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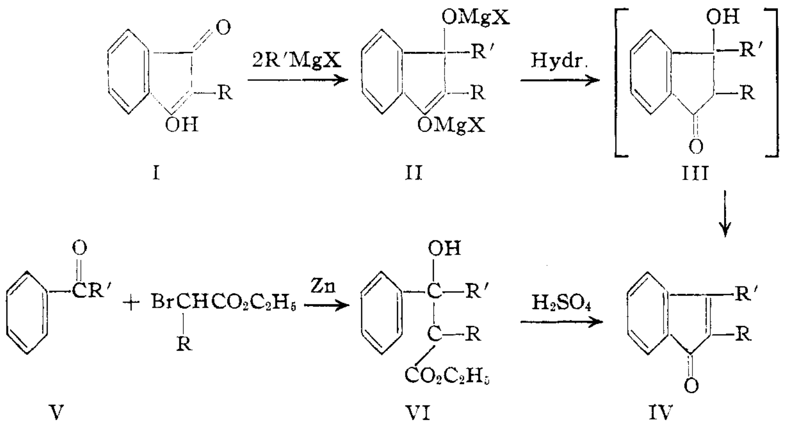
Some 2,3-Disubstituted Indones

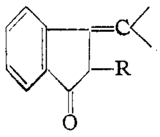
BY ROBERT L. FRANK, HENNING EKLUND, JOHN W. RICHTER, CLINTON R. VANNEMAN AND ARNOLD N. WENNERBERG

2,3-Disubstituted indones have been reported to be activators for alcoholic fermentation. According to Pirrone,[1] 2-ethyl-3-phenylindone, 2-methyl-3-phenylindone and 2,3-diphenylindone increase the rate of alcoholic fermentation by as much as 18%. The present research was undertaken in the hope of discovering other compounds that would produce this effect. Nine 2,3-disubstituted indones have been synthesized in which the substituents are alkyl, aryl or substituted aryl groups.

The indones in which the substituent on the 2-position is aromatic were prepared by the addition of excess Grignard reagent to 2-substituted indanediones according to the method employed by Jacobi[2] and by Koelsch[3] (I–IV). Those in which the substituent on the 2-position is aliphatic were prepared by the Reformatsky reaction followed by simultaneous dehydration and ring closure by means of concentrated sulfuric acid (V–VI–IV). This method has been carried out successfully by de Fazi.[4]



When the substituent in the 3-position is a primary or secondary aliphatic group, it is possible for the dehydration of the β-hydroxy ketone (III) to take place in such a way as to form the indone (IV) or the isomeric alkylidene indanone (VII).



VII

Weiss and Alberti[5] have shown that both types of dehydration products form when 2-phenylindane-1,3-dione is treated with benzylmagnesium chloride and the resulting product is dehydrated.

To establish definitely the structures of the indones of this type, the position of the double bond in 3-ethyl-2-phenylindone was determined by ozonolysis. Ozonization in acetic acid yielded two crystalline products. One of these was colorless and gave the correct combustion analysis for the ozonide (VIII). The other was yellow and had the composition of *o*-propionylbenzil (IX). This compound could only arise from the indone (IV) and not from the alkylidene indanone (VII).

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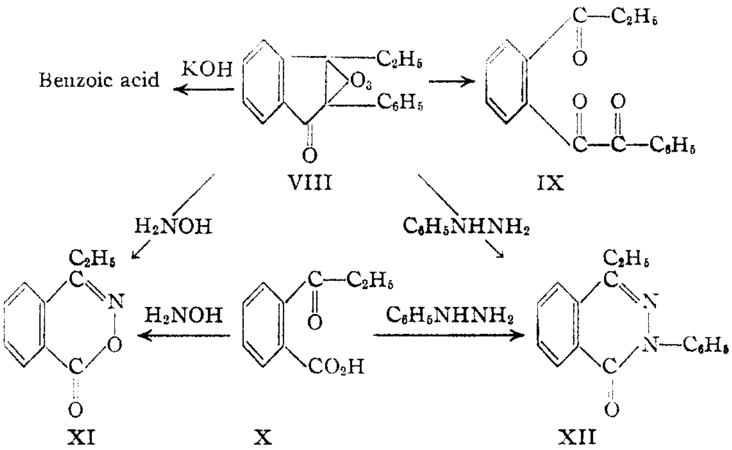
[1] Pirrone, *Ann. chim. appl.*, **22**, 501 (1932); *C. A.*, **27**, 159 (1933).

