CHAPTER IV

Silica-Gel Supported Semicarbazide and Girard-T Reagents

SILICA-GEL SUPPORTED SEMICARBAZIDE AND GIRARD-T REAGENTS

Abstract —— Semicarbazide-on-silica gel and Girard-T-on-silica gel are described and evaluated as convenient reagents for efficient isolation of aldehydes and ketones from mixtures with other usual neutral organic components. Semicarbazide-on-silica gel, which can be readily prepared, can effectively replace the classical Girard reagents, for the isolation of aldehydes and ketones in most cases.

SILICA-GEL SUPPORTED SEMICARBAZIDE AND GIRARD-T REAGENTS[++]

To deal with the problem of isolation of certain carbonyl compounds (aldehydes, ketones) from natural mixtures such as essential oils, plant extracts or mammalian physiological products, in which these compounds may occur only in trace quantities, a number of reagents have been developed,[1] of which the Girard reagents[1] have proved to be outstanding. In connection with our work[2] on the pharmacologically-active constituents of the Ayurvedic crude drug, Guggulu (gum- exudate from the tree *Commiphora mukul* Engl.), a need arose for the segregation of the neutral fraction into ketonic and non-ketonic cuts. Though, the separation could be effectively achieved[2e] with Girard-p reagent, the acid labile diterpenoids[2b] in the non-ketonic portion underwent extensive dehydration/isomerization, even under the rather mild conditions[3] involving use of an acid ion-exchange resin. To overcome this handicap[4] attention was directed towards the development of a reagent which could be used under neutral or slightly basic conditions,[5] Efforts were made to support this reagent in a solid matrix[6], such that the non-ketonic/non-aldehydic material would stay

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[++] *Tetrahedron*, in press

in the solution phase, when the condensation is carried out in a non-polar solvent, like hexane/toluene in which the semicarbazones are invariably insoluble.[7] Now the preparation and use of such a reagent, which permits separation of these carbonyl compounds from other neutral components in an expeditious manner, even on a large scale is described.[8] Separations with Girard-T-on-silica gel, which is equally effective, but has no special advantages over the more readily accessible semicarbazide-on-silica gel reagent have also been described in this Chapter.

1. Semicarbazide on silica gel

Using a 10% soln. of (-)-menthone in p-menthane as test material, preparations of semicarbazide-on-silica gel having silica gel/semicarbazide ratios of either 9:1 or 4:1, and prepared as described under Experimental, were evaluated (Table 1) to determine which ratio was more suitable as well as what was the molar equivalence of the reagent (in terms of active component) for complete removal of the ketone.[9] The reaction was carried out by heating the test material and the reagent in hexane at ~70° for 12 hr. The results have been summarised in Table 1. It is clear from Table 1 that a silica gel/

TABLE 1. Determination of molar equivalence: reaction[a] of menthone at 70° by various molar equivalents of semicarbazide on different amounts of silica-gel.

No.	Silica gel/ semicarbazide ratio	Mole equivalent of semicarbazide per one mole of menthone	Amount of menthone (%, GLC) in the soln. phase
1	9 : 1[b]	1.0	2.9
2	"	1.25	2.7
3	"	1.50	1.9
4	"	1.75	1.4
5	"	2.00	0.7
6	"	2.50	0.0
7	4 : 1[c]	1.00	3.4
8	"	1.50	2.2
9	"	2.00	1.6
10	"	3.00	0.9
11	"	3.00	0.0

[a] Reaction on a one mmole scale (hexane, 70 ± 2°, 12 hr).

[b] 1g of supported reagent ≡ 0.0542g of semicarbazide
≡ 0.723 mmole of semicarbazide

[c] 1g of supported reagent ≡ 0.105g of semicarbazide
≡ 1.40 mmole of semicarbazide.

semicarbazide ratio of 9:1 and a molar equivalence of 2.5 is quite suitable for the purpose on hand, and hence all further work was carried out using this preparation and conditions.

