described. A method for the quantitative formation of hydrogen sulfide-S^{35} from cadmium sulfide-S^{35} has been described. A method of labeling thiourea with S^{35} has been described. The thiourea possessed an activity of 0.535 mc./mg.

LOS ALAMOS, NEW MEXICO RECEIVED MAY 5, 1950

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Reduction of α-Haloketones to Halohydrins by Lithium Aluminum Hydride[1]

BY ROBERT E. LUTZ, ROSSER L. WAYLAND, JR., AND HAYWOOD G. FRANCE

The reduction of α-bromoketones by lithium aluminum hydride is of particular interest in connection with reductive elimination of bromine by the Grignard reagent which has been shown in one case to occur as a 1,4-reaction process or "reductive enolization."[2]

Trevoy and Brown[3] have reported the reduction of *p*-bromophenacyl bromide (I) to α-(*p*-bromophenyl)-ethanol using 30–100% excess of lithium aluminum hydride. In attempted repetitions of their experiment we obtained in addition to this (the predominant product) very small amounts of the *p*-bromophenylbromohydrin. By using an amount of reagent only slightly in excess of that needed for a one-stage reduction we obtained the bromohydrin in 69% yield of purified material. Desyl chloride (II) and *p*-chlorophenacyl bromide (III) under these conditions were reduced in 76 and 77% yields, respectively, to *erythro*-stilbene chlorohydrin and *p*-chlorophenyl bromohydrin. This synthesis of *erythro*-stilbene chlorohydrin appears to be more economical in respect to labor and materials than the synthesis through *meso*-hydrobenzoin.[4] Varying the temperature from 0–35° did not seem to affect the results appreciably, but reversing the order of addition, *e. g.*, adding the reducing agent slowly to desyl chloride, lowered the yield sharply, due doubtless to condensation between desyl chloride and the reaction product.

It is shown by the above results that in three typical instances the straightforward 1,2-reduction of the carbonyl group proceeds more rapidly than reductive replacement of the halogen of either the haloketone or the halohydrin. The preferential 1,2-reduction of the carbonyl groups of the α-bromoketones is in sharp contrast with the "reductive enolization" which is commonly brought about by the Grignard reagent.[1]

Some consideration has been given to the distinction between the first hydride reducing equivalent of the reagent and the other hydride hydrogens which may involve the equivalent of aluminum hydride.[5] It was found that the aliphatic halogen of one typical bromohydrin (the *p*-bromophenyl) was readily removed by the action of a molecular equivalent of lithium aluminum hydride, and the bromoketone was reduced to *p*-bromophenylethanol by reagent in which the first hydride reducing equivalent had been destroyed in advance. The formation of the halohydrins from the haloketones in reductions using close to one-fourth of a molecule of the rea-

TABLE OF RESULTS

Compound[a]	Mole $LiAlH_4$	Temp., °C.	Product	Yield, %
I	0.007	25	V	69[b]
I	.026	35	VI	[c]
I	.026	0	VI	[c]
I	.026[d]	35	VI	90[e,f]
V	.026	35	VI	90[e]
II	.007	25	VII	76[b]
II	.015	0	VII	60[b]
II	.015	34	VII	60[b]
II	.026	35	VII	50[b]
II	.007	35	VII[g]	30[b]
III	.007	25	VIII	77[b]
IV	.007	35	IX	10[h]

[a] The amount of compound used in each case was 0.02 mole. The compounds and products are as follows: I = p-$BrC_6H_4COCH_2Br$ (*p*-bromophenacyl bromide); II = $C_6H_5COCHClC_6H_5$ (desyl chloride); III = p-$ClC_6H_4COCH_2Br$; IV = $C_6H_5COCHBrC_6H_5$; V = p-$BrC_6H_4CHOHCH_2Br$; VI = p-$ClC_6H_4CHOHCH_3$; VII = $C_6H_5CHOHCHClC_6H_5$ (*erythro*); VIII = p-$ClC_6H_4CHOHCH_2Br$; IX = $C_6H_5CHOHCHBrC_6H_5$ (*erythro*). [b] Purified material, identified by the sharp and characteristic melting points (within one degree of reported values), and in the case of stilbene chlorohydrin by mixture melting points with an authentic sample. In view of losses entailed in purification of these products by crystallization methods, it is clear that the actual production of the halohydrin in all cases must have been higher than the yields stated. [c] The results were similar to those of Trevoy and Brown[3] except that a very small amount of the bromohydrin (V) was also isolated and identified. [d] In this reduction in two separate experiments the first hydride–hydrogen equivalent had been destroyed by addition of the calculated amount of (a) allyl iodide or (b) ethyl iodide (and refluxing for a half hour). [e] The product was isolated as a distilled oil and identified by boiling point,[f] and also by conversion to the phenylurethan.[3] [g] The lithium aluminum hydride solution was added slowly to the ether solution of desyl chloride. [h] This experiment was a preliminary one carried out by Mr. J. W. Baker, and it is cited only as evidence that the bromohydrin can be isolated here.

(1) This work was incidental to the synthesis of amino alcohols as tumor-necrotizing agents; supported in part by a grant from the National Institutes of Health.

(2) (a) Lutz and Kibler, THIS JOURNAL, **62**, 360 (1940); (b) Lutz and Reveley, *ibid.*, **63**, 3180 (1941).

(3) Trevoy and Brown, *ibid.*, **71**, 1675 (1949).

