Novel Lossen Rearrangements of 3-Benzenesulfonyloxy(1*H*- and 1-methyl)-2,4-quinazolinediones Induced by Alkoxide Ions[1]

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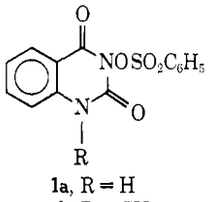
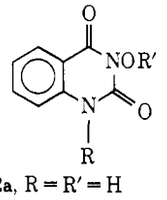
Unexpected Lossen rearrangement products are obtained when sodium alkoxides are added slowly to a solution of the title compounds, **1a** and **1b**, in either alcoholic or DMF media. The slow addition of sodium methoxide to a solution of **1a** in hot methanol furnished *o*-$C_6H_4(CO_2CH_3)NHNHCO_2CH_3$ (45%). A by-product of this reaction is 3-hydroxy-2,4-quinazolinedione (**2a**, 34%), which becomes the major product when **1a** is boiled (3 min) either in aqueous sodium hydroxide or a methanol solution containing sodium methoxide. However, the reaction of **1a** with sodium hydride or methoxide in DMF gave 2-benzimidazolone (88%). The 1-methyl analog, **1b**, was rearranged by various alkoxide ions to 3-indazolone derivatives (40–78%) together with 1-methyl-3-hydroxy-2,4-quinazolinedione (10–35%). Mechanisms are advanced to explain these rearrangements.

The almost spontaneous rearrangement of 3-benzenesulfonyloxy-5,6-dihydrouracil to give ethylenediamine takes place in an aqueous solution containing 1 equiv of sodium hydroxide.[2] In contrast, the aromatic analog, 3-benzenesulfonyloxy-2,4-quinazolinedione (**1a**), is quite stable in a cold 10% aqueous sodium hydroxide solution, but is hydrolyzed to the *N*-hydroxy heterocycle **2a** (77%) after the solution is boiled for several minutes.[2] This nucleophilic substitution reaction involves attack by the base on sulfur with the release of the anion of **2a**. The sulfonate group was also lost when a methanol solution of **1a** containing 2 equiv of sodium methoxide was boiled briefly to furnish **2a** in 78% yield.



1a, R = H
b, R = CH_3



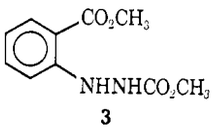
2a, R = R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = CH_3
d, R = R′ = CH_3

Rearrangements of 1a.—The *slow* addition of sodium methoxide to a solution of **1a** in hot methanol led to the interesting observation that, besides **2a** (34%), there is formed the *o*-hydrazino ester **3** (45%) and 3-methoxy-2,4-quinazolinedione (**2c**, 7%). The structure of **3** was established by pmr and mass spectra and its transformation to 3-indazolone (**4a**). The identity of **2c** was established by comparison with a sample synthesized by methylating **2a**.

A further departure from the reactions described so far was realized when a solution of sodium methoxide was added to a solution of **1a** in *N*,*N*′-dimethylformamide (DMF) at 100°. There was isolated 2-benzimidazolone (**5a**) in 88% yield. This rearrangement perhaps closely parallels the one described for the conversion of 3-benzenesulfonyloxy-5,6-dihydrouracil to ethylenediamine.[2] Confronted with three different reactions for **1a** with bases, we investigated this matter further as a function of the bases and solvents.

(1) Presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 10, 1973.

(2) C. M. Buess and L. Bauer, *J. Org. Chem.*, **20**, 33 (1955). Initially, this reaction produces water-soluble derivatives (probably ureas) since no amides were formed with benzoyl chloride. However, acid- or base-catalyzed hydrolysis formed ethylenediamine, characterized as the benzamide.