To evaluate the efficacy of the reagent, four more test mixtures (Table 2, entries 2-5) were subjected to separation by this method. In each case, the solution phase was analysed by GLC for the carbonyl component and the solid phase treated for the regeneration of the carbonyl compound. Though, a number of methods are available[10] for the regeneration of the carbonyl compound from its semicarbaze, we find stirring and refluxing of the solid phase with toluene/heptane and ~6% oxalic acid aq.[10b,11] most convenient and effective. It is clear from the data presented in Table 2, that the reagent is quite effective for the isolation of both aldehydes and ketones.

Further, the reagent was evaluated for the isolation of aldehydes/ketones from neutral mixtures. The essential oils of <u>Cedrus deodara</u> Loud. (wood),[12] <u>Cyperus rotundus</u> Linn. (tubers),[13] and <u>Eucalyptus citriodora</u> Hook. (leaves and terminal branchlets)[14] have been well-investigated for their ketones/aldehydes and these compounds have been well-characterised.[15] Table 2 summarises the results obtained

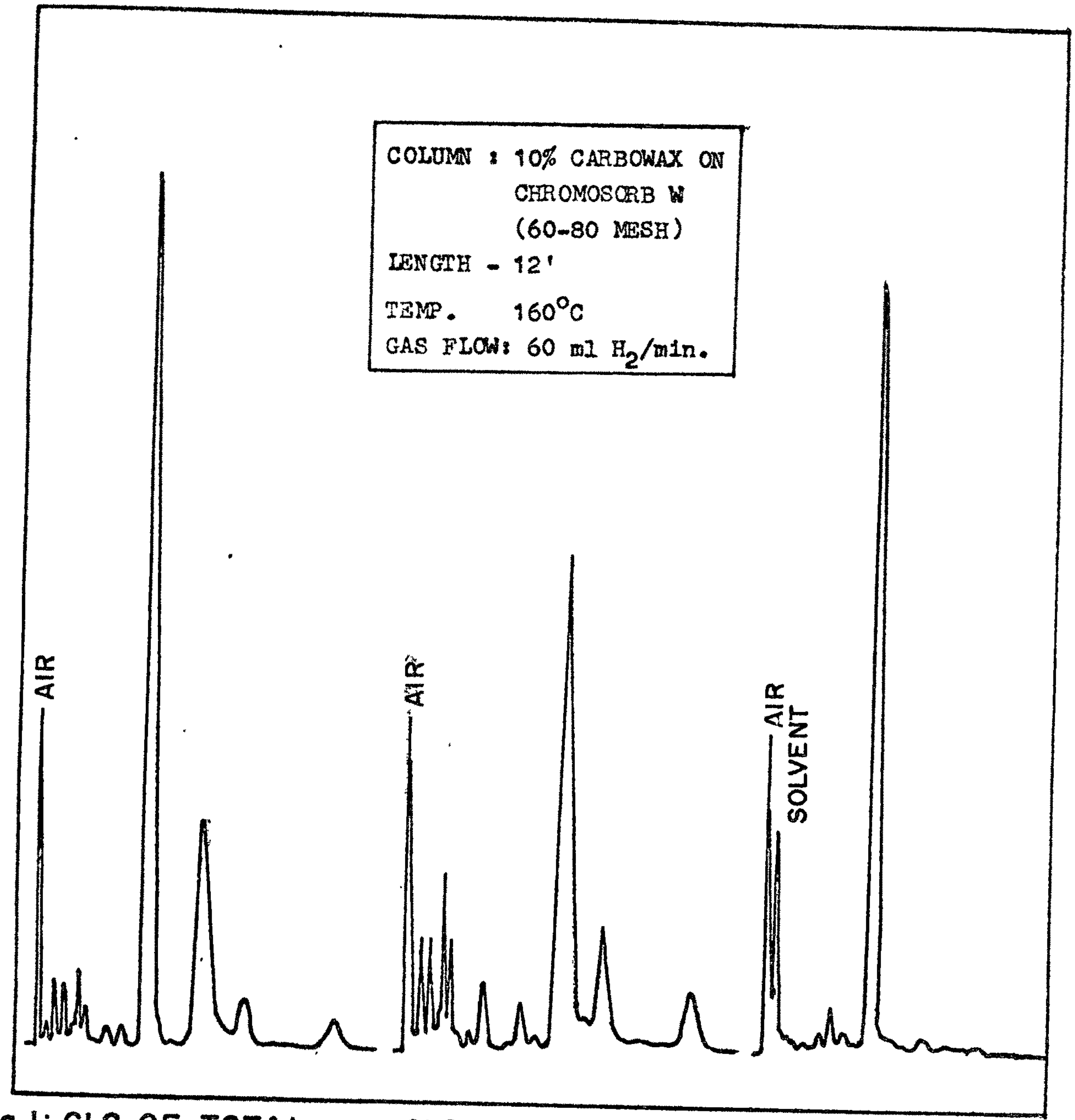

Fig.1: GLC OF TOTAL ESSENTIAL OIL OF EUCALYPTUS CITRIODORA HOOK

GLC OF NON-KETONIC PORTION

GLC OF KETONIC PORTION

TABLE 2. Isolation of aldehydes/ketones from test mixtures by reaction[a] with semicarbazide-on-silica gel

No.	Test Mixture (Aldehyde/ketone content, %)[b]	Material Recovery[c]			
		Carbonyl part		Non-carbonyl part	
		Wt (%)	Aldehyde/ ketone content, %[b]	Wt (%)	Aldehyde/ ketone content, %[b]
1	(-)-Menthone in p-menthane (10%)	94	100	92	0.0
2	Benzaldehyde in p-menthane (10%)	65[d]	100	90	0.0
3	Cinnamaldehyde in p-menthane (10%)	78[d]	98	91	0.0
