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Formation of Girard-T Derivatives[1]

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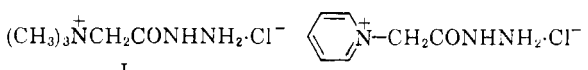
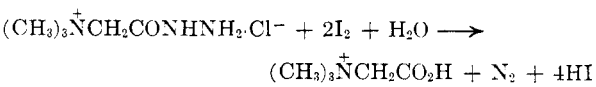
The Girard reagents,[3] Girard-T (I, *N*,*N*,*N*-trimethylammonium acetylhydrazine chloride) and Girard-P (II, pyridinium acetylhydrazine chloride), have been widely used for separating aldehydes and ketones from complex mixtures[4] since their introduction by Girard and Sandulesco in 1936, but no quantitative study has been made of the formation of Girard derivatives.



I II

Semicarbazide can be titrated iodometrically[5] and it seemed probable that the Girard reagents could be titrated similarly. An aqueous solution of the Girard-T reagent (I) is strongly acidic (*p*H 2) and reacts very slowly with iodine (Table I). However in a neutral buffer solution the reaction with iodine is rapid and corresponds to the utilization of two moles (4 g.-atoms) of iodine per mole of Girard-T reagent. Titrations at different *p*H (Table I) showed that there was an optimum *p*H for the reaction (*p*H 7–8); below this the reaction was very slow and incomplete and in strongly alkaline solution the iodine was consumed by the base. The stoichiometry of the reaction[5] is presumably the following:



Although the Girard-T reagent (I) can be readily determined in this manner, the Girard-P reagent (II) reacted incompletely with iodine in both acid and basic solution (Table II).

TABLE I

TITRATION OF GIRARD-T REAGENT

Buffer	*p*H	Ml. of 0.1*N* I_2 for 2 Ml. of 0.025*M* Girard	Ml. of 0.1*N* Thiosulfate for 2 Ml. of 0.1*N* I_2[a]
None	2	0.00	2.00
Chloride	2	0.00	
	3	0.04	
Acetate	4	1.00	
	5	1.02	
	6	1.05	
Phosphate	7	2.00	
	8	2.00	
	8.5	1.95	
	9	1.01	
Borate	9	0.60[b]	1.80
	10	0.40[b]	1.36

[a] With 10 ml. of buffer solution. [b] Corrected for blank.

TABLE II

TITRATION OF GIRARD-P REAGENT

Buffer	*p*H	Ml. of 0.05*N* I_2 for 2 Ml. of 0.04*M* Girard[a]	Same with 2½ × Excess I_2
Chloride	2	0.07	—
	3	0.13	0.37
Acetate	4	0.57	—
	5	0.55	—
	6	0.55	—
Phosphate	7	0.60	—
	8	0.65	1.58[b]
	9	0.78	—

[a] Solution titrated after 2–3 min. Theory 6.4 ml. [b] Used 2.95 ml. at 50°.

The kinetics of reaction of simple aldehydes and ketones with Girard-T reagent can be followed conveniently in 60% ethanol at 25° (Tables III and IV) by withdrawing samples at intervals, adding to an excess of iodine solution adjusted to *p*H 7 and titrating with thiosulfate in the usual manner. The reaction with cyclohexanone was essentially instantaneous in acid media at *p*H 3 and 25°, and measurements were accordingly made at *p*H 8 (Table III), where the reaction is much slower. The reactions showed good second order plots up to *ca.* 90%. The increases in rate in rate for cyclohexanone and cyclopentanone on increasing the temperature from 25° to 64° were only factors of 8 and 9, respectively, which corresponds to an energy of activation of 10.7 and 11.1 kcal/mole respectively.

TABLE III

RATES OF REACTION WITH CYCLIC KETONES[a]

	$k \times 10^4$ L. Mole^{-1} Sec.$^{-1}$ 25.0°	64.0°
Cyclohexanone	87	708
4-Methylcyclohexanone	55	—
Cyclopentanone	5.4	48
Cycloheptanone	5.8	—

[a] In 60% aqueous-ethanol at *p*H 8.5.

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(3) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

(4) *Cf.* A. Petit and S. Tallard, *Ind. Parf.*, **3**, 75 (1948).

(5) P. D. Bartlett, *J. Am. Chem. Soc.*, **54**, 2853 (1932).

TABLE IV

RATES OF REACTION WITH BENZALDEHYDES[a]

	$k \times 10^3$ L. Mole^{-1} Sec.$^{-1}$		
		*p*H 8.5	*p*H 6.0
	25.0°	64.0°	25.0°
Benzaldehyde	7.68	69.1	11.1
p-Anisaldehyde	2.30	14.5	16.1
p-Nitrobenzaldehyde	25.4	—	4.11

[a] In 60% aqueous ethanol.

