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Synthesis and Studies of Some Novel Analogues of Phthalein Dyes

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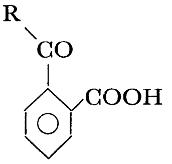
Some novel analogues of phthalein dyes have been synthesized by condensing a γ-keto acid, 2-(2-thenoyl) benzoic acid with various phenols. The dyes so obtained are unsymmetrically substituted phthalides where the central carbon atom is attached with two different rings and these dyes have been named as phthal-as-eins; -'as' representing unsymmetry, and-'ein' class of the compound (phthal-ein). The structures of these products have been established on the basis of their elemental analysis and chemical reactions. Absorption maxima of these new dyes have been determined and compared with those of true phthaleins.

The γ-keto acids have been found to exist in open **1** and cyclic **2** form due to keto-lactol tautomerism.[1] Generally it has been observed that γ-keto acids exist chiefly as lactol or equilibrium mixture of keto and ctol forms.a[2,3] These lactols give crystalline acetyl derivatives **3**[4,5] retaining their cyclic structure. Hence it has been concluded that the lactol form of the γ-keto acids is more stable than their open form.[5] The cyclic derivatives, pseudo chlorides (**4**)[6] and pseudo esters (**5**)[7–9] are obtained through the lactol form.



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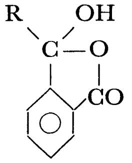

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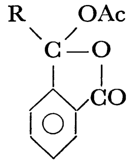

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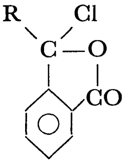

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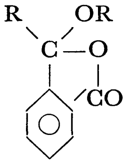

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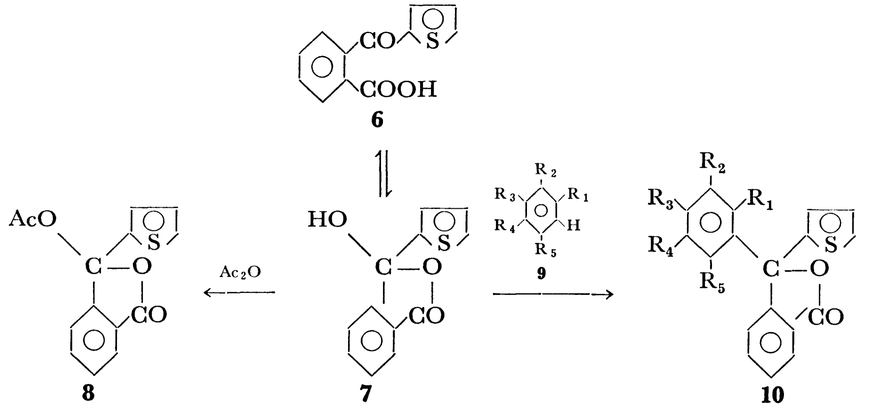
Many chemical reactions[10,11] of γ-keto acids have been explained on the basis of their cyclization to lactol. IR,[8,12] Raman,[9] and NMR[13] spectra have further confirmed the formation of cyclic isomers.

It has been observed that ring tautomerism of γ-keto acids is further exalted by changing R to larger alkyl or aryl groups.[14] It increases further when hydrogen atoms on carbon atoms α to carboxyl group (in γ-keto acids of the type, R–CO–CH$_2$–CH$_2$–COOH), are also changed to larger alkyl groups or α,β-ethylenic bond.[15] In continuation of previous work[16–23] on synthesis of mixed phthaleins and succineins, we report in this paper synthesis of a new series of phthal-as-eins from a γ-keto acid, 2-(2-thenoyl)benzoic acid.

