Analgesics. Basic Amides of α-Alkoxydiphenylacetic Acids[1]

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Twenty-six basically substituted amides of α-alkoxydiphenylacetic acids were prepared for evaluation as analgesics. Four of these compounds had higher analgesic activity than meperidine when tested in rats by the oral route.

The synthesis of a series of basic amides derived from benzilic acid has been reported previously and the compounds have been shown to possess antispasmodic activity.[2] Replacement of the hydroxyl group in some of these compounds by alkoxyl has yielded basic amides of α-alkoxyldiphenylacetic acids showing high analgesic activity.

Compound I, the prototype of this series, was readily prepared by either of two methods. The reaction of α-chlorodiphenylacetyl chloride with N,N,N′-trimethylethylenediamine gave the intermediate α-chloroamide. The latter was not isolated and purified but converted directly to the α-ethoxyamide I by treatment of the reaction mixture with ethanol.

$$(C_6H_5)_2CClCOCl + CH_3NHCH_2CH_2N(CH_3)_2 \longrightarrow (C_6H_5)_2CClCON(CH_3)CH_2CH_2N(CH_3)_2\cdot HCl \xrightarrow{C_2H_5OH} (C_6H_5)_2C(OC_2H_5)CON(CH_3)CH_2CH_2N(CH_3)_2\cdot HCl$$

I

In the alternate method, 2-ethoxy-N-methyl-2,2-diphenylacetamide was alkylated with 2-dimethylaminoethyl chloride, using sodamide as the condensing agent, to give I.

Most of the compounds of this series, listed in Table II, were prepared by the reaction of α-chlorodiphenylacetyl chloride with the appropriate diamines and alcohols. The yields in these reactions were usually about 80%. The analogs of I, in which the basic group is amino (**12**) or methylamino (**14**) were obtained by hydrogenolysis of the corresponding dibenzylamino (**11**) and benzylmethylamino (**13**) derivatives. The reaction of the free base of **14** with *p*-nitrophenethyl bromide and phenacyl chloride and with 2- and 4-vinylpyridine yielded compounds **20, 23, 24,** and **25.** Compound **21** was obtained by the catalytic reduction of the intermediate analog (**20**).

The compounds listed in Table II were evaluated for analgesic activity in rats by the oral route using a radiant heat procedure.[3] In this test, the ED_{50}[4] of **3** (I) was 56 mg./kg.[5] (LD_{50}, 565 mg./kg.) and the ED_{50} of meperidine was 48 mg./kg. (LD_{50},[6] 170 mg./kg.). Compounds **19, 21, 23,** and **24** were about one and one-half times as potent as **3** while compounds **8, 14, 16,** and **26** possessed about one-half the potency of **3.** Compound **19,** 2-ethoxy-N-methyl-N-[2-(methylphenethylamino)ethyl]-2,2-diphenylacetamide hydrochloride,[7] exhibited pharmacological actions similar to those reported for compound **3**[8]; it showed no physical dependence capacity (often equated with addiction liability) in the monkey at doses up to 24 mg./kg. (testing of higher doses was precluded by the low water solubility of the compound)[9] and was found to be an orally effective analgesic (150 mg. dose) in man.[10]

Analysis of the structure–activity relationships in this series of compounds reveals that the ethoxyl group, a methyl group attached to the amido nitrogen, and an ethylene bridge[11] separating the nitrogen atoms are essential for high analgesic activity. Maximum activity was obtained by replacement of a methyl group on the basic nitrogen of I by phenethyl, *p*-aminophenethyl, and 2-(or 4-)pyridylethyl.