Although the reactions at 25° proceeded to 100% completion, at 64.0° both cyclohexanone and cyclopentanone only reacted to 70–75% with a slight excess of Girard-T. This shows that the overall reaction is exothermic and suggests that it may be more convenient to prepare Girard derivatives by reaction at room temperature for a longer time.

The rates of reaction of benzaldehyde, *p*-anisaldehyde and *p*-nitrobenzaldehyde were similarly determined at 25° and at *p*H 6.0 and 8.5 (Table IV). Benzaldehyde and *p*-anisaldehyde showed increases of 9 and 6.5 times, respectively, on raising the temperature to 64° at *p*H 8.5, corresponding to energies of activation of 11.2 and 9.4 kcal/mole, respectively. In alkaline solution at 25° *p*-nitrobenzaldehyde reacted 3.3 times as fast as benzaldehyde, whereas *p*-anisaldehyde reacted at about $^1/_3$ the rate, while in acid solution *p*-anisaldehyde reacted 1.5 times as fast as benzaldehyde and *p*-nitrobenzaldehyde at about $^1/_3$ the rate.

Aqueous ethanol was not a suitable solvent for studying the reaction with high molecular weight ketones due to their low solubility. However 90%-isopropyl alcohol-water was found to dissolve sufficient inorganic salts to prepare buffered solutions. Steroid ketones were also reasonably soluble in this solvent and the rate of reaction of 3-cholestanone with Girard-T reagent at 25° and at various *p*H (buffers, chloride *p*H 2.0, 3.5, acetate *p*H 4.5, 5.5 and phosphate pH 8.5) has been determined (Table V).

TABLE V

RATES OF REACTION OF 3-CHOLESTANONE[a]

*p*H	$k \times 10^3$ L. Mole-1 Sec.$^{-1}$
2.0	4.2
3.5	1020
4.5	960
5.5	5.9
8.5	0.74

[a] In 90% isopropyl alcohol-water at 25.0°.

The reaction was extremely slow in alkaline-medium, but very rapid at *p*H 3.5. The rate, however, decreased again at higher acidity since the reaction is reversible and the hydrolysis of the Girard derivative is catalyzed by strong acids.[6]

(6) O. H. Wheeler and O. Rosado, forthcoming publication.

The first 80% or so of the reaction with 3-cholestanone followed second order kinetics, but steroid ketones were found to react with more than one equivalent of Girard-T reagent in isopropyl alcohol. The nature of this reaction and other aspects of reactions with steroid ketones will be discussed in a forthcoming publication.

EXPERIMENTAL

Titration of Girard-T reagent. Girard-T reagent (Arapohoe Chemicals) was recrystallized twice from ethanol and stored in a desiccator.

Various aqueous buffer solutions were prepared of total concentration 0.2*M* from A.R. salts. The phosphate buffer (*p*H7) used for the titrations was 0.62*M* disodium hydrogen hydrogen phosphate and 1*M* sodium hydrogen phosphate. Blank titrations of these buffers and the titration and the Girard-P are given in Tables I and II.

Kinetic measurements. The freshly distilled or recrystallized aldehyde or ketone (*ca.* 0.5 mM) was dissolved in absolute ethanol (10 ml.) (isopropyl alcohol in the case of 3-cholestanone), aqueous phosphate buffer *p*H7 (20 ml.) added and the solution allowed to attain thermal equilibrium in a constant temperature bath at 25° (or a boiling methanol bath at 64°), and 0.0125*M* Girard-T reagent in absolute ethanol (20 ml.) at the same temperature added. The resultant solution had an apparent *pH* of 8.5 (glass electrode). Aliquots (5 ml.) were withdrawn at intervals added to 0.05*N* iodine solution (5 ml.) in phosphate buffer *p*H7 (10 ml.), and the excess iodine titrated with 0.05*N* sodium thiosulfate using starch as indicator.

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Synthesis of Some Sulfur-Containing Acids and Their Derivatives. I. Derivatives of 10-Undecenoic Acid

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This paper reports the synthesis and reactions of some alkane bis(11-mercaptoundecanoic) acids. The alkane bis(11-mercaptoundecanoic) acids were prepared by the addition of alkane dithiols to 10-undecenoic acid under free radical conditions. The acids were esterified by methanol and oxidized to the corresponding disulfones by hydrogen peroxide in the presence of glacial acetic acid. The alkane bis(11-mercaptoundecanoic) acids were oxidized to the corresponding disulfone acids by hydrogen peroxide, and these compounds were then esterified by methanol.