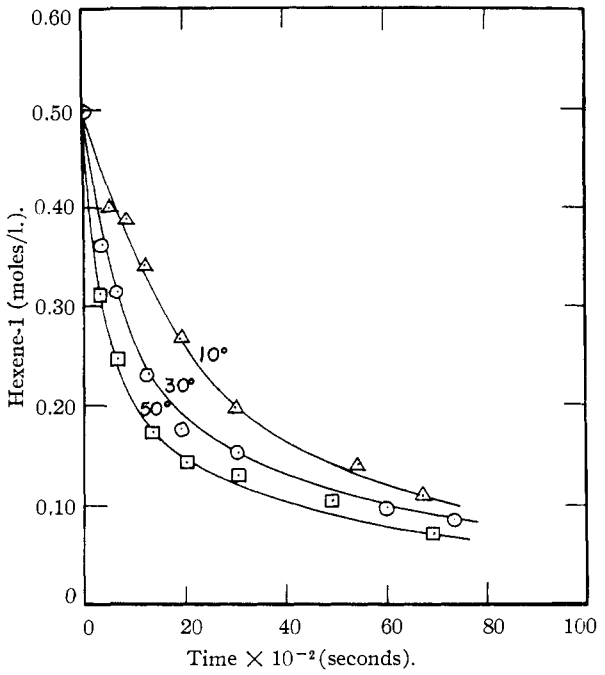


Fig. 2.—Hexene-1 polymerization, variation of rate with temperature; (catalyst, 20 mmoles $TiCl_4$, 10 mmoles Al $(i\text{-}C_4H_9)_3$; solvent, cyclohexane).

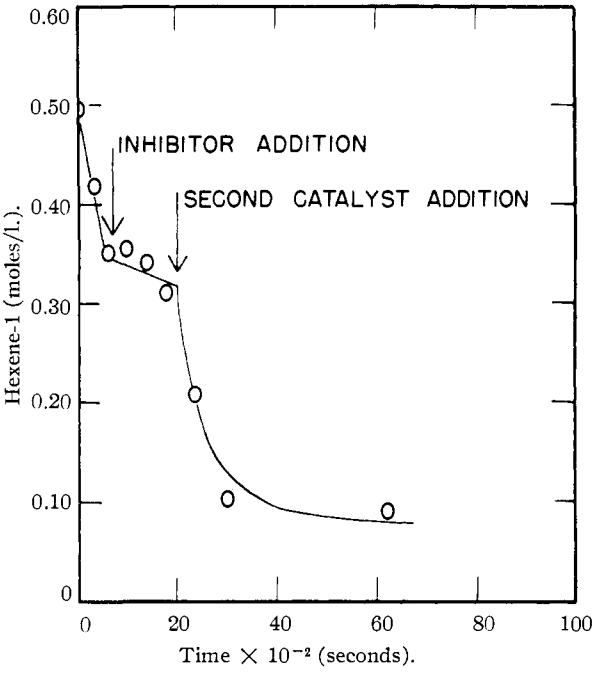


Fig. 3.—Hexene-1 polymerization at 30°. Inhibition (by triethylamine) followed by second catalyst addition (catalyst, 20 mmoles $TiCl_4$, 10 mmoles Al $(i\text{-}C_4H_9)_3$; solvent, cyclohexane).

oriented structure for catalyst ratios of 1:3 than for catalyst ratios of 2:1.

Brief mention may be made of an experiment designed to show the nature of inhibition. Early experiments showed that practically any reagent added to the reaction caused inhibition. This is particularly true of ethers, amines, ketones and alcohols. One would expect any electron donor molecule to coördinate readily with the catalyst molecules. It would be anticipated that addition of just sufficient inhibitor to complex the catalyst would lead to cessation of the reaction. Addition of fresh catalyst would be expected to start the reaction again provided the inhibitor–catalyst complex would remain as an inert substance. Results indicating that this occurs are shown in Fig. 3. Polymerization here was catalyzed at the start by 20 mmoles $TiCl_4$ and 10 mmoles Al$(i\text{-}C_4H_9)_3$. After 12.5 minutes, 2 mmoles of triethylamine was added. This amount was chosen since earlier experiments with ethylene showed that this amount would reduce the ethylene polymerization rate almost, but not quite, to zero. After 24 minutes in the dormant state, a fresh quantity of catalyst was added. This immediately recatalyzed polymerization at a rate equivalent to the initial rate.

