Experimental[9]

1-(2-Deoxy-5-*O*-trityl-β-D-lyxosyl)uracil (II).—To a cooled solution of 1.73 g. (3.68 mmoles) of 5'-*O*-trityl-2'-deoxyuridine[10] (I) in 10 ml. of dry pyridine was added 0.57 ml. (7.36 mmoles) of methanesulfonyl chloride and the mixture held at 5° for 16 hr. Water (2.0 ml) was added and, after 0.5 hr. at room temperature, the reaction mixture was poured into 500 ml. of stirred ice–water. The off-white solid was collected and washed with generous quantities of water. The air-dried product was dissolved in 80 ml. of 50% ethanol that contained 14.5 ml. of *N* sodium hydroxide and the solution was refluxed for 4 hr. The volume was then reduced *in vacuo* to *ca.* 40 ml.; the reaction mixture was then chilled and carefully acidified (pH 2) with dilute hydrochloric acid. The gelatinous product was collected, washed with water, and sucked dry. The dry product was readily transformed to a crystalline solid on stirring with 50 ml. of ethanol at room temperature for 0.5 hr., wt. 1.64 g. (95% yield), m.p. 225–228° Two recrystallizations from ethanol provided an analytical sample, m.p. 239–240°, $[\alpha]^{25}D$ −14.9° (*c* 0.93, DMF); λ_{max}^{EtOH} 262 mμ (ε 10,630), and λ_{min} 243 mμ (ε 6370).

Anal. Calcd. for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.96. Found: C, 71.30; H, 5.73; N, 5.69.

1-(2-Deoxy-β-D-lyxofuranosyl)uracil (III).—A solution of 1.45 g. (3.08 mmoles) of II in 10 ml. of 80% acetic acid was refluxed for 10 min. The reaction mixture was evaporated to dryness *in vacuo* and the residue was evaporated from three 10-ml. portions of ethanol. The product crystallized from methanol–ethyl acetate, 0.58 g. (two crops, 83% yield), m.p. 163–165°. A second recrystallization from methanol failed to alter the melting point; $[\alpha]^{25}D$ +58.2 (*c* 0.55, ethanol); in H_2O, λ_{max} 263 mμ (ε 10,620), and λ_{min} 232 mμ (ε 2760); 0.1 *N* HCl, λ_{max} 262 mμ (ε 9610), and λ_{min} 231 mμ (ε 2220); 0.1 *N* NaOH, λ_{max} 262 mμ (ε 7070), add λ_{min} 241 mμ (ε 4520).

Anal. Calcd. for $C_9H_{12}N_2O_5$: C, 47.36; H, 5.30; N, 12.28. Found: C, 47.22; H, 5.40; N, 12.09.

1-(2-Deoxy-β-D-lyxofuranosyl)-5-iodouracil (IV).[11]—A mixture of 0.25 g. (1.1 mmoles) of III, 0.25 g. (1 mmole) of iodine, 2.5 ml. of *N* nitric acid, and 1.3 ml. of chloroform was refluxed for 2 hr. On cooling, a colorless crystalline solid was deposited. The product was collected, washed free of iodine with ether, and recrystallized from water, 0.23 g. (57% yield), m.p. 180–181° dec., $[\alpha]^{25}D$ −4.9° (*c* 0.81, ethanol); in H_2O, λ_{max} 289 mμ (ε 6530) and λ_{min} 247 mμ (ε 970); 0.1 *N* HCl, λ_{max} 288 (ε 4330), and 255 mμ (ε 2010); 0.1 *N* NaOH, λ_{max} 278 mμ (ε 5310) and λ_{min} 254 mμ (ε 2830).

Anal. Calcd. for $C_9H_{11}IN_2O_5$: C, 30.52; H, 3.13; I, 35.84; N, 7.91. Found: C, 30.28; H, 2.88; I, 35.70; N, 8.09.