Experimental[12]

N-(2-Dimethylaminoethyl)-2-ethoxy-N-methyl-2,2-diphenylacetamide Hydrochloride (I).—A solution of 530 g. (2.0 moles) of α-chlorodiphenylacetyl chloride in 2.6 l. of benzene was maintained at 20–25° during the dropwise addition (90 min.) of a solution of 204 g. (2.0 moles) of N,N,N′-trimethylethylenediamine in 500 ml. of benzene. The mixture was stirred for 1 hr. at room temperature, refluxed for 2 hr., and then distilled to remove 2 l. of solvent while 1 l. of ethanol was being added to the reaction mixture. The residue was treated with 1.8 l. of ethanol and refluxed for 8 hr., and the mixture was concentrated to a volume of about 1 l. The residue was cooled and treated with 1 l. of cold water, and the resulting solution was treated with a cold solution of 120 g. of sodium hydroxide in 450 ml. of water. The base was extracted with ether and dried over a magnesium sulfate, and the solvent was evaporated. Fractionation of the residue gave 596 g. (86%) of nearly colorless distillate, b.p. 170–175° (0.3 mm.).

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: N, 8.24. Found: N, 8.27.

A solution of this material in 600 ml. of ethanol was cooled and treated with an equivalent quantity of hydrogen chloride in 400 ml. of ethanol. Dilution of this solution to 4 l. with anhydrous ether gave 577 g. (77%) of colorless product, m.p. 193–194°.

(1) Presented in part before the Division of Medicinal Chemistry, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1960.

(2) J. Krapcho, C. F. Turk, and E. J. Pribyl, *J. Am. Chem. Soc.*, **77**, 3632 (1955).

(3) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(4) According to a method described by N. B. Eddy and D. Leimbach, *ibid.*, **107**, 385 (1953).

(5) N. B. Eddy, *Chem. Ind.* (London), 1462 (1959), reported the ED_{50} of **3** and meperidine in mice (s.c.) as 9.0 and 8.6 mg./kg., respectively.

(6) O. W. Barlow and J. R. Lewis, *J. Pharmacol. Exptl. Therap.*, **103**, 147 (1951).

(7) This product is currently under clinical investigation. Detailed pharmacological and clinical studies of this compound will be reported elsewhere.

(8) G. L. Hassert, J. J. Piala, J. C. Burke, and B. N. Craver, *Fed. Proc.*, **20**, 311 (1961).

(9) G. A. Deneau and M. H. Seevers (Univ. of Michigan), Addenda to the Minutes of the 1963 Meeting of the Committee on Drug Addiction and Narcotics, National Research Council. Physical dependence capacity is defined as the capacity of a compound to suppress withdrawal symptoms in morphine-addicted monkeys.

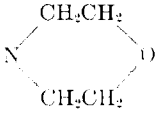
(10) Dr. Leo J. Cass, private communication.

(11) A related compound in which the ethylene bridge is part of a cyclic system, 1-(2,2-diphenyl-2-ethoxyacetyl)-4-methylpiperazine hydrochloride, exhibited no analgesic activity. The preparation of this compound was reported previously by O. Hromatka, O. Kraupp, and L. Stentzel, *Monatsh. Chem.*, **85**, 1208 (1954).

(12) The melting points are corrected.

TABLE I

$R'NHCH_2CH(R'')-B$

R'	R''	B	B.p., °C. (mm.)	Yield, %	Formula	% Nitrogen Calcd.	% Nitrogen Found
CH_3	H	$N(CH_3)CH_2C_6H_5$	71–72 (0.1)	66	$C_{11}H_{18}N_2$	15.72	15.65
CH_3	H	$N(CH_3)CH_2CH_2C_6H_5$	75–78 (0.2)	70	$C_{12}H_{20}N_2$	14.57	14.30
CH_3	H	$N(CH_3)(CH_2)_3C_6H_5$	86–87 (0.2)	58	$C_{13}H_{22}N_2$	13.58	13.53
CH_3	H	$N(CH_2C_6H_5)_2$	144–146 (3)	61	$C_{17}H_{22}N_2$	11.02	10.75
CH_3	H		67–70 (7)	55	$C_7H_{16}N_2O$	19.43	19.24
$CH_2CH{=}CH_2$	H	$N(CH_3)_2$	75–77 (50)	41	$C_7H_{16}N_2$	21.85	21.90
CH_3	CH_3	$N(CH_3)_2$	133–135 (760)	77	$C_6H_{16}N_2$	24.10	24.30

Crystallization from isopropyl alcohol did not change the melting point.