SUMMIT, NEW JERSEY

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, AMHERST COLLEGE, AND WASHINGTON AND LEE UNIVERSITY]

# A New Method for the Resolution of Racemic Carbonyl Compounds: Synthesis and Use of 4-(4-Carboxyphenyl)-semicarbazide

BY JAMES K. SHILLINGTON,[1] GEORGE S. DENNING, JR.,[2a] WILLIAM B. GREENOUGH, III,[2b] TRAFFORD HILL, JR., AND O. BERTRAND RAMSAY[2a]

RECEIVED AUGUST 6, 1957

A new approach has been developed for the resolution of carbonyl compounds possessing an asymmetric carbon atom by means of a bifunctional intermediate which possesses a free acid group and a group which reversibly condenses with the carbonyl compound. For this purpose, 4-(4-carboxyphenyl)-semicarbazide has been synthesized and its use assayed in a successful resolution of *dl*-3-methylcyclohexanone.

Resolution *via* the carbonyl group, as briefly reviewed by Leonard and Boyer,[3] has traditionally proceeded through the preparation and use of optically active carbonyl reagents. The present investigation was undertaken to synthesize a bifunctional intermediate which would give, upon reacting with the carbonyl group, a condensate, easily hydrolyzable for regeneration of the aldehyde or ketone, and which would be able to form re-

(1) Department of Chemistry, Washington and Lee University.

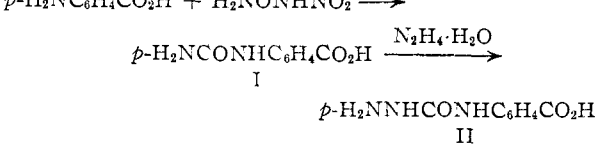
(2) Taken in part from theses presented by (a) George S. Denning, Jr., and O. Bertrand Ramsay to Washington and Lee University and by (b) William B. Greenough, III, to Amherst College in partial fulfillment for the degree of Bachelor of Science in Chemistry.

(3) N. J. Leonard and J. H. Boyer, *J. Org. Chem.*, **15**, 42 (1950).

solvable salts with readily obtained optically active bases.

After consideration of stability of derivatives in the presence of light and air, ease of handling and ease of hydrolysis, it was decided to attempt the synthesis of 4-(4-carboxyphenyl)-semicarbazide. Direct transamination of acetone semicarbazone with the desired amine, in this case *p*-aminobenzoic acid, and subsequent hydrolysis is perhaps the reaction that has been most widely employed, because of its apparent simplicity, for the production of the 4-substituted semicarbazides. However, a comparative study[4] of the transamination reaction *vs.* the hydrazination of substituted ureas and of isocyanates indicated that hydrazination of ureas gave better yields and that either of the two hydrazination reactions gave far better yields than the transamination process. Finally, the synthesis of the thio analog, 4-(*p*-carboxyphenyl)-thiosemicarbazide, by hydrazination of *p*-$HO_2CC_6H_4NHCS_2NH_4$ has been reported.[5]

**Results and Discussion.**—The following synthetic scheme was used



*p*-Ureidobenzoic acid (I), the starting compound, was first reported by Davis and Blanchard,[6] although no specific directions for its preparation, the yield, nor its specific physical constants are given in the literature. Buck and Ferry[7] suggest ethyl alcohol as a solvent for better yields from this reaction. We did not find this to be true in our case. The nitrourea must be recrystallized, for the sulfuric acid remaining in the crude material precipitates *p*-aminobenzoic acid as the bisulfate. The melting point of the product was reproducible in a sealed capillary tube.

The 4-(4-carboxyphenyl) semicarbazide (II) was prepared in the best yield with methyl alcohol as solvent.

