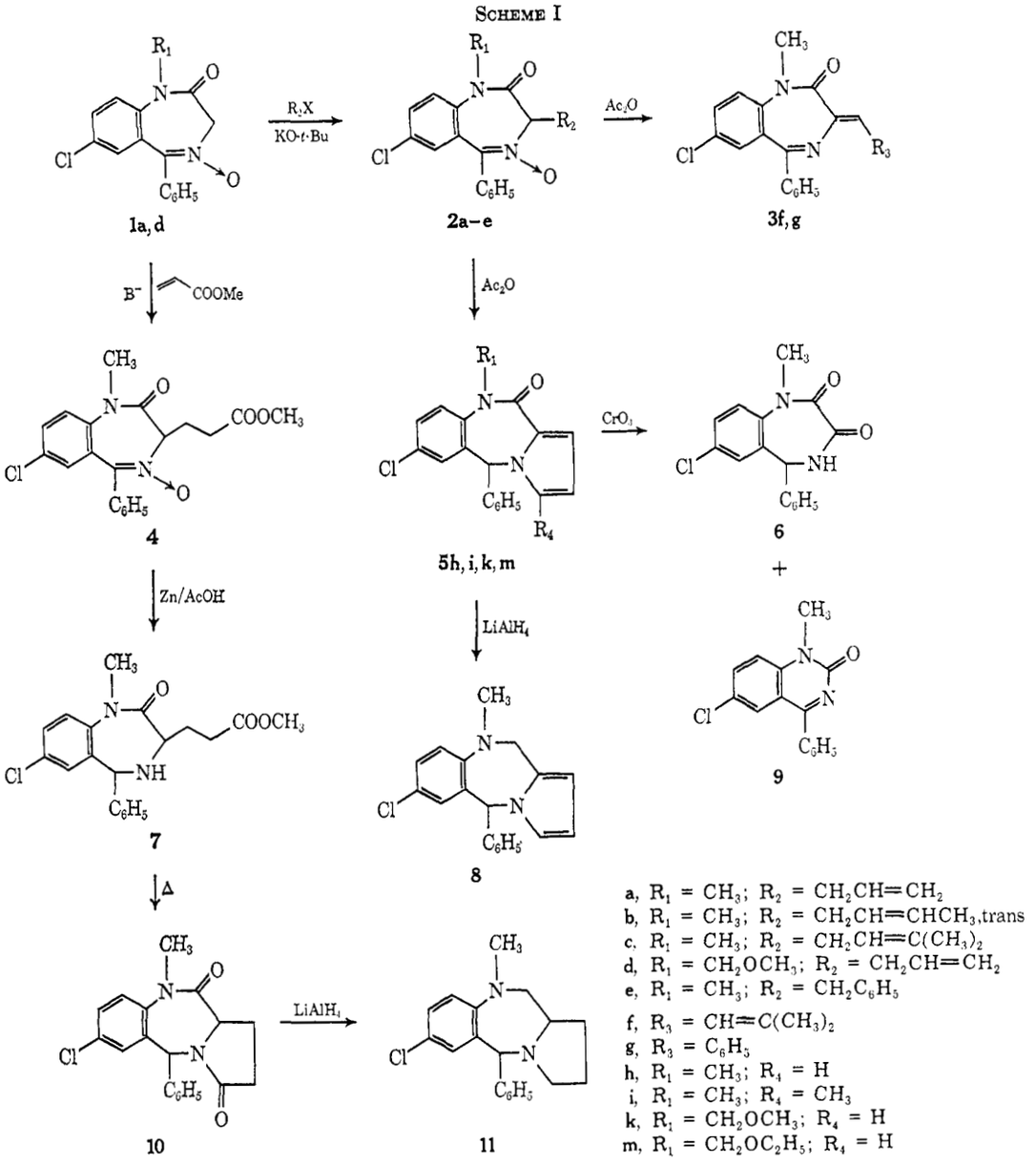
(3) A. Walser, G. Silverman, R. Ian Fryer, L. H. Sternbach, and J. Hellerbach, *J. Org. Chem.*, **36**, 1248 (1971).

(4) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(5) A. M. Felix, J. V. Earley, R. I. Fryer, and L. H. Sternbach, *J. Heterocycl. Chem.*, **5**, 731 (1968).

(6) E. Broger, unpublished work of these laboratories. Analysis provided by courtesy of E. Broger.