4	(+)-Carvone in p-menthane (10%)	93	98	93	0.2
5	β-Ionone in p-menthane (10%)	93	96	97	0.0
6	Essential oil: *Cyperus rotundus* (∿30%)	97	90	97	1.2
7	Essential oil: *Cedrus deodara* (∿40%)	96	90	93	0.5
8	Essential oil: *Eucalyptus citriodora* (∿63%)	74[d]	90	88	0.0
9	Neutral EtOAc extract of *Commiphora mukul* gum-resin (∿13%)	94	100	97	-

[a] Reaction on one mmole scale of aldehyde/ketone present in the mixture using 2.5 molar equivalents of reagent; solvent hexane except for entry 9, where toluene was used; temp., 70 ± 2°; time, 12 hr, except for entry 9, where reaction was carried out for 18 hr.

[b] For natural mixtures, the % is based on GLC (for essential oils), since the aldehyde/ketone components of these oils are well-known (see Text); for entry 9, the ketone content is based on isolation with Girard-P reagent.[2e]

[c] Represents isolated products, after distillation.

[d] Low recoveries are due to formation of the corresponding acid during the regeneration step; no special precautions were taken to avoid oxidation.

with these materials and as is evident, the reagent has given gratifying results. The GLC of the product (ketonic/non-ketonic) isolated from oil of *Eucalyptus citriodora* with this reagent is given in Fig. 1.

The gum-resin of *Commiphora mukul* Engl. contains a number of steroidal ketones, which have been earlier isolated by column chromatography.[2a] The neutral ethyl acetate extract of this material on treatment with Girard-D-reagent, in the usual manner,[3] gave the ketone fraction in a yield of 13% (w/w);[2e] the application of semicarbazide-on-silica gel for the isolation of these ketones gave a product of comparable purity (TLC; solvent: 25% EtOAc in C_6H_6) in almost the same yield (Table 2).

