

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Action of Grignard Reagents. XII.¹ Action of Organomagnesium Compounds on 5-Aralkylidene Derivatives of Rhodanine and of 3-Phenyl-2,4-thiazolidine

AHMED MUSTAFA, WAFIA ASKER, AHMED FATHY ABDEL-MAWGOUD SHALABY,
AND MOHAMED EZZ EL-DIN SOBHY

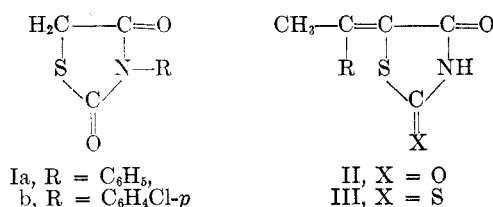
Received March 17, 1958

Treatment of 5-aralkylidene derivatives of rhodanine and of 3-phenyl-2,4-thiazolidinedione with Grignard reagents does not affect the hetero-ring opening and only the double bond of the lateral chain of IV and VI enters into reaction, yielding colorless products, believed to have structures like V and VII, respectively. Rhodanine and 3-phenyl-2,4-thiazolidinedione were proved to be stable when treated with phenylmagnesium bromide under similar conditions.

When Va was treated with aqueous sodium hydroxide solution, α -mercapto- β , β -diphenylpropionic acid was obtained.

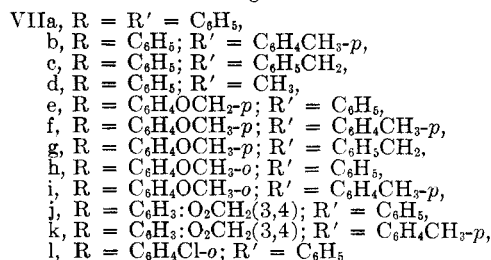
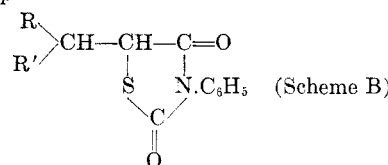
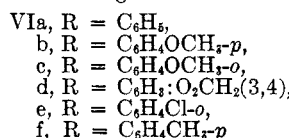
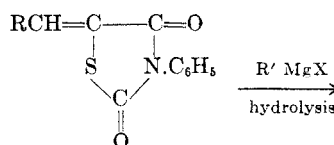
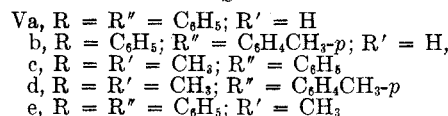
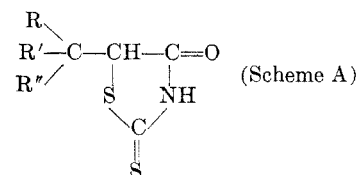
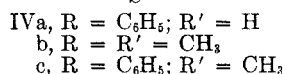
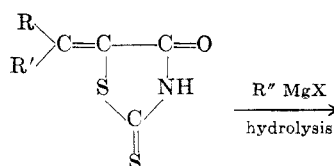
Recently, it has been reported that 3-aryl-2,4-thiazolidinediones, *e.g.*, 3-phenyl-(Ia) and 3-(4-chlorophenyl)-2,4-thiazolidinedione (Ib), possess fungistatic activity.² 5-(1-Methylalkylidene)-2,4-thiazolidinediones (II) show antimicrobial activity comparable to that of the most potent of the corresponding rhodanine derivatives (III).³

The fungicidal action of several organic sulfur compounds may be attributed to the presence of N—C—S linkage in II or III which is a characteristic of thiazole compounds. The latter compounds are known to possess considerable activity.⁴



We now have prepared derivatives of 5-methylrhodanine⁵ (V) and 5-methyl-3-phenyl-2,4-thiazolidinedione⁵ (VII) through the action of Grignard reagents on 5-aralkylidenerhodanones (IV) and 5-

aralkylidene-3-phenyl-2,4-thiazolidinediones (VI), respectively (*cf.* Scheme A and B).



(1) For parts X and XI *cf.* A. Mustafa and M. Kamel, *J. Am. Chem. Soc.*, **77**, 5630 (1955); *J. Org. Chem.*, **22**, 157 (1957), respectively.