SCHEME I



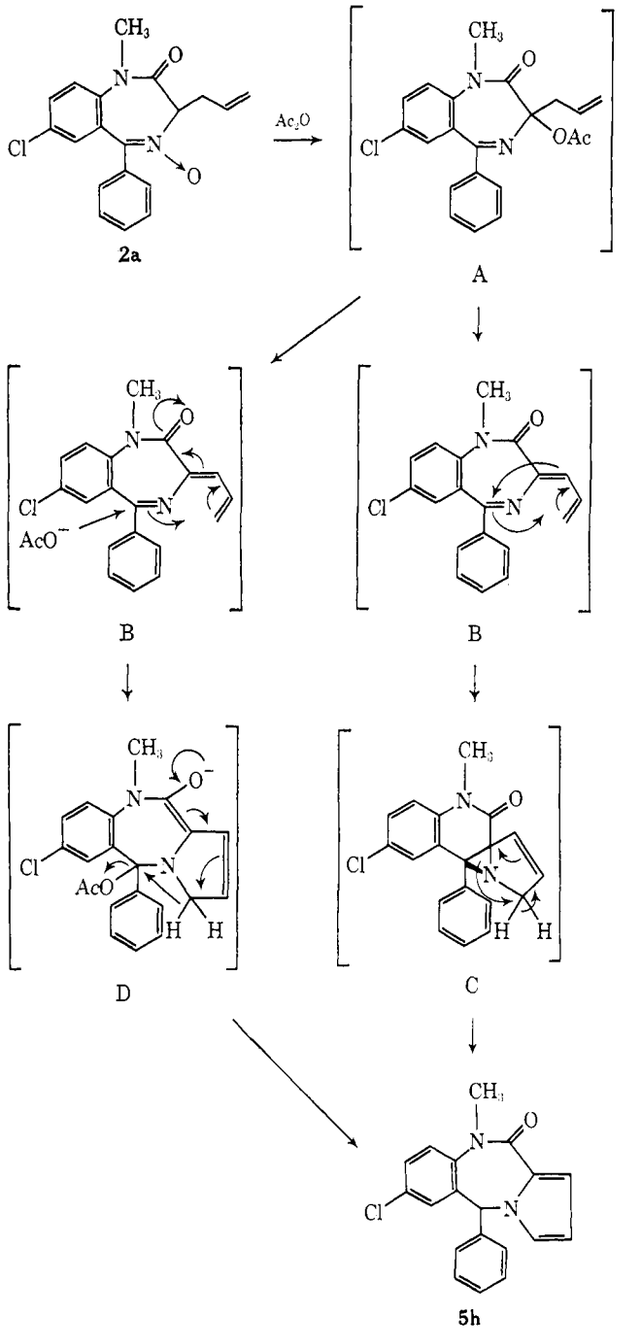
a, $R_1 = CH_3$; $R_2 = CH_2CH{=}CH_2$
b, $R_1 = CH_3$; $R_2 = CH_2CH{=}CHCH_3$,trans
c, $R_1 = CH_3$; $R_2 = CH_2CH{=}C(CH_3)_2$
d, $R_1 = CH_2OCH_3$; $R_2 = CH_2CH{=}CH_2$
e, $R_1 = CH_3$; $R_2 = CH_2C_6H_5$
f, $R_3 = CH{=}C(CH_3)_2$
g, $R_3 = C_6H_5$
h, $R_1 = CH_3$; $R_4 = H$
i, $R_1 = CH_3$; $R_4 = CH_3$
k, $R_1 = CH_2OCH_3$; $R_4 = H$
m, $R_1 = CH_2OC_2H_5$; $R_4 = H$

hydride produced the desired pyrrolidine **11**. Although the stereochemistry has not been unequivocally established it is believed that it is most likely that both the C_3 proton and the C_6 proton of compound **7** take a pseudoaxial orientation. This may also be true for the corresponding protons in the pyrrolidinobenzodiazepines **10** and **11**. The nmr spectra of **7**, **10**, and **11** do not contradict this assignment of stereochemistry.

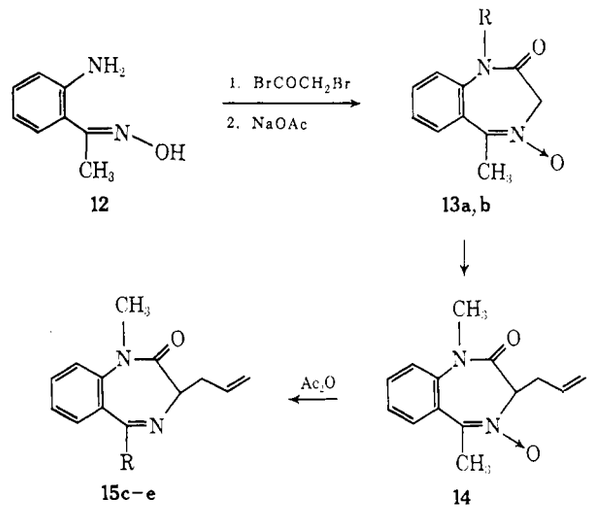
We also looked at the reaction of the 5-methyl analog of **2a**, compound **14**, with acetic anhydride. The benzodiazepine **14** was prepared as shown in Scheme III by alkylation of **13b** with allyl bromide. Compound **13b** was obtained by methylation of **13a**,[7] which in turn was accessible by bromoacetylation of the oxime **12** followed by cyclization of the intermediate bromo acetate. In this case treatment of **14** with acetic anhydride did not give the analogous pyrrolobenzodiazepine. The major product was found to be the 5-acetoxymethyl derivative **15c**. Methanolysis of this acetate produced the rather unstable alcohol **15d**, which was oxidized with manganese dioxide to give the aldehyde **15e**. We observed an unusual long-range coupling between the aliphatic protons of the C_5 substituent and one of the C_3 protons. If it is assumed that in compound **13b** the pseudoaxial proton in the 3 position is more shielded and appears therefore at higher field, then the pseudoequatorial proton would be responsible for the long-range coupling. If this is true it would follow that the allyl group in compounds **14**, **15c**, and **15d** would favor a pseudoaxial orientation. A proton-free 5 substituent seems to be required on the 1,4-benzodiazepine **2** in order to obtain a good yield of the pyrrolobenzodiazepines **5**, since in the Polonovsky reaction the *N*-oxide showed a preference for migration to the 5-methyl group rather than to the 3-methine moiety.

