with acetic anhydride according to the directions of Winstein.[33]

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NEWARK, DELAWARE

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

Reactions with Mercaptans. III.[1] Action of Aromatic Thiols on Coumarins, 4-Styrylcoumarins and 2-Styrylchromones

BY AHMED MUSTAFA, MOHAMED KAMEL, MOHAMED ALY ALLAM, ABDEL HAMID EL-SAYED HARHASH AND ALAA ELDIN ABDEL AZIZ HASSAN

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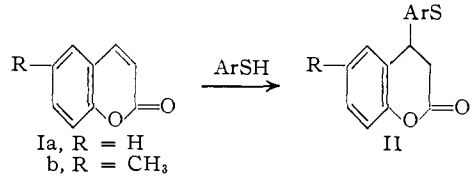
Coumarin and 6-methylcoumarin add aromatic thiols to give the 4-arylmercapto-3,4-dihydrocoumarins (II). Thioncoumarin is stable toward the action of aromatic thiols under parallel conditions. The treatment of 4-styrylcoumarins (III and V) with aromatic thiols results in the formation of the thiol adducts, believed to have structures like IVa or IVb, and VIa and VIb, respectively; they are readily oxidized to the corresponding sulfones. Whereas 2-methylchromone is stable toward the action of aromatic thiols, 2-styrylchromones (VIII), which may be regarded as vinylogs of chalcones, add the thiols to yield thiol adducts, believed to have a structure like IX. IX (R = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*) reacts with hydrazine hydrate to give the pyrazole derivative (XIa or XIb), and not the hydrazone derivative; similarly, it reacts with hydroxylamine hydrochloride in presence of pyridine to yield the corresponding isoxazole derivative (XIIIa or XIIIb).

In conjunction with a study of the pharmacological action of sulfur-containing compounds against Bilharziasis,[1,2] 4-arylmercapto-3,4-dihydrocoumarin (II,R = H) and 4-arylmercapto-6-methyl 3,4-dihydro-coumarin (II,R = CH_3) were prepared through the addition of aromatic thiols to coumarin (Ia) and 6-methylcoumarin (Ib), respectively.



Ia, R = H
b, R = CH_3

II

Although the addition of organic sulfur compounds to coumarin and its derivatives has not been investigated extensively, addition products have been obtained from coumarin and potassium cyanide,[3] and/or sodium bisulfite.[4] Similarly, coumarin adds cyanoacetamide, malonic ester and ethyl phenylacetate[5,6] to give substituted dihydrocoumarin derivatives. The unsaturated system in the pyrone ring functions as a dienophile in the Diels–Alder synthesis.[7]

The aromatic thiols employed in this investigation generally react with Ia and/or Ib in the presence or absence of piperidine[8] to give the corresponding addition product II in 75–95% yield. All the sulfides (*cf.* Table I) were sharp melting crystalline compounds.

The pure sulfides were stable under the normal conditions, but were decomposed into the original components by refluxing with 4% alcoholic potassium hydroxide solution. The regenerated thiol was readily characterized by the formation of a yellow lead salt with lead acetate. The adducts are almost insoluble in cold aqueous sodium hydroxide, and give no color reactions with alcoholic ferric chloride solution.

Coumarins in their reactions may behave as unsaturated lactones,[9] and in view of the well established mechanism for the conjugate addition of thiols to α,β-unsaturated compounds, *e.g.*, α,β-unsaturated ketones,[10] 1-cyanocyclohexene,[11] α,β-unsaturated esters[12] and allylacrylonitriles,[13] we have assigned structure II to the sulfides, particularly since the reactions were not carried out under the influence of peroxides.[14]

In agreement with the finding of Dey and Row[15] that alkyl groups inhibit the addition reaction of 4-methylcoumarin with sodium bisulfite, we have found that under the given experimental conditions, 4-methylcoumarin is stable toward the action of *p*-thiocresol in the presence or absence of piperidine. However, in contrast to the observation of Seshardi and Venkateswarlu[16] that the methyl group in the 6-position markedly slows down the addition of cyanoacetamide to 6-methylcoumarin (Ib), the latter reacts readily with aromatic thiols in a similar manner to Ia.

Whereas, Ia readily adds aromatic thiols, thioncoumarin is recovered almost unchanged when allowed to react with thiols in the presence or ab-

(1) A. Mustafa, A. H. E. Harhash and M. Kamel, THIS JOURNAL, **77**, 3860 (1955).

(2) N. O. Nolan, H. W. Bond and E. R. Mann, *Am. J. Trop. Med. and Hyg.*, **2** [4], 716 (1953).

(3) J. Bredt and J. Kallen, *Ann.*, **293**, 366 (1896).

(4) F. D. Dodge, THIS JOURNAL, **52**, 1724 (1930).

(5) T. R. Seshardi, *J. Chem. Soc.*, 166 (1928).

(6) R. Connor and Wm. R. McClelland, *J. Org. Chem.*, **3**, 570 (1939).

(7) R. Adams, W. D. McPhee, R. B. Carlin and Z. W. Wicks, THIS JOURNAL, **65**, 356 (1943); R. Adams and R. B. Carlin, *ibid.*, **65**, 360 (1943).

(8) R. M. Ross, *ibid.*, **71**, 3158 (1949).

(9) R. C. Elderfield, ed., "Heterocyclic Compounds," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 197.

