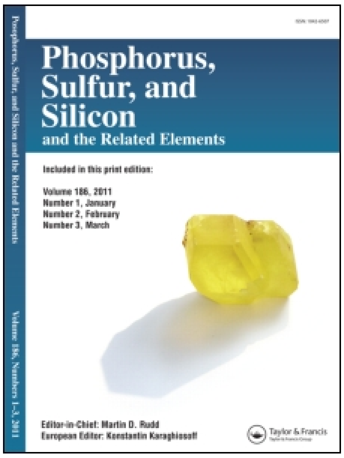

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THE CHEMISTRY OF STABILIZED 2H-THIOPYRANES

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THE CHEMISTRY OF STABILIZED 2H-THIOPYRANES

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Abstract 2H-Thiopyranes with a side chain in position 2 of the ring and a terminal formyl group are resonance stabilized compounds. They represent solid, coloured substances, both thermal stable and also reactive, especially against several nucleophilic reagents. The red coloured 2-(α-formylmethylene)-2H-thiopyranes are good available by cyclisation reactions starting with ß-thioxoaldehydes respectively their derivates, and acceptor substituted 2-chloro-propenes. The Z-s-cis configuration of the side chain was elucidated by ^{1}H-nmr spectroscopy and X-ray analysis. Several reactions lead to prolongation of the side chain, e.g. to the formation of purple 2-(γ-formylallylidene)-2H-thiopyranes. These compounds are very new educts for the synthesis of pentamethine dye stuffs with long wave light absorption maxima. Introduction of alkyl carboxylate groups by synthesis, e.g. use of dimethyl-2-chloro-propene-dicarboxylates, increase the solubility of resulting thiopyranes, but also cause an amazingly steric shielding effect of the formyl group against nucleophilic reagents.

INTRODUCTION

2H- and 4H-Thiopyranes are six membered heterocyclic sulfur compounds with relatively low thermal stability in case of the presence of hydrogen, alkyl or aryl substituents in positions 2,3,4,5,6 of the ring system. More stable compounds are available by introduction of electron acceptor groups, e.g. in position 3 of the ring ($-NO_2$, -CHO, $-COCH_3$, -CN, -COOR)[1]. Hydride ion abstraction by means of trityl perchlorate gives heteroaromatic thiopyrylium salts (FIGURE 1). In comparison with the

