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

Action of Grignard Reagents. XXII. Action of Organomagnesium Compounds on 2-Mercapto-4-arylidene-5-thiazolidones and on 4-Arylidene-2,5-thiazolidinediones. Reaction of 2-Mercapto-4-benzylidene-5-thiazolidone with Diazomethane

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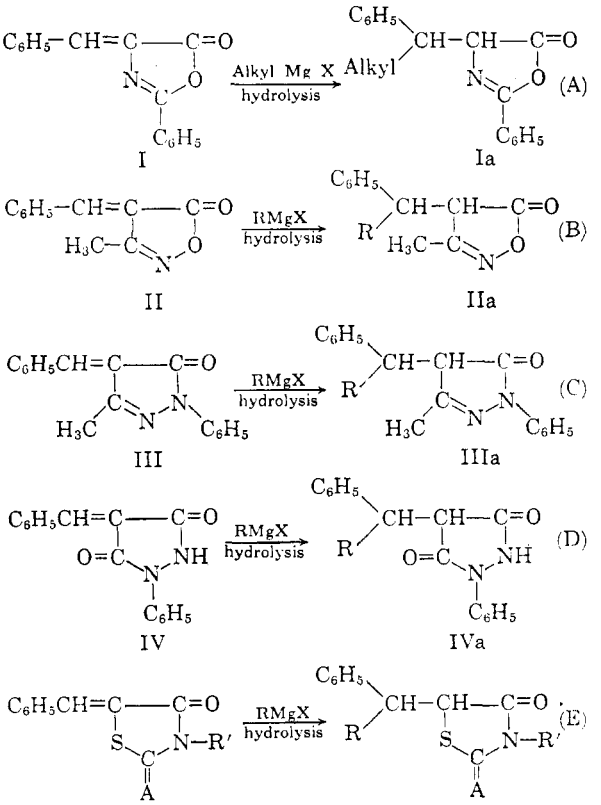
Treatment of 2-mercapto-4-arylidene-5-thiazolidones (VIa–d) with organomagnesium compounds does not affect the opening of the heterocyclic nitrogen ring, but only addition to the conjugation created by attachment of an exocyclic double bond in the 4-position takes place to give colorless products believed to have structures like VIIa–m (*cf.* Scheme F). 2-Mercapto-4-diphenylmethyl-5-thiazolidone (VIIa) now has also been obtained by the addition of benzene to the exocyclic double bond in VIa, in the presence of anhydrous aluminum chloride. Hydrolysis of the Grignard products (VIIa–m), exemplified by VIIa and VIId, with aqueous sodium hydroxide (10%) establishes a new route for the preparation of β,β-disubstituted alanines, namely, β,β-diphenyl-, β-phenyl-β-ethylalanine, respectively.

Similarly, addition of organomagnesium compounds to the exocyclic double bond in the newly prepared 4-arylidene-2,5-thiazolidinediones (IXa–b) takes place with the formation of colorless products believed to have structures like Xa–d. Hydrolysis of Xa with aqueous sodium hydroxide gave β,β-diphenylalanine.

The action of ethereal diazomethane solution on 2-mercapto-4-benzylidene-5-thiazolidone (VIa) leads to the formation of 2-methylmercapto-4-benzylidene-5-thiazolidone (XII) in good yield.

Recently Mustafa and Sallam,[1] in conjunction with the study of pharmacological and toxocological properties of thiazolidine derivatives,[2] have synthesized a series of new derivatives of 2-thio-4-methyl-5-thiazolidone (VI).[3]

The addition of organomagnesium compounds to the conjugation created by attachment of an exocyclic double bond in the 4-position of a heterocyclic nitrogen ring having a carbonyl function has been reported in the case of 2-phenyl-4-benzylidene-2-oxazoline-5-one (I),[4] 3-methyl-4-benzylideneisoxazolone(II),[5] its nitrogen analog, namely, 1-phenyl-3-methyl-4-benzylidene-5-pyrazolone (III),[6] 1-phenyl-4-benzylidene-3,5-pyrazolidinone (IV),[7] 5-benzylidenerhodanine (Va)[8a] and 5-benzylidene-3-*p*-tolyl-2,4-thiazolidinedione (Vb)[8b]



Va. A = S; R′ = C_6H_5
b. A = O; R′ = *p*-$C_6H_4CH_3$

Vc–d

(1) S. A. Tawab, A. Mustafa, and M. M. M. Sallam, *Arch. int. pharmacodyn.*, (1960), *cf.* also S. A. Tawab, A. Mustafa, and A. F. A. Shalaby, *Nature*, **183**, 607 (1959).