(10) T. Posner, *Ber.*, **35**, 809 1902); B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(11) R. M. Ross and F. W. Raths, *ibid.*, **73**, 129 (1951).

(12) B. H. Nicolet, *ibid.*, **57**, 1098 (1935).

(13) R. M. Ross, H. L. Bushey and R. J. Rolih, *ibid.*, **73**, 540 (1951).

(14) S. O. Jones and E. E. Reid, *ibid.*, **60**, 2452 (1938); M. S. Kharasch, A. T. Read and F. R. Mayo, *Chemistry & Industry*, 752 (1938).

(15) B. B. Dey and K. K. Row, *J. Chem. Soc.*, **125**, 554 (1924).

(16) T. R. Seshardi and V. Venkateswarlu, *Proc. Indian Acad. Sci.* **15A**, 424 (1942).

TABLE I

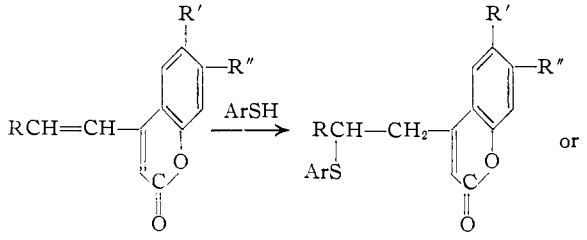
THIOL ADDUCTS II

No.	R =	Thiol Ar =	M.p.,[a] °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found
1	H	C_6H_5	110	91	$C_{15}H_{12}O_2S$	70.30	70.12	4.72	4.53	12.49	12.11
2	H	$C_6H_4CH_3$-*o*	111	78	$C_{16}H_{14}O_2S$	71.10	70.87	5.22	4.98	11.84	11.67
3	H	$C_6H_4CH_3$-*p*	151	85			70.94		4.86		11.71
4	CH_3	C_6H_5	96	94			71.00		5.12		11.54
5	CH_3	$C_6H_4CH_3$-*o*	122	78	$C_{17}H_{16}O_2S$	71.82	71.62	5.67	5.49	11.26	11.20
6	CH_3	$C_6H_4CH_3$-*p*	116	89			71.58		5.51		11.12
7	CH_3	$CH_2C_6H_5$	115	82			71.46		5.61		11.29

[a] Melting points are uncorrected.

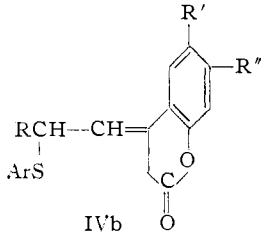
sence of piperidine under similar conditions. Similarly, the newly synthesized 7,8-benzothioncoumarin is proved to be stable toward thiols.

Action of Thiols on 4-Styrylcoumarins.—We have found that aromatic thiols are readily added to 6-methyl- (IIIa), and to 7-methyl-4-styrylcoumarin (IIIb) in the presence of piperidine leading to the formation of products believed to have structures like IVa or IVb.



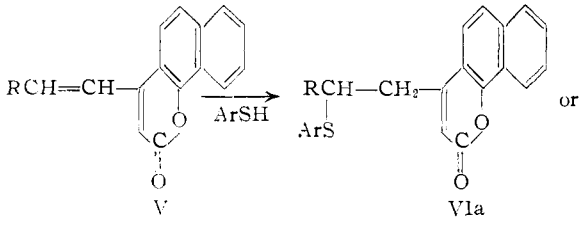
IIIa, R′ = CH_3, R″ = H
b, R′ = H, R″ = CH_3

IVa



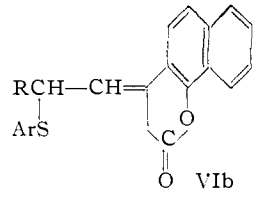
IVb

Similar reactions were carried out with 4-styryl-7,8-benzocoumarin (V), yielding addition products with structures like VIa or VIb.



V

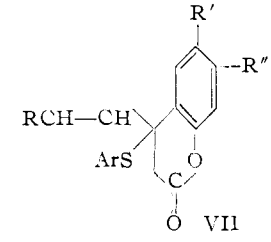
VIa



VIb

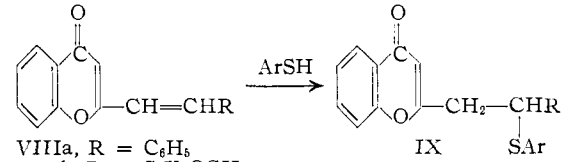
The finding that 4-methylcoumarin does not add thiols under the same conditions as does Ib should exclude the formation of addition products like VII. The ready oxidation of the sulfides to the corresponding sulfones (*cf.* Table III) may eliminate a vinyl sulfide structure for these sulfides.[17] Moreover, the finding that the reaction between thiols and the styrylcoumarin derivatives (III and V) is brought out in the presence of a basic catalyst may favor the isomerization of structure, *e.g.*, IVb to IVa.

The thiol adducts such as IV and VI (*cf.* Table II) are obviously of analogous structure. They are colorless compounds (whereas the corresponding styryls are usually colored yellow), insoluble in aqueous sodium hydroxide solution and give no color reaction with ferric chloride. When the adduct (IV, R = $C_6H_4OCH_3$-*p*, R′ = H, R″ = CH_3, Ar = $C_6H_4CH_3$-*p*) was treated with alcoholic potassium hydroxide followed by acidification, it yielded *p*-thiocresol and IIIb (R = $C_6H_4OCH_3$-*p*).



