Heterocyclic Studies. XXVI. Alkylation of 5-Methyl-6-phenyl-2,3-dihydro-4H-1,2-diazepin-4-one[1]

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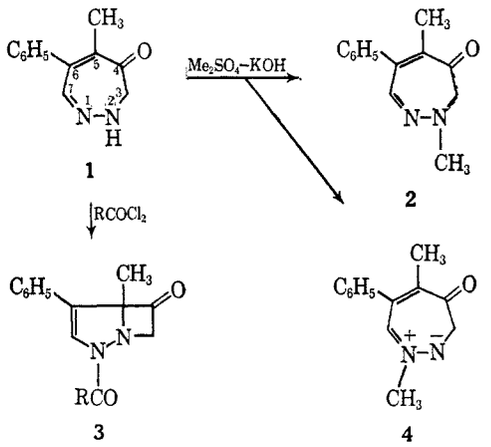
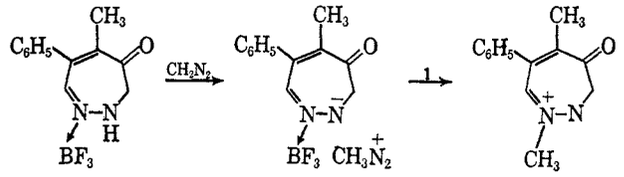
Alkylation and acylation of the diazepinone **1** have previously been shown to occur at both nitrogen atoms.[2,3] With methyl sulfate and aqueous alkali, the 2-methyl derivative **2** and the 1-methylbetaine **4** are obtained in equal amounts.[2] With acid chlorides in tertiary amine, substitution occurs exclusively at N-1, leading to bicyclic ketones **3**, but with anhydrides the 2-acyl derivatives are formed. In this Note we present some further observations on the position of electrophilic substitution in **1** (see Scheme I).

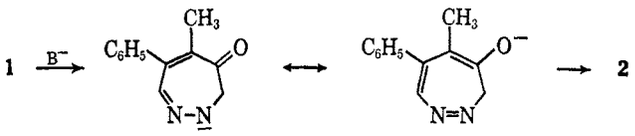
SCHEME I



Alternative methylation conditions have been found which permit the separate preparations of **2** and **4**. The diazepinone **1** is not sufficiently acidic to react with diazomethane alone, but in the presence of boron trifluoride, methylation proceeds rapidly, giving the betaine **4** as the only product. The site of coordination of BF_3 in the ketone **1** is N-1; this conclusion is based on the marked similarity of the infrared spectrum of a solution of **1** containing BF_3 ($\nu_{C=O}$ 1690 cm^{-1}) and the hydrochloride of **4** ($\nu_{C=O}^{KBr}$ 1670 cm^{-1}).[2] Following protonation of diazomethane, electrophilic attack by methyldiazonium ion again occurs at N-1. A very similar mode of reaction leading to a betaine has been observed in the methylation of guanosine.[4]



On treatment of **1** with methyl sulfate in *t*-butyl alcohol containing potassium *t*-butoxide, the 2-methyldiazepinone **2** was the sole product. Under these conditions, the diazepinone **1** is completely converted to the conjugate base **5**, and alkylation of the latter occurs cleanly at N-2.



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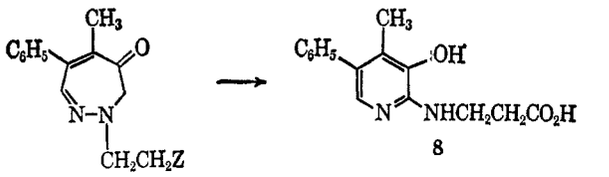
These results are in accord with the earlier suggestion[2] that, in the reaction of **1** with methyl sulfate in aqueous alkali, **2** and **4** arise from the anion and the neutral ketone, respectively. Another example of electrophilic attack of the anion **5** at N-2 is seen in the benzoylation of **1** under Schotten–Baumann conditions in aqueous alkali, which gave the 2-benzoyl derivative.

The base-catalyzed addition of **1** to electrophilic olefins gave the 2-cyanoethyl and 2-carboxyethyl derivatives **6** and **7** in excellent yields. Brief treatment of **6** and **7** with dilute methanolic alkali brought about ring contraction, as previously observed with **1** and **2**;[5,6] in both cases the product was the β-aminopropionic acid **8**. Conversion of the nitrile to the acid under such mild conditions evidently reflects assistance for hydrolysis by the *o*-hydroxyl group. The structure of the pyridine follows from analogy to the rearrangement of **2** and consistent spectral data (CCH_3 peak in alkaline D_2O 23 cps downfield from that of the diazepinone **1**)[5] and pK_A values (4.3, 6.5, and 10.5).