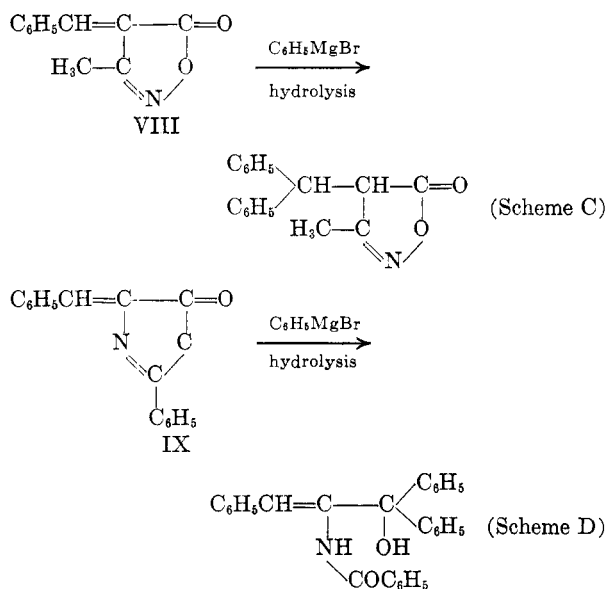
(2) N. K. Sundholm and J. B. Skaptason, U. S. Patent 2,510,725, June 6, 1950; *Chem. Abstr.*, **44**, 8045 (1950).

(3) *Cf.* F. C. Brown, C. K. Bradsher, and S. W. Chilton, *J. Org. Chem.*, **21**, 1269 (1956).

(4) M. K. Rout, B. Padhi, and N. K. Das, *Nature*, **173**, 516 (1954).

(5) In view of the marked interest in many derivatives of thiazolidone which proved to be useful as anaesthetics [A. R. Surrey, *J. Am. Chem. Soc.*, **71**, 3354 (1949)], anti-convulsants [H. D. Troutman and L. M. Long, *J. Am. Chem. Soc.*, **70**, 3436 (1948)] and amebicidal agents [A. R. Surrey and R. A. Cutler, *J. Am. Chem. Soc.*, **76**, 578 (1954)], the presence of a thiazolidine moiety in penicillin, the fungitoxic or bacteriotoxic activity shown by many derivatives of rhodanines [H. K. Pujari and M. K. Rout, *J. Sci. Ind. Res. (India)*, **14B**, 398 (1955)]; F. C. Brown and C. K. Bradsher, *Nature*, **163**, 171 (1951); F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, *J. Am. Chem. Soc.*, **78**, 384 (1956), the fungicidal activity of these compounds has been determined and the results will be published elsewhere.

The behavior of IV and VI toward organomagnesium compounds simulates that of 3-methyl-4-benzylideneisoxazolone⁶ (VIII) toward the action of phenylmagnesium bromide⁶ (*cf.* Scheme C). The isoxazolone ring in VIII is stable and only the double bond of the lateral chain enters into reaction. The stability of the 5-membered heterocyclic ring in IV and VI is in contrast to the ready opening of the oxazolone ring in 2-phenyl-4-*aralkylidene*-2-oxazolin-5-ones (IX; Scheme D⁷).



The structure of Va, which is taken as an example of compounds Va-e, is inferred from the fact that it is colorless, readily transformed by the action of aqueous sodium hydroxide (10%) into a colorless substance believed to have structure Xa.⁸

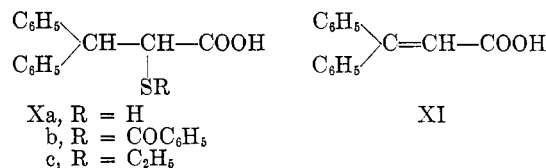
The structure of Xa is inferred from the fact that it has an acidic character and when its solution in aqueous sodium hydroxide is allowed to react with benzoyl chloride it gives the corresponding *S*-benzoyl derivative (Xb). Furthermore, when its solution in absolute alcohol is allowed to react with ethyl iodide, it gives the corresponding thioether (Xc). Xa gives an intense blue color when its alcoholic solution is treated with an alcoholic ferric chloride solution. Treatment of the solution of Xa in glacial acetic acid with hydrogen peroxide gives a sulfur-free compound, believed to be identical with XI.⁹

(6) Cf. L. Panizzi, *Gazz. chim. ital.*, **76**, 44 (1916).

(7) Cf. H. Pourrat, *Bull. soc. chim. France*, 828 (1955); A. Mustafa and A. H. E. Harhash, *J. Org. Chem.*, **21**, 575 (1956); L. Hörner and E. Lingnau, *Ann.*, **591**, 21 (1954).

