[Contribution from the Noyes Chemical Laboratory, University of Illinois]

5-(α-PHENYLETHYL)SEMIOXAMAZIDE AS A CARBONYL REAGENT

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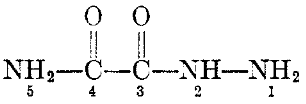
Received June 16, 1949

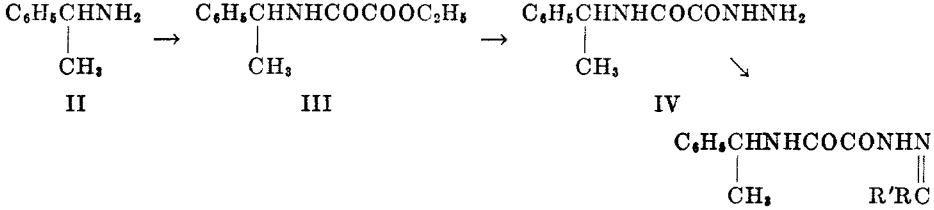
Derivatives (1) of semioxamazide (I) with carbonyl compounds possess the advantage of facile hydrolysis, thus permitting easy regeneration of the aldehyde or ketone. 5-Substituted semioxamazides have been suggested as reagents for the identification of carbonyl compounds, but 5-phenylsemioxamazide (2, 3) and 5-methylsemioxamazide (4) formed derivatives which had uniformly high melting points. We have found that representative carbonyl derivatives of 5-(α-phenylethyl)semioxamazide (IV) possess more satisfactory melting points. Optically active forms of this carbonyl reagent have also been obtained and the utilization of the asymmetric form in the resolution of carbonyl compounds has been demonstrated with 3-methylcyclohexanone.



$$\underset{5}{NH_2}—\underset{4}{\overset{\overset{O}{\|}}{C}}—\underset{3}{\overset{\overset{O}{\|}}{C}}—\underset{2}{NH}—\underset{1}{NH_2}$$

I

5-(α-Phenylethyl)semioxamazide (IV) was readily prepared from α-phenylethylamine (II), ethyl oxalate, and hydrazine. The reaction between α-phenylethylamine and ethyl oxalate at room temperature gave ethyl N-(α-phenylethyl)oxamide (III) in 91% yield, and that between III and hydrazine gave IV in 93% yield. 5-(α-Phenylethyl)semioxamazide formed derivatives (V) with numerous aldehydes and ketones, and the wide differences in the melting points of these derivatives suggest the feasibility of using this reagent for characterization purposes (see Table I).



$$\underset{\underset{CH_3}{|}}{C_6H_5CHNH_2} \rightarrow \underset{\underset{CH_3}{|}}{C_6H_5CHNHCOCOOC_2H_5} \rightarrow \underset{\underset{CH_3}{|}}{C_6H_5CHNHCOCONHNH_2} \searrow \underset{\underset{CH_3}{|}\qquad\quad \underset{R'RC}{\|}}{C_6H_5CHNHCOCONHN}$$

II III IV V

The optically active forms of 5-(α-phenylethyl)semioxamazide were readily obtained by the same process starting with *d*- and *l*-α-phenylethylamine. *l*-5-(α-Phenylethyl)semioxamazide was employed successfully for the resolution of 3-methylcyclohexanone. An optically pure derivative was obtained after five recrystallizations. This derivative was readily hydrolyzed to give *l*-3-methylcyclohexanone, which was characterized as the optically pure form by conversion to the semicarbazone (5). Other reagents which have been employed for the resolution of carbonyl compounds were mentioned by Woodward, Kohman and Harris (6) when they initiated the use of *l*-menthydrazide. Recently, Adams, and Garber (7) have introduced the bisulfites of optically active amines as aldehyde and ketone resolving agents. The *d* and *l* forms of 5-(α-phenylethyl)semioxamazide can now be added to those reagents which are applicable to carbonyl compound resolution.