The condensations of the carbonyl compounds with the reagent II were carried out under the usual conditions. The alkaloid[8] salts of the 3-methylcyclohexylidene derivative were easily formed and easily interchanged, one of the advantages expected of this process. Resolution of the brucine salt was carried out with methyl alcohol as a solvent.[9] Control of temperature proved to be important. The optically pure derivative was hydrolyzed readily to give 1,3-methylcyclohexanone, which was characterized as the optically pure form by conversion to the semicarbazone.[3,10,11]

**Acknowledgment.**—We wish to express our appreciation for a Dow fund grant (one summer) (WBG), for John M. Glenn Grant-in-aids (two summers) (J. K. S.) and to the National Science Foundation for a grant (2 years) (J. K. S.) which made possible the completion of this work.

## Experimental[12]

***p*-Ureidobenzoic Acid.**—The details for the preparation of this product are reported here since those of Davis and Blanchard[6] are sketchy at best. To 23.4 g. (0.17 mole) of *p*-aminobenzoic acid in a blender, was added 21.0 g. (0.20 mole) of recrystallized nitrourea[13] and the mixture slurried with 200 ml. of water. The blended mixture was heated on a steam-bath for 3 hours, cooled in an ice–salt-bath and filtered; yield 25–26 g. (81–85%), m.p. 274–278° (sealed), neut. equiv. 181. A sample recrystallized from dimethylformamide–water gave m.p. 276–279° (sealed), neut. equiv. 180.

*Anal.* Calcd. for $C_8H_8O_3N_2$: N, 15.55. Found: N, 15.53.

**4-(4-Carboxyphenyl)-semicarbazide: (*p*-(3-Aminoureido)-benzoic Acid).**—A mixture of 27 g. (0.15 mole) of *p*-ureidobenzoic acid, 195 ml. of 95% methanol and 37.5 ml. (0.49 mole) of 100% hydrazine hydrate was refluxed in an oil-bath at 82–83°, for 48 hours, cooled and filtered. The filtrate, cooled in an ice–salt-bath, was adjusted to *p*H 4–5, using 10% hydrochloric acid and allowed to stand one hour. The precipitate was collected, washed there times with water and dried at 110°. The crude material was triturated with cold water, collected, and dried, a sufficient number of times to bring it to purity, following the change by neutral equivalent (dimethylformamide as solvent); yield 10–15 g. (34–51%). Pure material obtained in this manner gave m.p. 218–20° (sealed), neut. equiv. 195.

*Anal.* Calcd. for $C_8H_9O_3N_3$: N, 21.53. Found: N, 21.58.

**4-(4-Carboxyphenyl)-semicarbazone of Acetone.**—A mixture of 5 ml. of methanol, 5 ml. of dimethylformamide, 0.5 g. (0.003 mole) of 4-(4-carboxyphenyl)-semicarbazide, 0.5 ml. (0.007 mole) of acetone and 0.35 g. (0.002 mole) of sodium acetate was refluxed for 0.5 hour, cooled and 25 ml. of water added. The chunky white precipitate was collected, dissolved in 5% sodium bicarbonate, reprecipitated with glacial acetic acid, filtered, washed with water and dried; yield 0.44 (73%), m.p. 252–253° (sealed), neut. equiv. 234.

*Anal.* Calcd. for $C_{11}H_{13}O_3N_3$: N, 17.86. Found: N, 17.80.

**4-(4-Carboxyphenyl)-semicarbazone of Benzaldehyde.**—In 10 ml. of dimethylformamide, 0.6 ml. (0.006 mole) of benzaldehyde and 0.5 g. (0.003 mole) of 4-(4-carboxyphenyl)-semicarbazide were refluxed at 100° for 6 hours, cooled, the product forced out with water, collected, dissolved in 5% sodium hydroxide, extracted with ether, reprecipitated with glacial acetic acid, collected, and dried; yield 0.25 g. (22%), m.p. 266–268° (sealed), neut. equiv. 282.

*Anal.* Calcd. for $C_{15}H_{13}O_3N_3$: N, 14.83. Found: N, 14.91.