[2] Jacobi, *J. prakt. Chem.*, **129**, 55 (1931).

[3] Koelsch, THIS JOURNAL, **58**, 1331 (1936); **65**, 1639 (1943).

[4] de Fazi, *Gazz. chim. ital.*, **45**, II, 143 (1915).

[5] Weiss and Alberti, *Monatsh.*, **59**, 220 (1932).



The ozonide from 3-ethyl-2-phenylindone was a remarkably stable compound, melting at 93° with no decomposition. It burned evenly and did not explode when heated in a flame. Treatment with hydrogen and platinum oxide for a long period did not alter it. These properties are perhaps due to the hindrance which might be expected from the groups around the double bond in 3-ethyl-2-phenylindone. Boiling with water converted the ozonide to a yellow oil, presumably due to the formation of the triketone (IX).

Alkaline hydrolysis of the ozonide yielded benzoic acid in 95% yield assuming the formation of one mole from each mole of ozonide. No *o*-propionylbenzoic acid (X), a product which might be expected from the cleavage of the ozonide (VIII), could be isolated from the reaction mixture.

Treatment of the ozonide with hydroxylamine hydrochloride resulted in the formation of a colorless crystalline product which showed no depression in melting point when mixed with a sample of the known 4-ethyl-1-keto-2,3,1-benzoxazine (XI).[6] The latter was obtained by the method of Daube[7] from hydroxylamine and *o*-propionylbenzoic acid (X). *o*-Propionylbenzoic acid (X) can be derived from the indone (IV) but not from the alkylidene indanone (VII).

The ozonide was also heated with phenylhydrazine and a crystalline product was isolated. The same product was obtained when *o*-propionylbenzoic acid (X) was heated with phenylhydrazine. The compound is evidently 1-ethyl-3-phenylphthalazone (XII), although it melts at 111–112°, whereas Gottlieb[8] reported a melting point of 102°.

Ultraviolet absorption spectra also indicate the structure IV rather than VII for these compounds. The spectrum of 3-ethyl-2-phenylindone shows a maximum at 255 mμ (log ϵ = 4.765 in 95% ethanol), very near the maximum of 259 mμ (log ϵ = 4.702 in 95% ethanol) in the spectrum of 2,3-diphenylindone, in which the double bond is definitely fixed.

Tests on these compounds as activators for alcoholic fermentation are being carried out by Dr. F. M. Clark of the Department of Bacteriology of this University and the results will be reported elsewhere.

Experimental

2-Phenylindane-1,3-dione.—This compound was prepared by the method of Nathanson[9] from 66 g. (0.30 mole) of benzalphthalide and 9 g. (0.39 mole) of sodium dissolved in 600 cc. of absolute methanol. The yield was 63.0 g. (95%), m. p. 144–145°.

2-Anisyl- and 2-Veratrylindane-1,3-diones.—2-Anisylindane-1,3-dione was prepared by the method of Koelsch[3] using 85 g. (0.634 mole) of phthalide, 85 g. (0.625 mole) of anisaldehyde and 20.5 g. (0.891 mole) of sodium dissolved in 400 cc. of absolute ethanol. The yield of product melting at 153–154° was 54.5 g. (34.6%).

2-Veratrylindane-1,3-dione was prepared in a similar manner from 100 g. (0.746 mole) of phthalide, 120 g. (0.723 mole) of veratric aldehyde and 20.5 g. (0.891 mole) of sodium in 400 cc. of absolute ethanol. The yield of light yellow needles, m. p. 188–190°, was 68.0 g. (33.4%).

Anal.[10] Calcd. for $C_{17}H_{14}O_3$: C, 72.33; H, 5.00. Found: C, 72.60; H, 5.21.