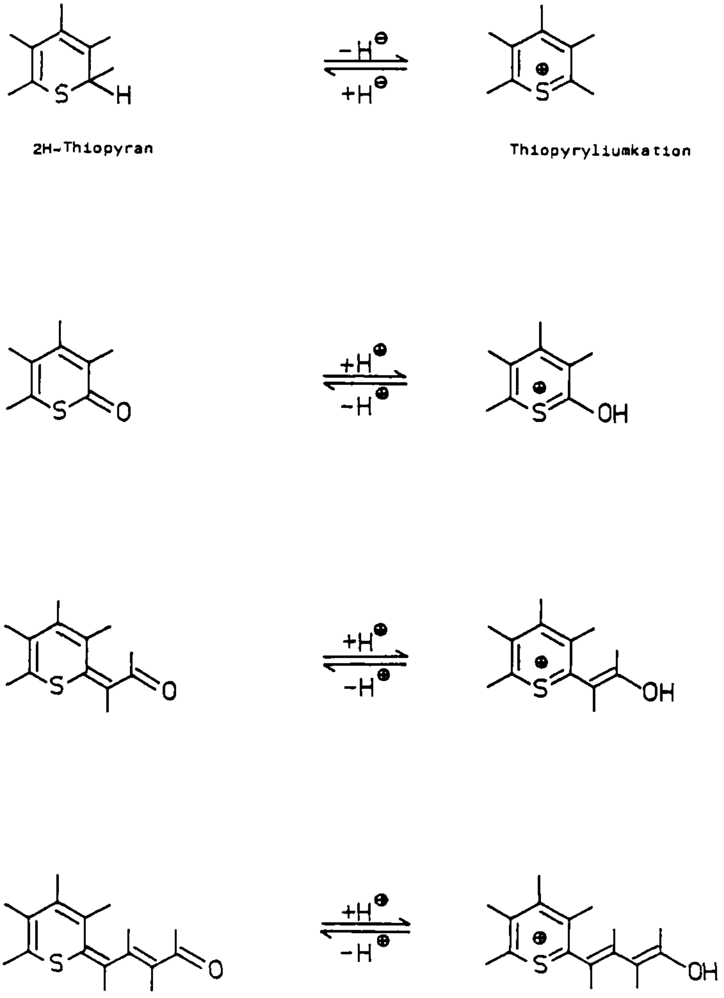


FIGURE 1

extensively investigated pyrylium salts the sulfur analogous compounds show a better thermal stability and lower reactivity. So, for example, ring opening and ring transformation reactions of thiopyrylium salts are not so strongly marked as in the substance class of pyrylium salts.

Another pathway to obtain stable thiopyrane derivatives is the introduction of an oxygen atom in positions 2 or 4 of the ring (2H-thiopyran-2-ones respectively 4H-thiopyran-4-ones)[2].

Great interest have the vinylogous compounds in FIGURE 1 with a formyl group in the side chain with regard to their physical behaviour, molecular structures and their reactivity, especially for the formation of compounds with dye stuff character.

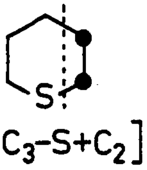
Our research work is concerned with syntheses, properties and possible reactions of such compounds (line 3 and 4 in FIGURE 1). Well known for several years are 2-acylmethylene-2H-thiopyranes. Lozach et al [3] synthesized such substances and investigated their molecular structure, especially the O-S-interaction between the acetyl or benzoyl group and the ring sulfur atom. As we found some years ago, these compounds are less reactive, but very stable [4]. We could show, that there is a great difference to 2-formylmethylene derivatives of 2H-thiopyranes. Their advantage is a very good availability, high thermal and photochemical stability and sufficient reactivity for many transformation reactions to compounds with an extensive conjugative system [5]. Most derivatives show amazingly long wave absorption maxima in the visible range of the spectrum respectively at the border to IR. In the last years it was possible to synthesize compounds in line 4 of FIGURE 1, 2-(γ-formylallylidene)-2H-thiopyranes [6] via two synthetic pathways.

RESULTS AND DISCUSSION

A) Syntheses

The formation of several 2H-thiopyrane derivatives depends on suitable building blocks with sufficient reactivity. So, after looking to a scheme of thiopyrane ring design, we selected $[C_3S+C_2]$cyclisation reactions as one of twelve possibilities (Formula A).

Some C_3S building blocks, e.g. monothio-1,3-dibenzoyl methane or eneaminothioketones [7], are well known, but



FORMULA A

their reactivity is not sufficient. Recently we have shown, that good availabla ß-thioxoaldehydes A and their derivatives are convenient for such syntheses, especially by reason of the excellent carbonyl reactivity of the aldehyde group, respectively the nitrogen masked carbonyl group (A, B and C, FIGURE 2). Often ß-thioxoaldehydes A are instable red oils, by treating the compounds with amines, they give compounds B or C, in last case mostly by use of dicyclohexyl amine [8]. Only compounds A with two phenyl or substituted phenyl groups are stable yellow solid substances (enethiol-formyl-form) [9].

Over a long time we investigated reactions between A, B or C and different substituted 3-chloro-crotonaldehydes [10]. For a better generalization of ring closure reactions to thiopyranes we now can introduce the principle of acceptor substituted 2-chloro-propenes (Formula B).

Electron with-drawing substituents R^3, R^4, R^5 cause two important effects in the chloropropene molecule:

a) activation of the chloro atom for a good leaving group during substitution reactions,

b) activation of the CH_2-group on basement of the vinylogous principle (increase of CH-acidity).