Preparation of I by Alternate Route. 2-Ethoxy-N-methyl-2,2-diphenylacetamide.—Interaction of 265 g. (1.0 mole) of α-chlorodiphenylacetyl chloride with 62 g. (2.0 moles) of monomethylamine in 1.8 l. of benzene and then treatment with ethanol according to the preceding procedure gave 202 g. (75%) of product, b.p. 151–157° (0.5 mm.). After crystallization of 178 g. of this material from 800 ml. of hexane, the colorless solid weighed 143 g. (60%), m.p. 98–100°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.95; H, 7.01; N, 5.12.

Preparation of I.—A solution of 27.0 g. (0.1 mole) of the above amide in 200 ml. of toluene was added to a slurry of 4.0 g. (0.1 mole) of sodamide in 100 ml. of toluene, and the mixture was refluxed for 30 min. This mixture was cooled, treated with a solution of 15.0 g. (0.14 mole) of 2-dimethylaminoethyl chloride in 150 ml. of toluene, refluxed for 3 hr., cooled, and washed with 50 ml. of water. The organic phase was then extracted with dilute hydrochloride acid. Treatment of the aqueous phase with excess sodium hydroxide solution liberated the base. The ether extracts of the base were dried over magnesium sulfate, filtered, and concentrated. Fractionation of the residue gave 19.3 g. (57%) of colorless product, b.p. 160–165° (0.1 mm.). The hydrochloride salt of this material had the same melting point, mixture melting point, and infrared spectrum as material from the previous procedure.

Anal. Found: Cl, 9.19; N, 7.32.

2-Ethoxy-N-methyl-N-(2-methylaminoethyl)-2,2-diphenylacetamide Hydrochloride (14).—To a warm solution of 35.0 g. (0.077 mole) of N-[2-(N-benzyl-N-methylamino)ethyl]-2-ethoxy-N-methyl-2,2-diphenylacetamide hydrochloride (**13**) in 205 ml. of ethanol was added 3 g. of 5% palladium–carbon, and the mixture was placed in a Parr apparatus under 3 atm. of hydrogen at room temperature. The theoretical quantity of hydrogen was consumed in 5 min. The mixture was diluted with 200 ml. of ethanol, heated to dissolve the crystallized product, and filtered. The filtrate was cooled and diluted with 200 ml. of ether to give 28.1 g. (100%) of colorless product, m.p. 200–201°. Recrystallization from 230 ml. of ethanol gave 24.7 g. (88%) of material, m.p. 202–203°. The free base, obtained by treatment of an aqueous slurry of the hydrochloride with an equivalent of alkali, melted at 40–42°. After crystallization from hexane, it melted at 44–46°.

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: N, 8.58. Found: N, 8.43.

2-Ethoxy-N-methyl-N-[2-(N-methyl-N-phenacylamino)-ethyl]-2,2-diphenylacetamide Hydrochloride (25).—A mixture of 12.0 g. (0.037 mole) of previously prepared base, 5.7 g. (0.037 mole) of phenacyl chloride, and 250 ml. of xylene was stirred and refluxed for 15 min. and then cooled; the crystalline product was filtered and washed with ether. This material represented the hydrochloride of the starting material and weighed 6.2 g., m.p. 200–201°. The filtrate was treated with a slight excess of alcoholic hydrogen chloride to give 8.2 g. of product, m.p. 175–180°. This material was suspended in 80 ml. of water, filtered, and dried to give 7.0 g. (39%) of product, m.p. 187–188°. Crystallization from acetonitrile did not change the melting point.

2-Ethoxy-N-methyl-N-{2-[methyl(2-(4-pyridyl)ethyl]amino}ethyl}-2,2-diphenylacetamide Dihydrochloride (24).—A mixture of 20.0 g. (0.061 mole) of the base of **14** and 20.0 g. (0.19 mole) of 4-vinylpyridine (freshly distilled) was heated at 150–155° for 4 hr., cooled, and extracted with 300 ml. of ether. The ether was decanted from the insoluble polymeric material and the solution concentrated. Fractionation of the residue gave 15.0 g. of product as a yellow sirupy liquid, b.p. 210–230° (0.2 mm.). A solution of the base in 50 ml. of ethanol was treated with 11.6 ml. of 6 *N* ethanolic hydrogen chloride and the resulting solution diluted to 500 ml. with ether to give an oily product. Trituration of this crude hydrochloride with 100-ml. portions of (a) ether, (b) butanone, and (c) acetonitrile, followed by crystallization from 30 ml. of ethanol gave 12.4 g. (37%) of colorless product, m.p. 213–215°.

