assayed for antihistaminic activity. On the basis of preliminary pharmacological data, the most active members of the series possessed an activity equal to one-fourth that of N,N-dimethyl-N'-benzyl-N'-(α-pyridyl)-ethylenediamine.

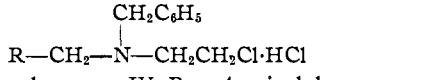
KALAMAZOO, MICHIGAN RECEIVED MARCH 18, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

The Preparation of β-Chloroethylamines Containing Heterocyclic Nuclei

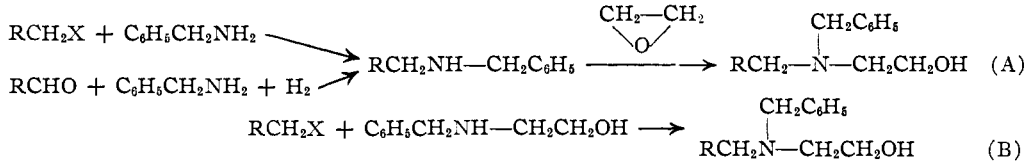
BY KENNETH N. CAMPBELL, JOSEPH F. ACKERMAN[1] AND BARBARA K. CAMPBELL

In view of the effectiveness of dibenzylaminoethyl chloride hydrochloride "Dibenamine"[2] as a sympatholytic drug,[3] it became of interest to prepare analogous substances in which one of the phenyl groups is replaced with a heterocyclic ring system. In this paper we are reporting the synthesis of five such compounds



I, R = α-thienyl
II, α = α-furyl
III, R = 4-imidazolyl
IV, R = 4-quinolyl
V, R = 4-methyl-5-thiazolylmethyl

All of these compounds were prepared from the corresponding amino alcohols by the action of thionyl chloride, with or without an inert solvent. The intermediate amino alcohols were made in one of the two following ways



The thiophene compound (I) was prepared by method A from α-chloromethylthiophene without difficulty. In the case of the furan derivative (II) it was found more convenient to use the aldehyde with benzylamine than to prepare α-chloromethylfuran; this synthesis likewise presented no difficulty.

When attempts were made to use 4-chloromethylimidazole in Method A for the synthesis of compound III, it was found very difficult to purify the imidazolylmethylbenzylamine from unreacted benzylamine, as the mixture could not be distilled, and the two substances had about the same solubilities. The amino alcohol was, therefore, prepared by Method B, and the crude amino alcohol was converted to the chloride (III) without purification. Compound III was separated from the benzylaminoethyl chloride hydrochloride which accompanied it by recrystallization from methanol.

It was originally planned to prepare the quinoline compound (IV) from cinchoninic aldehyde and benzylamine, by Method A. Cinchoninic aldehyde has been condensed successfully with other primary amines, and the aldimines reduced to secondary amines[4,5] but in the present case only poor yields of lepidylbenzylamine could be obtained by this procedure. The action of N-bromosuccinimide on lepidine was, therefore, investigated. Buu-Hoi[6] has reported that quinaldine and α- and γ-picolines are very easily brominated by this reagent, but he did not describe the products in detail nor establish their structures. We have found that lepidine reacts readily with N-bromosuccinimide in carbon tetrachloride, but the product is very unstable. It decomposes rapidly in hot solvents, and fairly rapidly even on standing, so that we were unable to purify it or analyze it. The product must be α-bromomethylquinoline, however, since it reacts rapidly with benzylaminoethanol, and behaves in other respects also as a reactive bromide. The N-lepidyl-N-benzylaminoethanol was converted, without difficulty, to the chloride (IV).

The thiazolyl compound (V) was prepared by Method B. Both the amino alcohol and the chloride in this series formed very hygroscopic salts, which made purification difficult; the oxalate of the chloride was found to be more easily handled than the hydrochloride.

Attempts were made to prepare a pyrimidine derivative by Method B, from 2-methyl-4-amino-5-bromomethylpyrimidine, but it was difficult to separate the reaction products from starting material and no satisfactory drug was obtained.

The authors wish to thank the Smith, Kline and French Co. of Philadelphia for a fellowship grant to support this work, and Dr. Fellows of Smith, Kline and French Co. for making the pharmacological tests. Most of the compounds

(1) Smith, Kline and French Fellow, 1947-1948.