(8) Cf. the easy opening of the hetero-ring in 5-*aralkylidene*denerhodanines by the action of aqueous sodium hydroxide [E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 32 (1956)].

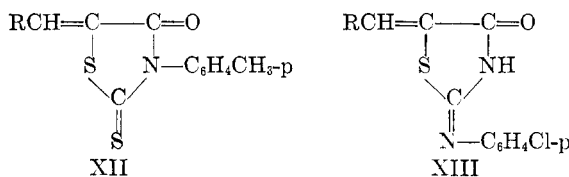
(9) The elimination of the mercapto group is analogous to the elimination of aromatic thiol from its adduct with ω ,*p*-dinitrostyrene by the action of hydrogen peroxide in acetic acid [A. Mustafa, A. H. E. Harhash, and M. Kamel, *J. Am. Chem. Soc.*, **77**, 3860 (1955)].



Similarly, a colorless product is obtained by the action of alcoholic potassium hydroxide on VIIa, which proved to be identical with XI, obtained by the action of hydrogen peroxide on Xa as described above.

The finding that VIIb is obtained by the action of phenylmagnesium bromide on VIa and by the action of *p*-tolylmagnesium iodide on VIa may be taken in favor of the assigned structure for the Grignard products (*cf.* VII).

Both rhodanine and 3-phenyl-2,4-thiazolidine-dione (Ia),¹⁰ the latter having less tendency for tautomerization, proved to be stable toward the action of phenylmagnesium bromide under similar conditions, thus showing the stability of the heteroring toward the action of Grignard reagents. The activity of the vinyl group in IV may be compared with the activity of the same group in 5-*aralkylidene*-3-*p*-tolylrhodanines (XII) and 5-*benzylidene*-2-*p*-chlorophenylimino-4-thiazolidone (XIII) toward the action of bromine¹¹ to give 5-bromo-5-*aryl*bromomethyl-*N*-*p*-tolylrhodanine and 5-bromo-5-*aryl*bromomethyl-2-(*p*-chlorophenylimino)-4-thiazolidone, respectively.



EXPERIMENTAL

*Action of Grignard reagents on benzylidenerhodanine (IVa), isopropylidenerhodanine (IVb), α -methylbenzylidenerhodanine (IVc), and 5-*aralkylidene*-3-phenyl-2,4-thiazolidinediones (VIa-f).* The following illustrates the procedure. To a Grignard solution (prepared from 0.9 g. of magnesium and 9.0 g. of bromobenzene in 50 ml. of dry ether) was added a solution of 1 g. of each of IVa, IVb, IVc, VIa-f in dry benzene (50 ml.). After evaporation of the ether, the mixture was heated for 3 hr. on a steam bath. After standing overnight at 25° it was poured slowly into 100 ml. of saturated aqueous ammonium chloride solution to which 3 ml. of concentrated hydrochloric acid was added, and extracted with ether. The ethereal layer was dried over anhydrous sodium sulfate, filtered, and evaporated. The solidified residues, after washing with light petroleum¹² in the case of IVa-c, and after washing with ethyl alcohol in the case of VIa-f, were crystallized from the appropriate solvents.

(10) F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, *J. Am. Chem. Soc.*, **78**, 384 (1956).

(11) Cf. H. K. Pujari and M. K. Rout, *J. Sci. Ind. Res. (India)*, **14B**, 398 (1955).

(12) Light petroleum is the fraction boiling at 40-60° and petroleum ether at 60-100°; the boiling ranges of other fractions are specified.

TABLE I
DERIVATIVES OF 5-METHYLRHODANINES (Va-c) AND 5-METHYL-3-PHENYL-2,4-THIAZOLIDINEDIONES (VIIa-l)

