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Studies on the Ultraviolet Absorption of Psoralene and Substituted Psoralenes

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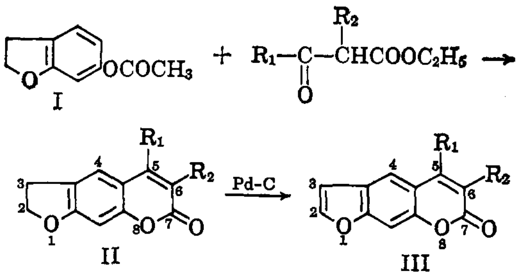
Psoralene, the active principle of *Psoralea corylifolia* Linn., has been widely used in the treatment of leucoderma.[1] Many psoralene derivatives obtained both naturally and synthetically have been studied and the photosensitizing activities have been found to vary according to the position as well as to the nature of the substituent.[2] In view of the demonstration of Pathak and Fellman[3] that there is a correlation between light absorption and photosensitizing activity, it was considered to be interesting to study the ultraviolet absorption spectra of psoralenes substituted at various positions. In this note we have dealt with psoralene derivatives substituted at the pyran ring (*viz.*, 5- and 6-positions).

Different methods employed for the syntheses of psoralene and its derivatives have been reviewed by Esse and Christensen[4] and we have employed 6-acetoxycoumaran (I) as a starting material for our syntheses. Compound I has been prepared according to Horning and Reisner's[5] method by condensing resorcinol and chloroacetonitrile, acetylating the product, and reducing catalytically the 6-acetoxybenzofuranone with palladized charcoal. We have also followed the method employed by Davies,[6] *et al.*, for the synthesis of 6-hydroxybenzofuranone from resorcinol and chloroacetyl chloride. Syntheses of substituted psoralenes (III) were accomplished by condensing 6-acetoxycoumaran (I) with an appropriate β-keto ester followed by dehydrogenation of the resulting dihydropsoralene (II) with palladium–carbon in refluxing diphenyl ether.[7]



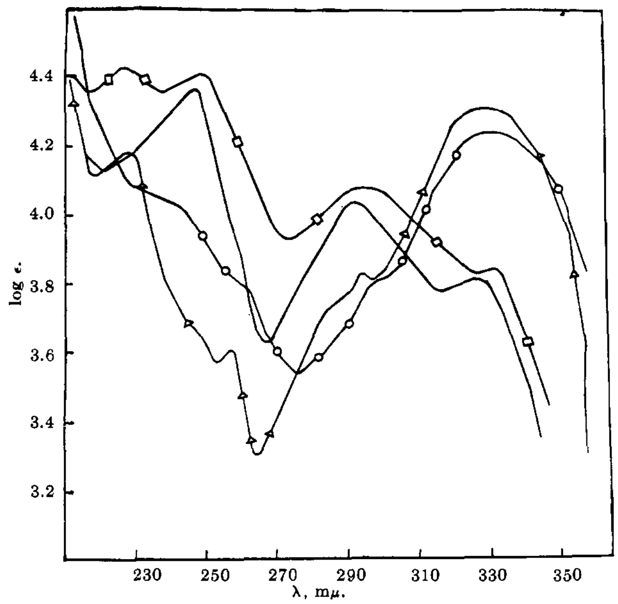


Fig. 1.—Ultraviolet absorption spectra of psoralene, ———; 5-phenylpsoralene (15), -□-□-; 5,6-cyclopenteno-2,3-dihydropsoralene (9), -△-△-; 5-phenyl-6-methyl-2,3-dihydropsoralene (7), -○-○-.

Experimental

Melting points are uncorrected. The compounds were repeatedly crystallized from the solvents until sharp and constant melting points were obtained.

Dihydropsoralenes[6] and psoralenes[7] prepared following the procedure of Horning, *et al.*, are listed in Tables I and II. Natural psoralene as a reference compound was obtained from the seeds of *Psoralea corylifolia* Linn. by the solvent extraction process.[8] The crude product after purification by chromatography and finally by crystallization from benzene, melted at 160–161°.[8]

Absorption was measured with a Uvispek Mark VII photoelectric spectrophotometer, using ethanol as solvent at a concentration of 5–6 mg./l. in the region 200–360 mμ.

