#### Experimental<sup>9</sup>

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<sup>10</sup> (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);  $\lambda_{\rm max}^{\rm EOH}$ 262 m $\mu$  ( $\epsilon$  10,630), and  $\lambda_{min}$  243 m $\mu$  ( $\epsilon$  6370). *Anal.* Caled. for C<sub>28</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>: C, 71.47; H, 5.57; N, 5.96.

Found: C, 71.30; H, 5.73; N, 5.69.

1-(2-Deoxy-B-p-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 drvness 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), nr.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<sub>2</sub>O,  $\lambda_{max}$  263 m $\mu$  ( $\epsilon$  10,620), and  $\lambda_{\min} 232 \ \text{m}\mu \ (\epsilon \ 2760); \ 0.1 \ N \ \text{HCl}, \ \lambda_{\max} \ 262 \ \text{m}\mu \ (\epsilon \ 9610),$ and  $\lambda_{\min}$  231 m $\mu$  ( $\epsilon$  2220); 0.1 N NaOH,  $\lambda_{\max}$  262 m $\mu$  ( $\epsilon$  7070), add  $\lambda_{\min}$  241 m $\mu$  ( $\epsilon$  4520).

Anal. Caled. for C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>: C, 47.36; H, 5.30; N, 12.28. Found: C, 47.22; H, 5.40; N, 12.09.

1-(2-Deoxy- $\beta$ -D-lyxofuranosyl)-5-iodouracil (IV).<sup>11</sup>—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.  $180-181^{\circ}$  dec.,  $[\alpha]^{25}D = 4.9^{\circ}$  (c 0.81, ethanol); in H<sub>2</sub>O,  $\lambda_{max} 289 \text{ m}\mu$  ( $\epsilon 6530$ ) and  $\lambda_{\min} 247 \,\mathrm{m}\mu$  ( $\epsilon 970$ ); 0.1 N HCl,  $\lambda_{\max} 288$  ( $\epsilon 4330$ ), and 255 m $\mu$ ( $\epsilon$  2010); 0.1 N NaOH,  $\lambda_{max}$  278 m $\mu$  ( $\epsilon$  5310) and  $\lambda_{min}$  254 m $\mu$ (e 2830).

Anal. Caled. for  $C_8H_{11}IN_2O_5$ ; 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, 111.

(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-2H-1,3,4-benzotriazepin-2ones

## Theodore S. Sulkowski and Scott J. Childress

Research and Development Division, Wyeth Laboratories Inc., Radnor, Pennsylvania

#### Received November 21, 1963

Because of our interest in 1,4-benzodiazepin-2-ones<sup>1</sup> and 3,1,4benzoxadiazepin-2(1H)ones,<sup>2</sup> it seemed desirable to prepare some aza analogs of these ring systems. Accordingly, several 5-aryl-1,3-dihydro-2H-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-2H-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. Caled. 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-2H-1,3,4-benzotriazepin-2-one, m.p.  $253-255^\circ$ , was prepared similarly from 2-amino-5-methyl-benzophenone hydrazone in a yield of 50%.

Anal. Caled. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O: 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-2H-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. standing there was obtained 1.6 g. of product, m.p. 246-248°

Anal. Caled. for  $C_{14}H_{10}ClN_{8}O$ : 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. Caled. for C16H16ClN3O2: 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.

# Quinazolines and 1,4-Benzodiazepines. XIX.<sup>1</sup> N-Alkyl Derivatives of Substituted 1,3,4,5-Tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-ones

R. IAN FRYER, B. BRUST, J. EARLEY, AND L. H. STERNBACH

Department of Chemical Research, Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey

#### Received January 16, 1964

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-2H-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)-1,3,4,5tetrahydro-2H-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.

<sup>(1)</sup> S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, J. Org. Chem., 27, 562 (1962).