(2) "Dibenamine" is the trade-mark for dibenzyl-3-chloroethylamine hydrochloride, Smith, Kline and French Laboratories.

(3) Nickerson, Goodman and Nomaguchi, *J. Pharmacol.*, **89**, 167 (1947).

(4) Campbell, Sommers, Kerwin and Campbell, THIS JOURNAL, **68**, 1851 (1946).

(5) Phillips, *ibid.*, **69**, 865 (1947).

(6) Buu-Hoi, *Ann.*, **556**, 5 (1944).

TABLE I

AMINO ALCOHOLS, $RCH_2—N(CH_2C_6H_5)—CH_2CH_2OH$

R	Method	Yield, %	B. p. °C.	Mm.	$n^{20}D$	HCl M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
α-Thienyl	A	74	135–145	0.07	1.5738	146–147	$C_{14}H_{17}NOS$	68.0	67.9	6.93	6.82	5.66	5.48
α-Furyl	A	62	122–126	.08	1.5481	152–154 (dec.)	$C_{14}H_{18}ClNO_2$[a]	62.8	62.7	6.77	6.60	5.23	5.04
4-Imidazolyl	B	94	Oil[b]		....	182–184 (dec.)	$C_{13}H_{19}Cl_2N_3O$[a]	..	..	..	..	13.8	14.0
4-Quinolyl	B	[c]											
4-Methyl-5-thiazolylmethyl[d]	B	65	174–175	.05	....	[e]	$C_{15}H_{20}N_2OS$	65.2	64.9	7.29	7.60	10.14	10.02

[a] Analyses carried out on the hydrochloride. [b] This oil could not be crystallized or distilled. [c] The amino alcohol was not isolated in this case. [d] The 4-methyl-5-(β-bromoethyl)-thiazole required was prepared by the method of Buchman, THIS JOURNAL, **58**, 1804 (1936). [e] The hydrochloride and oxalate salts were too hygroscopic to handle.

TABLE II

β-CHLOROETHYLAMINE HYDROCHLORIDES, $RCH_2—N(CH_2C_6H_5)—CH_2CH_2Cl\cdot HCl$

R	No.	Yield	Solvent[a]	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
α-Thienyl	I	43	A	177–178 dec.	$C_{14}H_{17}Cl_2NS$	55.6	55.7	5.67	5.79	4.64	4.69
α-Fury	II	44[b]	A	118–120 dec.	$C_{14}H_{17}Cl_2NO$	58.6	58.6	6.08	6.11	4.97	4.97
4-Imidazolyl	III	45[c]	M. E.	194–194.5 dec.	$C_{13}H_{18}Cl_3N_3$	48.4	48.2	5.62	5.71	13.05	13.23
4-Quinolyl	IV	19[c,d]	P. E.	155 dec.	$C_{19}H_{21}Cl_3N_2$	59.5	59.2	5.52	5.68	7.30	7.56
4-Me-5-thiazolyl-methyl	V	28	A	103–105[e]	$C_{19}H_{23}ClN_2O_8S\cdot H_2O$	46.2	46.2	5.07	4.75	5.68	5.22

[a] A = absolute alcohol, M. E. = methanol–ether, P. E. = *n*-propanol–ether. [b] The amino alcohol–thionyl chloride mixture was kept at 45° for fifteen minutes; higher temperatures and longer times gave tars. [c] Reaction carried out in chloroform solution. [d] Yield based on lepidyl bromide used. [e] Oxalate salt; the hydrochloride was an oil.

in this series showed some sympatholytic activity but were less active than 'Dibenamine.'

Experimental Part[7–9]

α-Thenylbenzylamine.—A solution of 25 g. (0.19 mole) of α-chloromethylthiophene[10] in 25 ml. of benzene was added dropwise to a solution of 46 g. (0.43 mole) of benzylamine in 50 ml. of benzene, while the temperature gradually rose to 65°. The mixture was stirred for three hours, the benzylamine hydrochloride removed, and the filtrate distilled to give 25.5 g. (68%) of product, b. p. 145–147° (2 mm.), $n^{20}D$ 1.5900.

Anal. Calcd. for $C_{12}H_{13}NS$: C, 70.89; H, 6.45; N, 6.89. Found: C, 71.06; H, 6.20; N, 7.00.