(2) In view of the marked interest many derivatives of thiazolidine which proved to be useful as anaesthetics [A. R. Surrey, *J. Am. Chem. Soc.*, **71**, 3354 (1949)]; anticonvulsants [H. D. Troutman and L. M. Long, *J. Am. Chem. Soc.*, **70**, 3436 (1948)]; and amebacidical agents [A. R. Surrey and R. A. Culter, *J. Am. Chem. Soc.*, **76**, 578 (1954)]; the presence of a thiazolidine moiety in penicillin, the fungi-toxic or bacteria-toxic 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*, **168**, 171 (1951); F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, *J. Am. Chem. Soc.*, **78**, 384 (1956)] and the antibacterial actions of a number of 2-mercapto-4-arylidene-5-thiazolidones have been reported recently [*cf.* W. Kashida and H. Yamanaka, *J. Pharm. Soc. Japan*, **73**, 949 (1953)].

(3) The fungicidal action of several organic sulfur compounds may be attributed to the presence of N—C—S linkage in Va; or characteristic of thiazole compounds which possess considerable activity (M. K. Rout, B. Padhi, and N. K. Das, *Nature*, **173**, 516 (1954)).

(4) L. Horner, and H. Schwahn, *Ann.*, **591**, 99 (1954).

(5) L. Panizzi, *Gazz. Chem. ital.* **76**, 44 (1926).

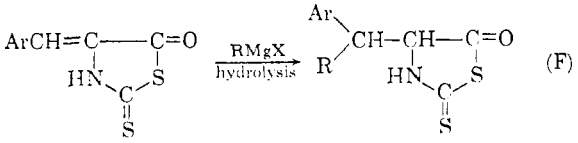
(6) A. Mustafa and A. H. E. Harhash, *J. Org. Chem.*, **21**, 575 (1956).

(7) A. Mustafa, M. Kira, and M. El-Essawi, *J. Org. Chem.*, **25**, 34 (1960).

(8)(a) A. Mustafa, W. Asker, A. F. A. Shalaby, and M. E. Sobhy, *J. Org. Chem.*, **23**, 1992 (1958). (b) A. Mustafa, W. Asker, and co-workers, *J. Am. Chem. Soc.*, **82**, 2029, 2597 (1960).

to yield Ia, IIa, IIIa, IVa and Vc—d respectively (*cf.* Scheme A–E).

In this investigation, the action of Grignard reagents on 2-mercapto-4-arylidene-5-thiazolidones (VIa–d) has now been undertaken with the formation of the reaction products (VIIa–m) (*cf.* Scheme F) needed for the pharmacological studies.

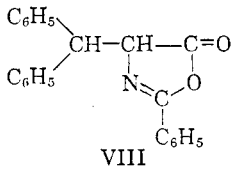


(F)

VIa. Ar = C_6H_5
b. Ar = *p*-$CH_3OC_6H_4$
c. Ar = *p*-$CH_3C_6H_4$
d. Ar = C_6H_5: O_2CH_2(3:4)
VIIa. Ar = R = C_6H_5
b. Ar = C_6H_5; R = *p*-$CH_3C_6H_4$
c. Ar = C_6H_5; R = CH_3
d. Ar = C_6H_5; R = C_2H_5
e. Ar = C_6H_5; R = *i*-C_3H_7
f. Ar *p*-$CH_3OC_6H_4$; R = C_6H_5
g. Ar = *p*-$CH_3OC_6H_4$; R = *p*-$CH_3C_6H_4$
h. Ar = *p*-$CH_3OC_6H_4$; R = CH_3
i. Ar = *p*-$CH_3OC_6H_5$; R = C_2H_5
j. Ar = *p*-$CH_3OC_6H_4$; R = C_6H_5
k. Ar = C_6H_3: O_2CH_2(3:4); R = C_6H_5
l. Ar = C_6H_3: O_2CH_2(3:4); R = *p*-$CH_3C_6H_4$
m. Ar = C_6H_3: O_2CH_2(3:4); R = CH_3

The Grignard reagents do not affect the hetero-ring opening and only addition to the conjugation created by attachment of an exocyclic double bond in the 4-position of a heterocyclic ring having a carbonyl function (VI) takes place.