The well investigated 3-chloro-crotonaldehydes are only one example of a variety of more than twenty five C_2-

building blocks in this generalized cheme, very good available by Vilsmeier reaction of ketones [11].

ß-Thioxoaldehydes and Derivatives
(C_3-S building blocks)

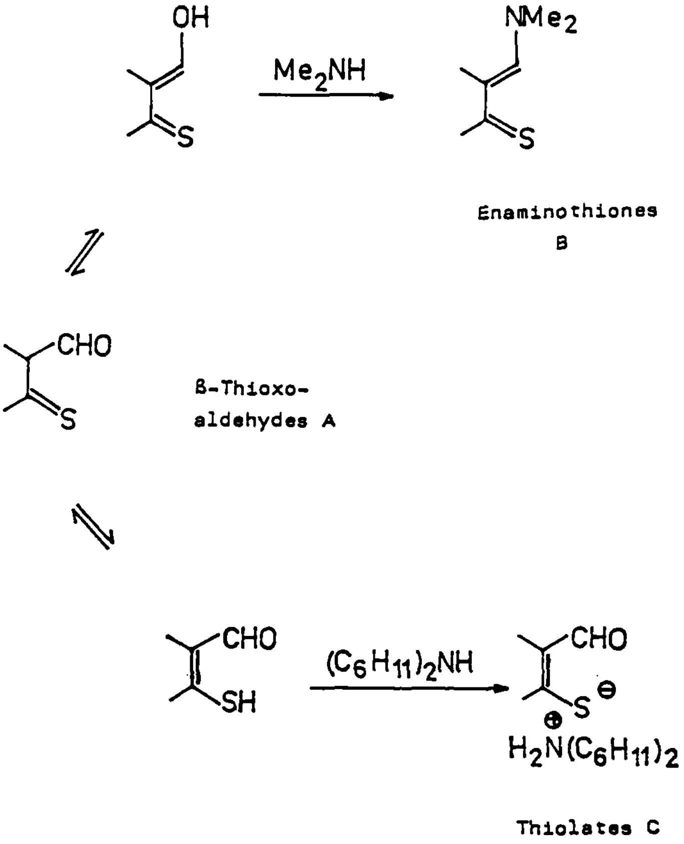
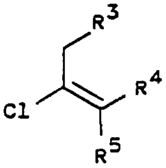


FIGURE 2

What we have done in the last years, is the variation of R^3, R^4 and R^5 using really good available compounds, e.g. dimethyl-2-chloro-propene-1,3-dicarboxylate, prepared from chlorination of dimethyl-3-oxo-glutarate, ethyl-3-chloro-2-formyl-crotonate, obtainable by Vilsmeier reaction of ethyl-acetoacetate, and other examples.

Acceptor substituted 2-Chloro-propenes



1: $R^3 = R^4 = H$, alkyl, aryl $R^5 = CHO$	3-Chloro-crotonaldehydes
2: $R^4 = H$ $R^3 = R^5 = COOMe$	Dimethyl-2-chloro-propene-1,3-dicarboxylate
3: $R^3 = H$ $R^4 = CHO$ $R^5 = COOEt$	Ethyl-3-chloro-2-formyl-crotonate
4: $R^3 = H$, alkyl $R^4 = CN$ $R^5 = COOEt$	Ethyl-3-chloro-2-cyano-crotonate

Variation of -CHO, -CN, -COOR : more than 25 compounds (C_2-building blocks)

FORMULA B

Best experimental results are obtained by reactions between 2-chloro-propene-1,3-dicarboxylates and eneaminothioketones B respectively thiolates C (FIGURE 2). Especially thiolates C are fit for the $[C_3S+C_2]$cyclisation reactions to 2H-thiopyranes with carboxylic ester groups (FIGURE 3). The resulting 2H-thiopyranes <u>1a-h</u> are red solid compounds with good crystallisation properties and remarkable thermal stability (TABLE 1). The introduction of a formyl group into the exomethylene group proceeds very easily via Vilsmeier reaction. Unfortunately the formyl group in 2H-thiopyranes <u>2a-h</u> shows less reactivity against nucleophilic reagents in comparison to alkyl substituted 2-(α-formylmethylene)-2H-thiopyranes. The reason is propably a steric shielding effect of the methoxy-carbonyl groups, especially in 3-position.