The hydrochloride melted at 248–250° (dec.) after recrystallization from absolute alcohol.

Anal. Calcd. for $C_{12}H_{14}ClNS$: Cl, 14.82. Found: Cl, 14.80.

The amine formed a phenylthiourea which was obtained as colorless needles from ethanol; m. p. 105–106°.

Anal. Calcd. for $C_{19}H_{16}N_2S_2$: N, 8.28. Found: N, 8.42.

Furfurylbenzylamine.—This was prepared by hydrogenation of furfurylidenebenzylamine[11] in absolute ethanol over Raney nickel at 48 p. s. i. The product had b. p. 115–124° (4 mm.), $n^{20}D$ 1.5543–1.5580, neut. equiv. (found) 187.5, (calcd.) 187.2. The hydrochloride melted at 208–212° (dec.).

Anal. Calcd. for $C_{12}H_{14}ClNO$: C, 64.42; H, 6.26; N, 6.26; Cl, 15.85. Found: C, 64.34; H, 6.00; N, 6.44; Cl, 15.90.

The phenylthiourea melted at 80–81° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{18}N_2OS$: N, 8.68. Found: N, 8.94.

Lepidyl Bromide.—Lepidine (15 g., 0.1 mole) was added with stirring to a suspension of 15 g. (0.08 mole) of N-bromosuccinimide[12] in 50 ml. of carbon tetrachloride kept at 60° and the mixture was refluxed for thirty minutes and filtered hot. The filtrate deposited 10 g. of white crystalline solid, which was washed thoroughly with water to remove occluded succinimide, and dried *in vacuo*. This material, m. p. 88–91°, decomposed to a high-melting red solid on standing for more than a few hours, and this same red product was obtained when efforts were made to recrystallize the crude lepidyl bromide; consequently the lepidyl bromide was used directly in the next step.

Preparation of Amino Alcohols, Method A.—The following procedure is typical. A mixture of 15 g. (0.074 mole) of α-thenylbenzylamine, 1.4 g. of water and 3.0 g. (0.07 mole) of ethylene oxide was heated under pressure at 100° for ten hours. The material was then taken up in ether, dried over magnesium sulfate and distilled.

Method B.—The heterocyclic alkyl halide was heated with 2–3 molar equivalents of benzylaminoethanol in benzene solution at 60–100° for several hours. Ether was added to precipitate the benzylaminoethanol hydrohalide, and the filtrate was evaporated to give the heterocyclic amino alcohol. The amino alcohols are recorded in Table I.

Preparation of β-Chloroethylamines.—The following example is typical: α-thenylbenzyl-N-(β-hydroxyethyl)-

(7) We wish to thank Mr. Charles A. Miller for carrying out some of the preparations reported in this paper.

(8) Microanalyses by Mr. Charles Beazley, Microtech Laboratory, Skokie, Illinois.

(9) All melting points are uncorrected.

(10) Blicke and Burckhalter, THIS JOURNAL, **64**, 478 (1942).

(11) de Chamot, *Ann.*, **271**, 12 (1892).

(12) Ziegler, *et al.*, *ibid.*, **551**, 109 (1942).

amine (9.5 g., 0.038 mole) was added gradually to 30 ml. of purified thionyl chloride. After the initial vigorous reaction had subsided the mixture was refluxed for one hour, and the excess thionyl chloride removed under reduced pressure. The residue was recrystallized from absolute ethanol. The data on this compound and the other members of the series are summarized in Table II.

Summary

1. Several heterocyclic analogs of dibenzylaminoethyl chloride have been prepared for testing as sympatholytic agents.

NOTRE DAME, INDIANA RECEIVED JANUARY 31, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORY, GENERAL ELECTRIC COMPANY]

A Study of Some Condensations of o-Methylolphenol

BY MURRAY M. SPRUNG AND MATTHEW T. GLADSTONE

The processes which occur during the formation of phenolaldehyde resins have been well systematized in recent years.[1] It is now generally agreed that three basic types of reactions occur: (1) Addition of aldehyde (formaldehyde) ortho or para to a phenolic hydroxyl group gives, as the simplest recognizable product, a methylol phenol.[2] (2) Condensation with a second molecule now gives a dinuclear reaction product. Repetition of these addition and condensation steps then yields polynuclear reaction products of varying structures, chain lengths and degrees of branching, depending upon the structures of the reactants and the conditions imposed upon them. (3) More complex condensations and rearrangements of these intermediates finally are involved, leading, usually at higher temperatures, to complex, highly condensed structures.