(7) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

SCHEME II



SCHEME III



a, R = H
b, R = CH_3
c, R = CH_2OAc
d, R = CH_2OH
e, R = CHO

Experimental Section

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian A-60 or Varian T-60 instrument in deuteriochloroform with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography.

3-Allyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (2a).—Potassium *tert*-butoxide (13.5 g, 0.12 mol) was added to a solution of 30 g (0.1 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (1a)[8] in 200 ml of dry dimethylformamide cooled to 0°. After stirring for 5 min under nitrogen the mixture was further cooled to −45°, when 14.5 g (0.12 mol) of allyl bromide was added. Cooling was discontinued and the reaction mixture was stirred until it reached room temperature, when it was poured into ice water. The precipitated product was collected, washed with water, and dissolved in methylene chloride. The solution was washed with water, dried over sodium sulfate, filtered, and evaporated. The residue was crystallized from ether to yield 24 g (70%) of product, mp 178–180°. The analytical sample was recrystallized from methanol: mp 183–185°; uv λ_{max} 240–241 mμ (ε 30,400) infl 270 (13,500), 316–317 (11,500); ir ($CHCl_3$) 1660 cm^{-1} (CO); nmr δ 3.05 (m, 2, $-CH_2-$), 3.45 (s, 3, NCH_3), 4.26 (t, 1, J = 7 Hz, C_3H), 4.9–6.3 (m, 3, olefinic H), 7–7.9 (m, 8, aromatic H).

Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 67.25; H, 4.08; N, 8.14.

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-3-(*trans*-2-butenyl)-2*H*-1,4-benzodiazepin-2-one 4-Oxide (2b).—7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide, 30 g (0.1 mol), in 200 ml of dimethylformamide was allowed to react for 20 min at room temperature with 13.5 g (0.12 mol) of potassium *tert*-butoxide and 11 g (0.12 mol) of crotyl chloride. Work-up as described in the previous procedure and crystallization from methanol yielded 10.5 g (30%) of product. The analytical sample was recrystallized twice from methanol: mp 164–167°; nmr ($CDCl_3$) δ 1.63 (d with fine structure, 3, J = 4.5 Hz, CH_3), 3.0 (m, 2, $-CH_2-$), 3.5 (s, 3, NCH_3), 4.2 (t, 1, J = 7 Hz, C_3H), 5.6 (m, 2, olefinic H), 7.1–7.9 (m, 8, aromatic H).

Anal. Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.40; N, 7.90. Found: C, 67.92; H, 5.50; N, 7.87.

7-Chloro-1,3-dihydro-3-(3-methyl-2-butenyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (2c).—Similarly, the alkylation of 30 g (0.1 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide with 12.5 g (0.12 mol) of 3-methyl-1-chloro-2-butene and 13.5 g (0.12 mol) of potassium *tert*-butoxide in 200 ml of dimethylformamide yielded 20 g (57%) of product, crystallized from methanol. The analytical sample was recrystallized from methanol: mp 149–151°; nmr ($CDCl_3$) δ 1.68 (s, 6, CH_3), 3.02 (m, 2, $-CH_2-$), 3.48 (s, 3, NCH_3), 4.15 (t, 1, J = 7 Hz, C_3H), 5.1 (broad t, 1, J = 6 Hz, CH=), 7.1–7.9 (m, 8, aromatic H).

Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; N, 5.74; N, 7.59. Found: C, 68.39; H, 5.81; N, 7.56.

3-Allyl-7-chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (2d).—A solution of 33 g (0.1 mol) of 7-chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (1d)[2] in 200 ml of dimethylformamide was cooled to −30°. Potassium *tert*-butoxide (13.5 g, 0.12 mol) was added with stirring under nitrogen. After 10 min the reaction mixture was cooled to −50° and 14.5 g of allyl bromide was added. When the temperature had reached 0°, the reaction mixture was poured into ice water. The resinous precipitate was extracted with methylene chloride.

(8) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

The combined extracts were washed with water, dried over sodium sulfate, and evaporated. Crystallization of the residue from ethanol yielded 18.5 g (50%) of product: mp 137–139°; nmr ($CDCl_3$) δ 3.06 (m, 2, $-CH_2-$), 3.4 (s, 3, OCH_3), 4.30 (t, 1, J = 7 Hz, C_3 H), 4.94 (d, 1) and 5.4 (d, 1) (AB system, J = 10.5 Hz, OCH_2N), 4.8–6.2 (m, 3, olefinic H), 7–7.8 (m, 8, aromatic H).

Anal. Calcd for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55. Found: C, 64.68; H, 5.43; N, 7.82.

7-Chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5h).—A mixture of 17 g (0.05 mol) of 3-allyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**2a**) and 200 ml of acetic anhydride was refluxed for 3 hr with slow distillation of 100 ml of the solvent (collected in a Dean–Stark trap). The reagent was evaporated under reduced pressure, at the end azeotropically with toluene. Crystallization of the residue from ether yielded 10.6 g (66%) of product, mp 221–222°. The analytical sample was recrystallized from CH_2Cl_2–hexane: mp 223–225°; uv λ_{max} 242 mμ (ε 15,650), 277–278 (10,150); ir ($CHCl_3$) 1620 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.0 (s, 3, NCH_3), 6.16 (s, 1, C_5 H), 6.2–7.6 (m, 11, aromatic H).