(9) Melting points are corrected. Ultraviolet spectra were recorded by a Cary Model 11 spectrophotometer. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(10) J. Smrt and F. Sorm, *Collection Czech. Chem. Commun.*, **25**, 553 (1960); *Chem. Abstr.*, **54**, 12145 (1960).

(11) This procedure is identical with that described by W. H. Prusoff, *Biochim. Biophys. Acta*, **32**, 295 (1959), for the preparation of 5-iodo-2'-deoxyuridine.

5-Aryl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-ones

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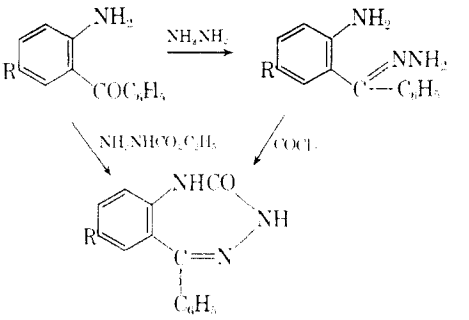
Because of our interest in 1,4-benzodiazepin-2-ones[1] and 3,1,4-benzoxadiazepin-2(1*H*)ones,[2] it seemed desirable to prepare some aza analogs of these ring systems. Accordingly, several 5-aryl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-ones have been prepared by two related methods, as shown in the reaction scheme.



Experimental

5-Phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-one.—A solution of 12 g. of 12.5% phosgene in benzene was added dropwise to a cooled solution of 3.2 g. of 2-aminobenzophenone hydrazone and 5 ml. of triethylamine in 50 ml. of benzene. After addition was completed, the mixture was stirred at room temperature for 1 hr. After separating the triethylamine hydrochloride by filtration, the solution was evaporated to dryness *in vacuo*. Recrystallization of the residue from ethanol afforded 1.4 g. of product, m.p. 238°.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.68; N, 17.70. Found: C, 70.69; H, 4.53; N, 18.04.

7-Methyl-5-phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-one, m.p. 253–255°, was prepared similarly from 2-amino-5-methylbenzophenone hydrazone in a yield of 50%.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.61; H, 5.43; N, 16.64.

7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-one.—A mixture of 5 g. of 2-amino-5-chlorobenzophenone and 5 ml. of ethyl hydrazinecarboxylate was heated at 190° for 1 hr. The mixture was cooled and dissolved in 75 ml. of ethanol. On standing there was obtained 1.6 g. of product, m.p. 246–248°.

Anal. Calcd. for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.72; Cl, 13.05; N, 15.47. Found: C, 61.65; H, 3.72; Cl, 13.27; N, 15.18.

Concentration of the mother liquor afforded 0.5 g. of 2-amino-5-chlorobenzophenone hydrazone ethyl carboxylate, m.p. 209°.

Anal. Calcd. for $C_{16}H_{16}ClN_3O_2$: C, 60.47; H, 5.07; Cl, 11.16; N, 13.23. Found: C, 60.16; H, 5.07; Cl, 11.25; N, 13.04.

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

(2) T. S. Sulkowski and S. J. Childress, *ibid.*, **27**, 4424 (1962).

Quinazolines and 1,4-Benzodiazepines. XIX.[1] N-Alkyl Derivatives of Substituted 1,3,4,5-Tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones

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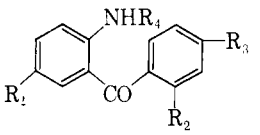
As a continuation of our investigation on psychotherapeutic agents of the 1,4-benzodiazepine class of compounds, we have prepared a series of 1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones and from these compounds a number of N-alkyl derivatives. For the sake of simplicity, the Experimental section of this paper will concern itself with the chemistry of only one of these compounds, namely, 7-chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one and its N-methyl derivatives. As shown in the Experimental, because of the difference in basicity between the two nitrogen atoms, we found it possible to alkylate the 1-nitrogen independently of the 4-nitrogen and *vice versa*. All other compounds and derivatives prepared by the same procedures will be found in Table III.