VII

Action of Aromatic Thiols on 2-Styrylchromones.—Whereas 2-methylchromone is stable or almost stable toward the action of aromatic thiols in the presence of piperidine, the densely colored 2-styrylchromones, namely, 2-(β-styryl-) (VIIIa), 2-(β-*p*-methoxystyryl-) (VIIIb), and 2-(β-3′,4′-methylenedioxystyryl)-chromone (VIIIc) react readily with aromatic thiols under the same experimental conditions, leading to the formation of products believed to have structures like IX.



VIIIa, R = C_6H_5
b, R = $C_6H_4OCH_3$-*p*
c, R = C_6H_3:O_2CH_2-3′,4′

IX

It has been shown[18] recently that 2-methylchromone may be regarded as a vinylog of A and this may explain the non-reactivity of 2-methylchromone toward aromatic thiols in the presence

(17) *Cf.* E. Campaigne and J. R. Leal, THIS JOURNAL, **76**, 1272 (1954); D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 1 (1951).

(18) A. Schönberg, M. M. Sidky and G. Aziz, THIS JOURNAL, **76**, 5115 (1954).

TABLE II

THIOL ADDUCTS (IV AND VI)

No.	Styryl-coumarin, R =	Thiol adduct IVa or IVb[a] Ar =	M.p.,[b] °C.	Yield, %	Color with H_2SO_4	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found
1	IIIa, C_6H_5	C_6H_5	65	93	Yell.-orange	$C_{24}H_{20}O_2S$	77.40	77.29	5.41	5.33	8.59	8.42
2		$C_6H_4CH_3$-*m*	95	78	Yellow	$C_{25}H_{22}O_2S$	77.70	77.56	5.74	5.61	8.28	8.13
3		$C_6H_4CH_3$-*p*	103	87	Yellow			77.47		5.43		8.22
4	$C_6H_4OCH_3$-*p*	C_6H_5	157	91	Red	$C_{25}H_{22}O_3S$	74.61	74.35	5.51	5.48	7.95	7.75
5		$C_6H_4CH_3$-*o*	110–111	71	Orange-red	$C_{26}H_{24}O_3S$	74.98	74.35	5.81	5.74	7.68	7.46
6		$C_6H_4CH_3$-*m*	114–115	83	Orange-red			74.74		5.72		7.55
7		$C_6H_4CH_3$-*p*	100	92	Orange-red			74.71		5.62		7.48
8	IIIb, C_6H_5	C_6H_5	136	94	Yellow	$C_{24}H_{20}O_2S$	77.40	77.41	5.41	5.33	8.59	8.45
9		$C_6H_4CH_3$-*o*	147	74	Yell.-green	$C_{25}H_{22}O_2S$	77.70	77.42	5.74	5.61	8.28	8.13
10		$C_6H_4CH_3$-*m*	133	70	Yell.-green			77.63		5.71		8.07
11		$C_6H_4CH_3$-*p*	130–131	89	Yellow			77.48		5.64		7.94
12	$C_6H_4OCH_3$-*p*	C_6H_5	115	85	Orange	$C_{25}H_{22}O_3S$	74.64	74.35	5.51	5.48	7.95	7.83
13		$C_6H_4CH_3$-*o*	118	80	Orange-red	$C_{26}H_{24}O_3S$	74.98	74.85	5.81	5.79	7.68	7.56
14		$C_6H_4CH_3$-*m*	114	77	Orange-red			74.91		5.62		7.43
15		$C_6H_4CH_3$-*p*	104	85	Orange-red			74.76		5.58		7.39
16	$C_6H_3(OH)OCH_3$-4,3	C_6H_5	102	95	Yellow	$C_{25}H_{22}O_4S$	71.76	71.58	5.30	5.30	7.64	7.50
17	$C_6H_3:O_2CH_2$-3′,4′	C_6H_5	130	91	Yellow	$C_{26}H_{26}O_4S$	72.10	71.94	4.84	4.68	7.68	7.62
18	V, C_6H_5	C_6H_5	134–135	94	Orange	$C_{27}H_{20}O_2S$	79.39	79.11	4.94	4.82	7.83	7.65
19		$C_6H_4CH_3$-*o*	132	74	Yellow	$C_{28}H_{22}O_2S$	79.60	79.38	5.25	5.16	7.57	7.43
20		$C_6H_4CH_3$-*m*	133	76	Yellow			79.46		5.21		7.52
21		$C_6H_4CH_3$-*p*	144	87	Yellow			79.51		5.20		7.46
22	$C_6H_4OCH_3$-*p*	C_6H_5	135–136	89	Orange-red	$C_{26}H_{22}O_3S$	76.70	76.58	5.06	4.87	7.30	6.98
23		$C_6H_4CH_3$-*o*	105	73	Red	$C_{29}H_{24}O_3S$	76.99	76.72	5.31	5.18	7.08	6.87
24		$C_6H_4CH_3$-*m*	122	72	Red			76.56		5.06		6.77
25		$C_6H_4CH_3$-*p*	139–140	83	Red			76.61		4.93		6.81

[a] All the adducts crystallize readily from a mixture of benzene and light petroleum, with the exception of no. 12, 22, 23, from absolute ethyl alcohol and no. 25 from petroleum ether (b.p. 80–100°). [b] Melting points are uncorrected.