Preparation of Indones by Addition of Grignard Reagents to Indanediones.—The indones prepared by this means are the first seven in Table I, in which the substituent on the 2-position (IV) is aromatic.

The Grignard reagents were prepared in amounts of 0.15 to 0.25 mole in three-necked round-bottomed flasks equipped with efficient stirrers. Equimolar amounts of magnesium and the organic halide were used in 200–400 cc. of anhydrous ether. The indanediones, dissolved in 200–400 cc. of anhydrous benzene or toluene, were added in one-fourth to one-third the molar amounts of Grignard reagent and the solutions were refluxed for one to two hours. It was necessary to use large amounts of benzene or toluene to dissolve the indanediones and also to keep the reaction mixture homogeneous during the addition. In the preparation of 3-ethyl-2-veratrylindone, for example, it was necessary to use a liter of dry benzene for 15 g. of 2-veratrylindane-1,3-dione. The color of the solutions became deep red as the indanediones were added, but this color disappeared as the reactions proceeded. The reaction mixtures were usually pink or colorless before they were worked up.

The Grignard complexes were decomposed by cold dilute sulfuric acid and the benzene (or toluene) layers were washed with dilute sodium carbonate solution and with water. The solvent was then removed by distillation and the residues were subjected to steam distillation for several hours. The taffy-like residues after steam distillation were separated by decantation and crystallized from ethanol or glacial acetic acid.

An alternate method of purification was distillation of the indones under reduced pressure rather than by steam distillation of the impurities. The products were then obtained as clear colored resins and could be crystallized.

Considerable variation in the ease of purification was encountered in the products. 3-Cyclohexyl-2-phenylindone, in particular, was obtained pure only after eight crystallizations from ethanol and methanol.

The phenylhydrazone or oxime of each indone was prepared and recrystallized from ethanol. The melting points and analyses are included in Table I.

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(6) Patterson and Capell, "The Ring Index," Reinhold Publishing Corporation, New York, N. Y., 1940, No. 950.

(7) Daube, *Ber.*, **38**, 206 (1905).

(8) Gottlieb, *ibid.*, **32**, 958 (1899).

(9) Nathanson, *ibid.*, **26**, 2576 (1893).

(10) The microanalyses reported in this paper were carried out by Miss Margaret McCarthy and Miss Theta Spoor.

TABLE I

2,3-DISUBSTITUTED INDONES

Product Formula IV R	R′	Description	M. p., °C.	Yield, %	Molecular formula	Calcd., % C	H	N	Found, % C	H	N
Phenyl	Methyl	Yellow-orange plates	67–68	40 (I-IV)	$C_{16}H_{12}O$	87.25	5.48		87.20	5.45	
(Phenylhydrazone)		Golden needles	120		$C_{22}H_{18}N_2$			9.03			9.15
Phenyl	Ethyl	Yellow-orange needles	97–98	42 (I-IV)	$C_{17}H_{14}O$	87.14	6.02		87.18	5.89	
(Phenylhydrazone)		Yellow needles	96–97		$C_{23}H_{20}N_2$			8.63			8.67
(2,4-Dinitrophenylhydrazone)		Orange needles	206–207		$C_{23}H_{18}N_4O_4$			13.52			13.16
Phenyl	Cyclohexyl	Yellow-orange needles	163–164	10 (I-IV)	$C_{21}H_{20}O$	87.46	6.99		86.99	7.07	
(Phenylhydrazone)		Yellow needles	166–167		$C_{27}H_{26}N_2$			7.40			7.48
Phenyl	Phenyl	Red plates	152–153[a]	48 (I-IV)							
(Phenylhydrazone)		Yellow plates	175–176[b]								
Anisyl	Ethyl	Orange rhombs	119–120	42 (I-IV)	$C_{18}H_{16}O_2$	81.79	6.10		81.97	5.98	
(Phenylhydrazone)		Yellow-orange granules	156–157		$C_{24}H_{22}N_2O$			7.91			7.93
Anisyl	Isopropyl	Yellow-orange needles	138–139	23 (I-IV)	$C_{19}H_{18}O_2$	81.99	6.52		81.98	6.48	
			(b. p. 198–203° (2 mm.))								
(Phenylhydrazone)		Golden plates	166–168		$C_{25}H_{24}N_2O$			7.61			7.60
Veratryl	Ethyl	Scarlet needles	111–112	27 (I-IV)	$C_{19}H_{18}O_3$	77.53	6.16		77.73	5.97	
			(b. p. 192–195° (4 mm.))								
(Phenylhydrazone)		Golden needles	188–190		$C_{25}H_{24}N_2O_2$			7.29			7.27
Ethyl	Phenyl	Yellow-orange rhombs	92–93[c]	22 (V-VI-IV)							
(Oxime)		Yellow needles	179–180[d]								
n-Propyl	Phenyl	Golden rhombs	72.5–73	50 (V-VI-IV)	$C_{18}H_{16}O$	87.06	6.50		87.18	6.55	
(Phenylhydrazone)		Brown needles	107–108		$C_{24}H_{22}N_2$			8.28			8.44