Results and Discussion

2-(2-Thenoyl)benzoic acid has also been found spectroscopically to exist as a mixture of keto **6** and lactol form **7**. IR spectrum of the acid shows notable absorption band at 1695, 1680, and 1740 (weak) cm^{-1} indicating the presence of carboxyl ${>}$C=O, diaryl ketonic ${>}$C=O, and lactonic ${>}$C=O respectively. Absorption peaks due to –OH of carboxyl group and –OH



11 $R_1=R_2=R_4=R_5=H$; $R_3=OH$
12 $R_2=R_4=R_5=H$; $R_1=R_3=OH$
13 $R_3=R_4=R_5=H$; $R_1=R_2=OH$
14 $R_2=R_3=R_5=H$; $R_1=R_4=OH$
15 $R_2=R_4=H$; $R_1=R_3=R_5=OH$
16 $R_4=R_5=H$; $R_1=R_2=R_3=OH$
17 $R_2=R_4=R_5=H$; $R_1=R_3=OCOCH_3$
18 $R_5=H$; $R_2=R_4=Br$; $R_1=R_3=OH$

Scheme 1.

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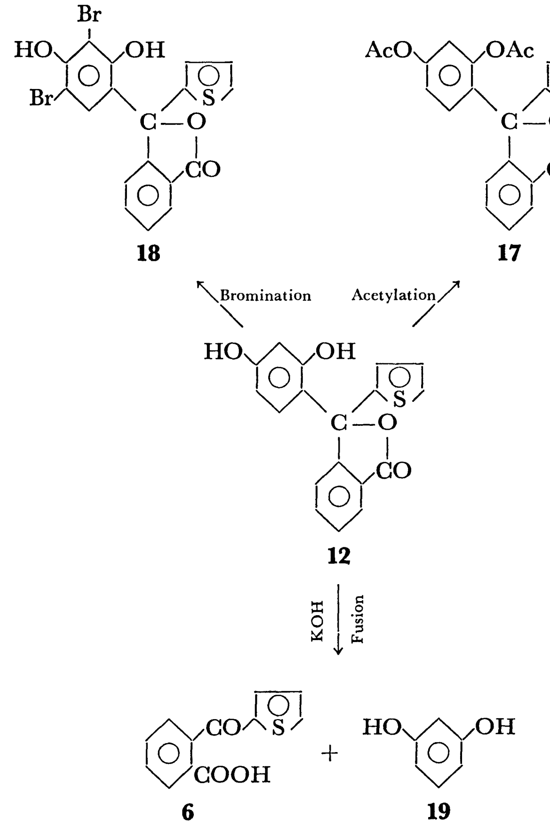
of lactol appear at 2640 (weak) and 3090 (broad) cm^{-1} respectively. In the NMR spectrum of the acid besides other peaks, there is a broad singlet of low intensity at τ 5.5 (1H) which may be assigned to hydroxyl proton of lactol form present in the acid.

IR spectrum of the acetyl derivative of the acid shows a very sharp peak at 1760 cm^{-1} which has been assigned to lactonic $>C=O$. Peaks at 1750, 1235, 1205, and 1010 cm^{-1} are due to presence of acetate group. Peaks present in the IR spectrum of the acid at 3090, 2640, 1695, and 1680 cm^{-1} are found to be absent in the IR spectrum of the acetyl derivative of the acid. In the NMR spectrum of the acetyl derivative there is no signal at τ 5.5 (present in the NMR spectrum of the acid) but there is new signal as a singlet at τ 7.5 (3H) due to acetate group.



Scheme 2.

On the basis of above spectral studies it has been concluded that acetyl derivative of the acid possesses a cyclic structure and its formation takes place through the lactol form **7** of the acid **6** (Scheme 1).

The phthal-as-eins have been prepared by condensing the acid with phenols (**9**). The condensation follows through the equilibrium process of lactol form **7** of acid (**6**) and with excess of phenols, the entire acid taken reacts as lactol. The purity of the dyes has been confirmed by TLC and paper chromatography. Their structures have been confirmed on the basis of elemental analysis, bromination, acetylation and KOH degradation studies. Formation of diacetyl derivative (**17**) and dibromo derivative (**18**) support the presence of only one resorcinol molecule in the dye molecule (**12**). KOH fusion of dye (**12**) gave acid (**6**) and resorcinol (**19**).

The absorption maxima (λ_{max}) of the phthal-as-eins are given in Table 2. Table 3 shows λ_{max} of true phthaleins prepared in similar manner. Absorption maxima of phthal-as-eins **11**, **12**, and **18** have been compared with those of phenolphthalein, fluorescein, and eosin respectively and a closeness has been observed.