Results and Discussion

Important features from the absorption spectra are summarized in Table III. Four types of absorption curves have been observed. One example of each type has been presented in Fig. 1. A study of the data given in Table III will show that substitution of hydrogen at the 5- and 6-positions by the alkyl group in psoralene does not produce any significant change of the absorption pattern; both λ_{max} and log ϵ remain materially unchanged.

A bathochromic shift as well as increase in log ϵ value has been observed at a lower wave length when the 5-position of psoralene is substituted by a phenyl group. A new minimum at 221 mμ (log ϵ 4.26–4.34) and a maximum at 225 mμ (log ϵ 4.42–4.43) have appeared. The usual minimum at 221 ± 1 has been shifted to 235 ± 1 mμ (log ϵ 4.24–4.33). The maximum at 245 ± 1 is found at 247–248 mμ (log ϵ 4.32–4.40), and the characteristic minimum at 265 ± 1 is shifted bathochromically to 270–271 mμ (log ϵ 3.68–3.91). There is a rather broad band at 297 ± 1 mμ (log ϵ 3.99–4.06) instead of at

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TABLE I. 2,3-DIHYDROALKYL AND -ARYL DERIVATIVES OF PSORALENE

Compd. no.	Reactants	Compd. II		M.p., ° C.	Crystn. solvent	Yield, %	Formula	Analysis, %			
								Carbon		Hydrogen	
		R_1	R_2					Calcd.	Found	Calcd.	Found
1	I + ethyl acetoacetate	CH_3	H	169–170[a]	Ethyl acetate	85[a]	$C_{12}H_{10}O_3$	71.29	71.39	4.95	5.23
2	1 + ethyl α-methylacetoacetate	CH_3	CH_3	185–186[b]	Ethanol	50[b]	$C_{13}H_{12}O_3$	72.22	71.92	5.55	5.68
3	1 + ethyl α-ethylacetoacetate	CH_3	C_2H_5	144–145[c]	Ethanol	40[c]	$C_{14}H_{14}O_3$	73.04	72.78	6.13	5.93
4	I + ethyl α-isopropylacetoacetate	CH_3	$(CH_3)_2CH$	184–185[d]	Ethanol	25[d]	$C_{15}H_{16}O_3$	73.77	73.58	6.55	6.63
5	I + ethyl α-*n*-butylacetoacetate	CH_3	$CH_3(CH_2)_3$	89–90	Ethanol	28	$C_{16}H_{18}O_3$	74.42	74.28	6.97	6.92
6	I + ethyl benzoylacetate	C_6H_5	H	200[e]	Ethyl acetate	61					
7	I + ethyl α-methylbenzoylacetate	C_6H_5	CH_3	239–240	Ethyl acetate	15	$C_{18}H_{14}O_3$	77.68	77.35	5.03	5.20
8	I + ethyl α-ethylbenzoylacetate	C_6H_5	C_2H_5	206–207	Ethyl acetate	15	$C_{19}H_{16}O_3$	78.18	78.08	5.50	5.70
9	I + ethyl cyclopentanone-2-carboxylate		$—CH_2$ $>CH_2$ $—CH_2$	185–186	Ethyl acetate	64	$C_{14}H_{12}O_3$	73.68	73.38	5.30	5.24

[a] Lit.[7] m.p. 170°, yield 88%. [b] Lit.[4] m.p. 186°, yield 21%. [c] Lit.[4] m.p. 143–144°, yield 35%. [d] Lit.[4] m.p. 185°, yield 25%. [e] Lit.[7] m.p. 202°.