The structure of VIIa, which is taken as an example of compounds VIIa–m is inferred from the fact that it is colorless (*cf.* the deep-yellow VIa) and readily transformed by the action of hot aqueous sodium hydroxide solution (10%)[9] into a colorless substance which was identified as β,β-diphenylalanine *via* the ready formation of its benzoyl derivative and the positive ninhydrin test for α-amino acids. Treatment of the *N*-benzoyl derivative of β,β-diphenylalanine with acetic anhydride in presence of fused sodium acetate resulted in the formation of 2-phenyl-4-diphenylmethyl-5(4H)oxazolone (VIII) which has been recently obtained after Filler and Hebron[10] *via*



VIII

the treatment of I with benzene in the presence of anhydrous aluminum chloride.

Similar treatment of VIId with hot aqueous sodium hydroxide gave β-phenyl-β-ethylalanine which was identical with the product obtained according to Horner and Schwahn[4] *via* the treatment of the reaction product, obtained by the action of ethylmagnesium iodide on I, with normal aqueous sodium hydroxide solution. Further identification was carried out by the identity of its *N*-benzoyl derivative with *N*-benzoyl-β-phenyl-β-ethylalanine.[4]

VIIa now has also been obtained by the action of benzene on VIa in the presence of anhydrous aluminum chloride.[10]

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

The absorption spectra for VIa and for VIIa give evidence for the assigned structure for the products obtained by the action of Grignard reagents on 2-mercapto-4-arylidene-5-thiazolidones (VI).

The ultraviolet curves clearly distinguish between the two samples. While the curves of both compounds show comparable bands in the 240–285 mμ range, only compound VIa has additional strong absorption at longer wave lengths (375 and 386 mμ) indicative of a more highly conjugated system. The absence of these bands at 375 and 386 mμ in compound VIIa indicates the destruction of this conjugation, thus supporting the contention that the Grignard reagent added *via* 1,4-addition.

The infrared data also distinguishes between the two samples. Both compounds (VIa and VIIa) show a band in the 3250 cm.$^{-1}$ region (3270 and 3230 cm.$^{-1}$, respectively) characteristic of the —NH group. That a carbonyl group is present in both molecules is shown in the 1700 cm.$^{-1}$ region. In compound VIa the band at 1684 cm.$^{-1}$ indicates a carbonyl conjugated to a double bond. Treatment with VIa with the Grignard reagent shifted the carbonyl band in VIIa to a higher frequency, 1735 cm.$^{-1}$, indicating an unconjugated carbonyl. In the curve of compound VIa there is strong absorption in the 1600 cm.$^{-1}$ region (bands at 1608 and 1592 cm.$^{-1}$) characteristic of both phenyl and C—C double bond absorption. The infrared data for compound VIIa show diminished absorption in that region (bands at 1600 and 1580 cm.$^{-1}$) indicative of only phenyl absorption.

Reactions of Grignard reagents with 4-arylidene-2,5-thiazolidinediones (IXa–b):

IXa–b have the added feature of an α,β-unsaturated carbonyl system and the activity of the exocyclic double bond in position 4 in IX may be

(9) *Cf.* the ready opening of the thiazolone ring of VIa with two equivalents of potassium hydroxide (R. Chatterjee, A. H. Cook, I. Heilbron, and A. L. Levy, *J. Chem. Soc.*, 1337 (1948)] and the ease of the reductive fission of VIa with red phosphorus and hydrogen iodide [J. D. Bilmoria and A. H. Cook, *J. Chem. Soc.*, 2323 (1949)].

(10) *Cf.* the addition of benzene to the conjugated exocyclic double bond in the 4-position of a heterocyclic ring having a carbonyl function (I) [R. Filler and L. M. Hebron, *J. Org. Chem.*, **23**, 1815 (1958)].