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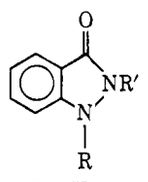
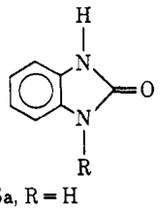
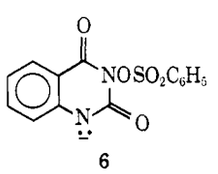


4a, R = R′ = H
b, R = CH_3; R′ = H
c, R = CH_3; R′ = CO_2CH_3



5a, R = H
b, R = $CO_2C_2H_5$
c, R = $CO_2CH(CH_3)_2$

On boiling **1a** in DMF for 3 hr, it was recovered unchanged, which indicated that a strong base was necessary to initiate these observed reactions. Sodium hydride in DMF was chosen as the least nucleophilic base and one most likely to neutralize the acidic NH proton of **1a** to form the anion **6**. Such a step would induce a Lossen rearrangement if **6** opens to **7**, which can be considered a precursor to *o*-benzene diisocyanate (**8**). Since solvents were removed prior to an aqueous work-up, it is suggested that **8** cyclized in DMF solution to benzimidazolone, *or* a substance capable of facile hydrolysis to benzimidazolone.



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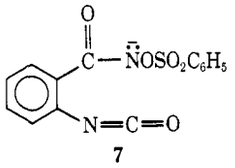

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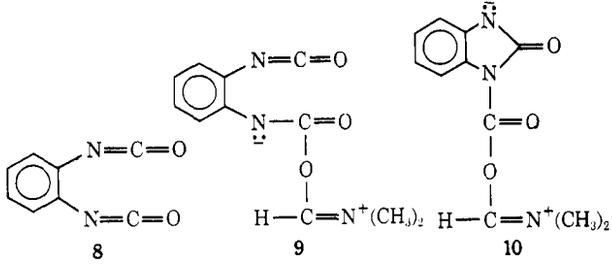
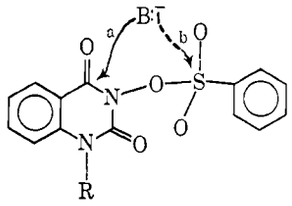


8 **9** **10**

The cyclization of **8** to **5a** in DMF can be explained if DMF, acting as a nucleophilic reagent, adds to **8** to create an intermediate, **9**, which cyclizes to **10**. The latter can be hydrolyzed during an aqueous work-up.

TABLE I

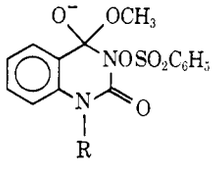
SUMMARY OF RESULTS OF NUCLEOPHILIC ATTACK OF A BASE B:⁻ ON 1



R	Base	Predominant solvent	Yield of product(s), %, due to attack on NH (R = H)	C-4 (path a)	S (path b)
H	NaH	DMF	82		
H	$NaOCH_3$	DMF	88		
H	$NaOCH_3$	CH_3OH		45	41
H	$NaOC_2H_5$	C_2H_5OH	93		5
H	$NaOCH(CH_3)_2$	$(CH_3)_2CHOH$	86		7
CH_3	$NaOCH_3$	CH_3OH		58	17
CH_3	$NaOCH_3$	DMF		78	10
CH_3	$NaOC_2H_5$	C_2H_5OH		41	32
CH_3	$NaOC_2H_5$	DMF		40	35
CH_3	$NaOCH(CH_3)_2$	$(CH_3)_2CHOH$		31	45

It would then appear that hydride or methoxide ions in DMF, acting as strong bases, neutralize, the acidic proton in **1a** and do not attack the sulfonate sulfur atom. In methanol, methoxide ion is less basic and considerably more solvated: the process of neutralization is suppressed while nucleophilic attack on the sulfonate group to give **2a** (path b, top of Table I) produces the anion of **2a** and methyl benzenesulfonate ($C_6H_5SO_3CH_3$). In this medium, the anion of **2a** can undergo an SN2 displacement reaction leading to **2c** and benzenesulfonate anion, which accounts for the 7% of **2c** isolated in that reaction.

However, nucleophilic attack on sulfur competes with one on the highly electrophilic carbon at position 4 in the quinazoline ring[3] (path a on top of Table I). Such an attack of methoxide anion on the C=O group at C-4 of **1a** would create a σ complex, **11** (R = H), which can collapse to form **12**. The latter is the Lossen type of precursor for **13**. The final step in the formation of **3** is the addition of methanol to the isocyanate group of **13** (R = H).



