reduced more easily than any reported type of organic compound. Reduction is effected at room temperature, atmospheric pressure and in the absence of any catalyst. The reaction is $RK + H_2 \longrightarrow RH + KH$.

The order of increasing ease of hydrogenolysis of the phenyl derivatives is: Ca, Li, Na, K, Rb, Cs. This series follows essentially the series of relative reactivities as established by other reactants.

The rates of hydrogenolysis appear to be unaffected by the presence of platinum and palladium.

The rates of hydrogenolysis have been established for a series of RLi compounds having different R groups.

AMES, IOWA RECEIVED JULY 14, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Urethans as Local Anesthetics. IV. Alkyl N-(*p*-Aminobenzyl)-carbamates

BY R. L. SHRINER AND JAMES M. CROSS

A study of the local anesthetic action of *p*-aminophenyl urethans (Formula I) showed that their anesthetic potency was high but that they were very irritating whether applied topically or intracutaneously.[1] It seemed possible that the irritation might be due to the *p*-phenylenediamine grouping present as a portion of the molecule since other derivatives of this compound have been found to cause irritation.[2]

In molecules of the type of alkyl N-(*p*-aminobenzyl)-carbamates (II) the urethan grouping is separated from the benzene ring by a methylene

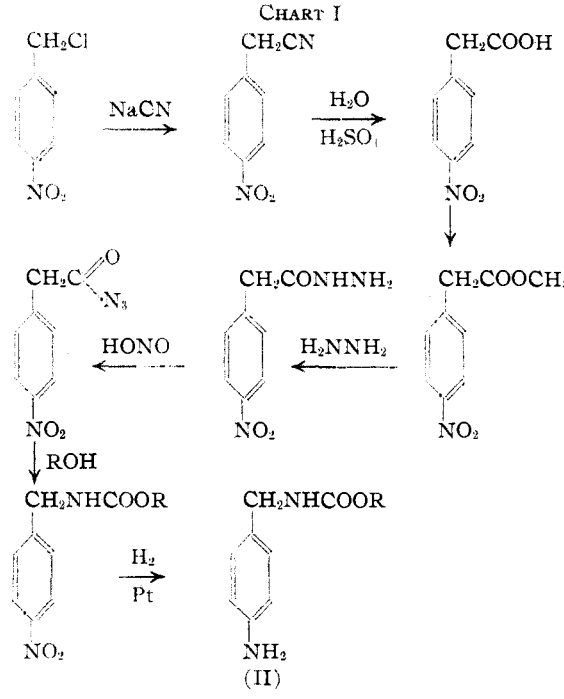
I $H_2NC_6H_4NHCOOR$
II $H_2NC_6H_4CH_2NHCOOR$
III $H_2NC_6H_4COO(CH_2)_xNR_2$

group and the *p*-phenylenediamine group is no longer present. The structure of urethans of type II is related to compounds of the novocaine type (III) in that each contains a *p*-aminophenyl radical attached to a carbon atom. Since the alkyl *p*-aminobenzoates are not especially irritating, it was considered of interest to synthesize the urethans of type II in order to determine whether this structure would be non-irritating to the tissues but still retain the superiority in topical and injection anesthetic potency of the urethans of type I over those of the *p*-aminobenzoates of type III.

The urethans were synthesized by means of the reactions summarized in Chart I.

Although the final compounds are new, each of the individual steps in the above synthesis represents well-known reactions which were adapted to the present compounds with slight modifications which are given in the experimental part.

CHART I



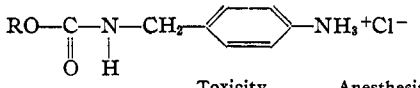
Through the courtesy of the Lilly Research Laboratories the pharmacological action of 1% aqueous solutions of the hydrochlorides of this series of urethans was determined. The data obtained are summarized in Table I.

The pharmacological data in Table I show that these urethans cause some local anesthesia when injected intracutaneously but that they are not especially active when applied topically. All of these urethans were irritating both to the skin and eyes and this fact probably accounts for the somewhat erratic results. These urethans are

(1) Horne, Cox and Shriner, THIS JOURNAL, **55**, 3435 (1933).
(2) Hanzlik, *J. Ind. Hyg.*, **4**, 386, 448 (1923); Erdmann and Bakken, *Arch. Exptl. Path. Pharm.*, **53**, 402 (1905).