Anal. Calcd for $C_{19}H_{15}ClN_2O$: C, 70.70; H, 4.68; N, 8.68. Found: C, 70.70; H, 4.70; N, 8.87.

7-Chloro-5,10-dihydro-3,10-dimethyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5i).—7-Chloro-1,3-dihydro-1-methyl-5-phenyl-3-(*trans*-2-butenyl)-2*H*-1,4-benzodiazepin-2-one 4-oxide (**2b**) (3.55 g) was refluxed in 40 ml of acetic anhydride for 48 hr under an atmosphere of nitrogen. The reagent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and aqueous ammonia. The methylene chloride layer was dried and evaporated. The residue was chromatographed over 200 g of silica gel with benzene–ether (1:1, v/v). Crystallization of the pure fractions from methylene chloride–petroleum ether (bp 30–60°) yielded 1.25 g (37%) of colorless product: mp 214–216°; uv λ_{max} 244 mμ (ε 17,800), infl 265 (10,400), 288 (12,800); ir ($CHCl_3$) 1630 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.40 (s, 3, CH_3), 2.97 (s, 3, NCH_3), 6.05 (d, 1, J = 4 Hz, pyrrole H), 6.20 (s, 1, C_5 H), 6.6–7.6 (m, 9, 8 aromatic H and pyrrole H).

Anal. Calcd for $C_{20}H_{17}ClN_2O$: C, 71.32; H, 5.09; N, 8.32. Found: C, 71.15; H, 5.10; N, 8.17.

7-Chloro-5,10-dihydro-10-methoxymethyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5k).—A mixture of 37 g (0.1 mol) of 3-allyl-7-chloro-1,3-dihydro-1-methoxymethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**2d**) and 300 ml of acetic anhydride was refluxed for 3 hr. The reagent was evaporated under reduced pressure and the residue was crystallized from benzene to yield 18.2 g (51%) of product: mp 196–198° after recrystallization from methylene chloride–ethanol; uv λ_{max} 239–240 mμ (ε 17,800), 279 (11,650); ir ($CHCl_3$) 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.30 (s, 3, OCH_3), 4.20 (d, 1) and 4.88 (d, 1) (AB system, J = 10.5 Hz, OCH_2N), 6.15 (s, 1, C_5 H) 6.25–7.8 (m, 11, aromatic H).

Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.08; H, 4.86; N, 7.94. Found: C, 68.27; H, 4.92; N, 8.08.

7-Chloro-5,10-dihydro-10-ethoxymethyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5m).—Ethanol (10 ml) containing 5% hydrogen chloride was added to a solution of 1 g of 7-chloro-5,10-dihydro-10-methoxymethyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**5k**) in 10 ml of methylene chloride. After sitting for 3 days at room temperature the solvents were removed under reduced pressure and the residue was crystallized from ethanol to yield 0.75 g (72%) of product: mp 148–151°; uv λ_{max} 238–239 mμ (ε 16,300), 277–278 (11,100); ir ($CHCl_3$) 1630 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.14 (t, 3, J = 7 Hz, CH_3), 3.5 (m, 2, OCH_2CH_3, protons not equivalent), 4.26 (d, 1) and 4.97 (d, 1) (AB system, J = 10.5 Hz, OCH_2N), 6.2 (s, 1, C_5 H), 6.25–8 (m, 11, aromatic H).

Oxidation of 7-Chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (5h) with Chromic Acid.—A solution of 6 g of chromium trioxide in 10 ml of water was added to a solution of 2 g of 7-chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one in 70 ml of glacial acetic acid. The mixture was stirred for 16 hr, diluted with ice water, made alkaline with aqueous ammonia, and extracted with methylene chloride. The extracts were dried and evaporated. The residue was chromatographed over 40 g of silica gel with 25% methylene chloride in ethyl acetate. The first eluted product, 0.6 g (32%), mp 224–228°, was found to be identical in every respect with 7-chloro-1-methyl-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepine-2,3-(1*H*)-dione (**6**).[4] The later eluted compound (0.1 g, 6%) melted at 227–230° and was found to be identical with 6-chloro-1,2-dihydro-1-methyl-4-phenylquinazolin-2-one (**9**).[5]

7-Chloro-1,3-dihydro-3-(3-methyl-2-butenylidene)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (3f).—A mixture of 1 g of 7-chloro-1,3-dihydro-3-(3-methyl-2-butenyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**2c**) and 10 ml of acetic anhydride was heated to reflux for 15 min. The excess reagent was removed under reduced pressure. The residue was partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was separated, dried, and evaporated. Crystallization of the residue from ether–petroleum ether yielded 0.43 g (45%) of deep yellow crystals, mp 157–161°. The analytical sample was recrystallized from methylene chloride–petroleum ether: mp 163–166°; uv λ_{max} 206 mμ (ε 34,600), sh 230 (26,800), 236 (27,100), sh 255 (22,500), 290 (17,900), 380 (5400); ir ($CHCl_3$) 1660 cm^{-1} (NCO); nmr ($CDCl_3$) δ 1.82 (s, 3, CH_3), 1.90 (s, 3, CH_3), 3.38 (s, 3, NCH_3), 6.25 (d with fine structure, 1) and 6.50 (d, 1) (AB system, J = 11 Hz, =CHCH=), 7–8 (m, 8, aromatic H).