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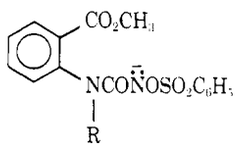

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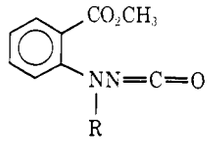

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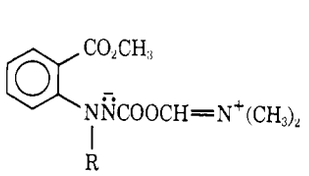
In anticipation that sodium ethoxide or isopropoxide, in their respective alcohols, would participate in similar reactions, it was rather surprising to discover that these alkoxide ions in their alcohols produced almost exclusively 2-benzimidazole derivatives **5** (see Table I). It is rather difficult to rationalize how a subtle structural change from methoxide to ethoxide ion would induce two different kind of reactions. The size of the solvated anion and the relative acidity of the methanol solution could expedite attack at C-4 *or* S, to the exclusion of the neutralization of NH in **1a**. The data in Table I summarize the results and the reaction in methanol appears outstandingly different.

Rearrangement of 1b.—The 1-methyl analog **1b** was subjected to a series of analogous reactions, to test if alkoxide ions would attack C-4 once the acidic proton was absent. Methylation of **1a** in cold DMF furnishes **1b** in excellent yield. The reaction of **1b** with sodium methoxide in DMF yielded fewer products than a comparable reaction in methanol. In DMF, there was formed **2b** (11%) and 1-methyl-3-indazolone (**4b**, 78%). The formation of **4b** is explained by attack of methoxide ion at C-4 of **1b** to create **11**–**13** (R = CH_3), which may cyclize in DMF *via* some plausible intermediates **14** and **15**. Methanolysis of the ester group at N-2 can then convert **15** to **4b**.



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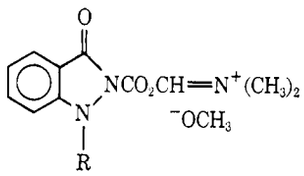

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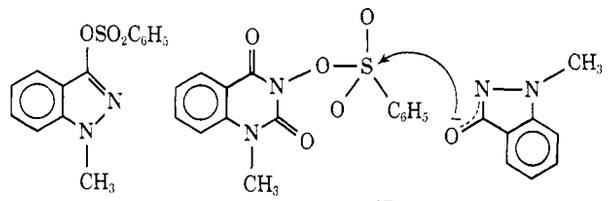
The analogous reaction of **1b** with methoxide ion in methanol furnishes **2b** (12%), **4b** (44%), **4c** (14%), and **2d** (5%). The formation of **4c** is visualized as proceeding *via* a urethane derived from **13** (R = CH_3) and subsequent cyclization. The mechanism suggested for the conversion of **1a** to a small quantity of **2c** (see above) can be applied to the transformation of **1b** to a small amount of **2d**.

We hypothesized that, in the absence of an acidic NH proton, ethoxide and isopropoxide ions would attack either C-4 or S. This premise was verified when **1b** was treated with sodium ethoxide in ethanol. As is evident (Table I) the attack on S increased over that on C-4 to give **2b** (32%) and **4b** (41%). However, the reaction of **1b** with sodium ethoxide in DMF

(3) The high electrophilicity at C-4 in quinazolines is discussed by A. Albert and W. L. F. Armarego in "Advances in Heterocyclic Chemistry," Vol. 4, A. R. Katrizky, Ed., Academic Press, New York, N. Y., 1965, p 1.

gave besides **2b** (35%) a mixture of 1-methyl-3-indazolone (11%) and its corresponding *o*-sulfonate **16** (29%).



16 **17**

A synthesis of **16** was accomplished by treating **1b** with **4b** in the presence of NaH in DMF. The ambident 1-methyl-3-indazolone anion attacks the sulfonate group as is drawn in **17**. It is therefore quite likely that, in DMF, the 3-indazolone anion, once produced, competes with the ethoxide ion in attacking **1b** to produce **16**.