TABLE I

PHARMACOLOGICAL ACTION OF ALKYL N-(*p*-AMINOBENZYL)-CARBAMATE HYDROCHLORIDES



Alkyl group R—	Toxicity (mice) mg./kg.	Anesthesia Skin (min.)	Anesthesia Eyes (min.)
Normal			
CH_3—	1000	30	None
CH_3CH_2—	340	25	None
$CH_3CH_2CH_2$—	250	21	None
$CH_3CH_2CH_2CH_2$—	140	38	6
$CH_3(CH_2)_4$—	125	11(?)	10
$CH_3(CH_2)_5$—	60	40	46
$CH_3(CH_2)_6$—	30	None	None
$CH_3(CH_2)_7$—	50	36	None
Iso			
$(CH_3)_2CHCH_2$—	175	23	None
$(CH_3)_2CHCH_2CH_2$—	100	10	None
$CH_3CH_2(CH_3)CHCH_2$—	90	45	22
Secondary			
$(CH_3)_2CH$—	400	28	None
$CH_3CH_2(CH_3)CH$—	230	23	None
$CH_3CH_2CH_2(CH_3)CH$—	200	21	None
$CH_3(CH_2)_5(CH_3)CH$—	35	None	None
$(CH_3CH_2)_2CH$—	125	120	None

not as potent local anesthetics as the *p*-aminophenylurethans previously described.

Experimental

Methyl *p*-Nitrophenylacetate.—Forty grams of *p*-nitrophenylacetic acid, prepared by the hydrolysis of *p*-nitrophenylacetonitrile,[3] was dissolved in 120 g. of absolute methanol and dry hydrogen chloride passed into the solution for two hours. The solution was refluxed for two hours and the excess methanol removed by distillation. The residue was extracted with warm ligroin and the resulting solution cooled in an ice-bath. The ester separated in the form of colorless needles which melted at 54°. The yield was 83.5%. This procedure is a modification of the one used by Curtius,[4] who obtained a 42% yield.

***p*-Nitrophenylacethydrazide.**—A mixture of 34 g. of the ester with 50 g. of 42% hydrazine hydrate solution was heated on a steam-bath for thirty minutes. At first a red coloration developed which gradually disappeared and the mixture solidified to a hard yellow cake. The product was washed with water and recrystallized from absolute ethanol. Thirty-three grams (97%) of needles was obtained melting at 167° which agreed with the value given by Curtius.[4]

***p*-Nitrophenylacetazide.**—Twelve grams of the hydrazide was dissolved in two liters of warm water and 8 cc. of concentrated hydrochloric acid added. This solution was cooled to 20° and 5 g. of sodium nitrite sifted in with vigorous mechanical stirring. The insoluble azide floated on the surface and was separated by filtration. Nine preparations using the above quantities and conditions gave an average yield of 10.6 g. (83.5%). The azide melted at 45° with decomposition. The azide decomposes upon standing and hence always was used within a few hours after it was prepared.

Alkyl N-(*p*-Nitrobenzyl)-carbamates.—A solution of 10 g. of the azide in 400 cc. of each of the anhydrous alcohols was refluxed for three to four hours, at the end of which time the evolution of nitrogen had ceased. The excess alcohol was removed by distillation and the residue chilled. In most cases the urethan solidified and was recrystallized from ligroin. Four of the urethans were oils (see Table II) which could not be crystallized satisfactorily and which decomposed upon attempted distillation *in vacuo*. The oils were washed with water and dried. The analyses of the oils indicated that they were not quite pure but they were sufficiently so for the next step. The data on the alkyl

