substance was prepared from 3β-acetoxyandrost-5-en-17-one as described by Levy and Jacobsen[7] in an over-all yield of 85%. The melting point of the lactone was found to be 169–170°, lit. m.p. 169.7–169.9°.

3β-Hydroxy-16-hydroxymethylene-17a-oxa-5α-D-homoandrostan-17-one[8] (X).—A mixture of 2.5 g. of IX, 150 ml. of dry thiophene-free benzene, 10 ml. of ethyl formate, and 2 g. of sodium hydride (50% in oil) was stirred in an atmosphere of nitrogen for a period of 5 hr. Excess reagent was decomposed by a few milliliters of methanol, and water added to the mixture. The aqueous alkaline layer was separated and the organic phase washed with water. The aqueous washing and the alkaline extract were mixed and acidified with cold 2 *N* hydrochloric acid. The precipitate was collected and dried to yield 2.55 g. of X, m.p. 291–292°, lit. m.p. 292–294°; ν_{max} 3340 (OH), 1690 (δ-lactone carbonyl), and 1610 cm.$^{-1}$ (hydroxymethylene); λ_{max} 250 mμ (log ε 4.05).

3β-Acetoxy-16-acetoxymethylene-17α-oxa-5α-D-homoandrostan-17-one (XI).—A solution of 2 g. of X in 25 ml. of pyridine and 5 ml. of acetic anhydride was kept at room temperature for 18 hr. Excess acetic anhydride was decomposed by adding a few ml. of methanol and the solution was poured into ice–water. The precipitate was collected and dried to give 2.4 g. of the diacetate XI, m.p. 105–105°. A sample was crystallized three times from ether–hexane for analysis to give needles, m.p. 108–110°; $[\alpha]^{22}D$ −122° (*c* 1.0, chloroform); λ_{max} 237 mμ (log ε 4.12); ν_{max} 1760 (16-acetoxy), 1740 (3-acetoxy), 1708 (conjugated δ-lactone), and 1630 cm.$^{-1}$ (double bond of acetoxymethylene).

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.02; H, 8.45.

3β-Acetoxy-17-oxa-5α-androstan-16-one (XII).—A solution of 2 g. of XI in a mixture of 30 ml. of ethyl acetate and of 30 ml. of acetic acid was cooled to −10° and then ozonized for a period of 75 min. After addition of 5 ml. of a 30% solution of hydrogen peroxide and 5 ml. of water the mixture was stored at 25° for 24 hr. It was then diluted with ether, washed with water, with sodium hydrogen carbonate solution, and water, and dried over sodium sulfate. Removal of solvent gave 2 g. of an oil which was dissolved in 10 ml. of benzene and adsorbed on a column of silica gel. Elution with mixtures of ethyl acetate, benzene (5% and 10%) yielded fractions melting in the range of 139–142°. These fractions were combined to give a total of 1.42 g. of XII (85%). No other compound of definite nature could be isolated by further elution of the column. An analytical sample was prepared by crystallizing from dichloromethane–hexane to give prisms, m.p. 146–148°; $[\alpha]^{23}D$ −59° (*c* 1.0, chloroform); ν_{max} 1776 (γ-lactone), 1730 (3-acetate), and 1236 cm.$^{-1}$ (3-acetate).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.68; H, 9.17.

Quinazolines and 1,4-Benzodiazepines. XVI.[1] Synthesis and Transformations of 5-Phenyl-1,4-benzodiazepine-2-thiones