[a] de Fazi [*Gazz. chim. ital.*, **45,** I, 554 (1915)] recorded 151–153°. [b] Orekhoff [*Bull. soc. chim.*, [4] **25,** 597 (1919)] recorded 175–176°. [c] de Fazi[4] recorded 92–93°. [d] de Fazi[4] recorded 182–183°.

All of the indones prepared give a deep green color with concentrated sulfuric acid, as described by de Fazi.[4]

2-Ethyl-3-phenylindone.—This compound was prepared by the method of de Fazi[4] from 6.8 g. (0.104 mole) of powdered zinc (purified by washing successively with 10% hydrochloric acid, water, alcohol, acetone, ether and anhydrous ether and dried at 100° *in vacuo*), 20 g. (0.110 mole) of benzophenone and 20 g. (15.1 cc.; 0.103 mole) of ethyl α-bromobutyrate in 60 cc. of dry benzene. The resulting white tufts were dissolved in 40 cc. of cold concentrated sulfuric acid and the green solution was allowed to stand for six hours and carefully diluted with ice water. The yield of yellow-orange crystals, recrystallized from ethanol, was 5.1 g. (22%), m. p. 92–93°.

3-Phenyl-2-*n*-propylindone.—α-Bromovaleric acid was prepared by the method of "Organic Syntheses"[11] for the preparation o α-bromocaproic acid from 50 g. (0.49 mole) of valeric acid and 78 g. (0.49 mole) of bromine, using 3 cc. of phosphorus trichloride as catalyst. The crude product was esterified by refluxing with absolute ethanol for five hours. The alcohol was then removed by evaporation and the residual liquid, after drying over "Drierite," was fractionally distilled, yielding 55.0 g. (54%) of ethyl α-bromovalerate, b. p. 92–94° (25 mm.); $n^{20}D$ 1.4496.

3-Phenyl-2-propylindone was prepared by the method of de Fazi[4] from 20 g. (0.110 mole) of benzophenone, 20.8 g. (0.099 mole) of ethyl α-bromovalerate and 9 g. (0.138 mole) of purified zinc powder in 60 cc. of dry benzene. Recrystallization of the intermediate product from high-boiling petroleum ether yielded 6.0 g. of white tufts, m. p. 112–113°.

Anal. C, 75.15, 75.18; H, 7.20, 7.26.

This analysis corresponds to the empirical formula of neither the β-hydroxy ester nor the α,β-unsaturated ester, but the compound nevertheless undergoes cyclization to the desired indone.

This material was cyclized by means of concentrated sulfuric acid in the same manner as the ethyl homolog. The yield of yellow-orange needles of 3-phenyl-2-propyl-indone was 5.6 g. (23%, based on ethyl α-bromovalerate), m. p. 72.5–73°. The analysis and phenylhydrazone are included in Table I.