In order to test the effect of increasing the bulk of the alkoxide ion, **1b** was treated with sodium isopropoxide in 2-propanol. Alcoholysis of the sulfonate group to give **2b** increased over the formation of indazole derivatives (**4b** and **16**) (Table I).

It is clear that the reactions of **1b** with ethoxide and isopropoxide ion still involve attack at C-4 and are not inhibited by the bulk of these nucleophiles.

Experimental Section[4]

Materials.—Methanol and ethanol refer to commercial grade absolute alcohols. Small quantities of sodium alkoxide solutions were prepared by diluting a stock solution of 1.2 g of sodium in 100 ml of the required alcohol.

3-Benzenesulfonyloxy-2,4(1*H*,3*H*)-quinazolinedione (1a).[5]—Finely powdered **2a**[6] (17.8 g, 0.1 mol) was dissolved in aqueous sodium hydroxide solution (8 g in 400 ml) and finally on a steam bath to dissolve traces of insoluble material. This solution was cooled to 5°, while benzenesulfonyl chloride (26 ml, 0.2 mol) was added dropwise, with stirring over 1 hr. The ice bath was then removed and the mixture was stirred at 25° for 3 hr. The solid was collected, washed with water and 95% ethanol, and recrystallized from 95% ethanol to give **1a** (25.8 g, 81%), mp 234–235° (lit.[2] mp 235–236°), ir identical with that of a literature sample.[2]

1-Methyl-3-benzenesulfonyloxy-2,4(1*H*,3*H*)-quinazolinedione (1b).—To a stirred solution of **1a** (9.7 g, 0.03 mol) in 100 ml of cold DMF and 20 ml of methyl iodide was added dropwise 0.03 mol of sodium ethoxide in 100 ml of ethanol over 2 hr at 25°. The mixture was stirred for 1 hr longer and then poured into 2 l. of ice–water. After 30 min, the white solid was collected, washed with water, and recrystallized from 95% ethanol to furnish pure **1b** (9.4 g, 93%): mp 187–189°; ir (Nujol) 1748, 1725 cm^{-1} (C=O); pmr (TFA) δ 8.46–7.40 (m, aromatic protons), 3.94 (s, NCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 334 (4), 333 (9), 332 (51), 176 (12), 161 (8), 142 (6), 141 (88), 134 (5), 133 (17), 132 (13), 105 (32), 104 (28), 92 (6), 90 (5), 78 (20), 77 (100), 64 (5), 51 (18), 50 (6), 39 (5).

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: N, 8.43. Found: N, 8.43.

Hydrolysis of **1b** (1 g) was achieved by heating it in 5% NaOH solution (10 ml) on a steam bath until a clear solution was obtained (about 5 min). The mixture was filtered to remove traces of insoluble material. The filtrate was cooled to 5° and acidified with concentrated HCl to pH 2. The wall of the flask was scratched and the solution was stored at 0° (3 days) and **2b** was deposited (0.37 g, 64%): mp 223–225° (lit.[7] mp 227°); its ir spectrum was identical with that of an authentic sample prepared by the other route;[7] mass spectrum (70 eV) *m/e* (rel intensity) 193 (12), 192 (100), 176 (27), 175 (6), 162 (38), 148 (5), 133 (11), 132 (62), 119 (5), 105 (32), 104 (33), 92 (80), 90 (8), 78 (16), 77 (28), 76 (8), 64 (10), 51 (13), 50 (10), 39 (8).

3-Methoxy-2,4(1*H*,3*H*)-quinazolinedione (2c).—A solution of **2a** (3.56 g, 0.02 mol) was stirred at 80°, while methyl sulfate (6.3 g, 0.05 mol) was added dropwise over 1 hr. After 2 hr another portion of methyl sulfate (6.3 g) was added and the mixture was stirred for 1 hr longer. The suspension was cooled, and the product (3.3 g 86%) was collected and washed with ice–water: mp 224–226°; ir (Nujol) 3250 (NH), 1750, 1720, 1690 cm^{-1} (C=O); pmr (TFA) δ 8.45–7.43 (4, m, aromatic protons), 4.41 (3, s, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 193 (4), 192 (31), 163 (7), 162 (41), 147 (6), 146 (46), 120 (12), 119 (100), 92 (30), 91 (9), 90 (20), 64 (13), 63 (11), 39 (6).