6, Z = CN
7, Z = CO_2H

From these and earlier results, a consistent pattern of electrophilic substitutions of **1** can be seen. With electrophiles having high SE1 reactivity such as a proton, boron trifluoride, methyl diazonium ion, or acylpyridinium ion, attack at N-1 is observed. The products depend upon the nature of the reagent, and may be the 1-aminopyridine resulting from protonation and

(1) Supported in part by Grant No. DA-CML-18-108-61-G-24 from the Army Chemical Corps.

(2) J. A. Moore and J. Binkert, *J. Am. Chem. Soc.*, **81**, 6029 (1959).

(3) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).

(4) J. A. Haine, C. B. Reese, and A. Todd, *J. Chem. Soc.*, 5281 (1962).

(5) J. A. Moore and E. C. Zoll, *J. Org. Chem.*, **29**, 2124 (1964).

(6) J. A. Moore, H. Kwart, G. Wheeler, and H. Bruner, *ibid.*, **32**, 1342 (1967).

ring contraction,[3] the bicyclo[3.2.0] system as in **3**, or the diazepinium betaine **4**, in which a driving force for 2 → 5 bridging is absent. In reactions of **1** in basic media, the anion **5** is the reactive nucleophile, and 2-substitution is observed. It may be noted that the diazepinone can be regarded as a vinylogous amide, and as such an ambident system would be expected to undergo these two types of electrophilic attack at the carbonyl oxygen and N-2, respectively.[7] The highly nucleophilic character of N-1, however, precludes the usual substitution at oxygen.

Experimental Section

Methylation of 1 with Diazomethane.—To a solution of 2.00 g (0.01 mole) of the diazepinone **1** in methylene chloride containing 0.8 ml of freshly distilled boron trifluoride etherate was added 125 ml of 0.4 *M* ethereal diazomethane. Nitrogen was evolved and a red oil separated. The mixture was then evaporated and the residue was treated with 12 ml of methanol and 18 ml of 2 *N* HCl. The resulting yellow solid was collected, washed, and dried to give 0.57 g of unreacted **1**, mp 125–130°. Recrystallization raised the melting point to 145–149°; tlc showed no spot corresponding to **2**. Addition of excess 40% KOH to the chilled acidic filtrate produced a red precipitate of betaine **4**, 1.05 g, mp 92–94° dec.

Methylation with Dimethyl Sulfate and Strong Base.—A solution of 200 mg (1 mmole) of **1** in 6 ml of *t*-butyl alcohol containing 2.8 mequiv of potassium *t*-butoxide (MSA Research Corp.) was treated with 0.16 ml of dimethyl sulfate. The solution remained clear, and the color did not deepen perceptibly. After dilution with water the mixture was extracted with ether and the ether solution was washed, dried, and evaporated to give 218 mg of red oil which showed two yellow spots, corresponding to **1** and **2**, on tlc. Chromatography on neutral alumina from hexane solution gave two yellow bands. The first band eluted gave 96 mg of yellow crystals of **2**, mp 72–73°, infrared and ultraviolet spectra being identical with those of an authentic sample. The slower moving zone gave 46 mg of yellow crystals of unreacted **1**, mp 147–150°.

2,3-Dihydro-2-(β-cyanoethyl)-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (6).—Addition of 0.4 ml of acrylonitrile to a solution of 200 mg of **1** in 1.5 ml of 10% KOH solution at 0° gave, after brief stirring and rubbing, 253 mg of yellow-orange solid, mp 113–116°. Recrystallization from ether gave yellow needles of **6**: mp 120–121°; ν^{KBr} 1640 cm^{-1}; nmr δ^{CDCl_3} 1.87 (s, 3), 2.78 (t, 2, J = 7.0 cps), 3.78 (t, 2, J = 7.0 cps), 3.82 (s, 2), 6.98 (s, 1), 7.33 ppm (m, 5).

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 71.12; H, 5.97; N, 16.59. Found: C, 70.75; H, 6.15; N, 16.70.