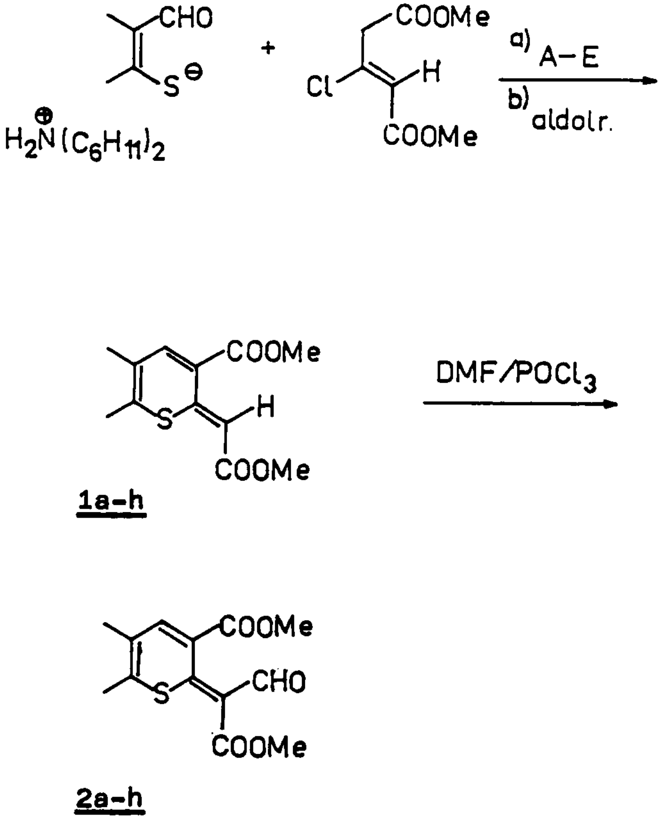
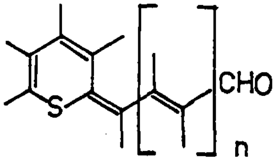


FIGURE 3

Concerning this fact, reactions of A, B or C with 3-chloro-2-formyl-crotonates rise in interest, because the product 3 (m.p.: 135-37 °C, yield: 40 %, λ_{max}: 438 nm) undergo carbonyl condensation reactions in a wide variety.

The aim of our investigations is to realize a wide variation of reactive and synthetic available 2-chloro-propene derivatives for ring closure reactions to several 2H-thiopyranes.

Another task is the prolongation of a reactive side chain in 2-position of the thiopyrane ring (Formula C).



n = 0 : 2-(α-Formylmethylen)2H-thiopyranes

n = 1 : 2-(γ-Formylallyliden)2H-thiopyranes

FORMULA C

In this connection all attempts to synthesize 2-(γ-formylallylidene)2H-thiopyranes by direct ring closure reactions of convenient building blocks have been unsuccessful. Therefore we developed two synthetic pathways starting either from formylmethylene thiopyranes or 2-alkyl-thiopyrylium salts:

a) Wittig reaction, followed by Vilsmeier reaction, starting from 2-(α-formylalkylidene)2H-thiopyranes as educts, yield directly the formylallylidene derivative 4a (m.p.: 160-62 °C, yield: 45 %, λ_{max}: 480 nm: 4a is the 3-phenyl-allylidene derivative) and 4b (m.p.: 223-24 °C, yield: 45 %, λ_{max}: 505 nm: 4b is the 3-formyl-3-phenyl derivative).

b) Similar compounds with a partially different substituent design are obtainable by condensation reactions of 2-alkyl respectively 2-benzyl thiopyrylium salts together with several 3-dimethylamino-acrolein derivatives. In a first step 2-(4-dimethylamino-butadienyl)2H-thiopyranes are available in good yields as deep coloured (purple) salts 5a-d (FIGURE 4).