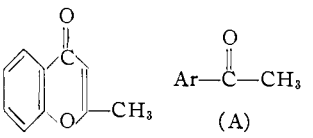
TABLE III

SULFONES OF THIOL ADDUCTS WITH 4-STYRYLCOUMARINS

Compound	Sulfone R	R′	R″	Ar	M.p.,[a] °C.	Yield, %	Solvent for cryst.[b]	Color with H_2SO_4	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found
IVa or IVb	C_6H_5	H	CH_3	C_6H_5	212	95	A	Pale-yell.	$C_{24}H_{20}O_4S$[c]	71.28	71.08	4.99	4.81	7.92	7.82
	C_6H_5	H	CH_3	$C_6H_4CH_3$-*p*	215	93	A	Pale-yell.	$C_{25}H_{22}O_4S$	71.76	71.52	5.30	5.13	7.64	7.53
VIa or VIb	$C_6H_4OCH_3$-*p*	..	..	$C_6H_4CH_3$-*o*	180	82	B	Orange	$C_{29}H_{24}O_5S$	71.89	71.76	4.99	4.67	6.60	6.43
	$C_6H_4OCH_3$-*p*	..	..	$C_6H_4CH_3$-*m*	175	86	A	Orange			71.82		4.83		6.55

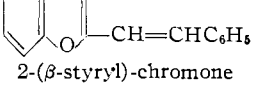
[a] Melting points are uncorrected. [b] A, ethyl alcohol; B, a mixture of acetic acid and water. [c] Mol. wt. calcd., 404; found, 385.

of basic catalyst.[19] According to the principle of vinylogy,[20] 2-styrylchromones (VIII) may be regarded as vinylogs of chalcones (B), and hence the ability of the carbon–carbon double bond of the styryl group to add the aromatic thiols,[10] used in this investigation, seems to be proved in principle.

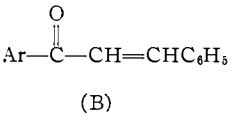


2-methylchromone

(A)



2-(β-styryl)-chromone



(B)

The sulfides, listed in Table IV, are colorless, insoluble in aqueous sodium hydroxide and give no color with ferric chloride. They give the correct molecular weight. When IX (R = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*) was refluxed with alcoholic potassium hydroxide for four hours, followed by acidification, *p*-thiocresol was regenerated, together with 2-*p*-methoxybenzylideneacetone and salicylic acid. Similar results have been obtained when 2-(β-*p*-methoxystyryl)-chromone (VIIIb) is allowed to react with alcoholic potassium hydroxide under the same experimental conditions, leading to the formation of salicylic acid and *p*-methoxybenzylideneacetone. Thus, it seems very probable that under the action of alkali, the thiol group in IX is eliminated with the formation of VIIIb which undergoes further hydrolysis to give the above-mentioned reaction products.[21]

The finding that 2-methylchromone is stable toward the action of aromatic thiols may eliminate the possibility of the addition of thiols to the unsaturated system of the chromone derivative to give addition compounds, having structures like X. Moreover, the behavior of IX (R = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*) toward hydrazine hydrate to give the pyrazole derivative (see below) and not a hydrazone derivative may, as well, be in favor of structure IX and not X.[22]

(19) *Cf.* the reactivity of ketones, *e.g.*, acetophenone toward thiols, *e.g.*, thiophenol in the presence of acid catalyst (ref. 17).

(20) R. C. Fuson, *Chem. Revs.*, **16**, 1 (1935).

(21) *Cf.* the action of alkali on chromones substituted in 2-position, leading to the formation of salicylic acid and the ketone $RCOCH_3$ (H. Simonis, *Ber.*, **50**, 779) 1917): ref. 9, p. 259.

(22) A compound with structure like X may be considered as a 4-chromanone derivative. 4-Chromanones behave like true ketones, forming oximes (K. V. Auwers and E. L. Lämmerhirt, *Ann.*, **421**, 1 (1920)), and phenylhydrazone derivatives (H. de Diesbach and H. Kramer, *Helv. Chim. Acta*, **28**, 1399 (1945)).

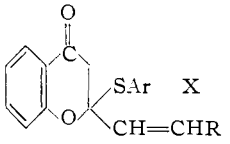
TABLE IV

THIOL ADDUCTS IX

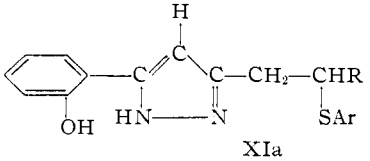
No.	Styryl-chromone	Thiol adduct Ar =	M.p.,[a] °C.	Yield, %	Color with H_2SO_4	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found
1	VIIIa[c]	C_6H_5	81	81	Yellowish-green	$C_{23}H_{18}O_2S$[b]	77.08	76.83	5.06	4.92	8.93	8.65
2		$C_6H_4CH_3$-*o*	89	67	Yellowish-green	$C_{24}H_{20}O_2S$	77.40	77.21	5.41	5.31	8.59	8.43
3		$C_6H_4CH_3$-*m*	91	72	Yellowish-green			77.36		5.29		8.52
4		$C_6H_4CH_3$-*p*	98	79	Yellowish-green			77.46		5.32		8.39
5	VIIIb[c]	C_6H_5	74	91	Orange	$C_{24}H_{20}O_3S$	74.21	73.96	5.19	5.06	8.24	8.13
6		$C_6H_4CH_3$-*o*	65	64	Orange	$C_{25}H_{22}O_3S$	74.61	74.52	5.51	5.43	7.95	7.86
7		$C_6H_4CH_3$-*m*	111	74	Orange			74.38		5.46		7.81
8		$C_6H_4CH_3$-*p*	95	78	Orange			74.49		5.42		7.69
9	VIIIc[d]	C_6H_5	121	89	Red	$C_{24}H_{18}O_4S$	71.63	71.58	4.51	4.36	7.95	7.78
10		$C_6H_5CH_3$-*o*	135	61	Red	$C_{25}H_{20}O_4S$	72.10	71.95	4.84	4.74	7.68	7.59
11		$C_6H_4CH_3$-*m*	136	69	Red			72.06		4.76		7.62
12		$C_6H_4CH_3$-*p*	99	84	Red			71.85		4.58		7.49