2. Girard-T on silica gel

The Girard-T (trimethylammonium acetylhydrazide chloride) was first prepared by A. Girard and G. Sandulesco.[1] The reagent was used by its discoverers to separate estrone from urinary extract and later by Reichstein with considerable success to separate the adrenal cortex steroids.[1] One disadvantage of Girard-T is its extremely hygroscopic nature and instability.[1] Conceivably, this handicap could be overcome by supporting it in a suitable solid matrix. It has been found that when Girard-T is supported on silica gel, in the manner outlined in the Experimental, is a stable non-hygroscopic reagent, which is convenient to handle for the isolation of aldehydes ketones. Aldehydes and ketones react on heating with Girard-T reagent in methanol in the presence of acetic acid for 20-30 minutes, or upto 1 hr or even 12 hr in case of less reactive ketones.[1] Use of acetic acid may not be good especially for some hydroxy groups containing steroid ketones, since hydroxy group under the condition of reaction, is likely to get acylated. Moreover, it has been found that with silica gel supported Girard-T reagent, no acid catalyst is necessary in the condensation reaction with carbonyl compounds.

To arrive at a convenient and useful silica gel/Girard-T ratio and to determine the molar equivalence of the resulting reagent for complete removal of the carbonyl component(s), studies exactly similar to those summarised in Table 1 for semicarbazide-on-silica gel were carried out. A silica gel/Girard-T ratio of 9:1 and a molar equivalence of 2.0 was found to be adequate. Results are depicted in Table 3.

This preparation was next evaluated for the isolation of β-ionone from a test mixture (10% β-ionone in p-menthane) and results compared with those obtained by using Girard-T reagent in the usual manner.[3] Girard-T-on-silica gel gave a 92% recovery of the ketone of 95% purity (GLC), where as the usual procedure furnished a material of 97% (GLC) purity in 84% yield. Thus, the performance of the Girard-T-on-silica gel reagent was quite comparable. In this context, it may be noted that recovery and purity of the product with semicarbazide-on-silica gel (Table 2, entry 5) was also similar.

Girard-T-on-silica gel was next used for the isolation of aldehydes/ketones from the same test mixtures (entries in Table 2) and results have been uniformly good (Table 4).

In view of the above results, both semicarbazide-on-silica gel and Girard-T-on-silica gel, and especially the former, are recommended for the separation of aldehydes and ketones from other usual neutral constituents. Chief advantages are: condensation is carried out in a convenient simple manner under essentially neutral conditions, and the exceptional ease of work-up.

TABLE 3. Determination of molar equivalence: reaction[a] of menthone at 70° by various molar equivalents of Girard-T on different amounts of silica-gel

No.	Silica gel/ Girard-T ratio	Mole equivalent of Girard-T per one mole of menthone	Amount of menthone (%, GLC) in the soln. phase.
1	9 : 1[b]	1.0	4.2
2	"	1.5	2.1
3	"	2.0	0.0
4	4 : 1[c]	1.0	8.2
5	"	1.5	4.3
6	"	2.0	1.8

[a] Reaction on a one mmole scale (hexane, 70 ± 2°, 12 hr)

[b] 1 g of supported reagent ≡ 0.0952 g of Girard-T ≡ 0.5685 mmole of Girard-T

[c] 1 g of supported reagent ≡ 0.1904 g of Girard-T ≡ 1.1367 mmole of Girard-T

Table 4. Isolation of aldehydes/ketones from test mixtures by reaction[a] with Girard-T-on-silica gel

No.	Test mixture (Aldehyde/ketone content, %)[b]	Material Recovery[c] Carbonyl part Wt(%)	Aldehyde/ketone content,%[b]	Non-carbonyl part Wt. (%)	Aldehyde/ketone content,%[b]
1.	(-)-Menthone in p-menthane (10%)	92	100	91	0.0
2.	Benzaldehyde in p-menthane (10%)	71	100	94	0.0
3.	Cinnamaldehyde in p-menthane (10%)	83	100	96	0.0
4.	(+)-Carvone in p-menthane (10%)	89	98	93	0.0
5.	β-Ionone in p-menthane (10%)	92	95	95	0.0
6.	Essential oil: *Cyperus rotundus* (30%)	94	89	93	4.0
7.	Essential oil: *Cedrus deodara* (40%)	93	92	93	2.0
8.	Essential oil: *Eucalyptus citriodora* (63%)	75	94	87	0.0
9.	Neutral EtOAc extract of *Commiphora mukul* gum-resin (13%)	98	100	95	-

[a] Reaction on one mmole scale of aldehyde/ketone present in the mixture using 2.0 molar equivalents of reagent; solvent hexane except for entry 9, where toluene was used; temp., 70 ± 2°.