**4-(4-Carboxyphenyl)-semicarbazone of 3-Methylcyclohexanone.**—To a mixture of 40 ml. of 95% ethyl alcohol and 5.0 g. (0.026 mole) of 4-(4-carboxyphenyl)-semicarbazide, was added dropwise, 55 ml. of 0.5 *N* sodium hydroxide solution and the *p*H adjusted to 7 using glacial acetic acid; 3.5 ml. (0.028 mole) of 3-methylcyclohexanone was added, the mixture refluxed for 30 minutes, cooled, 100 ml. of water and 15 ml. of saturated salt solution added, extracted with two 30-ml. portions of ether and the aqueous layer acidified with glacial acetic acid. The fine white precipitate was collected and dried; yield, after one recrystallization from eth-

(4) R. Barre and L. Piche, *Can. J. Research*, **19B**, 158 (1941).

(5) J. Klarer and R. Behnisch, German Patent 832,891, March., 1952 (to Farbenfabriken Bayer).

(6) T. L. Davis and K. C. Blanchard, THIS JOURNAL, **51**, 1790 (1929).

(7) J. S. Buck and C. W. Ferry, *ibid.*, **58**, 854 (1936).

(8) The alkaloid samples were very kindly supplied by the Mallinckrodt Chemical Works and the New York Quinine and Chemical Works, Inc.

(9) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, pp. 506–508.

(10) R. Adams, C. M. Smith and S. Loewe, THIS JOURNAL, **64**, 2087 (1942).

(11) R. Adams and J. D. Garber, *ibid.*, **71**, 522 (1949).

(12) Melting points are corrected.

(13) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 417–418.

anol, 2.5–3.0 g. (33–40%), m.p. 247–249° (sealed), neut. equiv. 289.

*Anal.* Calcd. for $C_{15}H_{18}O_2N_3$: N, 14.52. Found: N, 14.54.

**Resolution of the 4-(4-Carboxyphenyl)-semicarbazone of *dl*-3-Methylcyclohexanone.**—A mixture of 1400 ml. of methanol and 17.7 g. (0.06 mole) of the 4-(4-carboxyphenyl)-semicarbazone of *dl*-3-methylcyclohexanone was brought to boil and 26.6 g. (0.06 mole) of brucine,[8] dissolved in a small amount of methanol, was added. Solution of the derivative occurred immediately; the volume was reduced to 1100 ml. and allowed to stand overnight on a slowly cooling steam-bath. Any crystalline formation was redissolved by heating, the solution filtered hot, reduced to 1000 ml. and cooled slowly in an oven constant at 30°. The fine yellow crystals thus obtained were recrystallized three times from methanol at a solvent ratio of 22–25 ml./g. of salt and using a second crop from the previous recrystallization added to the following mother liquor.[9] The optically pure product, as golden rosettes, decomposed erratically when melted. The yield was 10.1 g. (24%), $[\alpha]^{20}D$ −22.2° (*c* 0.397 chloroform, 1 dm.).

*Anal.* Calcd. for $C_{38}H_{45}O_7N_5$: N, 10.27. Found: N, 10.19.

Slurrying 2.0 g. of the salt in 20 ml. of water, acidifying with 2 ml. of glacial acetic acid, collecting and drying gave quantitative recovery of the derivative, neut. equiv. 290.

Refluxing of 9.7 g. of the pure salt for 10 minutes with 19 ml. of 9 *N* sulfuric acid, cooling, extracting with ether, drying and removing the ether, left a residual oil, b.p. 167–169°, $n^{20}D$ 1.4444 (Adams, Smith and Loewe[10] report b.p. 164–168°, $n^{20}D$ 1.4449), which was converted to the semicarbazone in the usual manner. After one recrystallization from methanol, this semicarbazone of *l*-3-methylcyclohexanone melted at 183°, $[\alpha]^{20}D$ + 20.6° (*c* 1.159 absolute ethanol, 1 dm.); Leonard and Boyer[3] reported m.p. 179–180°, $[\alpha]^{20}D$ +20.6°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

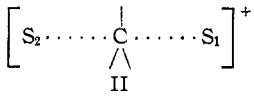
# Stereochemistry of the Primary Carbon. IX. Solvolysis of Optically Active 1-Butyl-1-*d* *p*-Nitrobenzenesulfonate in Dibutyl Ether–Acetic Acid[1-3]

BY A. STREITWIESER, JR., AND S. ANDREADES[4]