Anal. Calcd for $C_9H_8N_2O_3$: N, 14.58. Found: N, 14.50.

1-Methyl-3-methoxy-2,4-(1*H*,3*H*)-quinazolinedione (2d).—A mixture of **2a** (0.89 g, 0.005 mol) in 25 ml of water containing NaOH (0.8 g, 0.02 mol) and methyl sulfate (6.3 g, 0.05 mol) was stirred at 80° for 2 hr. The clear solution was chilled in an ice–water bath. The product was collected, washed with a little ice–water, and recrystallized from water to furnish **2d** (1.05 g, 100%): mp 150–152°; ir (Nujol) 1720, 1690 cm^{-1} (C=O); pmr ($CDCl_3$) δ 8.45–7.14 (4, m, aromatic protons), 4.10 (3, s, OCH_3), 3.65 (3, s, NCH_3); mass spectrum (70 eV) (rel intensity) 207 (9), 206 (82), 177 (10), 176 (51), 147 (11), 146 (5), 134 (19), 133 (29), 132 (34), 131 (7), 119 (9), 106 (10), 105 (100), 104 (70), 92 (10), 90 (10), 78 (25), 77 (36), 64 (10), 63 (10), 51 (13), 50 (7), 39 (8).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: N, 13.59. Found: N, 13.79.

Reactions of 1a with Sodium Alkoxides. A. Sodium Methoxide in Methanol (Slow Addition).—To a stirred boiling solution of **1a** (3.2 g, 0.01 mol) in methanol (300 ml) was added dropwise (1 hr) a solution of sodium methoxide (0.23 g of sodium in 78 ml of methanol). The suspension[8] was stirred for 0.5 hr longer and then evaporated to dryness *in vacuo*. The residue was extracted with chloroform (3 × 20 ml). The chloroform-insoluble material was suspended in 20 ml of water and acidified with HCl to pH 2. After 18 hr at 5°, there was obtained **2a** (0.6 g, 34%), identical with a prior sample.[2]

The combined chloroform solution was extracted successively with ice-cold 5% NaOH (2 × 20 ml), 5% HCl (2 × 20 ml), and water (2 × 20 ml) and then evaporated to dryness *in vacuo*. The oily residue was dissolved in 10 ml of hot 95% ethanol, and 30 ml of boiling water was added. The hot solution was scratched to effect crystallization. After several hours at 5°, **3** (1.0 g, 45%, mp 106–108°) was obtained as white needles: ir (Nujol) 3315 (NHNH), 1710 cm^{-1} (C=O); pmr ($CDCl_3$) δ 9.26 (1, s, one of the NHNH protons, the other one is buried among the aromatic proton multiplet, as is evident by D_2O exchange), 8.08 (1, dd, H-6, $J_{5,6}$ = 8.0, $J_{4,6}$ = 1.8 Hz), 7.72–6.70 (4, m, H-3, H-4, H-5, NH), 4.23 (3, s, CH_3), 4.08 (3 s, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 225 (8), 224 (56), 193 (6), 192 (30), 160 (7), 150 (5), 149 (9), 148 (57), 147 (10), 134 (17), 133 (100), 120 (5), 119 (12), 106 (7), 105 (74), 104 (16), 92 (10), 91 (10), 90 (6), 79 (5), 78 (14), 77 (91), 76 (15), 65 (8), 64 (9), 63 (8), 59 (55), 52 (9), 51 (25), 50 (10), 39 (9).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: N, 12.49. Found: N, 12.26.