(1) Paper XVIII: L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).

TABLE I

2-AMINOBENZOPHENONES

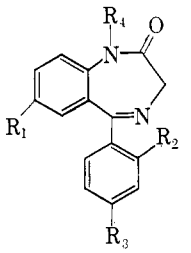


R_1	R_2	R_3	R_4	Method[a]	Crystd. from	M.p., °C.	Yield, %	Formula	—% Calcd.— C	H	—% Found— C	H
F	F	H	H	V A	Hexane	99–101	84	$C_{13}H_9F_2NO$	66.95	3.89	67.20	4.00
F	F	H	$COCH_2Br$	VI D	MeOH	116–118	92	$C_{15}H_{10}BrF_2NO_2$	50.87	2.85	50.62	2.80
F	H	Cl	H	V A	Hexane	96–97	52	$C_{13}H_9ClFNO$	62.54	3.63	62.64	3.62
F	H	Cl	$COCH_2Br$	VI D	MeOH	143–144.5	87	$C_{15}H_{10}BrClFNO_2$	48.61	2.72	48.43	2.92
Cl	Cl	Cl	H	V A	Hexane	81–83	89	$C_{13}H_8Cl_3NO$	51.95	2.68	52.21	3.01
Cl	Cl	Cl	$COCH_2Br$	VI D	MeOH	147–150	65	$C_{15}H_9BrCl_3NO_2$	42.74	2.15	42.72	2.41

[a] The letters denoting the method of preparation refer to the Experimental section of papers V and VI of this series[2,8] (*e.g.*, V A refers to method A in the Experimental section of paper V).

TABLE II

SUBSTITUTED 1,3-DIHYDRO-5-PHENYL-2*H*-1,4-BENZODIAZEPIN-2- ONES



R_1	R_2	R_3	R_4	Method[a]	Crystd.[b] from	M.p., °C.	Yield, %	Formula	—% Calcd.— C	H	—% Found— C	H
F	F	H	H	VI H[c]–N	Ac.	197–200	93	$C_{15}H_{10}F_2N_2O$	66.17	3.70	65.93	3.83
F	F	H	CH_3	VI S	Hex.	110–111	82	$C_{16}H_{12}F_2N_2O$	67.13	4.23	67.09	4.38
F	H	Cl	H	VI H[c]–N	Ac.	230–232	92	$C_{15}H_{10}ClFN_2O$	62.40	3.49	62.10	3.54
F	H	Cl	CH_3	VI S	Ac.–hex.	160–163	73	$C_{16}H_{12}ClFN_2O$	63.40	4.00	63.32	4.30
Cl	Cl	Cl	H	VI H[c]–N	Ac.	231–233	83	$C_{15}H_9Cl_3N_2O$	53.02	2.67	53.20	2.86
Cl	Cl	Cl	CH_3	VI S	Ac.–hex.	178–181	70	$C_{16}H_{11}Cl_3N_2O$	54.34	3.14	54.30	3.28

[a] The letters denoting the method of preparation refer to the Experimental section of paper VI in this series (see ref. 2). [b] Ac. = acetone, hex. = hexane. [c] As previously reported (see ref. 2) it was not necessary to isolate the intermediate aminoacetamidobenzophenones (method H) from the ammonolysis reaction. These compounds were cyclized (method N) directly to the 1,4-benzodiazepinones.

All but three of the parent benzodiazepinones used in these syntheses have been reported elsewhere.[2-7] The physical properties and the methods of preparation of the three, previously unknown, benzodiazepinones and their intermediates[8] are given in Tables I and II.

Experimental

All melting points were determined microscopically on a hot stage and are corrected. The infrared spectra of starting materials and reaction products were compared in every case in order to confirm or exclude structural changes. The infrared spectra were determined either in 2–4% chloroform solutions or in a potassium bromide pellet using a Perkin Elmer Model 21 spectrophotomer.