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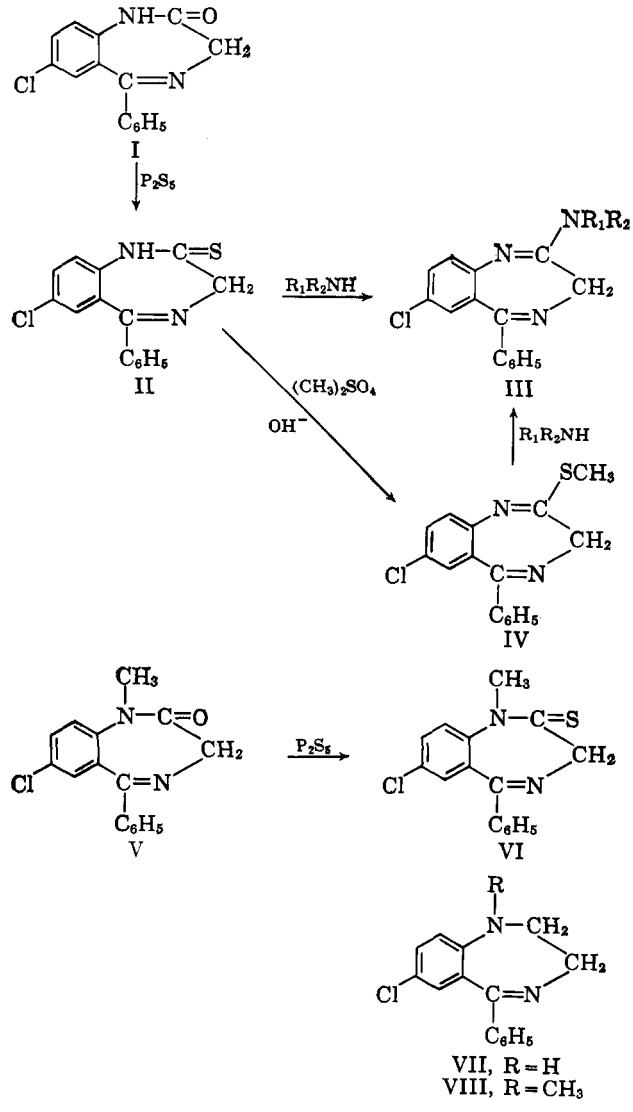
Received July 17, 1963

In continuation of our studies of the chemistry of 5-phenyl-1,4-benzodiazepin-2-ones, we examined methods for effecting transformations of the carbonyl grouping in position 2. Firstly we turned our attention to the synthesis and reactions of the thiolactam II. We expected the thione group in II to undergo nucleophilic replacement, when treated with a primary or secondary amine, to give aminobenzodiazepines of type III. This type of reaction has been used for the preparation of amino compounds from the corresponding thionamides, in the pyrimidine,[2] purine,[3] and quinazoline,[4,5] series, but had not been applied to 1,4-benzodiazepines.

Thiation of the lactam I was readily achieved by treatment with phosphorus pentasulfide in refluxing pyridine, to give the desired thiolactam II. Reaction of II with primary or secondary aliphatic amines, or with secondary heterocyclic amines, resulted in formation of compounds of type III, with evolution of hydrogen sulfide. Since it has been reported[6] that S-alkylthiopyrimidines react with amines more readily than do the corresponding thiopyrimidines, we were led to methylate II to the methylmercapto derivative (IV). That the product was in fact the S-methyl derivative, and not the isomeric N-methylthiolactam (VI), was proved by its ready acid hydrolysis to I and also by the unequivocal synthesis of VI from the N-methylbenzodiazepinone (V).



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(3) L. B. Townsend and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 3008 (1962).

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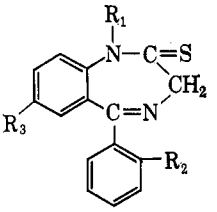
TABLE I