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

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

## TABLE I 2-Aminobenzophenones



					Crystd.	Crystd. Yield,			~~~% Calcd			
Rı	$\mathbf{R}_2$	$\mathbf{R}_3$	$R_4$	$\mathrm{Method}^a$	from	M.p., °C.	%	Formula	С	Н	С	н
$\mathbf{F}$	$\mathbf{F}$	Н	н	V A	Hexane	99 - 101	84	$C_{13}H_9F_2NO$	66.95	3.89	67.20	4.00
$\mathbf{F}$	$\mathbf{F}$	Η	$COCH_2Br$	VI D	MeOH	116 - 118	92	$\mathrm{C}_{15}\mathrm{H}_{10}\mathrm{BrF}_{2}\mathrm{NO}_{2}$	50.87	2.85	50.62	2.80
F	Η	Cl	н	V A	Hexane	96 - 97	52	C <sub>13</sub> H <sub>9</sub> ClFNO	62.54	3.63	62.64	3.62
$\mathbf{F}$	Η	Cl	$COCH_2Br$	VI D	MeOH	143 - 144.5	87	$\mathrm{C_{15}H_{16}BrClFNO_{2}}$	48.61	2.72	48.43	2.92
Cl	Cl	Cl	Н	V A	Hexane	81-83	89	$C_{13}H_8Cl_3NO$	51.95	2.68	52.21	3.01
$\mathbf{Cl}$	C1	Cl	$\rm COCH_2Br$	VI D	MeOH	147 - 150	65	$\mathrm{C_{15}H_9BrCl_3NO_2}$	42.74	2.15	42.72	2.41

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

 TABLE II

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



						3					
				Crystd. <sup>b</sup>		Yield,			lcd.—		und
R•	$\mathbf{R}_{3}$	$\mathbf{R}_4$	$\mathrm{Method}^a$	from	M.p., °C.	%	Formula	С	H	С	н
$\mathbf{F}$	H	Н	VI H <sup>e</sup> -N	Ac.	197 - 200	93	$\mathrm{C_{15}H_{10}F_2N_2O}$	66.17	3.70	65.93	3.83
$\mathbf{F}$	$\mathbf{H}$	$CH_3$	VI S	Hex.	110-111	82	$\mathrm{C_{16}H_{12}F_2N_2O}$	67.13	4.23	67.09	4.38
$\mathbf{H}$	Cl	H	VI H <sup>e</sup> –N	Ac.	230 - 232	92	$\mathrm{C}_{15}\mathrm{H}_{10}\mathrm{ClFN}_{2}\mathrm{O}$	62.40	3.49	62.10	3.54
н	Cl	$CH_3$	VIS	Achex.	160 - 163	73	$\mathrm{C}_{16}\mathrm{H}_{12}\mathrm{ClFN}_{2}\mathrm{O}$	63.40	4.00	63.32	4.30
Cl	$\mathbf{Cl}$	H	VI H°N	Ac.	231 - 233	83	$\mathrm{C_{15}H_9Cl_3N_2O}$	53.02	2.67	53.20	2.86
$\operatorname{Cl}$	Cl	$\mathrm{CH}_3$	VIS	Achex.	178 - 181	70	$\mathrm{C_{16}H_{11}Cl_3N_2O}$	54.34	3.14	54.30	3.28
	R. F F H Cl Cl	R- R <sub>s</sub> F H F H H Cl H Cl Cl Cl Cl Cl	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccc} & & & & & & & \\ R^{*} & R_{3} & R_{4} & & Method^{a} & & from \\ F & H & H & VI & H^{e}-N & Ac. \\ F & H & CH_{3} & VI & S & & Hex. \\ H & Cl & H & VI & H^{e}-N & Ac. \\ H & Cl & CH_{3} & VI & S & & Achex. \\ Cl & Cl & H & VI & H^{e}-N & Ac. \\ Cl & Cl & CH_{3} & VI & S & & Achex. \end{array}$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

<sup>a</sup> The letters denoting the method of preparation refer to the Experimental section of paper VI in this series (see ref. 2). <sup>b</sup> Ac. = acetone, hex. = hexane. <sup>c</sup> As previously reported (see ref. 2) it was not necessary to isolate the intermediate aminoacetamidobenzo-phenones (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.<sup>2-7</sup> The physical properties and the methods of preparation of the three, previously unknown, benzodiazepinones and their intermediates<sup>8</sup> 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-2H-1,4-benzodiazepin-2-one. Method A.—Hydrogenation<sup>9</sup> of a solution of 11.2 g. (0.0375 mole) of 7-chloro-5-(2-fluorophenyl)-1,3-dihy-

(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).