TABLE I

GRIGNARD PRODUCTS VII FROM 2-MERCAPTO-4-ARYLIDENE-5-THIAZOLIDONES (VI)

Arylidene Derivative	Grignard Product	Solvent of Crystallization[a]	M.P.[b]	Yield, %	Color with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
VIa[c]	VIIa	A	199–200	76	Yellow	$C_{17}H_{13}NOS_2$	64.18	64.24	4.38	4.50	4.68	4.68	21.42	21.24
VIa	VIIb	A	173	88	Yellow	$C_{17}H_{15}NOS_2$	65.14	65.51	4.82	4.69	4.46	4.48	20.45	19.84
VIa	VIIc	B	170	82	No color	$C_{11}H_{11}NOS_2$	55.66	55.52	4.67	4.58	5.90	5.81	27.02	26.91
VIa	VIId	C	157–158	79	No color	$C_{12}H_{13}NOS_2$	57.36	57.18	5.21	5.08	5.57	5.32	25.58	25.16
VIa	VIIe	B	214	76	No color	$C_{13}H_{15}NOS_2$	58.84	59.06	5.69	5.26	5.28	5.23	24.16	24.16
VIb[d]	VIIf	A	139	74	Yellow	$C_{17}H_{15}NO_2S_2$	61.98	62.15	4.59	4.42	4.26	4.26	19.47	19.18
VIb	VIIg	B	149	70	Orange	$C_{18}H_{17}NO_2S_2$	62.94	62.72	4.99	4.94	4.07	3.62	18.53	17.95
VIb	VIIh	C	175	72	No color	$C_{12}H_{13}NO_2S_2$	53.90	53.80	4.91	4.91	5.24	5.01	23.99	24.10
VIb	VIIi	B	167	78	No color	$C_{13}H_{15}NO_2S_2$	55.49	55.78	5.37	5.16	4.98	4.91	22.79	22.28
VIc	VIIj	A	173	68	Yellow	$C_{17}H_{15}NOS_2$	65.14	65.62	4.82	4.62	4.46	4.38	20.45	20.02
VId[e]	VIIk	B	212	71	Red	$C_{17}H_{14}NO_3S_2$	59.28	60.00	4.09	3.97	4.07	3.95	18.62	18.54
VId	VIIl	B	195	73	Red	$C_{18}H_{15}NO_3S_2$	60.48	60.86	4.23	4.41	3.92	3.58	17.94	17.67
VId	VIIm	B	184	72	Yellow	$C_{12}H_{11}NO_3S_2$	51.22	51.28	3.91	3.94	4.98	5.02	22.80	22.90

[a] A = Ethyl alcohol; B = benzene; C = benzene–pet. ether (b.p. 40–60°). [b] Not all melting points were corrected. [c] For the preparation, *cf.* Ref. No. 9. [d] *Cf.* A. H. Cook, G. Harris, J. R. A. Pollock, and J. H. Swan, *J. Chem. Soc.*, 1947 (1950), reported m.p. 212° dec.; and now obtained from ethyl alcohol as yellow crystals m.p. 216–217°. [e] M.p. 219° dec. as deep yellow crystals from benzene (*cf.* Y. Kashida and H. Yamanaka, *J. Pharm. Soc. Japan*, **73**, 949 (1953), reported m.p. 215° dec.).

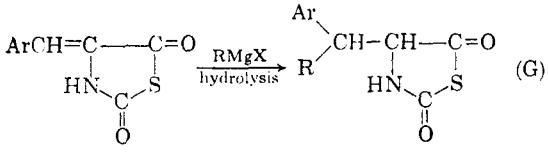
TABLE II

GRIGNARD PRODUCTS X FROM 4-ARYLIDENE-2,5-THIAZOLIDENEDIONE (IX)

Arylidene Derivative	Grignard Product	Solvent of Crystallization[a]	M.P.[b]	Yield, %	Color with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
IXa	Xa	B	136	82	Yellow	$C_{16}H_{13}NO_2S$	67.82	67.69	4.62	4.50	4.94	4.72	11.32	11.20
IXa	Xb	A	145	70	Orange	$C_{17}H_{15}NO_2S$	68.66	68.52	5.08	5.08	4.71	4.63	10.78	10.65
IXa	Xc	A	159	81	No color	$C_{11}H_{11}NO_2S$	59.71	59.62	5.01	4.78	6.33	6.24	14.48	14.75
IXb	Xd	A	149	73	No color	$C_{12}H_{13}NO_3S$	57.35	57.63	5.22	5.27	5.58	5.52	12.76	12.61

[a] A = Ethyl alcohol; B = benzene. [b] All melting points were not corrected.

compared with the activity of the double bond in VI. Thus, when IXa–b are treated with organomagnesium compounds, reaction products having structures like Xa–d are obtained (*cf.* Scheme G).