Experimental

All melting points are uncorrected. The absorption maxima (visible) have been measured with the help of model DU Beckman spectrophotometer in absolute ethanol (neutral and alkaline media). IR spectra were recorded in KBr on a Perkin Elmer infracord. NMR spectra were run in DMSO-d_6 on Varian A-60 spectrophotometer using TMS as internal standard. For TLC, plates coated with Alumina G-Silica gel G (1:1) layers were run in ethyl acetate–meth-

TABLE 1. PREPARATION AND PROPERTIES OF 3-(SUBSTITUTED PHENYL)-3-(2-THIENYL)PHTHALIDES (**10**)

	Substituents on phenyl group	Condensation Temp °C	Condensation Duration h	Appearance (Micro-crystalline)	Mp °C	Yield %	Formula	Found (%) Calcd (%) C	H	S
11[a)]	*p*-Hydroxy	160—170	6	Greyish white	210—211	57	$C_{18}H_{12}O_3S$	70.36 70.13	3.56 3.89	10.12 10.37
13	2,3-Dihydroxy	220—230	2	Brown	215—216	40	$C_{18}H_{12}O_4S$	66.31 66.66	3.98 3.70	9.62 9.87
14	2,5-Dihydroxy	230—240	3	Light brown	195—196	35	$C_{18}H_{12}O_4S$	66.89 66.66	3.46 3.70	9.97 9.87
15	2,4,6-Trihydroxy	190—200	2	Brown	>300 dec.	50	$C_{18}H_{12}O_5S$	63.64 63.82	3.26 3.52	9.23 9.41
16	2,3,4-Trihydroxy	180—190	$1^1/_2$	Blackish-brown	>300 dec.	50	$C_{18}H_{12}O_5S$	64.10 63.82	3.21 3.52	9.55 9.41
17	2,4-Diacetoxy	130—140	4	Light-yellow	175—176	50	$C_{22}H_{16}O_6S$	64.92 64.70	3.65 3.92	7.60 7.84
18	3,5-Dibromo-2,4-dihydroxy	130—140	1	Brick-red	235—236	67	$C_{18}H_{10}O_4SBr_2$		Br, Br,	33.32 33.15

All the compounds crystallized from rectified ethanol. a) Excess phenol after condensation was removed by steam distillation.

Table 2. Absorption maxima of 3-(substituted phenyl)-3-(2-thienyl)phthalide
(G. F.=Green Fluorescence)

Dyes	Color in ethanol		Color with 2% NaOH	λ_{max}/nm	
	Neutral	Alkaline		Neutral	Alkaline (pH)
11	Yellow-orange	Reddish-pink	Reddish-pink	510	540 (10.0)
12	Yellowish-brown (G. F.)	Red-brown ((G. F.)	Red-brown (G. F.)	480	490 (9.5)
13	Yellow	Green	Green	400	700 (10.5)
14	Yellow	Purple	Purple	a)	— —
15	Yellow	Red-brown	Red-brown	a)	— —
16	Yellow	Purple	Purple	a)	— —
17	Yellow	Yellow	Colorless	a)	— —
18	Red (G. F.)	Red (G. F.)	Dark red	520	520 (9.5)

a) Correct λ_{max} could not be measured due to decomposition of these dyes in solution.

Table 3. Absorption maxima of known phthaleins

Name of dye	Color in ethanol		Color with 2% NaOH	λ_{max}/nm	
	Neutral	Alkaline		Neutral	Alkaline (pH)
Phenolphthalein	Colourless	Pink	Pink	—	550 (10.5)
Fluorescein	Yellow red (G. F.)	Red (G. F.)	Reddish pink (G. F.)	480	500 (10.0)
Eosin	Light pink (G. F.)	Orange pink (G. F.)	Pink	530	530 (9.5)

anol–5 mol dm^{-3} aqueous ammonia solution (60:30:10) and spots were developed with 5% aqueous NaOH.