Compound **3** (100 mg) was dissolved in 2 ml of methanol and 3 ml of 5% NaOH. The clear solution was refluxed for 0.5 hr. The pH of the solution was then adjusted with concentrated HCl to 2 and the mixture was boiled under reflux for 10 min. It was then evaporated, *in vacuo*, almost to dryness. The resi-

(4) All melting points are uncorrected and were determined on a Thomas-Hoover Unimelt capillary melting point apparatus. Analyses for N were determined with the use of a Coleman nitrogen analyzer in this department. Infrared spectra were obtained on a Perkin-Elmer 337 recording infrared spectrophotometer. Pmr spectra were recorded by means of a Varian A-60 spectrometer in parts per million (δ), downfield from $(CH_3)_4Si$. Mass spectra were obtained at 70 eV by Mr. Richard Dvorak, using a Hitachi Perkin-Elmer RMU-6D single-focusing mass spectrometer. Usually, ions with 5% of base peak or more are recorded only, from *m/e* 39. Thin layer chromatographs (tlc) were developed on slides over 7.2 cm (15 min) coated with silica gel and a fluorescent indicator (Eastman chromagram sheet 6060) using the following solvent systems, designated by letters: A, ethyl acetate; B, methanol. Spots were detected by uv light.

(5) The original preparation of **1a** from sodium phthalohydroxamate (ref 2) has been modified and the method described by L. Bauer and C. S. Mahajanshetti [*J. Heterocycl. Chem.*, **4**, 325 (1967)] is perhaps more *a propos*.

(6) Prepared in 88% yield from *N*-benzenesulfonyloxyphthalimide, utilizing the method of E. Kühle and R. Wegler [*Justus Liebigs Ann. Chem.*, **616**, 183 (1958)].

(7) C. B. Shapira and S. Lamdan [*J. Heterocycl. Chem.*, **9**, 569 (1972)] have described the synthesis of 1-methyl-3-hydroxy-2,4(1*H*,3*H*)-quinazolinedione from *N*-methylanthranilic acid.

(8) The methanol-insoluble solid was shown to be the sodium salt of **2a** (ir comparison with an authentic sample).

due was dissolved in 2 ml of water and the pH was adjusted with sodium carbonate to 7. The crystalline product was collected, washed with ice-cold water, and recrystallized from methanol to give 3-indazolone (50 mg, 83%): mp 244–247° (lit.[9] mp 246–249°); tlc (solvent B) R_f 0.73; its ir was identical with that of the authentic sample prepared by the literature method,[9] and its mass spectrum was identical with the published one.[10]

The alkaline extract from the $CHCl_3$ solution above was acidified with HCl to pH 2 and extracted with chloroform (5 × 20 ml). After evaporation of the solvent, the residue was triturated with benzene to give **2c** (0.13 g, 7%), mp 220°, identical with the sample prepared above.

B. Sodium Methoxide in Methanol (Fast Addition).—A suspension of **2** (1.6 g, 0.05 mol) in 10 ml of boiling methanol was treated with sodium methoxide (0.23 g of sodium) in 18 ml of methanol, all at once. An emulsion resulted which was boiled for 3 min. After solvents were removed *in vacuo*, the residue was dissolved in 50 ml of water, acidified with HCl to pH 2, and stored at 0° for 18 hr to give **2a** (0.7 g 78%) identical with sample above.

C. Sodium Methoxide in DMF.—To a stirred solution of **1a** (3.1 g, 0.01 mol) in DMF (100 ml) on a steam bath was added sodium methoxide (0.23 g of sodium in 78 ml of methanol) dropwise over 2 hr, and the mixture was heated for an additional 0.5 hr. The solution was evaporated to dryness *in vacuo*, and the residue was diluted with ice-water. The product was filtered and recrystallized from methanol to give 2-benzimidazolone (1.15 g, 88%, white plates): mp 311–313° (lit.[11] mp 309–310°); tlc (solvent B) R_f 0.80; ir identical with that of a sample prepared by Hershenson, *et al.*[11]

D. Sodium Hydride in DMF.—To a solution of **1a** (3.18 g, 0.01 mol) in 100 ml of DMF was added 0.48 g of sodium hydride in mineral oil (50%). It was then stirred and heated on a steam bath for 1 hr. Solvent was removed *in vacuo*, and the residue was triturated with 25 ml of water and 25 ml of petroleum ether (bp 30–60°). The product proved to be **5a** (1.10 g, 82%).