Diamines.—The synthesis of many of the intermediate diamines has been reported.[2] The preparation of the new diamines, listed in Table I, is outlined.

N-(2-Chloroethyl)-N-methylphenethylamine Hydrochloride.—A solution of 110 g. (0.61 mole) of 2-(N-methyl-N-phenethylamino)ethanol[13] in 300 ml. of chloroform was stirred and treated dropwise with 90 ml. of thionyl chloride while the reaction temperature was maintained at 20–25°. The mixture was refluxed for 2 hr. and then concentrated until 165 ml. of liquid had distilled. The residue was cooled and diluted with 500 ml. of ether to give 144 g. (100%) of colorless crystalline product, m.p. 116–118°. The analytical sample was crystallized from acetonitrile–ether, m.p. 122–123°.

Anal. Calcd. for $C_{11}H_{17}Cl_2N$: Cl, 30.28; N, 5.98. Found: Cl, 30.32; N, 5.90.

N-(2-Chloroethyl)-N-methyl-3-phenylpropylamine Hydrochloride.—Interaction of 155 g. (0.8 mole) of 2-(N-methyl-3-phenylpropylamino)ethanol[13] with 110 ml. of thionyl chloride according to the preceding procedure gave 195 g. (99%) of colorless product, m.p. 125–127°. The analytical sample was crystallized from acetonitrile, m.p. 128–129°.

Anal. Calcd. for $C_{12}H_{19}Cl_2N$: Cl, 28.57; N, 5.64. Found: Cl, 28.89; N, 5.82.

N,N'-Dimethyl-N-phenethylethylenediamine.—To 300 g. of cold 40% aqueous monomethylamine was added 142 g. (0.61 mole) of 2-(N-methyl-N-phenethylamino)ethyl chloride hydrochloride, m.p. 116–118°, and then 100 ml. of ethanol. This mixture was stirred for 1 hr. at room temperature, heated at 70–90° for 4 hr., cooled, and treated with 100 g. of sodium hydroxide pellets. The mixture was extracted three times with 300-ml. portions of ether. The ether phases were combined and dried over potassium carbonate, and the solvent was evaporated. Fractionation of the residue gave 81 g. of product, b.p. 75–78° (0.2 mm.). A second fraction, **1,7-diphenethyl-1,4,7-trimethyldiethylenetriamine,** weighed 32.4 g., b.p. 178–180°° (0.2 mm.).

Anal. Calcd. for $C_{23}H_{35}N_3$: N, 11.89. Found: N, 11.84.

The trihydrochloride of this material, after crystallization from 80% ethanol, melted at 271° dec.

Anal. Calcd. for $C_{23}H_{38}Cl_3N_3$: Cl, 22.98; N, 9.08. Found: Cl, 23.26; N, 9.30.

Most of the other diamines listed in Table I were obtained in a similar manner by the reaction of methylamine with N-(2-chloroethyl)-N-methylbenzylamine hydrochloride[14]; N-(2-chloroethyl)-N-methyl-3-phenylpropylamine hydrochloride; dibenzylaminoethyl chloride hydrochloride[15]; and 4-(2-chloroethyl)-

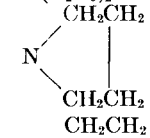
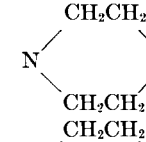
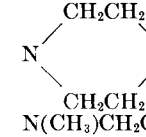
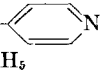
(13) R. W. Barnes and W. J. Rost, *J. Pharm. Sci.*, **51**, 146 (1962).

(14) J. B. Wright, E. H. Lincoln, R. V. Heinzelmann, and J. H. Hunter, *J. Am. Chem. Soc.*, **72**, 3536 (1950).