RECEIVED AUGUST 8, 1958

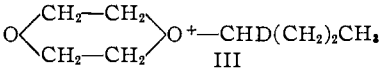
The acetolysis of optically active 1-butyl-1-*d* *p*-nitrobenzenesulfonate in 55% dibutyl ether–45% acetic acid (by volume) produces 71% of 1-butyl-1-*d* acetate with 97 ± 6% net inversion of configuration and 29% of undeuterated butyl acetate. The latter product presumably arises via a through a tributyloxonium ion intermediate. Under the reaction conditions 38% of the total product resulted from cleavage of the dibutyl ether by the *p*-nitrobenzenesulfonic acid produced in the solvolysis.

It has been previously demonstrated[5] that the solvolysis in acetic acid of optically active 1-butyl-1-*d* *p*-nitrobenzenesulfonate (I-*d*) proceeds with 85% inversion of configuration and 15% racemization. The significant amount of racemization which resulted was taken as evidence for the formation to some extent of symmetrically solvated primary carbonium ions (II, $S_1 = S_2$ = AcOH) in this system. The increased racemization found to result from the presence of dioxane or nitrobenzene was associated with the formation of carbonium ion intermediates (II) at least partially solvated by the addend solvent. The existence of II ($S_1 \neq S_2$) was inferred by



II

analogy with the II ($S_1 = S_2$) presumed to account for the racemization in pure AcOH.[6] The possible formation of intermediates such as the oxonium salt III in the dioxane case was recognized but was not determined. The formation and subsequent acetolysis of such intermediates in the mixed solvent would surely result in greater net racemization. Trialkyloxonium salts have been isolated and are known to be rather reactive.[7] Despite the many kinetic studies of solvolyses of various systems in solvents containing ethers, particularly dioxane, the possible role of such oxonium salts as



III

intermediates never has been evaluated. Alkoxy groups have been shown in many cases to provide neighboring group participation with the formation of cyclic oxonium ion intermediates[8]; these reactions, however, are intramolecular and involve a more favorable entropy change. In this paper we report experiments using deuterium simultaneously as an isotopic tracer and as a source of optical asymmetry which relate to the role of intermolecular oxonium ion formation in solvolysis reactions.

**Results and Discussion.**—1-Butanol-1-*d* having $\alpha^{25}D$ + 0.119 ± 0.008° (*l*4) was converted with acetyl chloride and pyridine to the acetate which had $\alpha^{25}D$ − 0.167 ± 0.003° (*l*2). The ratio of the rotations agrees within experimental error with values previously reported.[5] When the corresponding *p*-nitrobenzenesulfonate was solvolyzed in 55% dibutyl ether–45% acetic acid (by volume) for 5.5 half-lives at 100° the product acetate had $\alpha^{25}D$ + 0.071 ± 0.003° (*l*2), which corresponds to 42.5 ± 2.5% apparent net inversion (57.5 ± 2.5% racemization), but this product had lost 56 ± 1% of its deuterium. Hence, the 1-butyl-1-*d* acetate (IV-*d*)

(1) This paper was taken in part from the Ph.D. thesis of S. Andreades, University of California, 1958.

(2) Presented in part at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 16, 1958.

(3) This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

(4) National Science Foundation Predoctoral Fellow, 1957–1958.

(5) A. Streitwieser, Jr., and W. D. Schaeffer, THIS JOURNAL, **79**, 6233 (1957).

(6) See also E. D. Hughes, C. K. Ingold and A. D. Scott, *J. Chem. Soc.*, 1201 (1937); and A. Streitwieser, Jr., *Chem. Revs.*, **56**, 655 (1956).

(7) H. Meerwein, *et al.*, *J. prakt. Chem.*, **147**, 257 (1937); **154**, 83 (1939); *Ber.*, **89**, 2060 (1956).

(8) S. Winstein and R. B. Henderson, THIS JOURNAL, **65**, 2196 (1943); S. Winstein, C. R. Lindegren and L. I. Ingraham, *ibid.*, **75**, 147 (1953); D. S. Noyce and B. R. Thomas, *ibid.*, **79**, 755 (1957); S. Winstein, E. Allred, R. Heck and R. Glick, *Tetrahedron*, **3**, 1 (1958).