1,3-DIHYDRO-2*H*-1,4-BENZODIAZEPINE-2-THIONES

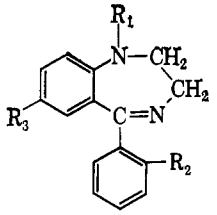


R_1	R_2	R_3	M.p., °C.[a]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
H	H	H	256–257	9	$C_{15}H_{12}N_2S$	71.40	71.35	4.79	4.65	12.70	12.54
H	H	Br	255–256	30	$C_{15}H_{11}BrN_2S$	54.39	54.29	3.35	3.24	9.68	9.71
H	H	Cl	245–247	40	$C_{15}H_{11}ClN_2S$	62.82	62.55	3.87	3.95	11.19	11.22
H	H	CH_3	260–261	28	$C_{16}H_{14}N_2S$	72.14	72.25	5.30	5.52	12.04	12.07
H	H	NO_2	209–214	13	$C_{15}H_{11}N_3O_2S$	60.59	61.07	3.73	4.27	10.78	10.69
H	Cl	Cl	251–253	40	$C_{15}H_{10}Cl_2N_2S$	56.08	56.43	3.14	3.25	9.98	9.81
H	F	Cl	229–232	29	$C_{15}H_{10}ClFN_2S$	59.12	58.88	3.30	3.52	10.52	10.12
H	OCH_3	Cl	222–224	38	$C_{16}H_{13}ClN_2OS$	60.66	60.49	4.13	4.36		
CH_3	H	Cl	162–164	73[c]	$C_{16}H_{13}ClN_2S$	63.88	63.96	4.36	4.55	10.66	10.86
CH_3	Cl	Cl	160–163	75	$C_{16}H_{12}Cl_2N_2S$	57.32	57.66	3.61	3.45	9.56	9.75
CH_3	F	Cl	144–146	48	$C_{16}H_{12}ClFN_2S$	60.28	60.24	3.79	3.77	10.06	9.80
CH_3[b]	CF_3	H	133–136	83	$C_{17}H_{13}F_3N_2S$	61.07	61.01	3.92	4.08	9.59	9.47

[a] The compounds described were crystallized from ethanol. [b] The starting material, 1,3-dihydro-1-methyl-5-(2-trifluoromethylphenyl)-2*H*-1,4-benzodiazepin-2-one, was made by methylation of the corresponding desmethyl compound [G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962)] by treatment with sodium methoxide and methyl iodide. The product crystallized from aqueous ethanol as colorless rhombs, m.p. 135–137°. *Anal.* Calcd. for $C_{17}H_{13}F_3N_2O$: C, 64.14; H, 4.12. Found: C, 64.45; H, 3.84. [c] The thiation of 1-substituted benzodiazepinones generally gave better yields of thiolactams than in the case of the unsubstituted lactams.

TABLE II

2,3-DIHYDRO-1*H*-1,4-BENZODIAZEPINES



R_1	R_2	R_3	Crystd.[a] from	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	H	CH_3	Aqueous alcohol	130–132	$C_{16}H_{16}N_2$	81.32	81.38	6.82	6.93				
H	OCH_3	Cl	Aqueous alcohol	190–191	$C_{16}H_{15}ClN_2O$	67.00	67.32	5.27	5.36				
H[b]	OCH_3	Cl	Methanol–ether	254–255 dec.	$C_{16}H_{15}ClN_2O \cdot HCl$	59.45	59.82	4.99	5.12			21.93	21.94
CH_3[b]	F	Cl	Methanol–acetone	245–247 dec.	$C_{16}H_{14}ClFN_2 \cdot HCl$	59.09	59.24	4.65	5.14	8.61	8.57		
CH_3	CF_3	H	Hexane	83–85	$C_{17}H_{15}F_3N_2$	67.09	67.25	4.97	4.86	9.21	9.16		
CH_3[b]	CF_3	H	Alcohol–ether	251–252	$C_{17}H_{15}F_3N_2 \cdot HCl$	59.91	59.97	4.73	4.68	8.22	8.19		

[a] Yields obtained were comparable with those obtained for the examples reported in the Experimental section. [b] Hydrochloride. The base was dissolved in the calculated amount of methanolic hydrogen chloride and the crystalline salt was precipitated by the addition of ether.

Compound IV reacted readily with primary or secondary amines to give aminobenzodiazepines of formula III. Reaction of IV with monomethylamine gave the methylaminobenzodiazepine III (R_1 = CH_3, R_2 = H), which was identical with that previously obtained[7] by deoxygenation of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (Librium®).