Ozonization of 3-Ethyl-2-phenylindone

In Acetic Acid.—Eight-tenths of a gram (0.0034 mole) of 3-ethyl-2-phenylindone dissolved in 65 cc. of glacial acetic acid was treated with 3% ozone for two hours at room temperature. It was then diluted with 65 cc. of water, causing a cloudy precipitate. After the addition of 0.24 g. of powdered zinc the mixture was allowed to stand in the icebox overnight, whereupon it became yellow. It was then diluted with water to 300 cc. and neutralized with sodium hydroxide, after which the neutral solution was extracted with one 50-cc. portion and three 25-cc. portions of benzene. The benzene solution was evaporated under an air jet to a yellow oil which was dissolved in ethanol. Two compounds crystallized from the ethanol solution on standing overnight. One of these formed large yellow tabular crystals (60 mg.) and the other formed an equal amount of large white rhombohedra. The crystals were separated by hand with the aid of a magnifying glass, and each compound was recrystallized from ethanol. The yellow compound melted at 93° and gave the correct combustion analysis for *o*-propionylbenzil (IX).

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.82; H, 5.30.

The white compound melted at 92–93° and gave the correct combustion analysis for the ozonide (VIII) of 3-ethyl-2-phenylindone.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.39; H, 4.81.

A mixture of the yellow and white crystals melted at 67–72°.

This experiment was repeated several times, but the yellow compound was obtained in crystalline form only in the one case described here.

In Chloroform.—Four grams (0.017 mole) of 3-ethyl-2-phenylindone dissolved in 100 cc. of dry chloroform was ozonized at 0° with 3% ozone. At the end of one and one-half hours the color became pale yellow and the reaction was stopped. Water was then added (100 cc.) and the chloroform was removed by boiling. The ozonide remaining in the water was then removed by ether extraction. The ether extract was evaporated and the resulting oil was crystallized from alcohol, yielding 4.0 g. (83%) of the white ozonide (VIII), m. p. 92–93°.

Attempted Hydrogenation of the Ozonide.—A mixture of 1.75 g. (0.0062 mole) of the ozonide with 125 mg. of platinum oxide catalyst in 200 cc. of ethanol was treated with two atmospheres of hydrogen at room temperature for fifteen hours. The ozonide was recovered and identified by mixed melting point.

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(11) Clarke and Taylor, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., second edition, 1941, p. 115.

Reaction of the Ozonide with Potassium Hydroxide.—One gram (0.0035 mole) of the ozonide was refluxed for two hours in 50 cc. of 10% alcoholic potassium hydroxide. The mixture was poured into water, acidified with hydrochloric acid, and extracted with ether. The ether layer was extracted with sodium hydroxide solution and this was then acidified with hydrochloric acid. "Darco" was added and the water was heated and filtered. Benzoic acid crystallized from the filtrate, yielding 0.40 g., m. p. 121–122°.

Reaction of the Ozonide with Hydroxylamine.—One gram (0.0035 mole) of the ozonide was refluxed for two hours with 1 g. (0.014 mole) of hydroxylamine hydrochloride, 10 cc. of pyridine and 10 cc. of absolute ethanol. The solvents were removed by evaporation under an air jet and the residual crystals were triturated with water. The product (XI) was recrystallized from ethanol, forming 0.36 g. (58%) of fine white needles, m. p. 117–119°.

Anal. Calcd. for $C_{10}H_9N_2O$: N, 8.00. Found: N, 7.82.

Reaction of the Ozonide with Phenylhydrazine.—One gram (0.0035 mole) of the ozonide was heated at 235–240° for two hours with 4 cc. (0.041 mole) of phenylhydrazine. The reaction mixture was poured into dilute acetic acid and the resulting oil was separated and twice crystallized from ethanol. The yield of product, m. p. 110–112°, was 0.03 g. (2.5%).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.86; H, 5.74; N, 11.36.

***o*-Propionylbenzoic Acid (X).**—The method was that of Gottlieb,[8] in which 66 g. (0.625 mole) of freshly fused sodium propionate, 130 g. (1.0 mole) of propionic anhydride and 100 g. (0.675 mole) of phthalic anhydride were refluxed at 170° for two and one-half hours. The product, ethylidene phthalide, was obtained as an oil (97 g.). Of this 46 g. (0.29 mole) was refluxed with 10% aqueous sodium hydroxide. The yield of *o*-propionylbenzoic acid was 23.4 g. (44%), m. p. 96–97°.

