[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

The Synthesis of 1- and 2-Pyrrolealkylamines

WERNER HERZ, D. S. RADEN, AND D. R. K. MURTY[1,2]

Received March 19, 1956

The synthesis of a number of 1- and 2-pyrrolealkylamines is reported.

The physiological activity of phenylalkylamines and related substances has led to the synthesis and pharmacological study of analogs containing the isosteric furan and thiophene nuclei,[3] but pyrrolealkylamines have received little attention. Mono- and di-alkylaminomethylpyrroles are readily accessible through the Mannich reaction[4,5,6] and the parent compound 2-aminomethylpyrrole was prepared much earlier.[7] The literature records only a brief mention of their lack of antimalarial activity. The antihistaminic properties of 2-(2-aminoethyl)pyrrole[8,9,10] have been commented upon[11,12] and a recent publication dealing with the synthesis of 1-(2-aminoethyl)pyrrole[13] testifies to continued interest in this field.

The present paper deals with the synthesis of a number of 2-N-alkyl-, 2-N,N-dialkyl-, 1-N-alkyl-, and 1-N,N-dialkylaminoalkylpyrroles and includes several related primary amines. Physiological properties of the products will be reported elsewhere.

2-Aminoethylpyrroles. The method adopted for the synthesis of the substances listed in Table I involved the acylation of 2-(2-aminoethyl)pyrrole followed by reduction with lithium aluminum hydride, reacylation of the resulting secondary amines, and subsequent reduction to the tertiary amines. An alternative method, the conversion of ethyl 2-pyrroleacetate to the appropriate amide followed by reduction with lithium aluminum hydride, was not satisfactory due to the poor yields encountered in the first step. Attempts to introduce the dialkylaminoethyl group directly by reaction of pyrrolemagnesium iodide with N,N-dialkylaminoethyl halides[14] were not successful. Methylation of 2-(2-aminoethyl)pyrrole by the Clarke-Eschweiler reaction[15] likewise could not be effected. This is not surprising when the ease of resinification of pyrrole under acidic conditions and its susceptibility to dipyrrylmethane formation in the presence of formaldehyde[16a] is considered.

1-Aminoalkylpyrroles. Reaction of potassium pyrrole with chloroacetonitrile, α-bromopropionitrile, β-chloropropionitrile, and γ-chlorobutyronitrile gave the appropriate cyanides in 25%, 33%, 63%,[17] and 6% yield. Reduction yielded the desired primary amines. While the yields were satisfactory only in the case of β-chloropropionitrile, this method, because of its convenience, offers advantages over the preparation of 1-(2-aminoethyl)pyrrole reported earlier.[13] The very low yield obtained with γ-chlorobutyronitrile, which could not be improved by substitution of the bromide, is paralleled by earlier results which indicate lack of reactivity when pyrroles are alkylated by halides of increasing chain length.[16b] Secondary amines were prepared by formylation followed by reduction. An attempt to improve the yields of 1-(1-methyl-2-aminoethyl)pyrrole and its N-methyl analog by proceeding *via* ethyl 2-(1-pyrrole)propionate failed in the last step due to our inability to reduce satisfactorily the amides obtained from this ester.

The tertiary amines described in Table II were prepared conveniently by alkylating pyrrole with 2-dimethylaminoethyl chloride, 2-dimethylaminoisopropyl chloride, and 2-diethylaminoethyl chloride.[18] Similarly, potassium pyrrole and 3-dimethylaminopropyl chloride furnished 1-(3-dimethylaminopropyl)pyrrole.

EXPERIMENTAL[19]

2-(2-Aminomethyl)pyrrole. This compound was made by

(1) Abstracted in part from the M.S. thesis of D. S. Raden, August 1955.

(2) Supported in part by grant RC-3097 from the United States Public Health Service, Department of Health, Education and Welfare.

(3) Burger, *Medicinal Chemistry*, Interscience, New York, N. Y., p. 289 *et seq.* (1951).

(4) Bachman and Heisey, *J. Am. Chem. Soc.*, **68**, 2496 (1946).