Anal. Calcd for $C_{21}H_{19}ClN_2O$: C, 71.89; H, 5.46; N, 7.98. Found: C, 71.65; H, 5.54; N, 7.92.

3-Benzylidene-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (3g).—A solution of 1.95 g (0.005 mol) of 3-benzyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide[3] in 30 ml of acetic anhydride was refluxed for 1 hr. The reagent was evaporated under reduced pressure. The residue was partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ether–petroleum ether yielded 1.3 g (70%) of yellow prisms: mp 189–192°; nmr ($CDCl_3$) δ 3.44 (s, 3, NCH_3), 6.47 (s, 1, $=CHC_6H_5$), 7–8 (m, 13, aromatic H).

Anal. Calcd for $C_{23}H_{17}ClN_2O$: C, 74.10; H, 4.60; N, 7.51. Found: C, 74.26; H, 4.65; N, 7.41.

The evaporated mother liquors were chromatographed over 20 g of silica gel using 5% ethyl acetate in methylene chloride. The fractions containing the slower moving spot were combined and evaporated. Crystallization from methylene chloride–ether–petroleum ether yielded 50 mg of yellow crystals: mp 207–212°; nmr ($CDCl_3$) δ 3.48 (s, 3, NCH_3), 6.2 (s, 1, $=CHC_6H_5$), 7–8 (m, 13, aromatic H).

7-Chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (8).—7-Chloro-5,10-dihydro-10-methyl-5-phenyl-11*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**5h**) (3.2 g, 0.01 mol) was added in portions to a suspension of 2 g (0.05 mol) of lithium aluminum hydride in 100 ml of ether. After 4 hr of reflux the reaction mixture was hydrolyzed by addition of 10 ml of water. The inorganic material was filtered and washed with methylene chloride. The filtrate was dried and evaporated. Crystallization of the residue from methylene chloride–petroleum ether yielded 2.15 g (70%) of colorless prisms: mp 150–153°; uv λ_{max} 272 mμ (ε 10,500), 310 (2200); nmr ($CDCl_3$) δ 2.78 (s, 3, NCH_3), 3.72 (d, 1) and 4.10 (d, 1) (AB system, J = 15 Hz, C_{11} H), 5.9–6.25 (m, 3, C_3 H and 2 pyrrole H), 6.6–7.5 (m, 9, aromatic H and 1 pyrrole H).

Anal. Calcd for $C_{19}H_{17}ClN_2$: C, 73.90; H, 5.55; N, 9.07. Found: C, 73.94; H, 5.65; N, 9.08.

7-Chloro-1,3-dihydro-3-(2-methoxycarbonylethyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (4).—A solution of 4.75 g (0.055 mol) of methyl acrylate in 20 ml of dimethylformamide was added to a mixture of 15 g (0.05 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**1a**), 0.75 g of potassium *tert*-butoxide, and 150 ml of dimethylformamide cooled to −35°. Cooling was discontinued after 10 min and the reaction mixture was stirred overnight under an atmosphere of nitrogen. After neutralization with acetic acid the product was precipitated by dilution with water. The collected precipitate was partitioned between methylene chloride and water. The organic phase was dried and evaporated. The residue was crystallized from ether and recrystallized twice from methylene chloride–methanol to leave 6.6 g (34%) of product: mp 179–182°; nmr ($CDCl_3$) δ 2.2–3.0 (m, 4, $-CH_2CH_2-$), 3.48 (s, 3, NCH_3), 3.62 (s, 3, OCH_3), 4.48 (t, 1, J = 6 Hz, C_3 H), 7.15 (d, 1, J = 2 Hz, C_6 H), 7.2–7.8 (m, 7, C_6H_5, C_8 H, C_9 H).

Anal. Calcd for $C_{20}H_{19}ClN_2O_4$: C, 62.10; H, 4.95; N, 7.24. Found: C, 62.37; H, 5.01; N, 7.24.

7-Chloro-3-(2-methoxycarbonylethyl)-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (7).—Zinc dust (30 g) was added in portions to a solution of 19.3 (0.05 mol) of 7-chloro-1,3-dihydro-3-(2-methoxycarbonylethyl)-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**4**) in 300 ml of glacial acetic acid. After addition, stirring was continued for 2 hr. The reaction mixture was filtered and the filtrate was made alkaline with ice and ammonia and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization from ether yielded 12.3 g (66%) of colorless product, mp 174–178°. The analytical sample was recrystallized from methylene chloride–ether: mp 177–180°; uv λ_{max} 240 mμ (ε 14,900), infl 290 (1300); ir ($CHCl_3$) 3300 (NH), 1740 (COOMe), 1670 cm^{-1} (NCO); nmr ($CDCl_3$) δ 2.06 (broad s, 1, NH), 1.8–2.7 (m, 4, $-CH_2CH_2-$), 3.35 (t, 1, J = 6.5 Hz, C_3 H), 3.52 (s, 3, NCH_3), 3.68 (s, 3, OCH_3), 5.25 (s, 1, C_5 H), 6.64 (d, 1, J = 2 Hz, C_6 H), 7.0–7.8 (m, 7, aromatic H).