[b] For natural mixtures, the % is based on GLC (for essential oils), since the aldehyde/ketone components of these oils are well-known (see Text); for entry 9, the ketone content is based on isolation with Girard-P reagent.[2e]

[c] Represents isolated products, after distillation.

3. EXPERIMENTAL

For general remarks see Chapter II.

All compounds described in this Chapter are known and after recovery from mixtures were distilled and the product recognized by IR, PMR and purity established by GLC (TLC).

3.1. Materials

Silica gel: The material as supplied by Beechem, Kanpur, was sieved and the fraction -80, + 200 mesh (bulk density, 0.71 g/ml) employed as the support.

Girard-T: Girard-T was prepared according to a standard procedure.[16]

Semicarbazide hydrochloride, oxalic acid, sodium hydroxide, hydrochloric acid (aq.), were all reagent grade.

Hexane, heptane were purified,[17] before use. All other solvents were distilled before use.

3.2. Preparation of reagents

3.2.1. (i) Semicarbazide-on-silica gel: Semicarbazide hydrochloride (5.0g; 0.045 mole) was added to a solution of NaOH (2.0g; 0.05 mole) in water-methanol (1:1; 60 ml) and to the resulting clear solution, silica gel (45 g) was introduced with stirring. The whole mixture was mechanically shaken (1 hr) at room temperature (30-35°) and water-methanol removed on a rotary evaporator (~90°/80-90 mm; 30-45 min) to get a white free-flowing powder. This material should weigh 60-63 g. The product is stored in a brown bottle at room temp. A two year old product had undergone no deterioration.

3.2.2. (ii) Girard-T-on-silica gel: To a solution of Girard-T (5.0g; 0.0299 mole) in *t*-BuOH and water (1:1; 60 ml), silica gel (45 g) was added and the mixture mechanically shaken for 1 hr at room temperature (30-35°). Most of *t*-BuOH/water were removed on a rotary evaporator (~90°/80-90 mm; 1 hr) to get a white free-flowing powder, which should weigh 52-55g. This material can be stored in a dark bottle at room temperature, without any deterioration (1 yr). When the yield of the reagent is 52.5 g, 1.0 g of it is equivalent to 0.0952 g of Girard-T (≡ 0.5685 mmole).

3.3. General procedure for Condensation

3.3.1. (i) With semicarbazide-on-silica gel: An amount of material containing ∼1 mmole of the ketone/aldehyde is dissolved in hexane or toluene (7 ml), and to the resulting soln. 3.5 g of reagent (1.0 g ≡ 0.0542 g of semicarbazide; 2.5 mmole semicarbazide) is added. The mixture is heated (70 ± 2°) and stirred for 12-18 hr and the absence of the carbonyl compound in the solution phase ensured by TLC (spray: 10% 2,4-dinitrophenylhydrazine in HCl aq.). The reaction mixture is cooled, filtered and the solid washed with the same solvent (5 ml x 4; at room temp.) The filtrate and washings are combined and processed in the usual manner for the non-carbonyl portion, while the solid part is treated for the regeneration of the aldehyde/ketone (see below).

3.3.2. (ii) With Girard-T-on-silica gel: The procedure as detailed above is followed except that Girard-T-on-silica gel (2.0 molar equivalent) is used instead of the semicarbazide reagent.

3.4. General procedure for regeneration

3.4.1. From semicarbazones: The solid phase containing the semicarbazone (∼1 mmole) is added to a solution of oxalic acid (0.9 g; 10 mmole) in water (16 ml), covered with a layer of heptane or toluene (10 ml) and the reaction mixture, stirred and refluxed for 4-5 hr. After cooling, the solvent and aqueous part are removed by decantation and the silica gel washed with heptane/toluene (5 ml x 2). The combined solvent layer is separated, the aqueous part extracted with the same solvent (10 ml x 2) and the extracts mixed with the main extract. The total solvent solution is washed with water (10 ml x 2), brine (5 ml), dried (Na_2SO_4) and the solvent removed at ~80°/200 mm through a short Vigreux column to get the regenerated carbonyl compound, which is appropriately processed further.