TABLE II. 5,6-ALKYL AND -ARYL DERIVATIVES OF PSORALENE

Compd. no.	Compd. III		M.p., °C.	Crystn. solvent	Yield, %	Formula	Analysis, %			
							Carbon		Hydrogen	
	R_1	R_2					Calcd.	Found	Calcd.	Found
10	CH_3	H	185–186[a]	Ethyl acetate	70					
11	CH_3	CH_3	235[b]	Ethyl acetate	50	$C_{13}H_{10}O_3$	72.89	72.69	4.71	4.92
12	CH_3	C_2H_5	178–179[c]	Ethyl acetate	60	$C_{14}H_{12}O_3$	73.68	73.63	5.26	5.30
13	CH_3	CH_3 $CH_3—CH$	143[d]	Petr. ether[e]	45	$C_{15}H_{14}O_3$	74.33	73.84	5.78	5.98
14	CH_3	$CH_3(CH_2)_3$	100–101	Ethanol	65	$C_{16}H_{16}O_3$	74.98	74.74	6.25	6.41
15	C_6H_5	H	177[f]	Ethanol	75					
16	C_6H_5	CH_3	160	Ethyl acetate–petr. ether	30	$C_{18}H_{12}O_3$	78.30	77.68	4.35	4.74
17	C_6H_5	C_2H_5	178	Ethanol–petr. ether	30	$C_{19}H_{14}O_3$	78.60	77.96	4.83	4.86
18		$—CH_2$ $>CH_2$ $—CH_2$	234	Ethyl acetate	40	$C_{14}H_{10}O_3$	74.33	73.94	4.42	4.68

[a] Lit.[7] m.p. 187°. [b] Lit.[4] m.p. 236°, yield 45%. [c] Lit.[4] m.p. 179°, yield 55%. [d] Lit.[4] m.p. 145–147°, yield 44%. [e] B.p. 60–80°. [f] Lit.[7] m.p. 178°.

TABLE III. ULTRAVIOLET ABSORPTION DATA OF PSORALENE AND ITS DERIVATIVES[a]

Compd. no.[b]	λ_{min} (log ε)	λ_{max} (log ε)	λ_{min} (log ε)	λ_{max} (log ε)	λ_{min} (log ε)	λ_{max} (log ε)	λ_{min} (log ε)	λ_{max} (log ε)
Psoralene[c]			221 (4.12)	246 (4.37)	266 (3.63)	290 (4.03)	316 (3.77)	328 (3.80)
1	215 (4.10)	225 (4.21)	252 (3.55)	254 (3.57)	264 (3.30)	294 (3.78)		332 (4.26)
2	216 (4.05)	225 (4.10)			266 (3.22)	296 (3.75)		332 (4.22)
3	216 (4.05)	226 (4.11)	254 (3.45)	256 (3.47)	265 (3.21)	295 (3.76)		332 (4.26)
4	216 (4.09)	226 (4.14)	253 (3.56)	255 (3.57)	265 (3.32)	295 (3.80)		332 (4.28)
5	217 (4.01)	226 (4.08)	254 (3.42)	256 (3.45)	265 (3.17)	296 (3.73)		332 (4.23)
6	230 (4.11)	235 (4.13)	255 (3.98)	261 (4.00)	292 (3.61)			337 (4.19)
7					279 (3.55)			335 (4.25)
8					277 (3.37)			335 (4.16)
9	218 (4.10)	227 (4.16)	253 (3.57)	255 (3.60)	265 (3.29)	295 (3.82)		332 (4.30)
10			220 (4.03)	244[d] (4.39)	264 (3.57)	289 (3.99)	312 (3.77)	329 (3.85)
11			221 (4.09)	245 (4.38)	266 (3.68)	290 (4.02)	312 (3.89)	329[e] (3.95)
12			221 (4.13)	245 (4.42)	266 (3.71)	290 (4.06)	312 (3.92)	329[e] (3.99)
13			220 (4.06)	245 (4.30)	266 (3.59)	290 (3.96)	312 (3.85)	329[e] (3.94)
14			221 (4.11)	244 (4.40)	266 (3.65)	290 (4.04)	312 (3.91)	328 (3.98)
15	215 (4.37)	225 (4.43)	236 (4.35)	248 (4.41)	271 (3.91)	298 (4.06)		331 (3.83)
16	221 (4.34)	225 (4.35)	236 (4.32)	247 (4.38)	270 (3.78)	296 (4.05)	317 (3.91)	328 (3.92)
17	222 (4.26)	225 (4.28)	234 (4.24)	247 (4.32)	270 (3.68)	296 (3.99)	318 (3.82)	328 (3.84)
18			222 (4.12)	246 (4.35)	266 (3.62)	298 (4.01)	310 (3.92)	326 (4.00)

[a] Values are in mμ. [b] The numbers of compounds are same as those in Tables I and II. [c] Compound III, $R_1 = R_2 = H$. [d] Twin peak at 422 and 244 mμ. [e] Twin peak at 326 and 329 mμ.