TABLE II

ALKYL N-(*p*-NITROBENZOYL)-CARBAMATES

Alkyl group	Yield, %	M.p., °C. (corr.)	Mol. formula	N Analyses, % Calcd.	Found
Methyl	68	104–105	$C_9H_{10}O_4N_2$	13.33	13.53
Ethyl	63	115–116	$C_{10}H_{12}O_4N_2$	Ref. 4	
n-Propyl	97	89–90	$C_{11}H_{14}O_4N_2$	11.76	11.95
Isopropyl	76	107–108	$C_{11}H_{14}O_4N_2$	11.76	11.75
n-Butyl	66	62–63	$C_{12}H_{16}O_4N_2$	11.11	11.06
Isobutyl	70	59–60	$C_{12}H_{16}O_4N_2$	11.11	10.94
2-Butyl	61	62–63	$C_{12}H_{16}O_4N_2$	11.11	11.24
n-Amyl	52	49–50	$C_{13}H_{18}O_4N_2$	10.52	10.77
Isoamyl	70	Oil	$C_{13}H_{18}O_4N_2$	10.52	10.03
2-Pentyl	70	50–51	$C_{13}H_{18}O_4N_2$	10.52	10.49
3-Pentyl	55	50–51	$C_{13}H_{18}O_4N_2$	10.52	10.72
2-Methyl-1-butyl	70	Oil	$C_{13}H_{18}O_4N_2$	10.52	10.10
n-Hexyl	61	Oil	$C_{14}H_{20}O_4N_2$	10.00	10.92
n-Heptyl	63	Oil	$C_{15}H_{22}O_4N_2$	9.52	9.29
1-Octyl	63	48–50	$C_{16}H_{24}O_4N_2$	9.09	9.00
2-Octyl	56	64–65	$C_{16}H_{24}O_4N_2$	9.09	8.94

TABLE III

ALKYL N-(*p*-AMINOBENZYL)-CARBAMATE HYDROCHLORIDES

Alkyl group	Decomposition temp.,[a] °C.	Mol. formula	Cl Analyses, % Calcd.	Found
Methyl	177–178	$C_9H_{13}O_2N_2Cl$	16.39	16.50
Ethyl	160–161	$C_{10}H_{15}O_2N_2Cl$	15.41	15.05
n-Propyl	153–155	$C_{11}H_{17}O_2N_2Cl$	14.51	14.90
Isopropyl	177–178	$C_{11}H_{17}O_2N_2Cl$	14.51	14.60
n-Butyl	156–158	$C_{12}H_{19}O_2N_2Cl$	13.84	13.84
Isobutyl	160–162	$C_{12}H_{19}O_2N_2Cl$	13.84	13.76
2-Butyl	153–154	$C_{12}H_{19}O_2N_2Cl$	13.84	14.05
n-Amyl	152–154	$C_{13}H_{21}O_2N_2Cl$	13.03	12.84
Isoamyl	157–159	$C_{13}H_{21}O_2N_2Cl$	13.03	13.20
2-Pentyl	140–146	$C_{13}H_{21}O_2N_2Cl$	13.03	13.70
3-Pentyl	149–150	$C_{13}H_{21}O_2N_2Cl$	13.03	13.15
2-Methyl-1-butyl	152–153	$C_{13}H_{21}O_2N_2Cl$	13.03	13.30
n-Hexyl	157–158	$C_{14}H_{23}O_2N_2Cl$	12.37	12.33
n-Heptyl	157–158	$C_{15}H_{25}O_2N_2Cl$	11.81	12.01
1-Octyl	159–161	$C_{16}H_{27}O_2N_2Cl$	11.29	11.39
2-Octyl	147–148	$C_{16}H_{27}O_2N_2Cl$	11.29	11.47

[a] In all cases these salts darkened 5 to 10° below the decomposition temperature.

(3) Robertson, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 398.

(4) Curtius, *J. prakt. Chem.*, **197**, 521 (1913).

N-(*p*-nitrobenzyl)-carbamates are summarized in Table II.

Alkyl N-(*p*-Aminobenzyl)-carbamates.—A solution of 5 g. of the alkyl N-(*p*-nitrobenzyl)-carbamate in 100 cc. of absolute ethanol was shaken with 0.2 g. of platinum oxide-platinum black and hydrogen at 3 atm. pressure. The reductions were complete in three to ten minutes. The platinum was removed by filtration and the filtrate saturated with dry hydrogen chloride. An equal volume of absolute ether was added to facilitate the separation of the hydrochloride. The hydrochloride salts were removed by filtration. The yields varied from 50 to 90%, most of the loss being due to the difficulties in causing complete separation of the hydrochlorides. Evaporation of the alcohol-ether mother liquor gave colored impure products which could not be obtained in a colorless condition by recrystallization. The data are summarized in Table III.