Com- pound	Grignard Reagent	Product	M.P., ^a °C.	Yield, %	Color with H ₂ SO ₄	Formula	Analysis							
							Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
IVa	Phenyl	Va	158	65	Yellow	C ₁₆ H ₁₃ NOS ₂	64.21	64.28	4.35	4.58	4.68	4.48	21.40	21.12
IVa	<i>p</i> -Tolyl	Vb	176	74	Yellow	C ₁₇ H ₁₅ NOS ₂	65.18	65.39	4.79	4.88	4.47	3.91	20.45	20.20
IVb	Phenyl	Vc	136	68	Pale yellow	C ₁₄ H ₁₁ NOS ₂	57.37	57.77	5.18	5.14	5.58	5.20	25.50	25.60
IVb	<i>p</i> -Tolyl	Vd	154	62	Yellow	C ₁₅ H ₁₂ NOS ₂	58.87	58.67	5.66	5.60	5.28	5.42	24.15	23.92
IVc	Phenyl	Ve	217	57	Deep violet	C ₁₇ H ₁₅ NOS ₂	65.18	65.35	4.79	4.77	4.47	3.88	20.45	20.45
VIa	Phenyl	VIIa	154	73	Yellow	C ₂₃ H ₁₇ NO ₂ S ^b	73.53	73.46	4.73	4.70	3.89	3.74	8.91	8.77
VIa	<i>p</i> -Tolyl	VIIb	145	71	Yellow	C ₂₃ H ₁₉ NO ₂ S	73.99	73.85	5.09	5.12	3.75	3.70	8.57	8.71
VIa	Benzyl	VIIc	152	69	Colorless	C ₂₃ H ₁₉ NO ₂ S	73.99	73.89	5.09	5.06	3.75	3.68	8.57	8.43
VIa	Methyl	VIIc	116	67	Colorless	C ₁₇ H ₁₃ NO ₂ S	68.68	68.91	5.05	5.13	4.71	4.69	10.77	10.61
VIb	Phenyl	VIIe	124	72	Yellow	C ₂₃ H ₁₉ NO ₂ S ^c	70.95	70.74	4.88	4.82	3.59	3.46	8.22	8.18
VIb	<i>p</i> -Tolyl	VIIe	152	70	Light orange	C ₂₄ H ₂₁ NO ₂ S	71.46	71.63	5.21	5.37	3.47	3.52	7.94	7.81
VIb	Benzyl	VIIe	134	68	Colorless	C ₂₄ H ₂₁ NO ₂ S	71.46	71.52	5.21	5.29	3.47	3.64	7.94	7.99
VIc	Phenyl	VIIg	113	67	Yellow	C ₂₃ H ₁₉ NO ₂ S	70.95	70.83	4.88	4.81	3.59	3.61	8.22	8.11
VIc	<i>p</i> -Tolyl	VIIh	187	69	Yellow	C ₂₃ H ₁₉ NO ₂ S	71.46	71.54	5.21	5.20	3.47	3.54	7.94	8.71
VIc	Phenyl	VIIi	134	73	Orange-red	C ₂₃ H ₁₇ NO ₄ S	68.48	68.32	4.21	4.17	3.47	3.41	7.94	7.97
VIc	<i>p</i> -Tolyl	VIIj	154	70	Orange-red	C ₂₃ H ₁₉ NO ₄ S	69.06	69.17	4.55	4.63	3.35	3.44	7.67	7.51
VIc	Phenyl	VIIk	174	74	Colorless	C ₂₃ H ₁₉ NO ₂ SCl ^d	67.09	67.21	4.06	4.12	3.55	3.61	8.13	8.37
VIc	<i>p</i> -Tolyl	VIIl	145	73	Yellow	C ₂₃ H ₁₉ NO ₂ S	73.99	73.76	5.09	5.13	3.75	3.73	8.57	8.61

^a All melting points are uncorrected. ^b Active H, Calcd.: 0.28, Found: 0.26. ^c Active H, Calcd.: 0.26, Found: 0.26. ^d Calcd.: Cl, 9.02, Found: Cl, 9.01.

The Grignard products listed in Table I were prepared similarly. Whereas Va-e are soluble in aqueous sodium hydroxide solution, VIIa-l are almost insoluble in the same reagent. The reaction products give no color with alcoholic ferric chloride and are generally soluble in hot benzene and/or alcohol, but are difficultly soluble in light petroleum.

Action of aqueous sodium hydroxide solution on Va. Two grams of Va and 20 ml. of aqueous sodium hydroxide solution (10%) were heated on a steam bath for 0.5 hr. until all the solid was dissolved. The reaction mixture was cooled, poured onto crushed ice, and solidified with dilute hydrochloric acid. The solid, so obtained, was filtered off and crystallized from aqueous ethyl alcohol (50%) as colorless crystals of Xa, m.p. 146°; yield, ca. 1.4 g.

Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.77; H, 5.43; S, 12.40. Found: C, 69.73; H, 5.27; S, 12.35.