(5) Herz, Dittmer, and Cristol, *J. Am. Chem. Soc.*, **69**, 1698 (1947).

(6) Herz and Rogers, *J. Am. Chem. Soc.*, **73**, 4921 (1951).

(7) Putokhin, *J. Russ. Phys.-Chem. Soc.*, **62**, 2226 (1930).

(8) Eiter, *Monatsh.*, **83**, 252 (1952).

(9) Kutscher and Klamerth, *Z. physiol. Chem.*, **289**, 229 (1952).

(10) Herz, *J. Am. Chem. Soc.*, **75**, 483 (1953).

(11) Lee and Jones, *J. Pharmacol. Exptl. Therap.*, **95**, 71 (1949).

(12) Grossman, Robertson and Rosiere, *J. Pharmacol. Exptl. Therap.*, **104**, 277 (1952).

(13) Klamerth and Kutscher, *Ber.*, **85**, 444 (1952).

(14) Hess and Wissing, *Ber.*, **47**, 1416 (1914).

(15) Clarke, Gillespie, and Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

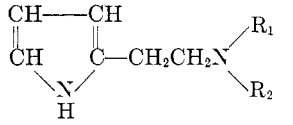
(16) (a) Fischer-Orth, *Die Chemie des Pyrrols*, Akademische Verlagsgesellschaft, Leipzig, Vol. I, p. 332 (1934). (b) Ref. 16a, p. 27.

(17) Clemo and Ramage, *J. Chem. Soc.*, 49 (1931).

(18) Eisleb, *Ber.*, **74**, 1433 (1941).

(19) Melting points and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England.

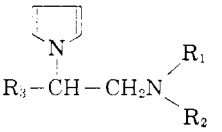
TABLE I

COMPOUNDS OF TYPE 

R_1	R_2	Yield, %	M.p. or B.p., °C.	Mm.	Formula	Analyses C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found	Picrate, M.p., °C.
CH_3	H	75	58–59[a]		$C_7H_{12}N_2$	67.70	67.49	9.77	9.92	22.5	22.2	157–158[b]
CH_3	CHO	69	138	0.6[c]	$C_8H_{12}N_2O$					18.4	18.2	
CH_3	CH_3	53.5	84	4[d]	$C_8H_{14}N_2$	69.52	69.13	10.21	9.89			112.5–113[e,f]
C_2H_5	H	91	82	1.2	$C_8H_{14}N_2$	[g]						167–168[g]
C_2H_5	$COCH_3$	46	62–63[h]		$C_{10}H_{18}N_2O$					15.4	15.5	
C_2H_5	C_2H_5	61	74	0.5[i]	$C_{10}H_{18}N_2$	72.24	72.04	10.91	10.65	16.8	16.7	[j]

[a] Sublimed. [b] Calc'd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28. Found: C, 43.72; H, 4.28. [c] n_D^{26} 1.5346. [d] n_D^{23} 1.5062. [e] Calc'd for $C_{14}H_{17}N_5O_7$: C, 45.77; H, 4.67; N, 19.1. Found: C, 45.57; H, 4.88; N, 18.8. [f] Methiodide recrystallized from anhydrous ether-methanol, m.p. 185–186°. Calc'd for $C_9H_{17}IN_2$: N, 10.0. Found: N, 9.8. [g] This substance could not be analyzed satisfactorily due to decomposition, but the *picrate* gave good results. Calc'd for $C_{14}H_{17}N_5O_7$: C, 45.77; H, 4.67; N, 19.1. Found: C, 45.66; H, 4.95; N, 19.1. [h] B.p. 129–135° (0.3). [i] n_D^{22} 1.5013. [j] This compound did not furnish a crystalline picrate but a *methiodide* of m.p. 110–111°. Calc'd for $C_{11}H_{21}IN_2$: N, 9.1. Found: N, 9.2.