(4) (a) Reulos and Letellier, *Compt. rend.*, **216**, 698 (1943); (b) *cf.* modifications of this method, Bauer, Master's thesis, University of Virginia, 1949 (to be published shortly).

(5) Johnson, Blizzard and Carhart, THIS JOURNAL, **70**, 3664 (1948).

gent must have involved in the main the lower level of the reducing equivalents. From the total of these results (see table) a relatively facile reducibility of the halogen of the halohydrin as compared with the reducibility of an ordinary alkyl halide is demonstrated. There may be some variation in the ratio of 1,2-reduction of the carbonyl group and direct or 1,4-reductive elimination of bromine from the bromo ketone or bromohydrin, depending on which hydrogens of the reducing agent are involved, but because of the facility of reduction of the bromohydrin this problem may not be easy to investigate. From these experiments it seems probable at the first reducing level of the reagent, and certain at the lower level, that 1,2-reduction of the carbonyl group is the dominant primary reaction in the three cases studied. Further studies on this problem are in progress.

Experimental

In a typical experiment a solution of 0.02 mole of the α-haloketone in 100 ml. of dry ether was added dropwise slowly to a stirred solution of lithium aluminum hydride in 100 ml. of dry ether. Stirring was continued for a half to one hour after the addition was complete. Water (25 ml.) was added, followed by 3 *N* hydrochloric acid, and the ether layer was separated, washed, dried over sodium sulfate and evaporated. The residue was recrystallized from ligroin.

Summary

Three typical α-haloketones undergo chiefly 1,2-reduction at the carbonyl group as the first step in the reaction with lithium aluminum hydride. Subsequent reduction of the bromine from a typical bromohydrin, proceeds with somewhat greater difficulty, by direct displacement, but occurs more easily than reduction of ordinary alkyl bromide.

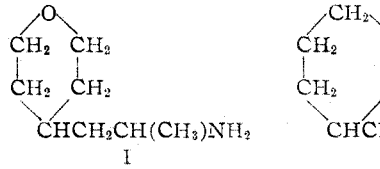
CHARLOTTESVILLE, VA. RECEIVED MAY 15, 1950

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

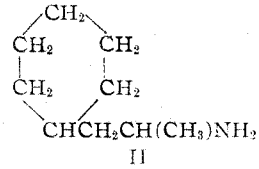
Some Derivatives of Tetrahydropyran as Potential Pharmacodynamic Agents. II[1]

BY ALFRED BURGER, LENNOX B. TURNBULL[2] AND J. GRAY DINWIDDIE, JR.

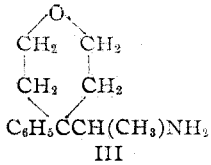
4-(1-Hydroxy-2-piperidinoethyl)-tetrahydropyran exhibits in rats a marked analgetic effect in a large proportion of the animals tested.[1] It appeared of interest to investigate whether a favorable pharmacodynamic behavior would be found in other derivatives of tetrahydropyran which contain suitable functional groups. We have prepared three types of compounds for this purpose. First, 1-(4-tetrahydropyranyl)-2-aminopropane (I) was to be compared with the isosteric local vasoconstrictor agent 1-cyclohexyl-2-aminopropane (II). Second, 1-(4-phenyl-4-



I

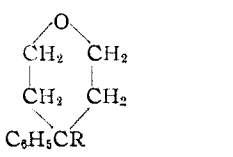


II

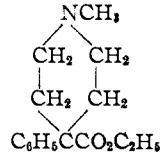


III

tetrahydropyranyl)-ethylamine (III) was to demonstrate the effect of incorporating the tetrahydropyran ring in derivatives of 1-phenyl-2-aminopropane. The third type included a series of 4-dialkylaminoacetyl-4-phenyltetrahydropyran (IV) and 1-(4-phenyltetrahydropyranyl)-2-dialkyl aminoethanol (V) derivatives which could be interpreted as analogs of the drug, Demerol (VI), the basic function having been removed into the side chain.



IV, R = $COCH_2NR_2$
V, R = $CHOHCH_2NR_2$



VI

1-(4-Tetrahydropyranyl)-2-aminopropane (I) was synthesized in seven steps starting from 4-carboxytetrahydropyran (VII). This acid was reduced to 4-tetrahydropyranylmethanol (VIII) with lithium aluminum hydride, the carbinol was converted to 4-tetrahydropyranylmethyl bromide (IX) and the latter was condensed with diethyl sodio methylmalonate. By hydrolyzing and decarboxylating the resulting diethyl methyl-(4-tetrahydropyranylmethyl)-malonate (X), α-methyl-β-(4-tetrahydropyranyl)-propionic acid (XI) was obtained which was degraded to the amine (I) by the Curtius method.

$C_5H_9O{\cdot}CO_2H \longrightarrow C_5H_9O{\cdot}CH_2OH \longrightarrow$
VII VIII
$C_5H_9OCH_2Br \longrightarrow C_5H_9O{\cdot}CH_2C(CH_3)(CO_2C_2H_5)_2 \longrightarrow$
IX X
$C_5H_9O{\cdot}CH_2CH(CH_3)CO_2H \longrightarrow$ I
XI

1-(4-Phenyl-4-tetrahydropyranyl)-ethylamine (III) was obtained conveniently by converting

(1) First article: Harnest and Burger, THIS JOURNAL, **65**, 370 (1943).

(2) du Pont Fellow, 1948-1950.