Summary

A series of alkyl N-(*p*-nitrobenzyl)-carbamates was prepared by the action of the alcohols from methyl to octyl on the azide of *p*-nitrophenylacetic acid. Catalytic reduction of these nitro compounds and subsequent treatment with hydrogen chloride produced the corresponding hydrochlorides of alkyl N-(*p*-aminobenzyl)-carbamates. Solutions of these hydrochlorides produced intracutaneous anesthesia but only a few caused surface anesthesia. All were quite irritating to the tissues.

URBANA, ILLINOIS RECEIVED JULY 15, 1938

[CONTRIBUTION OF THE G & A LABORATORIES, INC., SAVANNAH, GEORGIA]

Reactions Involved in the Sulfonation of Heat Treated Abietic Acid

BY TORSTEN HASSELSTROM AND JOHN D. MCPHERSON

Recent work of Fieser and Campbell[1] on dehydroabietic acid together with the investigations of Fleck and Palkin[2] and Littman[3] has produced evidence that α-pyroabietic acid heretofore regarded as an isomeric abietic acid is actually a mixture of dehydroabietic acid and hydrogenated abietic acids produced through the reactions of dehydrogenation and disproportionation of abietic acid.

In a previous communication[4] we reported that the sulfonation of heat treated abietic acid yields a crystalline sulfonic acid and as a by-product a lactone belonging to the tetrahydroabietic acid series of compounds. We have obtained evidence that the sulfonic acid[5] has the composition of $C_{20}H_{28}O_5S \cdot 3H_2O$ and hence may be established as a dehydroabietic acid sulfonate. This identity is established further by the preparation of the dimethyl ester, diethyl ester and diamide of this sulfonic acid. Since the lactone is saponified only with difficulty and easily regenerated,[4] it is apparently a γ-lactone formed from a $\Delta^{9,10}$-dihydroabietic acid as a result of hydration due to the sulfuric acid employed. Hence it is likely that the corresponding hydroxytetrahydroabietic acid has the hydroxyl in position 10. It is worthy of note that the addition of two atoms of hydrogen to abietic acid by catalytic means produces an easily lactonized dihydroabietic acid.[6] This lactone formation in the abietic acid series points to the fact that on saturation of one double bond of the original abietic acid, the remaining double bond moves to a position more favorable for hydration and lactonization.

The results obtained by us on the sulfonation of heat treated abietic acid do not agree with those previously recorded in the literature. On sulfonation of α-pyroabietic acid Fanica[7] obtained a crystalline monosulfonic acid for which the formula $C_{20}H_{30}O_5S$ was designated. He also reports as a residue a non-crystalline sulfur containing material.

Our findings that the sulfonation of heat treated rosin yields a dehydroabietic acid sulfonate and a lactone belonging to the tetrahydroabietic series of compounds are additional proof that the dehydrogenation and disproportionation of abietic acid occur on heat treatment.

Experimental

Dehydroabietic Acid Sulfonate.—The sulfonic acid was prepared from partially refined pseudopimaric acid according to Hasselstrom.[5a] It was recrystallized from water, glacial acetic acid and water; m. p. 223–224° (dec.). It was dried at 100° under vacuum.

Anal. Calcd. for $C_{20}H_{28}O_5S \cdot 3H_2O$: C, 55.29; H, 7.83;

(1) Fieser and Campbell, THIS JOURNAL, **60**, 159 (1938).
(2) Fleck and Palkin, *ibid.*, **60**, 921 (1938).
(3) Littman, *ibid.*, **60**, 1419 (1938).
(4) Hasselstrom, Brennan and McPherson, *ibid.*, **60**, 67 (1938).
(5) (a) Hasselstrom, U. S. Patent 2,121,032 (1938); (b) Hasselstrom, U. S. Patent 2,121,033 (1938).
(6) (a) Ruzicka and Meyer, *Helv. Chim. Acta*, **5**, 333 (1922); (b) Ruzicka, Waldman, Meier and Hösli, *ibid.*, **16**, 139 (1933).
(7) (a) Fanica, *Bull. inst. pin.*, **44**, 151 (1933); (b) *ibid.*, **45**, 181 (1933); (c) Greth, *Z. angew. Chem.*, **47**, 927 (1934).