The salts are fit for several condensation reactions to symmetrical or unsymmetrical pentamethine dye stuffs, respectively corresponding neutrocyanines, with long wave absorption maxima at the border of IR.

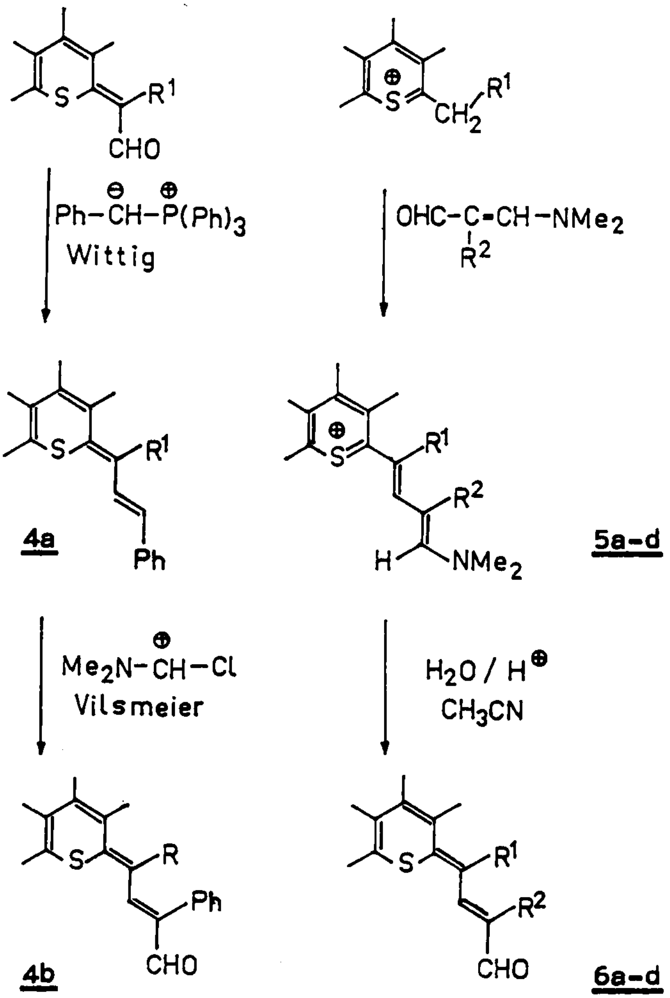


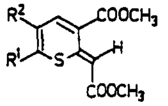
FIGURE 4

Hydrolysis with water/acetonitrile solvent mixture gives the desired 2-(γ-formylallylidene)2H-thiopyranes 6a-d (TABLE 2).

B) Structures, Properties and Reactions

2H-Thiopyrane derivatives 1 and 2 with different substituents, e.g. ester groups, are stable, red, solid compounds, similar to early described 2-(α-formylmethylene)-2H-thiopyranes with alkyl and aryl groups in the side chain [10]. The differences in λ_{max} values between the esters 1a-h and the formylated products 2a-h are small (TABLE 1) and in the expected range.

TABLE 1



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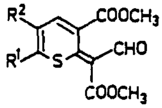
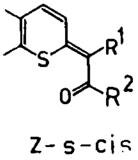