(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. dro-2*H*-1,4-benzodiazepin-2-one<sup>2</sup> 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-2H-1,4-benzodiazepine-2-one. Method B. From 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2one.<sup>2</sup>—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. Caled. 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-2H-1,4-benzodiazepin-2-one.—A solution of 10 g. (0.0334 mole) of the tetrahydro-1,4-benzodiazepinone in 50 ml. of N,Ndimethylformamide was stirred at 5° for 20 min. together with a methanolic solution of sodium methoxide<sup>10</sup> (0.0423 mole of NaOCH<sub>3</sub>). 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.

<sup>(4)</sup> L. H. Sternbach and E. Reeder, ibid., 26, 4936 (1961).

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

Substituted 1,3,4,5-Tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-ones



						Cryst. <sup>k</sup>	М.р.,	Yield.	e		'alcd		Found s
$\mathbb{R}_1$	$R_2$	$\mathbf{R}_{\delta}$	Ra	$R_{5}$	$Method^{o}$	from	°Ċ,	57	Formula	Ċ	11	C	Н
IT	H	Н	H	$\Pi^{d}$	А	Acpet.	$147 \cdot 148$	84	$C_{15}H_{14}N_2O$	75.60	5.92	75.88	5,60
H	П	Н	CHa	$C H_{2}$	E	$CH_2Cl_2$	115 - 116	32	$C_{17}H_{18}N_2O$	76.66	6.81	76.61	6.91
Br	11	H	H	11	E.	$DMF-H_2O$	191 - 192	79	$C_{15}H_{13}BrN_2O$	56.80	4.13	57.01	4.11
Br	Н	Н	CII	$CHs^{c}$	Е	MeOH-EtgO	166 - 172	20	$C_{17}H_{17}BrN_2O \cdot HCI$	53,49	4.49	53.20	4.48
Cl	H	11	H	$\mathbb{H}^d$	A	$DMF-H_{2}O$	185 - 186	73	$C_{1b}H_{13}C1N_2O$	66.06	4.80	65.87	4.80
C1	11	Н	H	CHa	D	$CH_2Cl_2$	205 - 206	38	$C_{16}H_{15}CIN_2O$	67.01	5.27	66.56	5.62
Cl	H.	Н	$CH_0$	$\Pi^d$	В	Et <sub>2</sub> O	144 - 145	76	$C_{16}H_{15}CIN_2O$	65.57	5.50	65.86	5 27
C1	П	ΗΓ	$C1I_3$	$CH_3$	E _	Hex.	9091	31	$C_{12}H_1;CIN_2O$	67.88	5.70	68.08	5.98
Cł	Н	H	$CH_3$	$CH_2CH==CH_2$	$F_{1}$	Hex.	108 - 109	57	$C_{19}H_{19}CIN_2O$	69.82	$5^{-}86$	69.95	6.11
Cl	H	H	$CH_2CH \sim CH_2$	−CH2CII-+CH9°	E'	$CH_2Cl_2$ ~ $Et_2O$	$190 \cdot 191$	4.3	$C_{21}H_{21}C[N_2O \cdot HC]$	64 - 78	5.70	64.41	5.58
$C F_{2}$	П	11	П	$\Pi^d$	4	MeOH	$152 \cdot 153$	72	$C_{13}H_{13}F_5N_2O$	62.74	1.28	62.65	4.27
C'E-	H.	11	CH:	CH	E	Hex.	77 - 79	48	$C_{18}H_{17}F_5N_2O$	64.66	5.13	65/09	1.71
$CH_3$	EL	11	II	11	A	EtOH	$174 \cdot 176$	50	$C_{2}H_{2}N_{2}O$	76.16	6.39	75,90	6.36
CHE	Н	11	$C \Pi_{0}$	CHa	E	Hex.	$71 \cdot 73$	1.5	$C_{18}H_{20}N_2O$	77.1I	7.19	76.84	7.13
Br	F	Н	11	$\Pi^{d}$	Α	MeOII	$224 \cdot 225$	87	$C_{15}H_{*2}BrFN_2O$	53.75	3.61	54.09	3 75