(15) Obtained from Givaudan-Delawanna, Inc., New York, N. Y.

TABLE II

$(C_6H_5)_2C(OR)CONR'(CH_2)_nB \cdot HCl$

Compound no.	R	R′	n	B	Base B.p., °C. (mm.)	HCl M.p., °C.	Solvent[a]	Formula	Analyses, % Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
1	CH_3	CH_3	2	$N(CH_3)_2$	174–176 (0.2)	201–203	A	$C_{20}H_{27}ClN_2O_2$	9.77	9.68	7.72	7.54
2	C_2H_5	H	2	$N(CH_3)_2$	180–183 (0.6)	172–174	BC	$C_{20}H_{27}ClN_2O_2$	9.77	9.89	7.72	7.79
3	C_2H_5	CH_3	2	$N(CH_3)_2$	170–175 (0.3)	193–194	A	$C_{21}H_{29}ClN_2O_2$	9.41	9.22	7.43	7.35
4	$(CH_2)_2CH_3$	CH_3	2	$N(CH_3)_2$	187–190 (0.7)	171–172	D	$C_{22}H_{31}ClN_2O_2$	9.07	9.10	7.17	7.33
5	$CH(CH_3)_2$	CH_3	2	$N(CH_3)_2$	175–180 (0.3)	166–168	AC	$C_{22}H_{31}ClN_2O_2$	9.07	8.95	7.17	7.15
6	$CH_2CH{=}CH_2$	CH_3	2	$N(CH_3)_2$	197–202 (1.0)	175–177	A	$C_{22}H_{29}ClN_2O_2$	9.12	9.19	7.20	7.16
7	$(CH_2)_3CH_3$	CH_3	2	$N(CH_3)_2$	173–175 (0.3)	158–159	AC	$C_{23}H_{33}ClN_2O_2$	8.76	8.87	6.92	6.83
8	C_2H_5	C_2H_5	2	$N(CH_3)_2$	174–177 (0.6)	185–187	A	$C_{22}H_{31}ClN_2O_2$	9.07	9.06	7.17	6.89
9	C_2H_5	$CH_2CH{=}CH_2$	2	$N(CH_3)_2$	170–175 (0.5)	207–208	B	$C_{23}H_{31}ClN_2O_2$	8.80	8.53	6.95	7.16
10	C_2H_5	CH_3	3	$N(CH_3)_2$	171–173 (0.2)	213–214	A	$C_{22}H_{31}ClN_2O_2$	9.07	9.26	7.17	7.07
11	C_2H_5	CH_3	2	$N(CH_2C_6H_5)_2$		87–89[b]	E	$C_{33}H_{36}N_2O_2$		[b]	5.69	5.63
12	C_2H_5	CH_3	2	NH_2		225–226	F	$C_{19}H_{25}ClN_2O_2$	10.16	9.94	8.03	8.07
13	C_2H_5	CH_3	2	$N(CH_3)CH_2C_6H_5$		162–164	D	$C_{27}H_{33}ClN_2O_2$	7.84	7.78	6.20	6.41
14	C_2H_5	CH_3	2	$NHCH_3$		202–203	B	$C_{20}H_{27}ClN_2O_2$	9.77	9.96	7.72	7.98
15	C_2H_5	CH_3	2	$N(C_2H_5)_2$	188–190 (0.7)	149–150	BC	$C_{23}H_{33}ClN_2O_2$	8.76	8.78	6.92	6.65
16	C_2H_5	CH_3	2		190–195 (0.2)	180–181	DC	$C_{23}H_{31}ClN_2O_2$	8.79	8.99	6.95	7.07
17	C_2H_5	CH_3	2		205–208 (0.3)	182–184	D	$C_{23}H_{31}ClN_2O_3$	8.46	8.40	6.69	6.33
18	C_2H_5	CH_3	2		205–209 (0.5)	191–193	G	$C_{24}H_{33}ClN_2O_2$	8.50	8.55	6.72	7.00
19	C_2H_5	CH_3	2	$N(CH_3)CH_2CH_2C_6H_5$		163–165	D	$C_{28}H_{35}ClN_2O_2$	7.59	7.56	6.00	6.08
20	C_2H_5	CH_3	2	$N(CH_3)CH_2CH_2$–C$_6$H$_4$–NO_2		177–178	DC	$C_{28}H_{34}ClN_3O_4$	6.92	6.92	8.21	8.07
21	C_2H_5	CH_3	2	$N(CH_3)CH_2CH_2$–C$_6$H$_4$–NH_2		189–190[c]	H	$C_{28}H_{37}Cl_2N_3O_2$	13.68	13.38	8.10	7.95
22	C_2H_5	CH_3	2	$N(CH_3)CH_2CH_2CH_2C_6H_5$		74–77	I	$C_{29}H_{37}ClN_2O_2 \cdot H_2O$[d]	7.11	7.21	5.62	5.51
23	C_2H_5	CH_3	2	$N(CH_3)CH_2CH_2$– 	205–210 (0.2)	173–175[c]	BC	$C_{27}H_{35}Cl_2N_3O_2$	14.06	14.18	8.33	8.10
24	C_2H_5	CH_3	2	$N(CH_3)CH_2CH_2$– 	210–230 (0.2)	213–215[c]	BC	$C_{27}H_{35}Cl_2N_3O_2$	14.06	14.20	8.33	8.23
25	C_2H_5	CH_3	2	$N(CH_3)CH_2COC_6H_5$		187–188	C	$C_{28}H_{33}ClN_2O_3$	7.35	7.25	5.82	5.99
26	C_2H_5	CH_3	[e]	$N(CH_3)_2$	170–175 (0.3)	164–166	D	$C_{22}H_{31}ClN_2O_2$	9.07	9.05	7.17	7.19