TABLE II

COMPOUNDS OF TYPE 

R_1	R_2	R_3	Yield, %	M.p. or B.p., °C.	Mm.	Formula	Analyses C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found	Picrate, M.p., °C.
H	H	H	58	68	3[a]	$C_6H_{10}N_2$	65.42	65.72	9.15	9.34	25.4	25.0	167–168[b]
H	CHO	H	87	119	0.35[c]	$C_7H_{10}N_2O$	60.85	60.81	7.30	7.54	20.3	20.0	
H	CH_3	H	43	46	0.8[d]	$C_7H_{12}N_2$	67.70	67.44	9.74	9.56	22.6	22.8	173–174[e]
CH_3	CH_3	H	35	110	37[f]	$C_8H_{14}N_2$	69.52	69.39	10.21	10.15	20.3	20.2	133–133.7[g,h]
C_2H_5	C_2H_5	H	38	98	14[i]	$C_{10}H_{18}N_2$	72.24	72.36	10.91	10.92	16.8	16.8	88–89[j]
H	H	CH_3	73	57	1.2[k]	$C_7H_{12}N_2$	67.70	67.11	9.74	9.54			175–177[l]
H	CHO	CH_3	87	129–131	0.7	$C_8H_{12}N_2O$	63.13	63.45	7.95	8.05	18.4	18.2	
H	CH_3	CH_3	75	50–52	1.2[m]	$C_8H_{14}N_2$	69.57	68.82	10.21	10.35	20.2	19.8	159.5–161.5[n]
CH_3	CH_3	CH_3	21	85–87	11[o]	$C_9H_{16}N_2$	71.03	71.20	10.59	10.77	17.6	18.4	157–158[p,q]

[a] n_D^{23} 1.5178. [b] Calc'd for $C_{12}H_{13}N_5O_7$: C, 42.48; H, 3.86; N, 20.7. Found: C, 42.89; H, 3.91; N, 20.6. [c] n_D^{22} 1.5336. [d] n_D^{22} 1.5050. [e] Calc'd for $C_{13}H_{15}N_5O_7$: N, 19.8. Found: N, 20.2. [f] n_D^{22} 1.4890. [g] Calc'd for $C_{14}H_{17}N_5O_7$: C, 45.77; H, 4.67; N, 19.1. Found: C, 45.80; H, 4.70; N, 19.2. [h] *Methiodide*, m.p. 245–246° from methanol. Calc'd for $C_9H_{17}IN_2$: C, 38.58; H, 6.12; N, 10.0. Found: C, 38.93; H, 6.20; N, 9.8. [i] Lit.[18] 80° (4). [j] Calc'd for $C_{16}H_{21}N_5O_7$: C, 48.61; H, 5.35; N, 17.7. Found: C, 48.27; H, 5.48; N, 17.6. [k] n_D^{25} 1.5062. [l] Calc'd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28; N, 19.8. Found: C, 44.35; H, 4.15; N, 19.7. [m] n_D^{27} 1.4895. [n] Calc'd for $C_{14}H_{17}N_5O_7$: C, 45.77; H, 4.67; N, 19.1. Found: C, 45.52; H, 4.45; N, 18.7; [o] n_D^{23} 1.4848. [p] Calc'd for $C_{15}H_{19}N_5O_7$: C, 47.28; H, 5.02. Found: C, 47.69; H, 4.97. [q] *Methiodide*, m.p. 249–250° from methanol. Calc'd for $C_{10}H_{19}IN_2$: C, 40.83; H, 6.51. Found: C, 41.17; H, 6.45.

the reduction of 2-pyrroleacetonitrile in 60–70% yield.[20] Its *methiodide* was prepared by stirring and heating at reflux a solution of 1.1 g. of the base in 50 ml. of anhydrous methanol, 2 ml. of methyl iodide, and 1.1 g. of lithium carbonate. After 24 hours, another 2 ml. of methyl iodide was added and the mixture was heated for an additional 12 hours. The solid obtained on cooling and the material obtained from the mother liquors was recrystallized five times from anhydrous methanol-anhydrous ether, yield 2.0 g. (71%) of silver-white platelets, m.p. 185–186° (dec.).

Anal. Calc'd for $C_9H_{17}IN_2$: N, 10.00. Found: N, 9.75.