Br	F	11	$CH_3$	СĦх	E	Et <sub>2</sub> O	$134 \cdot 135$	41	$C_{12}\mathrm{HesBrFN}_2\mathrm{O}$	56.21	4.46	56, 58	4 64
CL	C1	FL	П	$\mathbf{H}^{d}$	A	AcOH	$235 \cdot 237$	40	$C_{15}H_{12}Cl_2N_2O$	58.65	3.94	58.82	4.15
Cl	(1)	IT	$CH_3$	$CH^{*}$	E	AcEt <sub>2</sub> O	240 - 241	50	$C_1$ - $H_{16}$ $Cl_2$ $N_2$ O · H $Cl_2$	54.93	1-61	55.11	4 .53
Cl	Cl	11	CHa	$\Pi^{a}$	13	$CH_2CI_2$ -Et $_2O$	$169 \cdot 172$	51	$C_{10}H_{14}C_{12}N_2O$	59 - 83	1.39	59 - 94	F. OG
C1	Ł	н	14	I f"	л.,	Ac.	214 - 215	68	$C_{45}H_{12}CHFN_2O$	61.97	1.16	61.69	3 92
C1	ŀ.	H	$C_2 H_5$	If	$B'_{\pm}$	MeOH	165 - 167	87	$C_{12}\Pi_{10}ClFN_2O$	61 - 05	5.06	64.05	5.05
CI	Ŀ.	1 I	$C_2 H_b$	$CH_3$	12	Aches.	$132 \ 133$	57	$C_{18}H_{18}C1FN_2O$	64-96	5.45	65.19	5,30
Cl	F.	II	$C_2H_5$	CeHa	127	Hex.	92-93	47	$C_{19}H_{20}CIFN_2O$	65 80	5.81	65.63	6.05
Cl	CHa	11	11	$H^q$	.1	$DMF-H_2O$	248 249	91	$C_{16}H_{1\delta}C[N_2O]$	67.01	5,27	67.11	5,64
Cl	$CH_3$	11	CHa	CHe <sup>*</sup>	E	MeOH~EtgO	197 - 215	66	Cistf:gClNgO+HCl	61.54	5.71	61.69	5 16
E.	F	H	11	1£	A	Achex.	174-177	96	$C_{15}H_{12}F_2N_2O$	65.69	4.41	65.42	4.34
- F 	F	11	CH <sub>3</sub>	CHR	E	Hex.	118 - 120	84	$C_{17}H_{16}F_2N_2O$	67.45	5.33	67.58	5.26
F	F	H	CH:	H1 <sup>e</sup>	C	MeOH	219 - 239	35	$C_{16}H_{14}F_{2}N_{2}O \cdot HCl$	59.17	4.66	59.11	4 66
CI	H	CI	CHa	11"	В	Et <sub>2</sub> O	134 - 135	63	$C_{16}H_{14}Cl_2N_2O$	59.83	4 39	59.81	4.21
F	11	Cl		11	A	Cells	177-178	19	$C_{15}H_{12}ClFN_2O$	61.97	4.16	62.20	1.09
F	11	Cl	CHa	CHg	E	Hex.	109 - 112	60	$C_{17}H_{16}ClFN_2O$	64.05	5.06	64.59	4.86
1 Contraction	н	CI	C Ha	117	B	MeOH-Et <sub>2</sub> O	201 - 205	92	$C_{16}H_{14}ClFN_2O \cdot IICl$	56.49	4.15	56.35	4.46
(1	-CT	C1	H OTT	11	A	Ac.	208-210	7.5	CisHnClaN <sub>2</sub> O	52.74	3.25	52.66	3 59
() ()	-C]	C)	CHE	CH:	45	Hex.	150-153	30	CarH15ClaNeO	55.23	4.09	55.44	4.09
Cl	C1	C1		11	В	Achex.	169-172	69	$C_{18}H_{13}Cl_3N_2O$	54.03	3-68	54.40	3.86
11		11		14"	.1	CH <sub>2</sub> Cl <sub>2</sub>	162-163	92	C 5 H13F N2O	70.30	5.11	70.42	5.00
11	l'	11	CHa	CH:	E	flex.	119-122	-59	CarHirf NgO	71.81	$6_{-}03_{-}$	71.73	6.09
11	t	11	C 113	11	В	C112C1	123 - 124 - 5	ō0	$C_{16}H_{16}FN_2O$	71.09	5.59	70.77	5.72
11	Н	C1	H	$\Pi^d$	А	CH <sub>2</sub> Cl <sub>2</sub> -hex.	192 - 195	98	$C_{15}H_{15}ClN_2O$	66.06	4.80	66.28	5.07
П	Η	C1	CH:	$CH_3$	$\mathbf{E}$	Et <sub>2</sub> O-pet.	132 - 133	76	$C_{17}H_{17}ClN_2O$	67.88	5.70	68.04	5.68
	1 1	,		1 1 0									