3.4.2. From Girard hydrazones: The solid phase containing the hydrazone (~1 mmole) is added to hydrochloric acid (aqueous, 10% v/v; 15 ml), covered with ether (15 ml), well-swirled and the whole allowed to stand overnight (~12 hr) at room temperature (~25°). Ether and aqueous layer were decanted out and separated. Aqueous layer was again extracted with ether (10 ml x 2). The combined ether layer and extracts were given wash with water (10 ml x 2), brine (5 ml) and dried (Na_2SO_4). Careful removal of the solvent on steam bath and distillation of the residue afforded the desired product.

4. REFERENCES AND NOTES

1. See e.g.: [a]O.H. Wheeler, Chem. Rev. 62, 205 (1962); [b]O.H. Wheeler, J. Chem. Educ. 45, 435 (1968).

2. [a]V.D. Patil, U.R. Nayak and Sukh Dev, Tetrahedron 28 2341 (1972); [b] V.D. Patil, U.R. Nayak and Sukh Dev, ibid. 29, 341 (1973); [c]V.D. Patil, U.R. Nayak and Sukh Dev, ibid. 29, 1595 (1973); [d]R.S. Prasad and Sukh Dev, ibid. 32, 1437 (1976); [e]A.G. Bajaj, Ph.D. Thesis, M.S. University, Baroda (1980).

3. C.L. Teitelbaum, J. Org. Chem. 23, 646 (1958).

4. Dehydration/isomerization of certain hydroxy- and olefinic-ketones have been noted both at the condensation stage and at the stage of hydrolysis of the Girard hydrazones.[1]

5. See e.g.: P. Anziani, Bull. Soc. Chim. Fr. 6, 954 (1944); D.E. Pearson, K.N. Carter and C.M. Greer, J. Am. Chem. Soc. 75, 5906 (1953).

6. See: R.P. Singh, H.N. Subbarao and Sukh Dev, Tetrahedron 35, 1789 (1979).

7. This limits the application of the reagent to ketone/aldehyde-containing materials that are soluble in non-polar solvents such as hexane, toluene, etc.

8. The semicarbazide-on-silica gel has been used to get 90 g of ketones from 725g of the guggulu extract per batch.[2e]

9. This investigation was necessary, as conceivably some amount of the semicarbazide may not be available for semicarbazone formation, because of location at sites, in the silica gel matrix, which may be inaccessible to the aldehyde/ketone.

10. See e.g.: [a]L. Ruzicka, M.W. Goldbery and H. Brungger, Helv. Chim. Acta 17, 1389 (1934); [b]L. Ruzicka, M.W. Goldberg, J. Meyer, H. Brungger and E. Eichenberger, ibid. 17, 1395 (1934); [c]E.B. Hershberg, J. Org. Chem. 13, 542 (1948); [d]St. Goldschmidt and W.L.C. Veer, Rec. Trav. Chim. 65, 796 (1946); [e] V.R. Mattox and E.C. Kendall, J. Am. Chem. Soc. 70, 882 (1948); [f]D.H.R. Barton, D.J. Lester and S.V. Ley, Chem. Comm. 445 (1977).

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13. [a]A.E. Bradfield, B.H. Hegde, B.S. Rao, J.L. Simonsen and A.E. Gillam, J. Chem. Soc. 667 (1936); [b]V.H. Kapadia, V.G. Naik, M.S. Wadia and Sukh Dev, Tetrahedron Letters 4661 (1967).

14. P.S. Rao and K. Bhatia, Indian Forester 84, 162-63 (1958).

15. Authentic samples of atlantone (Cedrus deodara),[12b] α-cyperone (Cyperus rotundus)[13b] and citronellal (citronella oil)[14], which constitute the major carbonyl components of the respective oils, were available.

16. A. Girard, Organic Synthesis, Coll. vol. II, p. 85 (1969).

17. N.A. Sorensen, Chemist-Analyst 44, 24 (1955).