[a] Recrystallization solvents; A, isopropyl alcohol; B, ethanol; C, ether; D, acetonitrile; E, hexane; F, 95% ethanol; G, butanone; H, methanol; I, water. [b] Free base. *Anal.* Calcd.: C, 80.45; H, 7.37. Found: C, 80.34; H, 7.48. [c] Dihydrochloride. [d] *Anal.* Calcd.: C, 69.80; H, 7.88. Found: C, 69.96; H, 7.58. [e] $(CH_2)_n$ = $-CH_2CH(CH_3)-$.

morpholine hydrochloride.[16] The allyl compound listed in Table I was obtained by the reaction of 2-dimethylaminoethyl chloride hydrochloride with allylamine using isopropyl alcohol as a solvent in the same manner described for the preparation of the diethylamino analog.[2]

2-Dimethylamino-N-methylpropionamide.—A solution of 128 g. (0.77 mole) of 2-bromo-N-methylpropionamide[17] in 200 ml. of benzene was added to a cold solution of 150 g. (3.3 moles) of dimethylamine in 700 ml. of benzene. It was necessary to cool the mixture during the initial exothermic reaction. After standing at room temperature for 3 days, the mixture was heated at 55–65° for 4 hr., cooled, and treated with a cold solution of 40 g. of sodium hydroxide in 100 ml. of water. The layers were separated and the organic phase was dried over potassium carbonate. After evaporation of the solvent, the residue was fractionated to give 77 g. (77%) of colorless product, b.p. 71–72° (2 mm.).

Anal. Calcd. for $C_6H_{14}N_2O$: N, 21.52. Found: N, 21.57.

N^1,N^2,N^2-Trimethyl-1,2-propanediamine.—A solution of 39.0 g. (0.3 mole) of the preceding amide in 50 ml. of ether was added dropwise to a suspension of 15.0 g. (0.4 mole) of lithium aluminum hydride in 600 ml. of ether and the mixture was stirred for 20 hr. at room temperature. The product (Table I) was isolated in the usual manner.[2] This diamine is apparently the major product of the reaction of $ClCH(CH_3)CH_2N(CH_3)_2 \cdot HCl$[18] and excess aqueous CH_3NH_2; b.p. 134–137°; yield 67%.[19] Samples of compound **26**, obtained from the diamine prepared by either method, had identical melting points, mixture melting points, and n.m.r. spectra.[20]

Acknowledgment.—The authors are indebted to Mr. W. A. Lott for his interest and encouragement during this investigation, to Dr. John C. Burke and his associates for the pharmacological data, and to Mr. Joseph Alicino and his associates for the analyses reported herein.