[a] Melting points are uncorrected. [b] Mol. wt. calcd., 358; found, 341. [c] U. S. Cheema, K. C. Gulati and K. Venkataraman, *J. Chem. Soc.*, 925 (1932). [d] *Cf.* A. Mustafa and M. I. Ali, *J. Org. Chem.*, in press.

It has been established that the action of hydrazine hydrate on 2-methylchromone[23] and on chromone itself[24] leads to the formation of pyrazole derivatives and not hydrazones of the chromones in question, as previously described.



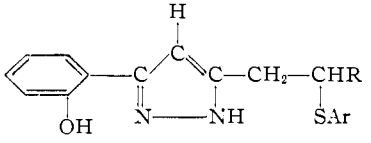
We have investigated the action of hydrazine hydrate on IX (R = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*) and believe, by analogy, that the reaction product is a pyrazole derivative (XIa or XIb).



or

XIa

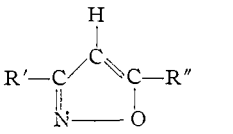
R = $C_6H_4OCH_3$-*p*
Ar = $C_6H_4CH_3$-*p*



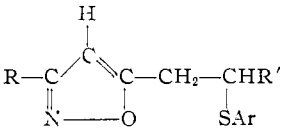
XIb

An alcoholic solution of XIa or XIb gives a violet color with ferric chloride. The pyrazole derivative, containing one active hydrogen atom in the phenolic hydroxyl group and one active hydrogen attached to a nitrogen atom, gives a diacetyl derivative when allowed to react with acetic anhydride. XIa or XIb was recovered unchanged when boiled with 10% alcoholic potassium hydroxide solution for four hours,[25] followed by acidification.

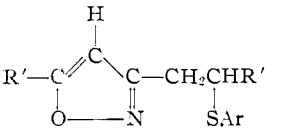
IX (R = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*) reacts readily with hydroxylamine hydrochloride in the presence of pyridine and ethyl alcohol at the boiling point of the reaction mixture. Flavone yields under similar conditions 3-*o*-hydroxyphenyl-5-isoxazole[24] (XII). By analogy, formula XIIIa is assigned to the reaction product, but we do not wish to exclude the corresponding formula XIIIb. The reaction product, though giving no color with ferric chloride, gives the Platkovskaya test[26] for hindered phenols.[27] It is recovered unchanged when boiled with 10% sodium hydroxide for three hours, followed by acidification. This stability toward alkali was to be expected; according to Claisen,[28] 3,5-substituted isoxazoles are very resistant to alkali.



XII, R′ = C_6H_4OH-*o*, R″ = C_6H_5



XIIIa
R = C_6H_4OH-*o*,



XIIIb
R′ = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*

Methods of Preparation.—6-Methylcoumarin-4-acetic acid, which was first prepared by Dey[29] in 20% yield, now has been obtained in 65% after the general procedure of Dey and Row[30] for the preparation of coumarin-4-acetic acids.[4] When the acid is allowed to condense with aromatic aldehydes, namely, benzaldehyde and *p*-methoxybenzaldehyde in the presence of pyridine and few drops of piperidine,[31] the new styryl derivatives IIIa (R = C_6H_5) and IIIa (R = $C_6H_4OCH_3$-*p*) are obtained in satisfactory yield.

Experimental

Preparation of New 4-Styrylcoumarins. General Procedure.—To a mixture of 6-methylcoumarin-4-acetic acid

(23) E. Koenigs and J. Freud, *Ber.*, **80**, 143 (1947).

(24) W. Baker, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.*, 1303 (1952).

(25) W. Baker and V. S. Butt, *ibid.*, 2150 (1949).

(26) V. M. Platkovskaya and S. G. Vatkina, *J. App. Chem.* (*U.S.S.R.*), **10**, 202 (1937); *C. A.*, **31**, 4232 (1937).

(27) A. Schönberg, A. Mustafa and A. F. A. M. Shalaby, THIS JOURNAL, **77**, 5756 (1955).

(28) L. Claisen, *Ber.*, **36**, 3672 (1903).

(29) B. B. Dey, *J. Chem. Soc.*, 1624 (1915).

(30) B. B. Dey and K. K. Row, *J. Indian Chem. Soc.*, **1**, 107 (1924).

(31) A. Mustafa and M. Kamel, THIS JOURNAL, **77**, 1828 (1955).