7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one. Method A.—Hydrogenation[9] of a solution of 11.2 g. (0.0375 mole) of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one[2] in 100 ml. of 60% acetic acid in the presence of 0.2 g. of platinum oxide gave, after filtration and removal of solvent under reduced pressure, 10.8 g. of a crystalline product. Recrystallization from acetone gave 10.3 g. (90.5%) of pure product, white needles, m.p. 216–217°.

Anal. Calcd. for $C_{15}H_{12}ClFN_2O$: C, 61.97; H, 4.16. Found: C, 61.69; H, 3.92.

7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-1-methyl-2*H*-1,4-benzodiazepine-2-one. Method B. From 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.[2]—A solution of 13.4 g. (0.0442 mole) of the 1,4-benzodiazepinone in 75 ml. of 60% acetic acid was hydrogenated and worked up as previously described to give, after recrystallization from an acetone–hexane mixture, 11 g. (81.5%) of product, white prisms, m.p. 136–138°.

Anal. Calcd. for $C_{16}H_{14}ClFN_2O$: C, 63.06; H, 4.63. Found: C, 63.31; H, 4.86.

Method C. From 7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one.—A solution of 10 g. (0.0334 mole) of the tetrahydro-1,4-benzodiazepinone in 50 ml. of N,N-dimethylformamide was stirred at 5° for 20 min. together with a methanolic solution of sodium methoxide[10] (0.0423 mole of $NaOCH_3$). Then 2.6 ml. (0.0423 mole) of methyl iodide was added slowly. The reaction mixture was allowed to warm to room temperature, stirred for 1 hr., and poured into 600 ml. of water. The product was extracted into dichloromethane which was washed with water, dried, and concentrated. Recrystallization of the residue from an acetone–hexane mixture gave 9.5 g.

(2) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.* **27**, 3788 (1962).

(3) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962).

(4) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

(5) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).

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

(7) L. H. Sternbach, G. Saucy, F. A. Smith, M. Müller, and J. Lee, *Helv. Chim. Acta*, **46**, 1720 (1963).

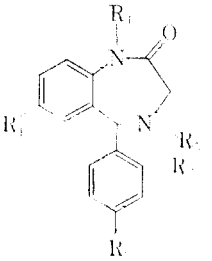
(8) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

(9) Hydrogenation was carried out at room temperature and at atmospheric pressure. One molar equivalent of hydrogen was adsorbed.

(10) This solution contained 4.2 mequiv. of sodium methoxide per ml. of absolute methanol.