(G)

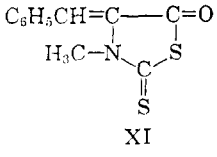
IXa. Ar = C_6H_5
b. Ar = p-$CH_3OC_6H_4$
Xa. Ar = R = C_6H_5
b. Ar = C_6H_5; R = p-$CH_3OC_6H_4$
c. Ar = C_6H_5; R = CH_3
d. Ar = p-$CH_3OC_6H_4$; R = CH_3

The assigned structure for the Grignard products (Xa–d) is inferred from the facts: (1) they are colorless, (2) hydrolysis of Xa with aqueous sodium hydroxide gives β,β-diphenylalanine, and (3) the analytical data agree with the expected values. The stability of the five-membered heterocyclic ring in IX toward the action of Grignard reagents parallels the behavior of that in IV and is in contrast to the ready opening of the oxazolone ring in I by the action of arylmagnesium halides.[11]

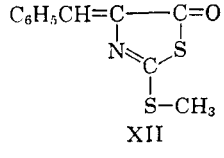
IXa–b, needed for this investigation, now have been obtained by the condensation of 2,5-thiazolidinedione with benzaldehyde and p-methoxybenzaldehyde respectively in presence of acetic acid and fused sodium acetate.

Action of diazomethane on 2-mercapto-4-benzylidene-5-thiazolidone (VIa):

Whereas the *N*-methyl derivative of VIa, namely, 2-thio-3-methyl-4-benzylidene-5-thiazolidone XI was obtained by the condensation of benzaldehyde with 2-mercapto-5-thiazolidone in presence of acetic acid and morpholine,[12] the *S*-methyl ether derivative namely 2-methylmercapto-4-benzylidene-5-thiazolidone (XII), was obtained by treatment of VIa with methyl iodide in presence of normal aqueous sodium hydroxide solution,[12] VIa is recovered unchanged on boiling with methyl iodide or dimethyl sulfate in ethanol solution. We now have found that 2-methylmercapto-4-benzylidene-5-thiazolidone (XII) is readily obtained in a good yield upon treatment of VIa with ethereal diazomethane solution. Fractional crystallization of the crude product does not reveal the presence of the *N*-methyl derivative (XI).



XI



XII

(11) *Cf.* A. Mustafa and A. H. E. Harhash, *J. Org. Chem.*, 21, 575 (1956); R. Filler and J. D. Wismar, *J. Org. Chem.*, 22, 853 (1957); H. Pourrat, *Bull. Soc. Chim. France*, 21, 575 (1956).

(12) A. H. Cook and S. F. Cox, *J. Chem. Soc.*, 2342 (1949).

EXPERIMENTAL

Preparation of 2-mercapto-4-(p-methylbenzylidene)-5-thiazolidone (VIc). Carbamylmethylammonium carbamylmethyldithiocarbamate is now obtained in a good yield after the following modification of the procedure described by Chatterjee, Cook, Heilbron, and Levy:[9] A solution of 4.9 g. of metallic sodium in 120 ml. of absolute ethyl alcohol was added during 2 hr. to a fine stirred suspension of 26 g. of aminoacetonitrile sulfate in 150 ml. of acetone until neutral to phenolphthalein. Sodium sulfate was filtered off, washed with 50 ml. of acetone, and 17 ml. of dried carbon disulfide was added to the filtrate, followed by the addition of 200 ml. of ether. The solid (*ca.* 18 g.), so obtained was collected and its solution in the least amount of warm water was added dropwise while stirring to *ca.* 300 ml. of acetone, colorless crystals (*ca.* 14.4 g.) m.p. 138–139° dec. were obtained.

When a solution of 1.0 g. of carbamylmethylammonium carbamyldithiocarbamate in 6.0 ml. of water was treated with a solution of 0.5 g. of p-tolualdehyde in 3.0 ml. of ethyl alcohol, and the reaction mixture was treated dropwise with 3.0 ml. of hydrochloric acid, VIc (*ca.* 0.15 g.) was obtained in yellow needles from benzene, m.p. 220–221°. It gives an orange color with sulfuric acid.