(0.02 mole) and the appropriate aldehyde (0.03 mole) in 30 ml. of freshly distilled pyridine was added 10 drops of freshly distilled piperidine. The reaction mixture was heated gradually to 125–130° (bath-temp.) and kept at that temperature for six hours. After it was cooled, water was added dropwise until the formation of a slight turbidity. The reaction mixture was then kept aside (ice-chest) for half an hour and the yellow styryl derivative was filtered off, washed with cold ethyl alcohol (*ca.* 30 ml.) and crystallized. 4-Styryl-6-methylcoumarin (IIIa, R = C_6H_5) was obtained in pale yellow crystals from petroleum ether,[32] m.p. 133°; yield *ca.* 30%. It gave a yellow color with sulfuric acid.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.44; H, 5.34. Found: C, 82.16; H, 5.18.

4-*p*-Methoxystyrylcoumarin (IIIa, R = $C_6H_4OCH_3$-*p*) was obtained as deep yellow crystals from a mixture of benzene and petroleum ether (b.p. 100–120°), m.p. 164°; yield *ca.* 40%. It gave a deep orange color with sulfuric acid.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.08; H, 5.47. Found: C, 77.87; H, 5.26.

Thiol Adducts. General Procedure.—A mixture of 0.5 g. of the substance under investigation, 0.5 g. of the aromatic thiol and two drops of freshly distilled piperidine[33] was warmed on a steam-bath for three hours, after which all the solid had melted. The cooled reaction mixture was washed with cold light petroleum (*ca.* 40 ml.) several times and the resulting solid crystallized from the proper solvent.

The thiol adducts, listed in Table I, are colorless, easily soluble in chloroform, benzene, but sparingly soluble in light petroleum, and are readily crystallized from a mixture of benzene and petroleum ether. They are insoluble in cold aqueous sodium hydroxide solution (10%) and their alcoholic solutions give no color with ferric chloride. They develop a yellow color with sulfuric acid.

The thiol adducts (IVa or IVb and VIa or VIb), listed in Table II, are colorless crystalline compounds, soluble in hot benzene, chloroform and glacial acetic acid, but sparingly soluble in light petroleum.

The thiol adducts IX, listed in Table IV, are colorless, easily soluble in benzene, chloroform, but difficultly soluble in light petroleum and are readily crystallized from a mixture of benzene and petroleum ether. They are insoluble in cold aqueous sodium hydroxide solution, and their alcoholic solutions did not give color with ferric chloride.

Sulfones.—The thiol adduct, dissolved in glacial acetic acid, was oxidized with hydrogen peroxide[34] (30%). The mixture was kept overnight at room temperature. The solid that separated out was filtered off and crystallized from the same solvent.

The sulfones, listed in Table III, are sharp melting crystalline compounds, easily soluble in hot glacial acetic acid, but difficultly soluble in light petroleum. The yields were almost quantitative.

Action of Potassium Hydroxide on: (a) II (**R = H, Ar = $C_6H_4OCH_3$-*p***).—A suspension of 0.5 g. of the sulfide in 50 ml. of 4% alcoholic potassium hydroxide solution was refluxed for a half-hour (steam-bath). After cooling, the reaction mixture was poured into ice and acidified with dilute hydrochloric acid, and extracted with ether. The ethereal layer was shaken with lead acetate solution and the yellow crystals so obtained were collected and identified as the yellow lead salt of *p*-thiocresol (m.p. and mixed m.p.[10]). The ethereal solution was then washed several times with cold water, dried and evaporated. The solid residue was crystallized from petroleum ether and identified as coumarin (*ca.* 0.28 g.) (m.p. and mixed m.p.).

(b) **VIa or VIb (R = C_6H_5, Ar = $C_6H_4CH_3$-*p*)**.—An identical procedure to that of Nicolet[10] was used. Half a gram of the sulfide was dissolved in 40 ml. of warm alcohol, and the solution rapidly cooled to 30–50°. A solution of 0.5 g. of lead acetate in 2.5 ml. of distilled water was then added, followed by a sufficient amount of potassium hydroxide solution to neutralize the acetic acid from the acetate and to leave the solution 0.5 *N* with regard to alkali. The yellow crystalline solid (*ca.* 0.3 g.) that separated out was filtered off, dispersed in alcohol, and treated with glacial acetic acid, whereby it became orange and then yellow. It melted at 205–208° and proved to be the lead salt of *p*-thiocresol.

The alkaline mother liquor was acidified with dilute acetic acid, and kept one hour at room temperature. The yellow solid so obtained was collected, crystallized from glacial acetic acid in yellow crystals (*ca.* 0.19 g.), m.p. 176°, and identified as V (R = C_6H_5) (m.p. and mixed m.p.).

(c) **IX (R = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*)**.—The sulfide (0.5 g.) was refluxed with 50 ml. of alcoholic potassium hydroxide solution (4%) for four hours. The reaction mixture was poured onto ice-cold water, and the alkaline solution was extracted with benzene (*ca.* 40 ml.). The benzene layer was washed several times with water, dried (Na_2SO_4), and evaporated. The oily residue was dissolved in hot petroleum ether and, on cooling, pale-yellow crystals (*ca.* 0.12 g.), m.p. 72°, of *p*-methoxybenzylideneacetone (m.p. and mixed m.p.) were obtained.