<sup>a</sup> The letters denoting the method of preparation refer to the Experimental section of this paper. <sup>b</sup> Ac. = acetone, pet. = petroleum ether, DMF = N,N-dimethylformamide, hex. = hexane, AcOH = acetic acid. <sup>c</sup> In most cases these experiments were carried out only once and optimal conditions were not established. <sup>d</sup> The starting material for this compound is described in one of the following references (1, 3-7). <sup>e</sup> Isolated, and purified as the hydrochloride salt. <sup>f</sup> 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//-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//-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. Caled. 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//-1,4-benzodiazepin-2-one. Method E. From 7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2one.—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<sub>3</sub>).<sup>10</sup> 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.  $(72^{C_{\ell}})$  of the product as white needles, m.p. 124–125°.

Anal. Caled. 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-2H-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-dimethylfornamide 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-1.4dimethyl-2H-1,4-benzodiazepin-2-one. Method G. From 7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetra-

Method G. From 7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-4-methyl-2//-1,4-benzodiazepin-2-one.-- A solution of New Compounds

3.55 g. (0.0116 mole) of the 4-methyl derivative in 15 ml. of N,Ndimethylformamide was treated with a methanolic solution of sodium methoxide (0.014 mole of NaOCH<sub>3</sub>)<sup>10</sup> 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.

Acknowledgments.—We are indebted to Dr. Al Steyermark and his staff for microanalytical data, to Dr. A. Motchane and Mr. S. Traiman for infrared determinations, and to Miss Barbara Petlack for the compilation of data in the tables.

## Derivatives of 2-(2-Pyrimidinyl)acetophenone<sup>1</sup>

#### FRANK F. EBETINO<sup>2</sup> AND E. D. AMSTUTZ

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania

#### Received February 4, 1964

Cyclic amidines and guanidines are well known classes of diuretic agents.<sup>3</sup> This paper reports the synthesis of some derivatives of 2-(2-pyrimidinyl)acetophenone (I),<sup>4–6</sup> 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<sup>7</sup>

 $\alpha,\alpha$ -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<sup>5</sup> 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. Caled. 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. Caled. 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% sulfurie 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.

(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.

(2) William S. Merrell Co. Fellow, 1951-1953. Author to whom inquiries should be addressed, Norwich Pharmacal Co., Norwich, N. Y.

(3) (a) W. L. Lipschitz and Z. Hadidian, J. Pharmacol. Exptl. Therap.,
81, 84 (1944); (b) W. L. Lipschitz and E. Stokey, *ibid.*, 83, 235 (1944); (c)
W. L. Lipschitz and E. Stokey, *ibid.*, 92, 131 (1948).

(4) J. M. Smith, Jr., and B. Roth, U. S. Patent 2,487,391 (1949).

(5) B. Roth and J. M. Smith, Jr., J. Am. Chem. Soc., 71, 616 (1949).

(7) Melting points are corrected.

2-(2-Hydroxy-2,2-diphenylethyl)-1-methylpyrimidinium Iodide.—A mixture of 2.0 g. (0.0073 mole) of  $\alpha, \alpha$ -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 C19H19IN2O: 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. Caled. for C13H13IN2O: 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- $\alpha$ -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. Caled. 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.<sup>8</sup> m.p. 237°).

(8) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 229.

# Synthesis of Some Derivatives of 5-Aminoindole-3-acrylic Acid<sup>1a</sup>

JOSEPH DEGRAW AND LEON GOODMAN

Life Sciences Research, Stanford Research Institute, Menlo Park, California

#### Received September 30, 1963

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

<sup>(6)</sup> A. Dornow and E. Neuse, Ber., 84, 296 (1951).

<sup>(1)(</sup>a) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, under Contract No. SA-43-ph-1892. The opinions expressed in this article are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. The authors are indebted to Mr. O. P. Crews and his staff for the large scale preparation of intermediates. They are also indebted to Dr. Peter Lim and his staff for spectral measurements and interpretations. (b) J. DeGraw and L. Goodman, J. Org. Chem., **27**, 1395 (1962). (c) J. DeGraw and L. Goodman. *ibid.*, **27**, 1728 (1962).