2-[2-(N-Methylamino)ethyl]pyrrole. A solution of 9 g. of 2-(2-formamidoethyl)pyrrole[20] in 25 ml. of anhydrous tetrahydrofuran was added to a slurry of 2.5 g. of lithium aluminum hydride in 75 ml. of anhydrous ether. After two hours of stirring at reflux, the mixture was decomposed by the addition of water. The ether extracts were washed, dried, and distilled. Sublimation of the residue *in vacuo* (bath temperature 50–60°) furnished 6.1 g. (75%) of colorless crystals whose properties are described in Table I.

Other reductions of amides with lithium aluminum hydride were carried out in a similar manner.

2-(2-Acetamidoethyl)pyrrole. This compound, described earlier[20] as a liquid, crystallized on distillation, b.p. 163° (1 mm.), in the course of the present work. Crystallization from a mixture of benzene and hexane furnished prisms, m.p. 68–69°.

2-Pyrrole-N-methylacetamide. A mixture of 2 g. of ethyl 2-pyrroleacetate and 13 ml. of 25% aqueous methylamine solution was allowed to stand for five days. The homogeneous solution was extracted with benzene and the dried extracts were concentrated *in vacuo*. The residue crystallized on rubbing with petroleum ether. Sublimation at 0.5 mm. (bath temperature 65°) furnished 0.3 g. (16%) of a white

(20) Herz and Tocker, *J. Am. Chem. Soc.*, **77**, 6353 (1955).

solid, m.p. 65–66°, which decomposed on standing. Attempts to improve the yield by heating the reagents in a sealed tube for various periods of time failed.

Anal. Calc'd for $C_7H_{10}N_2O$: N, 20.3. Found: N, 20.5.

The infrared spectrum exhibited an amide carbonyl band at 1670 cm.$^{-1}$.

2-Pyrrole-N,N-dimethylacetamide. A mixture of 5 g. of ethyl 2-pyrroleacetate and 45 ml. of 25% aqueous dimethylamine solution furnished, after seven days, 0.8 g. (16%) of white crystals which after repeated sublimation (bath temperature 90°) melted at 93–94° and decomposed on standing.

Anal. Calc'd for $C_8H_{12}N_2O$: N, 18.4. Found: N, 18.3.

The infrared spectrum exhibited an amide band at 1645 cm.$^{-1}$.

1-Pyrroleacetonitrile. In a three-neck flask fitted with dropping-funnel, stirrer, and reflux condenser was placed 100 ml. of freshly distilled pyrrole. A total of 16.1 g. of potassium, cut into small pieces, was added and the mixture was heated for 15 minutes by which time it appeared that reaction was complete. At this point 200 ml. of anhydrous toluene was added, the mixture was heated to reflux, stirring was started, and a solution of 31.5 g. of chloroacetonitrile in 150 ml. of anhydrous toluene was added. Refluxing was continued for 24 hours with stirring. The mixture was cooled, decomposed with water, and the water was extracted with toluene and the combined organic layers were dried and fractionated. The product, wt. 10.7 g. (25%), was collected at 137–144° (45 mm.). The analytical sample boiled at 90° (4.5 mm.), n_D^{23} 1.5122. The compound exhibited the typical C≡N frequency near 2240 cm.$^{-1}$ and evolved ammonia on heating with base. A previous report[21] listed no yield and no properties other than the b.p.

Anal. Calc'd for $C_6H_6N_2$: N, 26.4. Found: N, 26.6.

The reduction of this and related nitriles was carried out in the manner described earlier.[10]

3-(1-Pyrrole)propionitrile. Alkylation of potassium pyrrole with 43.8 g. of β-chloropropionitrile in the same manner furnished 39 g. (63%) of a liquid, b.p. 90–96° (0.4 mm.). The preparation of this compound, reported b.p. 140° (20 mm.), by a more circuitous route has been reported earlier.[17]

4-(1-Pyrrole)butyronitrile. Alkylation of potassium pyrrole by the method of Clemo and Ramage,[17] using either γ-bromo- or γ-chlorobutyronitrile, gave a disappointing 6% yield, b.p. 98–100° (0.3 mm.). The b.p. of material prepared by a different method was reported[17] as 152° (23 mm.).