EXPERIMENTAL

Ethyl N-(α-phenylethyl)oxamide. The preparation of this compound was carried out according to the method which Tierie (4) employed for the formation of ethyl N-methyloxamide. To 15 g. (0.12 mole) of distilled α-phenylethylamine in 150 cc. of absolute ethanol at room temperature was added slowly with stirring 38 cc. (0.25 mole) of distilled ethyl oxalate. The reaction mixture was allowed to stand for twenty-four hours, and a small amount of diamide was removed by filtration. Ethanol was removed by distillation, and unreacted ethyl oxalate, by vacuum-distillation. The residue, which solidified, was purified by recrystallization from absolute ethanol to give 23.2 g. (91%) of glistening colorless needles, m.p. 54°.

Anal. Calc'd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83.
Found: C, 64.86; H, 6.68.

5-(α-Phenylethyl)semioxamazide. The method of preparation was similar to that employed by Tierie (4). To a solution of 20 g. (0.10 mol) of ethyl N-(α-phenylethyl)oxamide in 200 cc. of absolute ethanol was added with stirring 6.0 g. (0.10 mole) of 85% hydrazine hydrate. A precipitate formed immediately and the entire contents of the reaction flask became a semi-solid mass. The crude product was dissolved in the minimum amount of hot 95% ethanol, and the solution was filtered to remove traces of the dihydrazide of oxalic acid. The very fine needles which separated from the filtrate were recrystallized from ethanol to give 20.5 g. (93%) of 5-(α-phenylethyl)semioxamazide, m.p. 157°.

Anal. Calc'd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28.
Found: C, 58.09; H, 6.27; N, 20.04.

Condensation of 5-(α-phenylethyl)semioxamazide with aldehydes and ketones. The procedure used by Wilson and Pickering (1) for preparing ketonic semioxamazones was found most successful. To 0.1 g. of the aldehyde or ketone in 20 cc. of anhydrous benzene was added 0.2–0.5 g. of the reagent. A crystal of iodine was added and the reaction mixture was refluxed for five to ten minutes (or until the disappearance of undissolved 5-(α-phenylethyl)semioxamazide). Rigorously anhydrous conditions were necessary for success in the formation of the ketone derivatives. The derivative usually crystallized out when the benzene solution was cooled. If the derivative was too soluble in benzene, the addition of low-boiling petroleum ether was used to cause precipitation. Aqueous ethanol was a satisfactory solvent for recrystallization of the aldehyde derivatives, but benzene or benzene-petroleum ether was necessary for the ketone derivatives, all of which were readily susceptible to hydrolysis. In Table I are recorded a number of representative products (all colorless needles) of 5-(α-phenylethyl)semioxamazide with aldehydes and ketones, formed under the conditions described above. It should be pointed out that under these conditions, a number of complex carbonyl compounds *failed* to give derivatives: benzoin, benzalacetophenone, benzil, mesityl oxide, acetoacetic ester, and levulinic acid.

Resolution of α-phenylethylamine. The method outlined briefly by Betti (8) and described in detail by Campbell, Houston, and Kenyon (9) was utilized for obtaining *l*-α-phenylethylamine. The directions given in "Organic Syntheses" (10) for the resolution of racemic α-phenylethylamine were used to obtain the *d* isomer.

d- and l-5-(α-Phenylethyl)semioxamazide. Following the procedure for the preparation of racemic 5-(α-phenylethyl)semioxamazide, the *d* and *l* forms were obtained from the corresponding optically pure forms of α-phenylethylamine in yields identical with those reported for the racemate.

d-5-(α-Phenylethyl)semioxamazide, m.p. 167–168°. A solution containing 1.0395 g. of the reagent in 100 cc. of chloroform gave α_D^{25} + 1.06° (*l*, 1), or $[\alpha]_D^{25}$ + 102.0°.

Anal. Calc'd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32.
Found: C, 57.99; H, 6.51.

l-5-(α-Phenylethyl)semioxamazide, m.p. 167–168°. A solution containing 0.6249 g. of the reagent in 100 cc. of chloroform gave α_D^{25} −0.64° (*l*, 1), or $[\alpha]_D^{25}$ −102.5°.

Anal. Calc'd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32.
Found: C, 57.98; H, 6.35.