TABLE III

SUBSTITUTED 1,3,4,5-TETRAHYDRO-5-PHENYL-2*H*-1,4-BENZODIAZEPIN-2-ONES



R_1	R_2	R_3	R_4	R_5	Method[a]	Crystd. from	M.p., °C.	Yield,[c] %	Formula	Calcd. C	Calcd. H	Found C	Found H
H	H	H	H	H[d]	A	Ac.-pet.	147–148	84	$C_{16}H_{14}N_2O$	75.60	5.92	75.88	5.60
H	H	H	CH_3	CH_3	E	CH_2Cl_2	115–116	32	$C_{17}H_{16}N_2O$	76.66	6.81	76.61	6.91
Br	H	H	H	H	A	DMF–H_2O	191–192	79	$C_{15}H_{11}BrN_2O$	56.80	4.13	57.01	4.11
Br	H	H	CH_3	CH_3[e]	E	MeOH–Et_2O	166–172	20	$C_{17}H_{17}BrN_2O \cdot HCl$	53.49	4.49	53.20	4.48
Cl	H	H	H	H[d]	A	DMF–H_2O	185–186	73	$C_{15}H_{11}ClN_2O$	66.06	4.80	65.87	4.80
Cl	H	H	H	CH_3	D	CH_2Cl_2	205–206	38	$C_{16}H_{13}ClN_2O$	67.01	5.27	66.56	5.62
Cl	H	H	CH_3	H[d]	B	Et_2O	144–145	76	$C_{16}H_{13}ClN_2O$	65.57	5.50	65.86	5.27
Cl	H	H	CH_3	CH_3	E	Hex.	90–91	31	$C_{17}H_{15}ClN_2O$	67.88	5.70	68.08	5.98
Cl	H	H	CH_3	$CH_2CH{=}CH_2$	F[f]	Hex.	108–109	57	$C_{19}H_{17}ClN_2O$	69.82	5.86	69.95	6.11
Cl	H	H	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$[e]	F[f]	CH_2Cl_2–Et_2O	140–141	43	$C_{21}H_{21}ClN_2O \cdot HCl$	64.78	5.70	64.41	5.58
CF_3	H	H	H	H[d]	A	MeOH	152–153	72	$C_{16}H_{11}F_3N_2O$	62.74	1.28	62.65	1.27
CF_3	H	H	CH_3	CH_3	E	Hex.	77–79	48	$C_{18}H_{15}F_3N_2O$	64.66	5.33	65.09	1.71
CH_3	H	H	H	H	A	EtOH	173–176	50	$C_{16}H_{14}N_2O$	76.16	6.39	75.90	6.36
CH_3	H	H	CH_3	CH_3	E	Hex.	71–73	15	$C_{18}H_{18}N_2O$	77.11	7.19	76.84	7.13
Br	F	H	H	H[d]	A	MeOH	221–225	87	$C_{15}H_{10}BrFN_2O$	53.75	3.61	54.09	3.75
Br	F	H	CH_3	CH_3	E	Et_2O	131–135	41	$C_{17}H_{14}BrFN_2O$	56.21	4.16	56.58	1.61
Cl	Cl	H	H	H	A	AcOH	235–237	10	$C_{15}H_{10}Cl_2N_2O$	58.65	3.99	58.82	1.15
Cl	Cl	H	CH_3	CH_3[e]	E	Ac.–Et_2O	240–241	50	$C_{17}H_{16}Cl_2N_2O \cdot HCl$	51.93	1.61	55.14	1.53
Cl	Cl	H	CH_3	H[d]	B	CH_2Cl_2–Et_2O	169–172	51	$C_{16}H_{14}Cl_2N_2O$	59.83	4.39	59.91	1.06
Cl	F	H	H	H[d]	A	Ac.	214–215	68	$C_{15}H_{10}ClFN_2O$	61.95	4.16	61.69	3.92
Cl	F	H	C_2H_5	H	B[f]	MeOH	165–167	87	$C_{17}H_{15}ClFN_2O$	61.05	5.06	61.05	5.05
Cl	F	H	C_2H_5	CH_3	F[f]	Ac.–hex.	132–133	57	$C_{18}H_{17}ClFN_2O$	61.96	5.15	65.19	5.30
Cl	F	H	C_2H_5	C_2H_5	F[f]	Hex.	92–93	47	$C_{19}H_{19}ClFN_2O$	65.80	5.81	65.63	6.05
Cl	CH_3	H	H	H[d]	A	DMF–H_2O	248–249	91	$C_{16}H_{13}ClN_2O$	67.01	5.25	67.11	5.64
Cl	CH_3	H	CH_3	CH_3[e]	E	MeOH–Et_2O	197–215	66	$C_{18}H_{17}ClN_2O \cdot HCl$	61.51	5.71	61.60	5.16
F	F	H	H	H	A	Ac.–hex.	174–177	96	$C_{15}H_{12}F_2N_2O$	65.69	4.41	65.12	1.31
F	F	H	CH_3	CH_3	E	Hex.	118–120	84	$C_{17}H_{16}F_2N_2O$	67.15	5.33	67.58	5.26
F	F	H	CH_3	H[e]	C	MeOH	219–239	35	$C_{16}H_{14}F_2N_2O \cdot HCl$	59.17	4.66	59.15	4.66
Cl	H	Cl	CH_3	H[d]	B	Et_2O	131–135	63	$C_{16}H_{14}Cl_2N_2O$	59.83	4.39	59.81	1.21
F	H	Cl	H	H	A	C_6H_6	177–178	19	$C_{15}H_{12}ClFN_2O$	61.97	4.16	62.20	1.09
F	H	Cl	CH_3	CH_3	E	Hex.	109–112	60	$C_{17}H_{16}ClFN_2O$	61.05	5.06	61.59	1.86
F	H	Cl	CH_3	H[e]	B	MeOH–Et_2O	201–205	92	$C_{16}H_{15}ClFN_2O \cdot HCl$	56.49	1.15	56.35	1.16
Cl	Cl	Cl	H	H	A	Ac.	208–210	75	$C_{15}H_9Cl_3N_2O$	52.74	3.25	52.66	3.59
Cl	Cl	Cl	CH_3	CH_3	E	Hex.	150–153	30	$C_{17}H_{15}Cl_3N_2O$	55.23	4.09	55.41	4.09
Cl	Cl	Cl	CH_3	H	B	Ac.–hex.	169–172	69	$C_{16}H_{13}Cl_3N_2O$	54.03	3.68	54.40	3.86
H	F	H	H	H[d]	A	CH_2Cl_2	162–163	92	$C_{15}H_{11}FN_2O$	70.30	5.11	70.42	5.00
H	F	H	CH_3	CH_3	E	Hex.	119–122	59	$C_{17}H_{17}FN_2O$	71.81	6.03	71.73	6.09
H	F	H	CH_3	H[e]	B	CH_2Cl	123–124.5	50	$C_{16}H_{15}FN_2O$	71.09	5.59	70.77	5.72
H	H	Cl	H	H[d]	A	CH_2Cl_2–hex.	192–195	98	$C_{15}H_{13}ClN_2O$	66.06	4.80	66.28	5.07
H	H	Cl	CH_3	CH_3	E	Et_2O–pet.	132–133	76	$C_{17}H_{17}ClN_2O$	67.88	5.70	68.01	5.68