E. Sodium Ethoxide in Ethanol.—A stirred suspension of **1a** (3.2 g, 0.01 mol) in boiling ethanol (300 ml) was treated with sodium ethoxide (0.23 g of sodium in 78 ml of ethanol) dropwise (1.5 hr). The turbid solution was evaporated to dryness *in vacuo*. The residue was extracted with chloroform (4 × 30 ml) and then ether (20 ml) and after removal of these, the oily residue was crystallized by the addition of 2 ml of 95% ethanol. After 1 hr at 5°, the white needles were collected and washed several times with ice-cold 95% ethanol. These proved to be **5b** (1.0 g, mp 148–152°); a second batch (0.2 g, mp 148–154°) was obtained from the mother liquors and ethanol washings after 18 hr at 5°. The combined yield of **5b** was 59%, tlc (solvent A) R_f 0.53. The product was recrystallized from ethanol (50% recovery): mp 158–160°; ir (Nujol) 3275 (NH), 1790 cm^{-1} (C=O); pmr (DMSO-d_6) δ 8.10–7.60 (1, m, H-7), 7.14–6.94 (3, m, H-4, H-5, H-6), 4.66 (2, q, CH_2), 1.49 (3, t, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 206 (23), 147 (7), 135 (9), 134 (100), 133 (12), 106 (39), 105 (7), 79 (9), 78 (11), 52 (7), 51 (8).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: N, 14.43. Found: N, 14.21.

The chloroform-insoluble residue was triturated with 10 ml of water, and the precipitate was collected, washed with ice-cold water several times, and then dissolved in 15 ml of 5% NaOH. The solution was filtered to remove insoluble substances. The filtrate was acidified with acetic acid to produce, after 30 min at 0°, 2-benzimidazolone (0.45 g, 34%).

The aqueous solution from triturating the chloroform-insoluble residue was acidified with HCl to pH 2 to yield some **2a** (0.08 g, 4.5%), mp 325°.

The structure of **5b** was proved by heating a suspension of it (0.10 g) with 3 ml of 5% NaOH at 95° for 30 min. The solution was then acidified with glacial acetic acid to produce 2-benzimidazolone (0.05 g, 73%), identical with the product of C.

F. Sodium Isopropoxide in 2-Propanol.—The reaction of **1a** (3.2 g, 0.01 mol) with sodium isopropoxide in boiling 2-propanol, as described under E, provided, from the corresponding chloroform extract, **5c**, which was crystallized from 50% ethanol (1.52 g, 69%): mp 149–151°; ir (Nujol) 3150 (NH), 1780, 1700 cm^{-1} (C=O); pmr (DMSO-d_6) δ 1.38 (6, d, CH_3) 5.15 (1, q, CH), 7.09–7.49 3, m, H-4, H-5, H-6), 7.75–8.02 (1, m, H-7); mass spectrum (70 eV) *m/e* (rel intensity) 221 (2), 220 (15), 178 (11), 161 (6), 160 (6), 135 (10), 134 (100), 133 (8), 106 (15), 43 (18). The analytical sample was recrystallized from 20% ethanol, mp 152–153.5°.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: N, 12.72. Found: N, 12.82.

In another run, the oily residue, after 2-propanol was removed, was hydrolyzed directly by refluxing with 30 ml of 10% NaOH for 30 min. Acidification with acetic acid gave **5a** (1.15 g, 86%).

Reactions of 1b with Sodium Alkoxides. G. Sodium Methoxide in DMF.—Addition of $NaOCH_3$ to **1b** (3.22 g, 0.01 mol) was carried out as described for C. The residue, after solvents were evaporated, was extracted with boiling ether (5 × 50 ml). Removal of ether afforded 1-methyl-3-indazolone (**4b**, 1.15 g, 78%), mp 146–150°, tlc (solvent A) R_f 0.38. Recrystallization from aqueous acetone (80% recovery) provided a pure sample, mp 154–155° (lit.[12] mp 151–153°) with ir and mass spectra identical[10] with those of a sample prepared by the literature method.[12]

The ether-insoluble material was suspended in water (10 ml), acidified with 1:1 HCl to pH 2, and collected after 18 hr at 5° (0.2 g, 10%), identical with **2b**.