Anal. Calcd for $C_{20}H_{21}ClN_2O_3$: C, 64.43; H, 5.67; N, 7.51. Found: C, 64.45; H, 5.54; N, 7.50.

7-Chloro-5,10-dihydro-10-methyl-5-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-3,11(2*H*,11a*H*)-dione (10).—A solution of 15 g of 7-chloro-3-(2-methoxycarbonylethyl)-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**9**) in 100 ml of quinoline was heated at 225–235° for 2 hr. After cooling the reaction mixture was partitioned between 2 *N* hydrochloric acid and methylene chloride. The methylene chloride layer was washed twice with 2 *N* hydrochloric acid and once with water. It was dried and evaporated. Crystallization of the residue from ether–petroleum ether after treatment with charcoal yielded 7.4 g (54%) of product. For analysis it was recrystallized from methylene chloride–methanol: mp 193–195°; uv λ_{max} 240 mμ (ε 11,020), 253 (11,150), infl 290 (800); ir ($CHCl_3$) 1700, 1680 cm^{-1} (NCO); nmr ($CDCl_3$) 1.6–2.9 (m, 4, $-CH_2CH_2-$), 3.41 (s, 3, NCH_3), 4.33 (d, 1, J = 6 Hz, C_3 H), 5.70 (s, 1, C_5 H), 6.46 (d, 1, J = 2 Hz, C_6 H), 7–7.6 (m, 7, aromatic H).

Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.93; H, 4.94; N, 8.26.

7-Chloro-10-methyl-5-phenyl-1,2,3,5,11,11a-hexahydro-10*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (11).—7-Chloro-5,10-dihydro-10-methyl-5-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-3,11-(2*H*,11a*H*)-dione (**10**) (6.8 g, 0.02 mol) was added in portions to a suspension of 5 g (0.125 mol) of lithium aluminum hydride in 250 ml of ether. After addition, the mixture was stirred at room temperature for 15 min and was then heated to reflux for 6 hr. The hydride was hydrolyzed by addition of 25 ml of water. The inorganic material was filtered off and washed with methylene chloride. The filtrate was dried and evaporated. Crystallization of the residue from ether yielded 4 g (64%) of product: mp 145–148° after recrystallization from methylene chloride–methanol; uv λ_{max} 263 mμ (ε 11,030), sh 300 (2390); nmr ($CDCl_3$) δ 2.86 (s, 3, NCH_3), 1.3–3.9 (m, 9, $-CH_2-$, CH), 5.1 (s, 1, C_5 H), 6.60 (d, 1, J = 2 Hz, C_6 H), 6.76 (d, 1, J = 9 Hz, C_9 H), 7.15 (q, 1, J_{AB} = 9, J_{AX} = 2 Hz, C_8 H), 7.35 (broad s, 5, C_6H_5).

Anal. Calcd for $C_{19}H_{21}ClN_2$: C, 72.95; H, 6.76; N, 8.95. Found: C, 72.85; H, 6.81; N, 8.96.

1,3-Dihydro-5-methyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (13a).[7]—Bromoacetyl bromide (120 g, 0.6 mol) was added slowly to a vigorously stirred two-phase mixture of 60 g (0.4 mol) of 2-aminoacetophenone oxime, 500 ml of methylene chloride, and 1 l. of saturated sodium bicarbonate solution. After complete addition, stirring was continued for 15 min. The methylene chloride layer was separated, washed with bicarbonate solution and water, dried over sodium sulfate, and evaporated. The residue was dissolved in 1 l. of ethanol. Glacial acetic acid (50 ml) and 50 g of anhydrous sodium acetate were added. The mixture was refluxed with stirring for 1 hr. The solvent was evaporated under reduced pressure and the product was precipitated by addition of water. It was collected, washed with water, and crystallized from acetone–methanol to yield 24 g (31.5%), mp 235–240°.

1,3-Dihydro-1,5-dimethyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (13b).—Potassium *tert*-butoxide (12.5 g, 0.11 mol) was added to a solution of 19 g (0.1 mol) of 1,3-dihydro-5-methyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**13a**) in 500 ml of dimethylformamide cooled to 0°. After stirring for 5 min, 15.6 g (0.11 mol) of methyl iodide was added and the mixture was stirred at room temperature for 90 min. Most of the dimethylformamide was removed under reduced pressure. The residue was crystallized by addition of water. The crystals were collected, washed with water, and recrystallized from methylene chloride–ethyl acetate to leave 12.5 g (61%) of product, mp 255–260°. The analytical sample was recrystallized from ethyl acetate–methanol: mp 268–271°; nmr (DMSO) δ 2.50 (d, 3, J = 1 Hz, C_5 CH_3), 3.56 (s, 3, NCH_3), 4.46 (d, 1, J = 14 Hz, C_3 H), 4.95 (d with fine structure, 1, J = 14 Hz, C_3 H) 7.1–7.7 (m, 4, aromatic H).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.93; H, 5.97; N, 13.78.