2

	R^1	R^2	yield (%)	m.p. (°C)	UV-VIS (EtOH) λ_{max}(nm)(lg ε)
1a	C_6H_5	H	84	106-107	465 (3.68)
1b	4-Br-C_6H_4	H	87	125-126	445 (3.76)
1c	4-Cl-C_6H_4	H	77	135-136	450 (3.76)
1d	4-NO_2-C_6H_4	H	85	193-195	— —
1e	4-CH_3O-C_6H_4	H	81	116-117	455 (3.88)
1f	4-Me_2N-C_6H_4	H	87	195-196	495 (4.16)
1g	C_6H_5	CH_3	70	123-125	430 (3.81)
1h	C_6H_5	C_6H_5	82	127-128	442 (3.68)
2a	C_6H_5	H	79	205-207	490 (3.80)
2b	4-Br-C_6H_4	H	90	170-172	475 (4.02)
2c	4-Cl-C_6H_4	H	75	160-161	475 (4.02)
2d	4-NO_2-C_6H_4	H	78	188-191	473 (3.95)
2e	4-CH_3O-C_6H_4	H	70	143-145	490 (4.00)
2f	4-Me_2N-C_6H_4	H	85	ab 116 (Z.)	560 (4.15)
2g	C_6H_5	CH_3	48	139-141	435 (4.02)
2h	C_6H_5	C_6H_5	82	159-160	460 (3.93)

Remarkable is the influence of the dimethylamino group in 1f and 2f indicating the donor-acceptor-character of the compounds, which is increased by donator groups in position 6 of the thiopyrane ring.

^{1}H-nmr and X-ray-investigations indicate conformably Z-configuration and a nonbonding interaction between the ring sulfur atom and the carbonyl oxygen atom in the side chain (FORMULA D) for 1a-h. For 2a-h we believe, that the above mentioned interaction occurs between the sulfur atom and the oxygen atom of the formyl group, as elucidated in former research work [12].



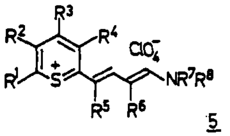
FORMULA D

This means, that the configuration has changed during the Vilsmeier reaction. Unfortunately we not yet have any exact proof for this assumption with exception of i.r. spectra.

2-(γ-Formylallylidene)2H-thiopyranes 4b and 6a-d with several substituents in the ring system and in the side chain represent deeply coloured, purple, solid compounds with λ_{max} values in the expected part of the visible spectrum (TABLE 2). Reactions with amines, e.g. dimethylamine, in presence of acids, leads to substituted 2-(δ-aminobutadienyl) thiopyrylium salts, which are preferable synthesized by condensation reactions starting with simple 2-alkyl thiopyrylium salts (FIGURE 4). These salts (5a-d) exhibit high reactivity and therefore they are excellent educts for the formation of pentamethine dye stuffs with long wave absorption maxima in the near infrared range of the electron spectrum. So we measured values for λ_{max} between 855 and 1010 nm in dependence of the substituent design.

The prolongation of the side chain in 2-position of a 2H-thiopyrane ring system is of general interest. Beside the convenient synthesis of polymethine dye stuffs for several special purposes we discovered another examle for application of special thiopyrane derivatives in the field of diazotypie. So it was possible to develope

TABLE 2



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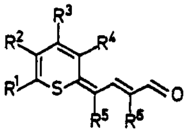


6

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	yield (%)	m.p. (°C)	UV-VIS(CH$_3$CN) λ_{max}(nm)(lgε)
5a	C$_6$H$_5$	H	C$_6$H$_5$	H	H	H	C$_6$H$_5$	CH$_3$	74	246-247	630 (4.38)
5b	C$_6$H$_5$	H	C$_6$H$_5$	-(CH$_2$)$_2$-		H	C$_6$H$_5$	CH$_3$	75	ab 180	730 (4.23) 672 (4.42) 625 (4.34)
5c	C$_6$H$_5$	H	C$_6$H$_5$	-(CH$_2$)$_3$-		H	C$_6$H$_5$	CH$_3$	99	240-241	636 (4.34)
5d	C$_6$H$_5$	H	C$_6$H$_5$	H	H	CN	CH$_3$	CH$_3$	96	250-252	588 (4.59)
6a	C$_6$H$_5$	H	C$_6$H$_5$	H	H	H	-	-	40	121-122	555 (3.94) 513 (4.03)
6b	C$_6$H$_5$	H	C$_6$H$_5$	-(CH$_2$)$_2$-		H	-	-	29	152-155	503 (4.20)
6c	C$_6$H$_5$	H	C$_6$H$_5$	-(CH$_2$)$_3$-		H	-	-	61	155-157	495 (3.80)
6d	C$_6$H$_5$	H	C$_6$H$_5$	H	H	CN	-	-	—	—	580 (qual.)