The alkaline layer was acidified with dilute hydrochloric acid, extracted with ether, and the ethereal solution gave on shaking with aqueous lead acetate solution yellow crystals (*ca.* 0.11 g.) of the lead salt of *p*-thiocresol. The ethereal solution, after thorough washing with water, followed by drying, gave on concentration colorless crystals (*ca.* 0.16 g. m.p. 156°, which were identified as salicylic acid (m.p. and mixed m.p.; color reaction with ferric chloride).

(d) **VIIIb.**—The experiment, using 0.5 g. of VIIIb, was carried out as described above. *p*-Methoxybenzylideneacetone (*ca.* 0.14 g.) and salicylic acid (*ca.* 0.21 g.) were obtained. Identification of the reaction products was carried out as described above.

7,8-Benzothioncoumarin.[35]—A reaction mixture of 2 g. of 7,8-benzocoumarin,[36] 5 g. of powdered phosphorus pentasulfide and 40 ml. of dry xylene (over sodium) was refluxed for four hours.[37] The yellowish-orange xylene solution was filtered while hot and concentrated to a small bulk. The yellow residue, obtained on cooling, was extracted with hot absolute ethyl alcohol (50 ml.) and filtered off while hot from any insoluble phosphorus pentasulfide. The alcoholic extract gave, upon concentration and cooling, golden yellow needles (*ca.* 1.2 g.), m.p. 158°. Recrystallization from petroleum ether (b.p. 100–120°) gave m.p. 159°.

Anal. Calcd. for $C_{13}H_8OS$: C, 73.58; H, 3.77; S, 15.09. Found: C, 73.60; H, 3.74; S, 14.85.

Action of Hydrazine Hydrate on: (a) **7,8-Benzothioncoumarin.**—A solution of 1 g. of the thioncoumarin in 50 ml. of ethyl alcohol was treated with 0.25 g. of hydrazine hydrate. The reaction mixture was heated (steam-bath) for 15 minutes, cooled and diluted with ice-cold water, when a yellow deposit was obtained. It was filtered off, crystallized from petroleum ether in yellow needles (*ca.* 0.8 g.), m.p. 160° and analyzed correctly for the expected hydrazone.[38]

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.28; H, 4.76; N, 13.33. Found: C, 74.60; H, 4.38; N, 13.21.

(b) **IX (R = $C_6H_4OCH_3$-*p*; Ar = $C_6H_4CH_3$-*p*)**.—To a solution of the sulfide in 30 ml. of ethyl alcohol, was added one gram of hydrazine hydrate. The reaction mixture was refluxed (steam-bath) for one hour. The colorless crystals (*ca.* 0.49 g.) that separated out on cooling were collected, and recrystallized from ethyl alcohol; m.p. 138°. The pyrazole derivative (XIa or XIb) gave a violet color when its alcoholic solution was treated with ferric chloride, and a yellowish-green color with sulfuric acid.

Anal. Calcd. for $C_{25}H_{24}N_2O_2S$: C, 72.10; H, 5.81; N, 6.73; S, 7.69; act. H, 0.48. Found: C, 71.93; H, 5.67; N, 6.23; S, 7.34; act. H, 0.46.

(32) Light petroleum is the fraction boiling at 50–60° and petroleum ether is that boiling at 60–80°.

(33) Ib and *p*-thiocresol were heated for three hours on a steam-bath without piperidine; the same reaction product was obtained in an almost quantitative yield. A similar product has also been obtained when Ib was allowed to react with freshly distilled thiophenol in a sealed tube in dry nitrogen atmosphere for three hours.

(34) H. Gilman and N. J. Beaber, THIS JOURNAL, **47**, 1450 (1925).

(35) This experiment was carried out with S. M. A. E. Omran.

(36) K. Bartsch, *Ber.*, **36**, 1966 (1903).

(37) *Cf.* the standard procedure for transforming coumarins into thioncoumarins after A. Clayton (*J. Chem. Soc.*, **93**, 524 (1908); A. Clayton and W. Godden (*ibid.*, **101**, 210 (1912)).

(38) Thioncoumarins are used to prepare the oxime and phenylhydrazone of coumarins since these compounds cannot be prepared directly from coumarins (Ch. Chmelewsky and P. Friedlander, *Ber.*, **46**, 1903 (1913); R. C. Elderfield, Editor, "Heterocyclic Compounds," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 213).

Acetylation.—A solution of 0.5 g. of the pyrazole derivative in 30 ml. of acetic anhydride was refluxed for two hours. The excess of acetic anhydride was removed under reduced pressure, and the cooled oily residue was treated with crushed ice and kept aside for a half-hour. The solid (*ca.* 0.39 g.), was filtered off, washed thoroughly with cold water and crystallized from alcohol in colorless crystals, m.p. 109°. The acetyl derivative is insoluble in aqueous sodium hydroxide solution (10%) and gave no color with ferric chloride. It gave an orange color with sulfuric acid.

Anal. Calcd. for $C_{29}H_{28}N_2O_4S$: C, 69.60; H, 5.60; N, 5.60; S, 6.40. Found: C, 70.02; H, 5.58; N, 5.60; S, 6.43.