(16) J. P. Mason and H. W. Block, *J. Am. Chem. Soc.*, **62**, 1443 (1940).
(17) W. E. Weaver and W. M. Whaley, *ibid.*, **69**, 1144 (1947).
(18) Purchased from Michigan Chemical Corp., St. Louis, Mich.
(19) A mixture of N^1,N^1,N^2-trimethyl-1,2-propanediamine and N^2,N^2,N^3-trimethyl-1,2-propanediamine was expected from this reaction. The cyclization of $ClCH(CH_3)CH_2N(CH_3)_2$ to the ethylenimonium ion and subsequent reaction with the anion of diphenylacetonitrile yielded a mixture of isomeric products; see E. M. Schultz and J. M. Sprague, *J. Am. Chem. Soc.*, **70**, 48 (1948), and references cited therein.
(20) The authors are indebted to Dr. A. Cohen for the deconvolution and interpretation of the n.m.r. spectra.

Synthesis of 5-Substituted Pyrimidines[1,2]

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Synthesis of a series of 5-substituted pyrimidines through the halogen–lithium exchange reaction has been reported. 2,4-Diethoxy-5-arylhydroxymethylpyrimidines prepared in this manner have been oxidized and then hydrolyzed to 5-acyluracils. The 5-acyluracils have been reduced successfully to 5-arylhydroxymethyluracils. The stability of 5-arylhydroxymethyluracils is discussed.

Many biologically active synthetic pyrimidines have been reported and most of them exert their effects on the nucleic acid metabolism of the cells.[3] The compounds reported in the literature are considered analogs of the naturally occurring pyrimidines or their nucleosides which are pyrimidines substituted with a carbohydrate moiety in the 1-position. However, more recently[4,5] a remarkably different type of nucleoside was isolated from soluble ribonucleic acid (RNA) of yeast. This is an isomer of uridine and is chemically identified as 5-ribosyluracil (pseudouridine) in which the base–ribosyl linkage is C–C instead of the usual N–C.

Little work has been done in synthesizing structural analogs of this nucleoside with potential antimetabolic activity. We wish to report here the synthesis of a series of 5-substituted pyrimidines where C-5 of the pyrimidine carries a noncarbohydrate grouping. These were prepared in order to test the dual possibility that they may be effective as (i) antimetabolites in systems where 5-ribosyluridylic acid has been implicated, as for example in the ability to incorporate C^{14}-amino acids (leucine) into RNA by certain fractions of soluble RNA which characteristically contain substantially large amounts of 5-ribosyluridylic acid,[6,7] and (ii) as antagonists of nucleic acid metabolism in bacterial and/or mammalian systems.

The method of synthesis employed here is an extension of the ones used by Langley[8] in the synthesis of 6-substituted pyrimidines and by Ulbricht[9] in the case of thymine and thymidine, where advantage is taken of the ability of pyrimidines to undergo halogen–metal interconversion reactions. Using this method Langley[8] also synthesized 2,4-dimethoxypyrimidine-5-carboxylic acid. Attention here has been focused on the reaction of 5-pyrimidinyllithium with aryl aldehydes to prepare a series of 5-substituted pyrimidines.

Our starting material, 2,4-diethoxy-5-bromopyrimidine (I), was synthesized according to the sequence of reactions reported by Hilbert and Jansen.[10] Langley's procedure[8] was adopted to synthesize the pyrimidyllithium compound (II). Reaction of II with an ether solution of an aryl aldehyde resulted in 2,4-diethoxy-5-arylhydroxymethylpyrimidine (III). These compounds were characterized by their ultraviolet and infrared absorption spectra and also elemental analysis (Table I).

The next step in the sequence was the attempted hydrolysis of the ethoxy groups of III to obtain the

(1) Abstracted from the Ph.D. thesis of T. V. Rajkumar, 1963.
(2) Presented in part before the Medicinal Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962.
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