diazonium salts with a relatively high thermal stability and sufficient sensitivity on red light via the synthetic steps in FIGURE 5, that means condensation of several 2-formylmethylene thiopyranes with 4-nitro-benzylcanides in a Knoevenagel reaction followed by selective reduction of the nitro group and diazotation reaction of the resulting amines. Compounds 7a-e and 8a-c (TABLE 3) are typical donor acceptor systems with remarkable physical properties. The aromatic nitro compounds show long wave absorption maxima, esp. 7a, and after reduction and formation of the diazonium function there is to observe a large bathochromic shift till to 740/790 nm, measured in solid layers. The photochemical dediazonation reaction is proceeding with light of the above mentioned wave length, but unfortunately the photolyse products are not yet colourless as desired and necessary for technical purposes.

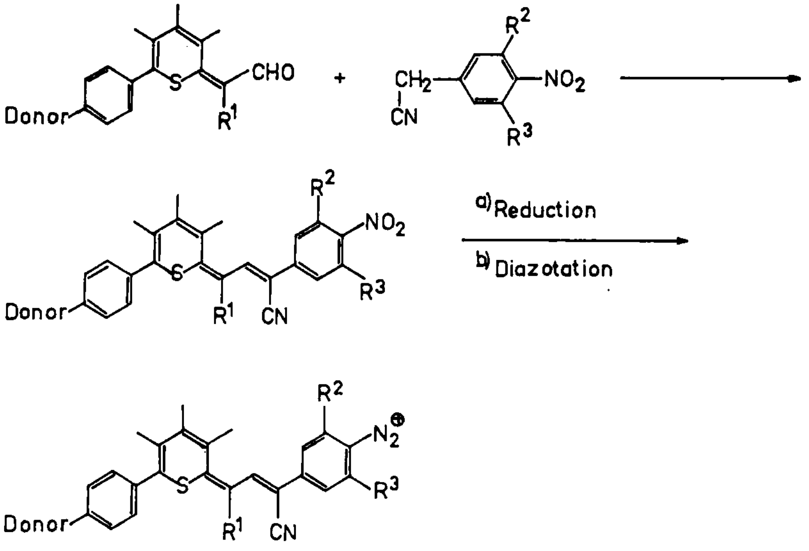
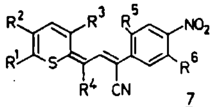


FIGURE 5

TABLE 3



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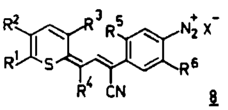

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	R^1	R^2	R^3	R^4	R^5	R^6	X^-	yield (%)	m.p. (°C)	UV-VIS λ_{max}(nm)(lg ε)
7a	4-CH_3O-C_6H_4	H	H	C_6H_5	H	H	-	56	189-190	568· (4.25)
7b	C_6H_5	C_6H_5	-$(CH_2)_3$-		H	H	-	71	199-201	565 (4.34)
7c	C_6H_5	C_6H_5	H	CH_3	H	H	-	73	261-263	520 (4.47)
7d	CH_3	CH_3	H	CH_3	H	H	-	27	249-250	540 (4.20)
7e	CF_3	C_6H_5	H	CH_3	H	H	-	35	175-177	450 (4.15)
8a	4-CH_3O-C_6H_4	H	H	C_6H_5	H	H	BF_4			740 a)
8b	C_6H_5	C_6H_5	-$(CH_2)_3$-		H	H	1/2 $ZnCl_4$			740 a)
8c	C_6H_5	C_6H_5	-$(CH_2)_3$-		OCH_3	OCH_3	BF_4			790 a)

a) measured in solid layer

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