[a] The letters denoting the method of preparation refer to the Experimental section of this paper. [b] Ac. = acetone, pet. = petroleum ether, DMF = N,N-dimethylformamide, hex. = hexane, AcOH = acetic acid. [c] In most cases these experiments were carried out only once and optimal conditions were not established. [d] The starting material for this compound is described in one of the following references (1, 3–7). [e] Isolated, and purified as the hydrochloride salt. [f] Where required allyl bromide or ethyl iodide was substituted for methyl iodide in this reaction.

(91%) of a pure compound shown to be identical with that obtained by Method B.

7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-4-methyl-2*H*-1,4-benzodiazepin-2-one. Method D.—A solution of 16 g. (0.054 mole) of 7-chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one in a mixture of 30 ml. of benzene and 10 ml. of N,N-dimethylformamide was heated under reflux for 1 hr. with 7.6 ml. (0.1 mole) of methyl iodide. The reaction mixture was cooled, poured into 400 ml. of water, and extracted with three 50-ml. portions of dichloromethane. The organic fractions were combined, washed with water, dried, and evaporated. Recrystallization of the residue from a mixture of dichloromethane and petroleum ether (b.p. 30–60°) gave 7.5 g. (44.6%) of the product as white prisms, m.p. 185–186°.

Anal. Calcd. for $C_{16}H_{14}ClFN_2O$: C, 63.08; H, 4.60; N, 9.19. Found: C, 62.67; H, 4.86; N, 9.21.

7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-1,4-dimethyl-2*H*-1,4-benzodiazepin-2-one. Method E. From 7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one.—A solution of 13 g. (0.0435 mole) of the tetrahydrobenzodiazepinone in 30 ml. of N,N-dimethylformamide was stirred for 1 hr. at room temperature with a methanolic solution of sodium methoxide (0.055 mole of $NaOCH_3$).[10] The sodio derivative thus formed was treated with 20 ml. (0.336 mole) of methyl iodide and the solution heated for 2 hr. at 60°. The reaction mixture was poured into 1 l. of water and extracted with four 140-ml. portions of dichloromethane. The extracts were combined, washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated. Recrystallization of the residue from ether gave 10 g. (72%) of the product as white needles, m.p. 124–125°.