H. Sodium Methoxide in Methanol.—The reaction of **1b** (3.22 g, 0.01 mol), as performed under the conditions of A, worked up as described under G, gave from the ether-insoluble material **2b** (0.23 g, 12%).

The ether extract was worked up differently. The crystalline residue, after removal of ether, was suspended in benzene and was extracted with 5% NaOH. The aqueous alkaline layer yielded, upon acidification with acetic acid, **4b** (0.65 g, 44%) identified as in G.

The benzene extract was concentrated to 1 ml and chromatographed on a column (54 × 2.5 cm) of silica gel (70–325 mesh ASTM, Brinkmann) packed in benzene–ethyl acetate (3:1). Elution (1 ml/min) with the same solvent mixture was monitored every 20 ml by tlc. The fraction from 225 to 275 ml was evaporated *in vacuo* to produce **4c** (0.28 g, 14%): mp 93–95°; ir (Nujol) 1740 cm^{-1} (C=O); pmr ($CDCl_3$) δ 8.00–7.05 (4, m, aromatic protons), 4.04 (3, s, CH_3), 3.33 (3, s, CH_3); tlc (solvent A) R_f 0.39; mass spectrum (70 eV) *m/e* (rel intensity) 207 (15), 206 (54), 175 (5), 162 (25), 161 (7), 148 (23), 147 (100), 133 (7), 119 (27), 105 (34), 104 (13), 92 (5), 78 (13), 77 (25), 76 (20).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: N, 13.59. Found: N, 13.92.

A suspension of **5c** (0.2 g) in 3 ml of 5% NaOH was refluxed for 1 hr, and the solution was just acidified with HOAc to yield, after 18 hr at 5°, **5b** (0.11 g, 77%).

From the eluent, 300–335 ml, there was obtained **2d** (0.1 g, 5%), tlc (solvent A) R_f 0.34, identical with specimen prepared above.

I. Sodium Ethoxide in Ethanol.—This experiment, when carried out as per A and G, gave on acidifying the ether-insoluble material **2b** (32%). The ether-soluble material was hydrolyzed with 5% NaOH for 1 hr and worked up as for 1-methyl-3-indazolone (41%).

J. Sodium Ethoxide in DMF.—This experiment was performed as under C and G. The residue, after removal of DMF, was extracted with ether (3 × 50 ml) and acetone (30 ml). The insoluble material was suspended in water and acidified to produce **2b** (35%). The organic extract was evaporated, triturated with water (10 ml) and 1-methyl-3-benzenesulfonyloxyindazole (**16**, 0.83 g, 29%), and recrystallized from 50% aqueous MeOH to give product (90% recovery): mp 103–105°; its ir spectrum (Nujol) lacked bands above 1620 cm^{-1} indicative of the sulfonate ester rather than the sulfonamide type, **4** (R = CH_3; R′ = $SO_2C_6H_5$); pmr ($CDCl_3$) δ 3.90 (3, s, CH_3) and aromatic protons 7.11–7.55 (7, m), 7.90 (1, d), 8.06 (1, d); mass spectrum (70 eV) *m/e* (rel intensity) 288 (11), 147 (100), 119 (4), 105 (13), 77 (14), 76 (10).

Anal. Calcd for $C_{14}H_{12}N_2O_3S$: N, 9.72. Found, N, 9.66.

From the aqueous filtrate of **16** there was deposited on standing (24 hr) some additional **4b** (0.16 g, 11%).

Synthesis of 16.—A solution of the sodium salt of **4b** in DMF was prepared by adding 96 mg of 50% sodium hydride in oil to a solution of **4b** (269 mg, 0.0018 mol) in 20 ml of DMF. There

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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

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