Resolution of 3-methylcyclohexanone with l-5-(α-phenylethyl)semioxamazide. To a solution of 25 g. (0.2 mole) of 3-methylcyclohexanone in 50 cc. of benzene was added 21 g. (0.1 mole) of *l*-5-(α-phenylethyl)semioxamazide and a crystal of iodine. The mixture was refluxed a few minutes, or until a clear solution was obtained. The solution was concentrated and cooled, and the solid product thus obtained was recrystallized five times from benzene. The colorless needles melted at 179–180°, and the melting point did not change on further recrystallization. The yield of optically pure product was 4.1 g. (27%). A solution of 1.264 g. in 100 cc. of purified chloroform gave an initial reading of α_D^{25} −1.75° (*l*, 1), or $[\alpha]_D^{25}$ −139.0°. While the solution remained in the stoppered polarimeter tube, the rotation was observed to change gradually to a constant reading, after eight hours, of α_D^{25} −1.45°, or $[\alpha]_D^{25}$ −114.7°. Evaporation of this chloroform solution gave a solid, m. p. 179–180°, identical with the original derivative. When the solid was redissolved in chloroform, the shift in rotation during eight hours was again observed from $[\alpha]_D^{25}$ −139.0° to a constant value of −115.0°. Further recrystallization failed to eliminate this shift in rotation. The infrared absorption spectrum of the derivative was identical with that of the material which had remained eight hours in chloroform solution.

TABLE I

CARBONYL COMPOUND	M.P., °C.	RECRYST. SOLVENT	MOLECULAR FORMULA	ANALYSIS			
				Calc'd		Found	
				C	H	C	H
Derivatives of 5-(α-Phenylethyl)semioxamazide							
n-Butyraldehyde	154–155	ethanol	$C_{14}H_{19}N_3O_2$	64.37	7.33	64.30	7.60
Isovaleraldehyde	161–162	ethanol	$C_{15}H_{21}N_3O_2$	65.43	7.69	65.24	7.69
Furfural	221–222	ethanol	$C_{15}H_{15}N_3O_3$	63.15	5.30	63.44	5.47
Benzaldehyde	237	ethanol	$C_{17}H_{17}N_3O_2$	69.12	5.80	69.39	5.83
Cinnamaldehyde	248–249	ethanol	$C_{19}H_{19}N_3O_2$	71.01	5.96	70.97	6.19
Biacetyl	126–127	benzene	$C_{14}H_{17}N_3O_3$	61.07	6.23	61.60	6.37
Acetophenone	187	methanol	$C_{18}H_{19}N_3O_2$	69.88	6.19	69.82	6.00
Cyclohexanone	173–174	benzene	$C_{16}H_{21}N_3O_2$	66.88	7.37	67.04	7.45
Derivatives of *l*-5-(α-Phenylethyl)semioxamazide							
l-3-Methylcyclohexanone	179–180	benzene	$C_{17}H_{23}N_3O_2$	67.74	7.69	67.75	7.88
Cyclopentanone	161–162	benzene-pet. ether	$C_{15}H_{19}N_3O_2$	65.91	7.01	66.20	7.17
Cycloheptanone	142–143	benzene-pet. ether	$C_{17}H_{23}N_3O_2$	67.74	7.69	67.82	7.76
Formaldehyde	199–200	benzene-pet. ether	$C_{11}H_{13}N_3O_2$	60.26	5.98	60.22	6.04

Hydrolysis of the pure condensation product proceeded rapidly (a few minutes) when 0.8 g. was refluxed in an excess of 20% sulfuric acid. The solution was cooled and filtered free from hydrazine sulfate. The filtrate was extracted several times with 5-cc. portions of ether. The combined ethereal extracts were dried and the ether was removed. The residual oil was converted to the semicarbazone in the usual manner. After one recrystallization from ethanol, the *semicarbazone of l-3-methylcyclohexanone* melted at 179–180°. A solution in absolute ethanol gave $[\alpha]_D^{25}$ +20.6°. Adams, Smith, and Loewe (5) and Adams and Garber (7) reported $[\alpha]_D^{20}$ +20.8° for the semicarbazone of *l-3*-methylcyclohexanone.

SUMMARY

5-(α-Phenylethyl)semioxamazide has been investigated in its racemic form as a reagent for the characterization of aldehydes and ketones and in its optically active form as a resolving agent for carbonyl compounds possessing an asymmetric carbon atom.

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