3-Allyl-1,3-dihydro-1,5-dimethyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (14).—A solution of 20.5 g (0.1 mol) of 1,3-dihydro-1,5-dimethyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**13b**) in 1 l. of dimethylformamide was cooled to −20° with stirring under nitrogen. Potassium *tert*-butoxide (14 g, 0.125 mol) was added and stirring was continued for 5 min. After the solution was cooled further down to −50°, 15 g (0.125 mol) of allyl bromide was added. The reaction mixture was allowed to reach room temperature and was neutralized with glacial acetic acid and evaporated under reduced pressure. The residue was partitioned between methylene chloride and water. The methylene chloride layer was separated, dried, and evaporated. Crystallization of the residue from ether yielded 14 g (57%) of product. The analytical sample was recrystallized from ethyl acetate–hexane: mp 138–141°; nmr ($CDCl_3$) δ 2.47 (d, 3, J = 2 Hz, 5 CH_3), 3.04 (m, 2, $-CH_2-$), 3.45 (s, 3, NCH_3), 4.14 (t, 1, J = 7 Hz, C_3 H), 4.9–6.3 (m, 3, $CH=CH_2$), 7.2–7.8 (m, 4, aromatic H).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.84; H, 6.60; N, 11.46. Found: C, 68.98; H, 6.55; N, 11.54.

5-Acetoxymethyl-3-allyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (15c).—A mixture of 12.2 g (0.05 mol) of 3-allyl-1,3-dihydro-1,5-dimethyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**14**), 50 ml of acetic anhydride, and 250 ml of toluene was heated to reflux for 3 hr. During this period 100 ml of toluene was removed by distillation. The reaction mixture was then evaporated and the residue was crystallized from ether–hexane to yield 8.6 g (60%) of product. Recrystallization from ether–hexane yielded colorless crystals: mp 82–84°; uv λ_{max} 227 mμ (ε 34,000), infl 250 (6500), 300 (1600); ir ($CHCl_3$) 1750 (OAc), 1680 cm^{-1} (NCO); nmr ($CDCl_3$) δ 2.05 (s, 3, $COCH_3$), 2.92 (m, 2, $-CH_2-$), 3.4 (s, 3, NCH_3), 3.5 (m, 1, C_3 H), 5.15 (d, 2, J = 2 Hz, $-CH_2OAc$), 4.9–6.3 (m, 3, $-CH=CH_2$), 7–7.8 (m, 4, aromatic H).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.33; N, 9.78. Found: C, 67.07; H, 6.51; N, 9.82.

3-Allyl-1,3-dihydro-5-hydroxymethyl-1-methyl-2*H*-1,4-benzodiazepin-2-one (15d).—Sodium methoxide (0.6 g, 11 mmol) was added to a solution of 2.86 g (10 mmol) of 5-acetoxymethyl-3-allyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**15c**) in 50 ml of methanol. After the solution had stood at room temperature for 1 hr the methanol was evaporated and the residue was partitioned between methylene chloride and water. The methylene chloride layer was dried and evaporated. The product was crystallized from ether–hexane and recrystallized from methylene chloride–ether–hexane to yield 1.5 g (61%): mp 100–106°; uv λ_{max} 225 mμ (ε 34,300), infl 250 (6200), 297 (1750); ir ($CHCl_3$) 3375 (OH), 1670 cm^{-1} (NCO); nmr ($CDCl_3$) δ 2.90 (t, 2, J = 7 Hz, $-CH_2-$), 3.40 (s, 3, NCH_3), 3.60 (m, 1, C_3 H), 3.87 (broad s, 1, OH), 4.33 (q, 1, J_{AB} = 17, J_{AX} = 2 Hz), and 4.94 (q, 1, J_{AB} = 17, J_{AX} = 2 Hz) (CH_2OH), 4.9–6.3 (m, 3, $CH=CH_2$), 7–7.8 (m, 4, aromatic H).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found: C, 68.73; H, 6.50; N, 11.44.

This compound was sensitive to air and discolored to red.

3-Allyl-1,3-dihydro-5-formyl-1-methyl-2*H*-1,4-benzodiazepin-2-one (15e).—A mixture of 1 g of 3-allyl-1,3-dihydro-5-hydroxymethyl-1-methyl-2*H*-1,4-benzodiazepin-2-one (**15d**), 7 g of manganese dioxide, and 30 ml of methylene chloride was stirred at room temperature for 1 hr. The manganese dioxide was removed by filtration. The filtrate was evaporated and the residue was chromatographed over 30 g of silica gel using 2.5% (v/v) ether in methylene chloride. Crystallization of the combined homogenous fractions from ether–hexane yielded 0.55 g (55%) of product: mp 68–71°; uv λ_{max} 234 mμ (ε 19,700), sh 275 (2800), 324 (1180); ir ($CHCl_3$) 1720 (CHO), 1680 cm^{-1} (NCO); nmr ($CDCl_3$) δ 3.07 (t, 2, J = 7 Hz, $-CH_2-$), 3.40 (s, 3, NCH_3), 3.77 (t, 1, J = 7 Hz, C_3 H), 4.9–6.3 (m, 3, $CH=CH_2$), 7.1–7.9 (m, 4, aromatic H), 9.77 (s, 1, CHO).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.68; H, 5.81; N, 11.27.