Anal. Calcd. for $C_{11}H_{10}NOS_2$: C, 55.90; H, 4.26; N, 5.93; S, 27.14, Found: C, 56.26; H, 3.97; N, 5.79; S, 26.86.

Action of Grignard reagents on 2-mercapto-4-arylidene-5-thiazolidones (VIa–d). 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 suspension of 1.5 g. of each of VIa–d in dry benzene (50 ml.); after evaporation of the ether, the mixture was heated for 1 hr. on a steam bath. It was kept at room temperature for 3 hr., poured slowly onto 100 ml. of saturated aqueous ammonium chloride solution to which 3 ml. of hydrochloric acid was added, and extracted with benzene. Evaporation of the solvent gave solid residues which were crystallized from the appropriate solvent.

The Grignard products (VIIa–m) listed in Table I were prepared similarly. They are all colorless, soluble in cold aqueous sodium hydroxide (10%), give no color with alcoholic ferric chloride, and are generally soluble in hot benzene, but are difficulty soluble in petroleum ether (b.p. 00–00°).

Action of aqueous sodium hydroxide on (a) VIIa. One gram of VIa and 10 ml. of aqueous sodium hydroxide solution (10%) were refluxed for 15 min. The yellow reaction mixture solution was cooled, poured onto crushed ice, and acidified with dilute acetic acid, when a marked smell of hydrogen sulfide was detected. It was then concentrated and kept aside overnight at room temperature. The solid so obtained was crystallized from water as colorless needles (*ca.* 0.55 g.), m.p. 234–235° dec.[13].

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.26; N, 5.85. Found: C, 74.24; H, 6.10; N, 5.58.

It gives positive ninhydrin test for α-amino acids. It is soluble in hot water and ethanol, but is difficultly soluble in benzene.

When hydrochloric acid was used for acetic acid for the acidification in the above experiment, the corresponding hydrochloride was obtained as colorless crystals from dilute ethyl alcohol, m.p. 227° dec.

Anal. Calcd. for $C_{15}H_{16}ClNO_2$: C, 64.86; H, 5.70; N, 5.04; Cl, 12.77. Found: C, 64.67; H, 4.91; N, 4.59; Cl, 12.97.

A solution of 0.5 g. of β,β-diphenylalanine in 5.0 ml. of aqueous sodium hydroxide (10%) was treated with 0.4 ml. of benzoyl chloride. The reaction mixture was shaken thoroughly for 15 min., cooled, poured onto crushed ice, and acidified with dilute hydrochloric acid. The solid so obtained was triturated with 3 ml. of hot carbon tetrachloride,

(13) C. R. Harington and W. McCartney, *J. Chem. Soc.*, 896 (1929), gave m.p. 236° dec. for β,β-diphenylalanine.

and was crystallized from dilute alcohol as colorless crystals (*ca.* 0.35 g.), m.p. 190–191°.

Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.05. Found: C, 76.13; H, 5.54; N, 3.92.

The benzoyl derivative is soluble in alcohol and acetone, but is difficulty soluble in benzene.

To a mixture of 0.5 g. of the benzoyl derivative and 0.3 g. of freshly fused sodium acetate was added 0.5 ml. of acetic anhydride. The reaction mixture was heated on a steam bath for 0.5 hr., cooled, and the solid that separated was crystallized from a mixture of benzene and petroleum ether (b.p. 50–60°) as colorless crystals (*ca.* 0.15 g.), m.p. 158°; identified as 2-phenyl-4-diphenylmethyl-5(4H)oxazolone (VIII) by melting point and mixed melting point determination.

Anal. Calcd. for $C_{22}H_{17}NO_2$: N, 4.28. Found: N, 4.35.

(b) VIId. Similarly, treatment of 1.0 g. of VIId with aqueous sodium hydroxide, as described above, resulted in the formation of colorless crystals (*ca.* 0.6 g.) of β-phenyl-β-ethylalanine from water, m.p. 222–223° dec. (m.p. and mixed m.p.[4]). It gives a positive ninhydrin test for α-amino acids.

Benzoylation of β-phenyl-β-ethylalanine (0.5 g.) with benzoyl chloride (0.4 ml.) in the presence of aqueous sodium hydroxide (5 ml., 10%), as described above, gave colorless crystals of the benzoyl derivative (*ca.* 0.3 g.) from ethyl alcohol, m.p. 193°.[14]

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.62; H, 6.41; N, 4.90.