Despite the wealth of chemical evidence adduced in support of the above generalizations, relatively little use has been made of kinetics in the study of phenol-aldehyde resinification. Such attempts have indeed been discouraged by the heterogeneous nature of the phenomena involved and by the lack of simple or distinctive analytical tools. Previous efforts have in general concerned themselves with the so-called primary (addition) reactions alone; or have involved measurements of the rates of many consecutive or integrated processes involved in resinification or in resinification and "curing" combined.[3]

Several years ago, there was reported[4] the reaction between various phenols and paraformaldehyde in virtual absence of water or other solvent and with triethanolamine as catalyst. The disappearance of formaldehyde under these conditions (the addition step, 1) apparently followed a first order rate law. Preliminary attempts to estimate the rates of the condensation reactions (step 2) were also described. It was observed that the condensation reactions are relatively slow compared to formaldehyde addition, and that phenols which readily form methylol derivatives also undergo subsequent condensations with relative ease.

Nordlander's extensive studies[3g] of the ammonia catalyzed reaction between phenol and formaldehyde indicated first order kinetics over a wide range of concentrations of reactants and catalysts. In contrast, most other aqueous alkaline catalyzed reactions show second order kinetics.[5] von Euler and Kispeczy[6] studied 2,4- and 2,6-dimethyl phenol in each of which only one position is available for reaction. With formaldehyde, in aqueous ethanol with hydrocbloric acid as catalyst, second order kinetics were observed. A specific rate constant some 75% greater was observed for phenol under similar conditions.

Recently Jones[7] reported on the initial phases of the phenol–formaldehyde reaction. Under acidic conditions, second order rates were observed between 80 and 100°, but a reversion to first order at low temperatures (30°) was noted. In presence of alkali (NaOH) the reactions were first order during the first 45% at 40°. (This interpretation, however, has been criticized by Goldblum.)[8]

In the present work the starting material is o-methylol phenol (saligenin) a crystalline substance which can easily be obtained pure by a method independent of aldehyde addition. This effectively eliminates step (1) in the generalized reaction scheme. Its reactions with itself, with phenol and with resorcinol have been studied under a variety of conditions.

Materials.—Saligenin was obtained from Hynson, Westcott and Dunning, Inc., as a colorless, crystalline solid (produced by catalytic reduc-

(1) (a) Zinke and co-workers, *Ber.*, **77B**, 264 (1944), and previous articles; (b) H. v. Euler and co-workers, *Arkiv. Kemi Mineral. Geol.*, **15A**, No. 11 (1942), and previous articles; (c) K. Hultzsch and co-workers, *Ber.*, **75B**, 363 (1942), and previous articles; (d) T. S. Carswell, "Phenoplasts," pages 12-29. Dr. Carswell has presented an admirable summary of much of the above and pertinent related material.

(2) Hemi-acetals (hemi-formals) may apear as precursors, but no unequivocal demonstration of their presence or of the role they play has yet been given.

(3) (a) Novak and Cech, *Ind. Eng. Chem.*, **20**, 796 (1928); (b) Megson, *J. Soc. Chem. Ind.*, **57**, 189 (1938); **58**, 131 (1939); (c) Holmes and Megson, *ibid.*, **52**, 415T (1933); (d) Granger, *Ind. Eng., Chem.*, **29**, 1305 (1937); (e) Tsuruta, *J. Soc. Chem. Ind. Japan*, **40**, 125B (1937); (f) Dubrisay, *Ind. Plastiques*, **1**, 132 (1945); (g) Nordlander, *Oil, Paint, Drug Rept.*, **130**, *3*, 27 (1936).

(4) M. M. Sprung, THIS JOURNAL, **63**, 334 (1941).

(5) K. B. Goldblum, private communication.

(6) von Euler and Kispeczy, *Z. physik. Chem.*, **A189**, 109 (1941).

(7) T. T. Jones, *J. Soc. Chem. Ind.*, **65**, 264 (1946).

(8) K. B. Goldblum, *J. Soc. Chem. Ind.*, in press.