Xa is readily soluble in ethyl alcohol, but difficultly soluble in cold water and dissolves in boiling water. It is soluble in aqueous sodium hydroxide solution and in sodium carbonate solution; its alcoholic solution gives an intense blue color with ferric chloride solution.

Reaction of Xa with (a) Ethyl iodide. One gram of Xa was dissolved in 10 ml. of ethyl alcohol, treated with 4 ml. of aqueous sodium hydroxide solution (10%) and with 3 ml. of freshly distilled ethyl iodide. The reaction mixture was refluxed on a water bath for 0.5 hr., set aside to cool, and then poured into 100 ml. of cold water. It was filtered off and the filtrate was acidified with cold dilute hydrochloric acid. The solid, so obtained, was crystallized from petroleum ether as colorless crystals (ca. 0.9 g.), m.p. 136°.

Anal. Calcd. for $C_{17}H_{16}O_2S$: C, 71.33; H, 6.29; S, 11.19. Found: C, 71.49; H, 6.18; S, 10.54.

Xb is sparingly soluble in cold ethyl alcohol. It is soluble in aqueous sodium hydroxide solution and aqueous sodium carbonate solution and its alcoholic solution gives no color with ferric chloride.

(b) Benzoyl chloride. A solution of 1 g. of Xa in 10 ml. of aqueous sodium hydroxide solution was treated gradually with 2 ml. of benzoyl chloride. The reaction mixture was vigorously shaken for 20 min., then poured into 200 ml. of cold water and acidified with dilute hydrochloric acid. The solid, so obtained, was collected and crystallized from dilute ethyl alcohol as colorless crystals (ca. 0.61 g.), m.p. 178°.

Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 72.93; H, 4.97; S, 8.84. Found: C, 73.09; H, 4.93; S, 9.15.

Xc is soluble in aqueous sodium hydroxide solution and aqueous sodium carbonate solution, and its alcoholic solution gives no color with ferric chloride.

(c) Hydrogen peroxide. A mixture of 0.5 g. of Xa and 10 ml. of glacial acetic acid and 2 ml. of hydrogen peroxide

was kept aside at room temperature for two days. It was poured onto crushed ice and the solid, that separated, was collected and crystallized from dilute acetic acid as colorless crystals (ca. 0.23 g.), m.p. 155°; not depressed with an authentic sample of XI.¹³

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.35; H, 5.31. Found: C, 80.30; H, 5.25.

XI is soluble in ethyl alcohol, ether, and chloroform. It is easily soluble in aqueous sodium hydroxide and sodium carbonate solutions, gives no color with concentrated sulfuric acid and its alcoholic solution develops no color with ferric chloride.

Action of potassium hydroxide solution on VIIa. Treatment of VIIa with an alcoholic potassium hydroxide solution (10%) as described in the case of Va and extending the heating period for 3 hr., gave, after acidification, an impure colorless substance having a wide range of melting point.

The reaction was repeated using 0.5 g. of VIIa and 20 ml. of an alcoholic potassium hydroxide solution (20%) and was refluxed for 10 hr. The solid that separated during refluxing, was collected, dissolved in water and acidified with cold dilute hydrochloric acid. The solid, that separated, was crystallized from aqueous alcohol, as colorless crystals (ca. 0.7 g.), m.p. 155° (not depressed when mixed with XI prepared as above).

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.35; H, 5.31. Found: C, 80.30; H, 5.25.

Action of potassium permanganate on XI. A solution of 0.5 g. of the reaction product, obtained as above by the action of potassium hydroxide solution on VIIa, in 30 ml was treated portionwise with 40 ml. of 5% aqueous potassium permanganate solution. The reaction mixture was refluxed for 2 hr., cooled, and poured into ice cold water. It was extracted with ether, dried, and evaporated. A solution of the oily residue in 4 ml. absolute alcohol was treated with a concentrated alcoholic solution of 2,4-dinitrophenylhydrazine containing few drops of hydrochloric acid. The reaction mixture was refluxed for 10 min. and the separated crystals, upon cooling, were collected and identified as benzophenone-2,4-dinitrophenylhydrazone (melting point and mixed melting point).

Similar results were obtained when 0.5 g. of Xa was treated with potassium permanganate as described above.

GIZA, CAIRO, EGYPT

(13) Prepared after E. P. Kohler and C. Heritage [*Am. Chem. J.*, **33**, 21 (1905)]; E. P. Kohler and R. M. Johnston, [*Am. Chem. J.*, **33**, 35 (1905)].