Anal. Calcd. for $C_{17}H_{16}ClFN_2O$: C, 64.05; H, 5.06; Found: C, 64.21; H, 5.17.

Method F. From 7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.—A solution of 1.9 g. (0.00625 mole) of the 1-methyl derivative in 15 ml. of N,N-dimethylformamide was treated with 0.8 ml. (0.0125 mole) of methyl iodide and worked up as described under D to give 1.2 g. (60%) of 7-chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-1,4-dimethyl-2*H*-1,4-benzodiazepin-2-one.

Method G. From 7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-4-methyl-2*H*-1,4-benzodiazepin-2-one.—A solution of

3.55 g. (0.0116 mole) of the 4-methyl derivative in 15 ml. of N,N-dimethylformamide was treated with a methanolic solution of sodium methoxide (0.014 mole of $NaOCH_3$)[10] and then with 1.05 ml. (0.0168 mole) of methyl iodide as described under C. The mixture was worked up as described under C and yielded 2.7 g. (73%), of a compound identical in every respect with that obtained under F.

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Derivatives of 2-(2-Pyrimidinyl)acetophenone[1]

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Cyclic amidines and guanidines are well known classes of diuretic agents.[3] This paper reports the synthesis of some derivatives of 2-(2-pyrimidinyl)acetophenone (I),[4-6] a cyclic amidine, as potential diuretic agents. When the ketone I was reacted with an equimolar amount of phenylmagnesium bromide the phenylcarbinol was obtained in 31% yield, with recovery of 67% of I; phenyllithium gave similar results. If one assumes that part of the Grignard reagent complexes with the pyrimidine ring nitrogens, then excess reagent should increase the yield of carbinol. This was found to be true, as the yield increased to 61% and 81% for 2:1 and 3:1 *M* ratios, respectively, of Grignard reagent to ketone.

Catalytic hydrogenation of the methochloride of I produced a tetrahydro carbinol. The structure assignment was based on the formation of benzaldehyde (retroaldol) on treatment with dilute sodium hydroxide solution. Stopping the hydrogenation after 2 moles of hydrogen were added yielded a compound which did not yield benzaldehyde when reacted with base; therefore, the tetrahydro ketone structure was assigned to the product.

Experimental[7]

α,α-Diphenyl-2-pyrimidineethanol. A.—To 14.9 g. (0.082 mole) of phenylmagnesium bromide in 85 ml. of ether was added over 3 min., 5.4 g. (0.0273 mole) of the ketone I[5] in 225 ml. of benzene and 60 ml. of ether. The solution was heated at reflux for 30 min., cooled, acidified with 50 ml. of 10% sulfuric acid, and the solid filtered to give 7.9 g. (81%), m.p. 221–224° dec., of the **hydrobromide** salt, after two recrystallizations from nitromethane, m.p. 231° dec.

Anal. Calcd. for $C_{18}H_{16}N_2O \cdot HBr$: C, 60.51; H, 4.80; N, 7.84. Found: C, 60.11; H, 4.86; N, 7.80.

The **free base** melted at 141–143°.

Anal. Calcd. for $C_{18}H_{16}N_2O$: N, 10.14. Found: N, 10.07.

B.—To 1.71 g. (0.0204 mole) of phenyllithium in 50 ml. of ether was added over 10 min. 3.6 g. (0.0182 mole) of I in 150 ml. of benzene and 50 ml. of ether. The solution was diluted with 50 ml. of ether, stirred for 30 min., adjusted to pH 5 with 5% sulfuric acid, and the solid filtered. The yield of hydrobromide salt was 1.6 g. (25%), m.p 231–233° dec. From the aqueous and organic layers 56% of I was recovered.