Action of Hydroxylamine Hydrochloride on (a) 7,8-Benzothioncoumarin.—A solution of 1 g. of the thioncoumarin in 40 ml. of ethyl alcohol was treated with a solution of 0.3 g. of hydroxylamine hydrochloride, and 0.5 g. of sodium carbonate in 5 ml. of water. The reaction mixture was refluxed (steam-bath) for four hours, during which time yellow crystals separated out. The reaction mixture was cooled, filtered off and the reaction product was crystallized from ethyl alcohol as pale-yellow needles (*ca.* 0.95 g.), m.p. 222° (brown melt), and analyzed correctly for the expected oxime.[38]

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.93; H, 4.26; N, 6.63. Found: C, 74.10; H, 4.38; N, 6.65.

(b) IX (R = $C_6H_4OCH_3$-*p*, Ar = $C_6H_4CH_3$-*p*).—A mixture of 0.5 g. of the sulfide, 0.1 g. of hydroxylamine hydrochloride 30 ml. of ethyl alcohol and five drops of freshly distilled pyridine was refluxed for three hours (steam-bath). The cooled reaction mixture was poured into ice-cold water, and acidified with dilute acetic acid; the deposit formed was filtered (*ca.* 0.41 g.), and crystallized from ethyl alcohol in colorless crystals, m.p. 162°. The isoxazole derivative (XIIIa or XIIIb) was soluble in hot benzene; its alcoholic solution gave no color with sulfuric acid.

Anal. Calcd. for $C_{25}H_{23}NO_3S$: C, 71.94; H, 5.51; N, 3.35; S, 7.67. Found: C, 71.82; H, 5.36; N, 3.24; S, 7.51.

Acetylation.—The acetyl derivative of the isoxazole derivative (XIIIa or XIIIb) was similarly obtained as previously described in the case of (XIa or XIb). It was obtained in colorless crystals from ethyl alcohol; m.p. 119°. It was insoluble in aqueous sodium hydroxide solution (10%) and gave an orange color with sulfuric acid.

Anal. Calcd. for $C_{27}H_{25}NO_4S$: C, 70.59; H, 5.45; N, 3.05; S, 6.97. Found: C, 70.53; H, 5.43; N, 3.02; S, 6.76.

GIZA, CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF STANFORD UNIVERSITY]

Synthesis of the Racemic *p*-Dimethylaminobenzylidene-N,N′-bis-(1-phenylethyl)-malonamides

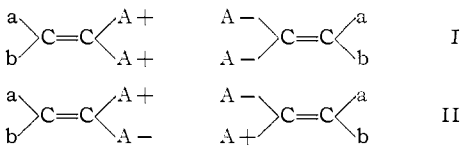
BY C. R. NOLLER, A. G. YARTZOFF AND W. N. JONES, JR.[1]

RECEIVED APRIL 27, 1956

Examples of the racemic forms of compounds having the structure abC=CA_2, where a and b are different non-dissymmetric groups and A is a dissymmetric group, have been prepared. Attempts to resolve one of the racemic forms were unsuccessful because of the instability of its salts.

It has been pointed out[2] that whereas a ketone having the structure $A_2C{=}O$, where A is a dissymmetric group, should exist in a racemic and a *meso* modification, the oxime of the *meso*-ketone as well as that of the racemic ketone should be resolvable, because the *syn* and *anti* forms of the *meso*-ketone are non-superposable mirror images. Apparently examples of *syn* and *anti* or of *cis* and *trans* isomerism arising from two enantiomorphic groups have not been reported in the literature.

The present work reports the preparation of the racemic forms I and II of a compound of the type abC=CA_2.



The compound chosen for study was the *p*-dimethylaminobenzylidene derivative of N,N′-bis-(1-phenylethyl)-malonamide. The malonamide of (1-phenylethyl)-amine should exist in a racemic and a *meso* modification. Reaction of racemic (1-phenylethyl)-amine with ethyl malonate gave two forms, one melting at 163–165° and the other at 139.5–140.° In order to determine which form was *meso* and which racemic, the active amides were prepared from the active amines. They melted at 135–136° and when mixed in equal amounts, they gave the racemic amide melting at 164–165°. Hence the amide melting at 139.5–140° is the *meso* form.

Condensation of the amides with *p*-dimethylaminobenzaldehyde gave two benzylidene derivatives, both of which are racemic. Since the benzylidene derivative from the racemic amide was the more easily prepared, initial attempts at resolution were made on this form. However, no stable salts could be obtained with (+)-tartaric, (−)-malic, (−)-mandelic, or (+)-camphor-10-sulfonic acid. A colorless hydrochloride was obtained when dry hydrogen chloride was passed into a benzene solution of the amine, but when the hydrochloride was added to water the yellow amine precipitated. Apparently, the two amide groups acting through the conjugated system reduce the basicity of the *p*-dimethylamino group to the point where salt formation does not take place in hydroxylic solvents.

Accordingly the amine was converted to the methiodide, and the quaternary iodide converted to the (+)-camphor-10-sulfonate. Attempts to separate the salt into its diastereoisomers were not promising. Because of these difficulties no attempt was made to resolve the racemic form of the benzylidene derivative from the *meso*-amide. It is hoped to prepare the carboxylic analog of these compounds, because the factors that reduce the basicity of the dimethylamino group should increase the acidity of the carboxyl group and permit easier resolution.

(1) Professor of Chemistry, McMurry College, Abilene, Texas, and Ford Foundation Fellow, 1953–1954.

(2) R. L. Shriner and R. Adams, p. 240 in Gilman's Organic Chemistry, 2nd Ed., 1943, John Wiley and Sons, New York, N. Y.