4-Ethyl-1-keto-2,3,1-benzoxazine (XI).[6]—The method of Daube[7] was used, starting with 3 g. (0.017 mole) of *o*-propionylbenzoic acid, 3 g. (0.043 mole) of hydroxylamine hydrochloride and 10 cc. of 10% potassium hydroxide solution. The yield of product, m. p. 115–117°, was 1.9 g. (64%).

The melting point was not lowered when this compound was mixed with the reaction product of the ozonide with hydroxylamine.

1-Ethyl-3-phenylphthalazone (XII).[8]—One gram (0.0056 mole) of *o*-propionylbenzoic acid was refluxed with 4 cc. (4.4 g.; 0.041 mole) of phenylhydrazine at 235–240° for two hours. The reaction mixture was poured into dilute acetic acid, whereupon crystals formed. These were recrystallized from ethanol, forming 0.35 g. (40%) of long white needles, m. p. 111–112°.

The same product was formed when *o*-propionylbenzoic acid was treated with phenylhydrazine according to the directions of Shriner and Fuson[12] for preparing phenylhydrazones.

The melting point was not lowered when this compound was mixed with the reaction product of the ozonide with phenylhydrazine.

Summary

1. Seven new 2,3-disubstituted indones are described.

2. The dehydration products after the addition of the Grignard reagents of primary and secondary alkyl halides to 2-substituted indanediones have been shown to be indones rather than alkylidene indanones.

(12) Shriner and Fuson, "The Systematic Identification of Organic Compounds;" John Wiley and Sons, Inc., New York, N. Y., second edition, 1940, p. 64.

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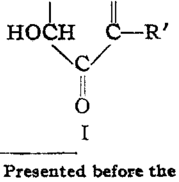
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Preparation of Cyclopentenones from Lactones[1]

BY ROBERT L. FRANK, PETER G. ARVAN, JOHN W. RICHTER AND CLINTON R. VANNEMAN

A method for preparing substituted cyclopentenones has been reported by Plattner and St. Pfau[2] which consists in the removal of the elements of water from γ,δ-unsaturated acids or the corresponding lactones. This reaction has also been reported in the patent literature[3] and has been studied recently by Bryusova and Osipova.[4] It was thought that if the yields for this transformation on a laboratory scale could be improved, it might afford a means of preparing hydroxycyclopentenones similar to pyrethrolone (I, R = CH_3; R′ = C_5H_7), the alcohol portion of the pyrethrins, by the sequence of reactions shown on the following page.



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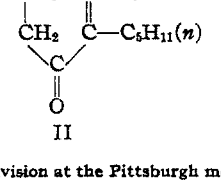

II

Such compounds could be used in studies relating chemical structure to pyrethrin-like insecticidal activity.

In order to investigate the reaction, γ-methyl-γ-decanolactone (III) was prepared in 28–31% yields by the addition of *n*-hexylmagnesium chloride or bromide to ethyl levulinate. The lactone was formed directly in this reaction due to the splitting out of ethoxymagnesium halide from the Grignard complex.[5] An attempt to prepare the lactone by the use of *n*-hexylzinc chloride was unsuccessful.

The use of phosphorus pentoxide as the dehydrating agent caused the transformation of γ-methyl-γ-decanolactone (III) to dihydrojasmone

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(1) Presented before the Organic Division at the Pittsburgh meeting of the American Chemical Society, September 6–10, 1943.

(2) Plattner and St. Pfau, *Helv. Chim. Acta*, **20**, 1474 (1937).

(3) Maschmeijer, French Patent 765,515 (June 12, 1934); I. G. Farbenindustrie, A.-G., French Patent 785,540 (Dec. 8, 1935); English Patent 453,518 (Aug. 10, 1936); Givaudan and Co., German Patent 639,455 (May 12, 1936).

(4) Bryusova and Osipova, *Sintezy Dushistykh Veshchestv, Sbornik Statei*, 295 (1939); *C. A.*, **36**, 3789 (1942).

(5) Grignard, *Compt. rend.*, **135**, 627 (1902).