2-(2-Thenoyl)benzoic acid was prepared according to reported procedure.[24] Its acetyl derivative prepared by refluxing it with acetic anhydride in presence of fused sodium acetate. The phenols (phenol, resorcinol, catechol, hydroquinone, phloroglucinol, and pyrogallol) have been taken in slight excess of molecular proportion than the acid (**6**) and concentrated sulfuric acid (4—5 drops) has been used as condensing agent throughout. Analogous to phthaleins, the condensation is supposed to have taken place as shown in Scheme 1.

*Synthesis of 3-(2,4-Dihydroxyphenyl)-3-(2-thienyl) phthalide (**12**).* An intimate mixture of 2-(2-thenoyl)benzoic acid (4.6 g) and resorcinol (3.0 g) was taken in a hard glass boiling tube and heated to 240 °C. Concentrated sulfuric acid (4—5 drops) was added and heating was continued between 240—250 °C for about 2 h till the contents became hard and brittle on cooling. The condensed mass was crushed, and washed thoroughly with water to remove excess of resorcinol. Then it was extracted with 2% aqueous sodium hydroxide and filtered. The dye was precipitated from red-brown (green fluorescent) filtrate by acidification with dilute hydrochloric acid. It was filtered, washed with water and purified by repeated crystallization from rectified ethanol, dried in an oven at 120 °C and then in a vacuum desiccator (3.6 g, 56% of the theoretical yield).

The yellow-brown dye, mp >300 °C is microcrystalline. The ethanolic solution is yellowish brown with light green fluorescence which on addition of alkali gives red-brown color with intensified green fluorescence. Found: C, 66.92; H, 3.50; S, 9.52%; mol wt, 315.00 (Rast). Calcd for $C_{18}H_{12}O_4S$: C, 66.66; H, 3.70; S, 9.87%; mol wt, 324.

The preparation of rest of the dyes, given in Table 1 has been done in the identical manner as already described.

*Paper Chromatography of Dye (**11**).* On test paper Whatman No. 1, 1-butanol–ammonia was allowed to run for 13 h (descending) to give two corresponding red-pink spots of the dye (**11**) and reference dye phenolphthallein, R_f: (**11**), 0.89, phenolphthalein, 0.91 (lit,[26] R_f, 0.92).

*Acetylation of Dye (**12**).* The dye (XII) (1.0 g) was refluxed with acetic anhydride (15 ml) and fused sodium acetate (3.0 g) at 130—140 °C for 4 h to give yellowish white microcrystalline diacetyl compound (0.6 g), mp, 175—176 °C (from rectified ethanol). It is soluble in ethanol, acetone, and acetic acid. Found: C, 64.92; H, 3.65; S, 7.60; acetyl, 20.70%. Calcd for $C_{22}H_{16}O_6S$ or $C_{18}H_{10}O_4S\ (COCH_3)_2$: C, 64.70; H, 3.92; S, 7.84; Acetyl, 20.58%.

*Bromination of Dye (**12**).* The dye (XII) (1.0 g) and 10% solution of bromine in acetic acid (10 ml) were refluxed at 130—140° for 1 h. The reaction mixture on cooling and dilution with water gave brick red dibromo compound (1.0 g), mp 235 °C (from rectified ethanol). The ethanolic solution of the dibromo compound is red with light green fluorescence which is intensified on addition of alkali. Found: Br, 33.32%. Calcd for $C_{18}H_{10}O_4SBr_2$: Br, 33.15%.

*Caustic potash treatment of Dye (**12**).* The dye (XII) (1.5 g) was taken in a platinum crucibllle and mixed with a paste of caustic potash pellets (10.0 g). The contents were heated at aobut 250 °C for 3 h until the red color of the dye disappeared completely. The residue was cooled and dissolved in water (50 ml) and filtered. The excess of alkali was just neutralized by dilute hydrochloric acid when a yellowish brown residue (A) settled down which was filtered and washed with water. The filtrate was further acidified by adding an excess of hydrochloric acid giving a white residue (B); it was also filtered and washed with water. The filtrate was shaken with ether and on evaporation of excess of solvent a brownish red residue (C) was obtained. Residues A, B, and C were identified as unreacted residual dye (**12**), acid (**6**), and resorcinol (**19**) respectively by direct comparison (m. m. p, co-TLC, co-IR) with their authentic samples.

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