2,3-Dihydro-2-(β-carboxyethyl)-5-methyl-6-phenyl-4H-1,2-diazepin-4-one (7).—A solution of 500 mg of **1** in 3 ml of 10% aqueous KOH was treated with 0.67 ml of methyl acrylate. After standing for 5 hr at 25° the solution was acidified with 6 *N* HCl and extracted with ether. Evaporation of the dried ether solution gave 225 mg of orange prisms, mp 130–132°. Recrystallization from ether gave deep yellow needles of **7**: mp 133–134°; ν^{KBr} 1740, 1590 cm^{-1}; δ^{CDCl_3} 1.87 (s, 3), 2.83 (t, 2, J = 7 cps), 3.87 (s, 2), 3.93 (t, 2, J = 7 cps), 6.97 (s, 1), 7.38 (m, 5), 9.52 ppm (s, 1, exchanged by D_2O).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.93; H, 6.22; N, 10.23.

2-(β-Carboxyethylamino)-3-hydroxy-4-methyl-5-phenylpyridine (8).—A mixture of 100 mg of the cyanoethyldiazepinone **6** and 2 ml of 5% aqueous NaOH was heated at 90° for 2 min. After cooling, the solution was neutralized by addition of 6 *N* HCl and a white precipitate (89 mg, mp 110–120°) was collected. Recrystallization from ethanol gave 62 mg of **8** as a microcrystalline powder: mp 155–156°; ν^{KBr} 3480, 2976 (broad), 1661 cm^{-1}; λ_{max}^{MeOH} 263 mμ (ε 7560), 311 mμ (9900); $\lambda_{max}^{MeOH + acid}$ 258 mμ (ε 7620), 313 mμ (ε 11,000); $\lambda_{max}^{MeOH + base}$ 320 mμ (ε 12,700); pK_A' = 4.3, 6.4, and 10.5.

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.83; H, 6.01; N, 10.25.

(7) R. Gompper, *Angew. Chem.*, **76**, 412 (1964).

In a similar procedure, 130 mg of the pyridine was obtained from 154 mg of the diazepine acid (**7**).

Benzoylation of 1 in Aqueous Base.—To a solution of 200 mg of the diazepinone **1** in 1.5 ml of 10% aqueous KOH at 20° was added 0.15 ml of benzoyl chloride. After a few minutes the resulting orange oil crystallized. The solid was worked up with methanol and ether to give 150 mg of the 2-benzoyldiazepinone,[2] mp 147–148°.

Registry No.—**1**, 1706-26-9; **2**, 4084-21-3; **4**, 10137-58-3; **6**, 10137-59-4; **7**, 10137-60-7; **8**, 10137-61-8.

Stereochemistry of a Nucleophilic Displacement at Phosphorus

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There has been wide spread interest in the stereochemistry of displacement reactions involving nucleophilic attack at the phosphorus atom.[1] The majority of the work has involved nucleophilic displacements at asymmetric phosphoryl centers which in the case of the phosphono analogs suffer from partial racemization during the reaction or work-up.[2] Therefore, although it is generally agreed that nucleophilic displacements at phosphorus proceed with predominate inversion, partial racemization has led to inconclusive results. In the present work a simple system which does not depend upon optical activity and purity has been developed.

In a previous publication[3] it was shown that bicyclic phosphites undergo an Arbuzov ring opening with an alkyl halide to give a single isomer whose formation is a consequence of the bridged structure of the phosphite and the mechanism of the reaction. Advantage is taken of this phenomena to study the steric course of a substitution at phosphorus by replacing chloride in a cyclic phosphorochloridate whose configuration as a consequence of ring opening is known.

2-Chloromethyl-2-ethyl-1,3-propanediol phosphorochlorochloridate (I, Scheme I) was prepared by treating ethyl bicyclic phosphite with chlorine gas as previously described.[3] The distilled product darkened on standing but upon redistillation gave the same infrared spectrum and index of refraction as freshly prepared material. Treatment of the phosphorochloridate with piperidine using methylene chloride as solvent gave after removal of the hydrochloride and solvent a white crystalline solid, II. Treatment of the bicyclic phosphite with N-chloropiperidine in CCl_4 also gave a sharp melting solid, III. The reaction of phosphites with chloroamines to give an Arbuzov reaction is well documented.[4]

The infrared spectra of II and III were as expected and identical except for the fingerprint region where

(1) R. F. Hudson and M. Green, *Angew. Chem. Intern. Ed. Engl.*, **2**, 11 (1963); W. E. McEwen, in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, Chapter I.

(2) H. S. Aaron, R. T. Vyeda, H. F. Frack, and J. I. Miller, *J. Am. Chem. Soc.*, **84**, 617 (1962).

(3) W. S. Wadsworth, Jr., and W. D. Emmons, *ibid.*, **84**, 610 (1962).

(4) K. A. Petrov and G. A. Sokol'skii, *Zh. Obshch. Khim.*, **26**, 3378 (1956).