2-(1-Pyrrole)propionitrile. Alkylation of potassium pyrrole, prepared from 80 ml. of pyrrole and 25 g. of potassium, with 68 g. of α-bromopropionitrile[22] furnished 20 g. (33%) of a fraction, b.p. 72–74° (1.5 mm.), n_D^{25} 1.4940.

Anal. Calc'd for $C_7H_8N_2$: C, 69.97; H, 6.71; N, 23.3. Found: C, 70.18; H, 6.63; N, 22.8.

Ethyl 2-(1-pyrrole)propionate. Alkylation of potassium pyrrole, prepared from 34 g. of pyrrole and 20 g. of potassium, with 100 g. of ethyl α-bromopropionate furnished 56 g. (67%) of a fraction boiling at 74° (1 mm.).

Anal. Calc'd for $C_9H_{13}NO_2$: C, 64.42; H, 7.82. Found: C, 64.65; H, 7.84.

The *amide* was prepared in 90% yield by mixing 10 g. of ester with 200 ml. of aqueous ammonia and allowing the mixture to stand in the refrigerator for several days. Repeated crystallization from ethanol furnished needles melting at 96°.

Anal. Calc'd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.3. Found: C, 61.22; H, 7.35; N, 20.2.

The *methylamide* was prepared in 81% yield by mixing 8 g. of ester with 180 ml. of 25% aqueous methylamine solution and allowing the mixture to stand in the refrigerator for several days. The solution was concentrated *in vacuo* and the residual crystals were recrystallized from alcohol to a constant m.p. of 71.5–72°.

Anal. Calc'd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.4. Found: C, 63.28; H, 7.79; N, 18.3.

Lithium aluminum hydride reduction of the above two amides gave very low yields of two amines, prepared in better yield by reduction of 2-(1-pyrrole)propionitrile and 1-(1-methyl-2-formamidoethyl)pyrrole respectively.

1-(3-Aminopropyl)pyrrole. Lithium aluminum hydride reduction[10] of 3-(1-pyrrole)propionitrile furnished a 58% yield of this amine, b.p. 82° (4 mm.), n_D^{23} 1.5121. The literature[23] reports b.p. 117–120° (30 mm.), but no refractive index or analysis.

Anal. Calc'd for $C_7H_{12}N_2$: C, 67.70; H, 9.74; N, 22.5. Found: C, 67.58; H, 9.82; N, 22.2.

The *picrate* melted at 138.5–139°, lit. 135–137°.[23]

Anal. Calc'd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28; N, 19.8. Found: C, 43.97; H, 4.53; N, 19.8.

1-(3-Dimethylaminopropyl)pyrrole. Alkylation of potassium pyrrole with N,N-dimethylaminopropyl chloride in the usual manner gave this amine in 47% yield, b.p. 87–88° (11 mm.), n_D^{23} 1.4820.

Anal. Calc'd for $C_9H_{16}N_2$: C, 71.03; H, 10.59; N, 18.4. Found: C, 71.36; H, 10.80; N, 17.7.

The *picrate* melted at 88–89°.

Anal. Calc'd for $C_{15}H_{19}N_5O_7$: C, 47.28; H, 5.02. Found: C, 47.50; H, 5.02.

1-(4-Aminobutyl)pyrrole. Lithium aluminum hydride reduction of 4-(1-pyrrole)butyronitrile yielded 80% of this amine, b.p. 78° (0.3 mm.). A crystalline picrate could not be obtained.

Anal. Calc'd for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.3. Found: C, 69.53; H, 10.36; N, 19.7.

Acknowledgment. We wish to thank E. I. DuPont de Nemours and Co., Inc., and the Michigan Chemical Company for the gift of chemicals.

TALLAHASSEE, FLORIDA

(21) Ochiai and Ikuma, *J. Pharm. Soc. Japan*, **56**, 379 (1936).

(22) C. Moureu and R. Brown, *Bull. soc. chim.*, **27**, 901 (1920).

(23) Corse, Bryant, and Shonle, *J. Am. Chem. Soc.*, **68**, 1911 (1946).