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Registry No.—1a, 2888-64-4; 1d, 28506-53-8; 2a, 41075-53-0; 2b, 40973-75-9; 2c, 40973-76-0; 2d, 41075-54-1; 2e, 28199-30-6; 3f, 40973-78-2; *cis*-3g, 40973-79-3; *trans*-3g, 40973-80-6; 4, 40973-81-7; 5h, 40973-82-8; 5i, 40973-83-9; 5k, 40973-84-0; 5m, 40973-85-1; 6, 3294-96-0; 7, 40973-87-3; 8, 40973-88-4; 9, 20927-53-1; 10, 40973-90-8; 11, 40973-91-9; 12, 4964-49-2; 13a, 40973-93-1; 13b, 40973-94-2; 14, 40973-95-3; 15c, 40973-96-4; 15d, 40973-97-5; 15e, 40973-98-6; allyl bromide, 106-95-6; crotyl chloride, 625-35-4; 1-chloro-3-methyl-2-butene, 503-60-6.

Carboxyalkylthioacrylates[1]

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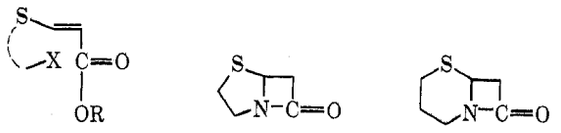
Base-catalyzed addition of mercaptoalkanoic acids and esters to propiolic acid and its esters gives, under mild conditions, carboxyalkylthioacrylic acids and their mono- and diesters. Reaction in protic polar solvents gives predominantly cis thioacrylates whereas aprotic solvents strongly favor the trans products.

It is well known that thioacrylates (I) are produced when thiols add to propiolic acid and its esters.[2]

$$RSH + HC{\equiv}CCOOR' \longrightarrow RSCH{=}CHCOOR'$$

Our interest in these compounds stemmed from the observation that the S—C=C—C=O moiety which they contain simulates a major structural feature of the penicillins (II) and cephalosporins (III). Thus,



I II III

suitably constructed thioacrylates might well be useful intermediates in the synthesis of such fused β-lactam antibiotics, the group X providing the nitrogen atom, and either X or the thioacrylate function the carbonyl group. Thioacrylates, moreover, are conveniently prepared in either the cis or the trans geometry, and preservation of this geometry during cyclization might permit a stereoselective penicillin–cephalosporin synthesis.

Alkyl, as opposed to aryl, thioacrylates seem to have been little studied. We report here upon one group of such compounds, the carboxyalkylthioacrylic acids (I, R = H, X = –COOH), their esters and half-esters, and other derivatives. The compounds (**1–15**) prepared are listed in Table I.

TABLE I

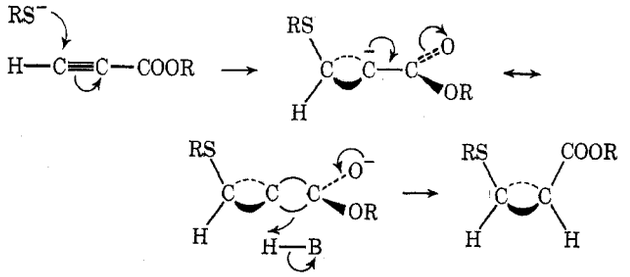
CARBOXYALKYLTHIOACRYLIC ACIDS AND ESTERS

A—CH_2CH_2—S—CH=CH—B

Compound		Group	
cis	trans	A	B
1	2	CO_2H	CO_2Et
3	4	CO_2H	CO_2H
5	6	CO_2Me	CO_2Et
7	8	CH_2CO_2H	CO_2H
9	10	CH_2CO_2H	CO_2Et
11		CO_2Me	CO_2H
12	13	COCl	COCl
14		$CONHC_6H_5$	CO_2Et
15		$CONHC_6H_5$	CO_2Et

The reaction of thiols with propiolates is very slow in the absence of catalysts but is accelerated remarkably by bases. Thus neutral alkanethiols such as benzyl mercaptan, methyl β-mercaptopropionate, and methyl γ-mercaptobutyrate react completely with propiolate esters in alcohol, aqueous alcohol, acetonitrile, or diethyl ether within 30–60 min after addition of catalytic amounts of pyridine or triethylamine at room temperature. Free mercaptoalkanoic acids neutralized to pH ~8 with rather more than 1 mol of aqueous base react equally readily, the pH of the reaction mixture rising to 10–12 as the buffering effect of the thiol group disappears. The reactive entity undoubtedly is the thiolate ion. Rather surprisingly, salts of propiolic acid react with thiols almost as readily as do esters. The carboxylate anion would hardly be expected to activate the acetylene to nucleophilic addition as much as the ester group does, and the question is open as to whether the propiolate anion or the small amount of free propiolic acid in equilibrium with it (at pH 8–9) is the entity which actually undergoes nucleophilic addition.

The predominant initial products from reactions effected in aqueous and alcoholic solvents were the cis alkylthioacrylates. The trans isomers usually could be recovered from mother liquors, with or without deliberate or fortuitous isomerization of residual cis material. The well-known rule of trans addition[3] thus is obeyed. The generally accepted rationalization of this rule involves coordination of thiolate ion at the β carbon of the acetylene to give a resonance-stabilized anion which subsequently accepts a proton from the protic solvent (HB) on its least-hindered side.



(1) A grant from Bristol Laboratories, Syracuse, N. Y. 13201, in support of this work is gratefully acknowledged.

(2) A comprehensive list of references is given in a recent paper by W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, **37**, 2391 (1972).

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