Reaction of VIa *with benzene in the presence of aluminum chloride.* To a cooled mixture of 9.5 g. of anhydrous aluminum chloride and 125 ml. of dry thiophene-free benzene which was stirred for 1 hr. at 10°, was added dropwise a suspension of 6.0 g. of VIa in 200 ml. of dry benzene. The temperature of the reaction mixture was maintained at 10–20° during the addition. Stirring was continued for an additional 3 hr. at room temperature. The complex was decomposed with 250 ml. of dilute (1:15) hydrochloric acid. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene extracts were washed thoroughly with dilute hydrochloric acid, then with water, until neutral to litmus. Benzene was evaporated and the yellow oily residue was dissolved in ether and precipitated with petroleum ether (b.p. 00–00°). The pale yellow precipitate was collected and crystallized from benzene as colorless crystals (*ca.* 4.1 g.), m.p. 199–200°; identified as VIIa by melting point and mixed melting point with an authentic specimen of VIIa prepared as above.

Preparation of: (a) *4-Benzylidene-2,5-thiazolidinedione* (IXa). To a mixture of 5 g. of 2,5-thiazolidinedione,[15] 5 ml. of benzaldehyde, and 20 ml. of acetic acid was added 3 g. of freshly fused sodium acetate. The reaction mixture was refluxed for 0.5 hr., cooled, and then poured onto ice cold water (200 ml.). The solid (*ca.* 3.2 g.) so obtained was collected and crystallized from ethyl alcohol as pale yellow crystals, m.p. 165°.

Anal. Calcd. for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82; S, 15.62. Found: C, 58.52; H, 3.31; N, 7.04; S, 15.81.

IXa is soluble in hot chloroform and benzene, but is sparingly soluble in petroleum ether, and gives yellow color with sulfuric acid.

(b) *4-p-Methoxybenzylidene-2,5-thiazolidinedione* (IXb). Similarly, refluxing a mixture of 5 g. of 2,5-thiazolidinedione, 5 ml. of *p*-methoxybenzaldehyde, 20 ml. of acetic acid, and 3 g. of fused sodium acetate for 0.5 hr., as described above, gave yellow crystals from ethyl alcohol (*ca.* 2.9 g.), m.p. 168°.

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.95; S, 13.63. Found: N, 6.02; S, 13.94.

IXb is soluble in hot benzene, but sparingly soluble in petroleum ether, and gives an orange color with sulfuric acid.

Action of Grignard reagents on 4-arylidene-2,5-thiazolidinediones (IXa–b). The procedure was like that described in the case of VIa–d. The Grignard products (Xa–d) listed in Table II are all colorless, soluble in cold aqueous sodium hydroxide (10%), give no color with alcoholic ferric chloride, and are generally soluble in hot benzene, but are sparingly soluble in petroleum ether.

Action of aqueous sodium hydroxide on Xa. Treatment of 1.0 g. of Xa with 10 ml. of aqueous sodium hydroxide (10%) as described in the case of VIa, gave *ca.* 0.45 g. of β-β-diphenylalanine, m.p. 235° which proved to be identical with an authentic sample obtained as above. It gives a positive ninhydrin test for α-amino acids, and was further identified by the ready formation of the benzoyl derivative obtained as above.

Action of an ethereal diazomethane solution on VIa. To a suspension of 1.0 g. of VIa in 50 ml. of dry ether was added an ethereal solution of diazomethane (prepared from 6.0 g. of nitrosomethylurea). The reaction mixture was kept aside at 0° overnight, and the resulting solution was allowed to evaporate slowly. The yellow residue, that separated was collected and crystallized from petroleum ether (b.p. 80–100°) as yellow needles (*ca.* 0.8 g.), m.p. 101°; it was proved to be identical with XII.[12]

Anal. Calcd. for $C_{11}H_9NOS_2$: C, 56.14; H, 3.83; N, 5.95; S, 27.25. Found: C, 56.51; H, 3.75; N, 5.81; S, 27.01.

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(14) L. Horner and H. Schwahn (ref. 4) reported m.p. 181° for the benzoyl derivative.

(15) P. Aubert and E. B. Knott, *Nature*, 166, 1039 (1950).