2-(2-Hydroxy-2,2-diphenylethyl)-1-methylpyrimidinium Iodide.—A mixture of 2.0 g. (0.0073 mole) of α,α-diphenyl-2-pyrimidineethanol and 10 ml. of methyl iodide was allowed to stand in a closed flask for 1 week. Removal of excess methyl iodide by evaporation yielded 3.0 g. (99%), m.p. 235–240° dec., of yellow methiodide. One recrystallization from 30 ml. of water yielded 2.22 g. (73.3%), m.p. 239–240° dec.

Anal. Calcd. for $C_{19}H_{19}IN_2O$: I, 30.34. Found: I, 29.92.

1-Methyl-2-phenacylpyrimidinium Iodide.—A mixture of 5.1 g. (0.0257 mole) of the ketone I and 25 ml. of methyl iodide was heated in a sealed tube in a water bath at 60–80° for 5 hr. The yield of yellow solid after filtration was 8.0 g. (91.5%), m.p. 189–191°. After 2 recrystallizations from a mixture of ethyl acetate and ethanol the methiodide melted at 190.5–191°.

Anal. Calcd. for $C_{13}H_{13}IN_2O$: N, 8.24. Found: N, 8.24.

The methochloride was prepared by treating a suspension of silver chloride in water with an aqueous solution of the methiodide.

2-(1,4,5,6-Tetrahydro-1-methyl-2-pyrimidinyl)acetophenone Hydrochloride.—A solution of 1.5 g. (0.0064 mole) of the methochloride of I in 25 ml. of absolute ethanol was reduced over 70 mg. of platinum oxide catalyst in a low pressure hydrogenation apparatus. The hydrogenation was stopped after 2 *M* equiv. of hydrogen was added (10 min.). The catalyst was filtered and the filtrate evaporated *in vacuo* to give 1.44 g. (95%) of solid, m.p. 250–253°. This was recrystallized from 2-propanol and then butanol to give white crystals, m.p. 252–253°.

Anal. Calcd. for $C_{13}H_{16}N_2O \cdot HCl$: C, 61.77; H, 6.78; Cl, 14.03. Found: C, 60.90; H, 6.77; Cl, 13.83.

1,4,5,6-Tetrahydro-1-methyl-α-phenyl-2-pyrimidineethanol Hydrochloride.—A solution of 1.5 g. (0.00604 mole) of I-methochloride in 25 ml. of absolute ethanol was reduced over 70 mg. of platinum oxide catalyst in a low pressure hydrogenation apparatus. The reduction was stopped after 3.5 *M* equiv. of hydrogen was added (160 min.) and the catalyst filtered. The filtrate was evaporated in vacuo, and the residual gum (1.4 g.) when added to 2-propanol crystallized to give 0.5 g. (32.5%), m.p. 223–224°, of white solid. This was recrystallized to constant melting point (223–224°) from 2-propanol.

Anal. Calcd. for $C_{13}H_{18}N_2O \cdot HCl$: C, 61.29; H, 7.52; Cl, 13.92. Found: C, 61.44; H, 7.36; Cl, 13.84.

When the hydrochloride salt was treated with 10% sodium hydroxide solution an odor of benzaldehyde was produced, and when this solution was acidified and reacted with 2,4-dinitrophenylhydrazine, a hydrazone was obtained, m.p. 238–239° (no depression with benzaldehyde 2,4-dinitrophenylhydrazone, lit.[8] m.p. 237°).

(1) Taken in part from the thesis of F. F. Ebetino submitted in partial fulfillment of the requirements for the Master of Science degree at Lehigh University, 1953.

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Synthesis of Some Derivatives of 5-Aminoindole-3-acrylic Acid[1a]

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Recently we have reported on the preparation of the 5-nitrogen mustards of tryptophan[1b] and other indole-3-alkanoic acids.[1c] As a continuation of this series we have undertaken the preparation of the corresponding mustard (I) of indole-3-acrylic acid. A

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