Reaction of II or IV with piperidine gave the piperidinobenzodiazepine (III, R_1R_2N = piperidino).[8]

Another reaction of the thiolactams II and VI was their desulfurization, by treatment with Raney nickel in boiling acetone, to give the dihydrobenzodiazepines (VII and VIII). Both these compounds have been obtained by other methods; the former by reduction of I with lithium aluminum hydride,[9] the latter by methylation of VII[9] and also by a four-step synthesis from 2-chloro-5-nitrobenzophenone.[10,11]

A number of analogs of the thiolactams II and VI were made by the method described in the Experimental section; their properties are given in Table I. The 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones used as starting materials have been described in the literature.[10,11]

(7) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(8) Benzodiazepines having a tertiary amino group in position 2 were not previously accessible by the route described[7] for preparation of benzodiazepines having a primary or secondary amino group in position 2. See also S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).

(9) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

(10) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

(11) L. H. Sternbach, R. Ian Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

Some of the thiolactams listed in Table I were desulfurized by treatment with Raney nickel, as described in the Experimental section, to give the 2,3-dihydrobenzodiazepines shown in Table II.

Experimental

All melting points are corrected. The infrared and ultraviolet absorption spectra of starting materials and reaction products were compared in order to establish structural changes. The infrared spectra were determined in 3% chloroform solutions or in potassium bromide pellets, using a Perkin-Elmer Model 21 spectrophotometer; the ultraviolet absorption spectra were determined in isopropyl alcohol and in 0.1 *N* hydrochloric acid.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (II).—A solution of 271 g. of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (I)[12] and 242 g. of phosphorus pentasulfide in 2 l. of anhydrous pyridine was stirred and heated under reflux for 45 min., with protection from atmospheric moisture. The mixture was then rapidly chilled in an ice bath and poured slowly into 5 l. of a well stirred, ice-cold saturated sodium chloride solution. The resulting precipitate was separated by filtration, washed with water, dried *in vacuo*, and dissolved in methylene chloride. The solution was filtered through a bed of activated alumina and concentrated. Addition of petroleum ether (b.p. 40–60°) gave compound II which was recrystallized from alcohol and obtained as pale yellow prisms (40%), m.p. 244–246°.

Anal. Calcd. for $C_{15}H_{11}ClN_2S$: C, 62.82; H, 3.87; S, 11.19. Found: C, 62.55; H, 3.95; S, 11.22.

7-Chloro-2-methylmercapto-5-phenyl-3*H*-1,4-benzodiazepine (IV).—To a stirred solution of 2.87 g. of II in a mixture of 12 ml. of aqueous 1 *N* sodium hydroxide and 15 ml. of methanol was added within 30 min. a solution of 1.39 g. of dimethyl sulfate in 5 ml. of methanol. Stirring was continued for 10 min., then the mixture was diluted with water and made strongly basic with sodium hydroxide solution. The precipitated product was separated by filtration, washed with water, and recrystallized from alcohol, to give pale yellow prisms, m.p. 132–134° (76%).

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88; H, 4.36; S, 10.66. Found: C, 63.52; H, 4.39; S, 10.86.

Acid Hydrolysis to I.—A solution of 1 g. of IV in a mixture of 100 ml. of alcohol and 20 ml. of 1 *N* hydrochloric acid was kept at 20–25° for 6 days. Methyl mercaptan was evolved (detected by its characteristic odor, and yellow coloration with lead acetate paper). The solution was diluted with 100 ml. of water and neutralized (pH 7) with dilute sodium hydroxide. The resulting precipitate was filtered and recrystallized from methylene chloride–hexane to give 0.63 g. (70%) of I, identical[13] with an authentic sample.

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (VI).—A solution of 14.3 g. of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[12] (V) and 11.1 g. of phosphorus pentasulfide in 100 ml. of anhydrous pyridine was stirred and heated under reflux for 1 hr., with protection from atmospheric moisture. The solution was evaporated *in vacuo*, the resulting tarry residue was dissolved in methylene chloride and filtered through a bed of activated alumina. Concentration of the filtrate and addition of petroleum ether gave the product, which was recrystallized from alcohol and formed pale yellow prisms (73%), m.p. 162–164°.

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88; H, 4.36; S, 10.66. Found: C, 63.96; H, 4.55; S, 10.86.

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (III, $R_1 = CH_3$; $R_2 = H$).—Monomethylamine gas was bubbled slowly through a refluxing solution of 25 g. of IV in a mixture of 300 ml. of alcohol and 50 ml. of dimethyl sulfoxide. After the evolution of methyl mercaptan had ceased (18 hr.), the solution was concentrated *in vacuo*, and the residue dissolved in dilute hydrochloric acid. The aqueous acidic layer was extracted with ether, made basic with sodium hydroxide, and extracted with methylene chloride. The methylene chloride solution was concentrated to give the nearly pure product, which was recrystallized from acetone and formed colorless prisms (91%), m.p. 238–240°, identical[13] with an authentic sample.[7]

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

(13) Identity was established by comparison of melting points, infrared spectra, and mixture melting point.

7-Chloro-5-phenyl-2-piperidino-3*H*-1,4-benzodiazepine (III, NR_1R_2 = Piperidino). A. From II.—A solution of 28.7 g. of II and 17 g. of piperidine in a mixture of 250 ml. of methanol and 50 ml. of dimethyl sulfoxide was refluxed on the steam bath until evolution of hydrogen sulfide ceased (after 1.5 hr.). The solution was concentrated, and the product isolated in the manner described in the previous experiment. Recrystallization from aqueous alcohol gave colorless prisms (60%), m.p. 115–116°. The yield was not increased by longer reaction periods.

Anal. Calcd. for $C_{20}H_{20}ClN_3$: C, 71.12; H, 5.96; N, 12.44. Found: C, 71.47; H, 6.23; N, 12.47.

B. From IV.—A mixture of 3.01 g. of IV and 21 g. of piperidine was refluxed until evolution of methyl mercaptan ceased (after 1.5 hr.). The resulting solution was concentrated, and the product isolated as previously, to give colorless prisms (89%), m.p. 115–116° (from alcohol), identical[13] with the authentic sample prepared by method A. The yield was unaffected by prolongation of the reaction time.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (VIII).—A mixture of 20 g. of VI, 500 ml. of acetone, and 160 g. of wet Raney nickel was stirred and refluxed for 2 hr. Filtration and evaporation of the filtrate gave the crude product, which was purified by dissolving it in dilute hydrochloric acid and extracting the solution with ether to remove nonbasic impurities. The acidic solution was then made basic with dilute sodium hydroxide and extracted with methylene chloride, to give VIII (69%), which was identical[13] with an authentic sample.[9]

7-Chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (VII).—Desulfurization of II with Raney nickel, followed by purification of the product in the manner described previously, gave VII as yellow plates (52%), m.p. 166–167° (from aqueous ethanol), identical[13] with an authentic sample.[9]

Acknowledgment.—We are indebted to Dr. A. Motchane, Mr. S. Traiman, and Dr. V. Toome for the infrared and ultraviolet spectra, and to Dr. Al Steyermark and his staff for the microanalyses. Mr. L. A. Dolan was helpful in the preparation of larger amounts of starting materials and intermediates.

Autoradiolysis of 6,7,8,9,10,10-Hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepine 3-Oxide-5a,9a-C^{14}

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Received June 13, 1962

The autoradiolysis of compounds containing radioactive isotopes is a well known phenomenon.[2] We wish to report a new and interesting observation of this sort of behavior with C^{14}-labeled samples of the insecticide Thiodan (I).

The infrared spectra of samples of Thiodan-5a,9a-C^{14} (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepine 3-oxide-5a,9a-C^{14}) taken shortly after preparation[3] showed no indication of the presence of Thiodan ether (II) (4,5,6,7,8,8-hexachloro-1,3,3a,4,7,7a-hexahydro-4,7-methanoisobenzofurane). The radio-Thiodan was stored in vials kept in a desiccator which was placed in a darkened cabinet. About 2.5 years later new infrared spectra showed the presence of Thiodan ether.

(1) Niagara Chemical Division, Middleport, N. Y.

(2) A. Murray, III, and D. L. Williams, "Organic Syntheses with Isotopes," Part I, Interscience Publishers, Inc., New York, N. Y., 1958, p. 19.

(3) S. E. Forman, B. L. Gilbert, G. S. Johnson, C. A. Erickson, and H. Adelman, *J. Agr. Food Chem.*, **8**, 193 (1960).