290, and the minimum at 317–318 mμ (log ϵ 3.82–3.91) corresponds to that of psoralene. A very weak band at 328–330 mμ is also present which corresponds to the similar band of psoralene in this region.

The spectra of 2,3-dihydropsoralenes present very interesting features. Reduction of the furano ring caused the appearance of a band at 226 mμ (log ϵ 4.08–4.20). This has been considered to be due to the formation of a saturated ether which causes a bathochromic effect, offsetting the effect of the loss of conjugation.[9] The minimum at 221 and maximum at 245 mμ of psoralene is shifted to 253 and 256 mμ (log ϵ 3.41–3.60), resulting in a very weak band. The very sharp minimum at 265 ± 1 mμ (log ϵ 3.31–3.32) is characteristic for this group of compounds also. A very small band at 295 ± 1 mμ (log ϵ 3.75–3.80) is present and the maximum at 332 mμ (log ϵ 4.22–4.30) though broad is very characteristic.

In case of 5-phenyl-6-alkyl derivatives of dihydropsoralene, the characteristic minimum at 265 is shifted to 277 mμ (log ϵ 3.37–3.55), whereas in case of 5-phenyl dihydropsoralene, unsubstituted at the 6-position, the minimum occurs at 292 mμ (log ϵ 3.61). A broad band at above 335 mμ is present in all the three compounds.

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Alkylation and Metalation of Perylene with *n*-Butyllithium. 1-*n*-Butylperylene

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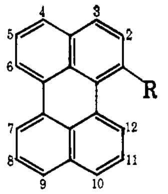
Recently Dixon and Fishman reported that aromatic hydrocarbons undergo alkylation with alkyllithium reagents to form mono- and dialkylated arenes in decalin at elevated temperatures.[2] During the course of metalation studies[3] on perylene (Ia) with *n*-butyllithium, at room temperature, we observed the alkylation reaction. One of the hydrocarbons which was isolated is thought to be 1-*n*-butylperylene and constitutes the first reported substitution of perylene at a position other than position three.

Two monosubstituted *n*-butylperylenes were isolated after column chromatography over alumina. One of these isomers (m.p. 138–139°) has an infrared spectrum which is difficult to distinguish from the spectrum for the known 3-*n*-hexylperylene.[4,5] The ultraviolet spectrum of this material compares favorably with the spectrum for the known 3-alkylperylenes[6,7] listed in Table I despite the fact that it was isolated in small amount and contained a difficult-to-remove impurity.



Ia, R = H
b, R = n-C$_4$H$_9$ –

The other *n*-butylperylene isomer (13.2%, m.p. 66.5–67.0°) has been assigned the structure 1-*n*-butylperylene (Ib) because its infrared spectrum differs from the spectra of the presumed 2-ethyl- and 2-*n*-hexylperylene in the region of 10–15 μ.[8] Furthermore, comparison of the n.m.r. spectrum of this butylperylene isomer with the spectrum of 3-*n*-hexylperylene shows an appreciable lower field chemical shift of 0.2 p.p.m. for the α-methylene signals.[9] Interestingly, the difference in chemical shift is greater (0.37 p.p.m.) for a comparison of 1-*n*-butylperylene and the presumed 2-ethyl- and 2-*n*-hexylperylene. This deshielding suggests that the *n*-butyl group is not at the 3-position and is predicted for the 1-position because of the increased ring-current effect expected for this position.

The ultraviolet spectrum of the new hydrocarbon bears a closer resemblance to the reported spectrum for 1-methylperylene[7] than for the spectrum of the presumed 2-ethylperylene (see Table II).

The n.m.r. spectrum[9] of 1-*n*-butylperylene exhibits proton signals: (1) at 0.9 and 1.0 p.p.m. from internal tetramethylsilane having an intensity ratio of 1:2.96 (theoretical = 1:2.86); (2) at 2.98 p.p.m. (center of a triplet), intensity ratio of 1:9.9 (theoretical = 1:10);

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[1] National Science Foundation Undergraduate Research Participant, spring semester and summer, 1963.

[2] J. A. Dixon and D. Fishman (a) *J. Am. Chem. Soc.*, **85**, 1356 (1963); (b) Abstracts of Papers, Division of Organic Chemistry, 145th National Meeting of the American Chemical Society, Sept. 1963, paper no. 101, p. 54Q.

[3] The solvent was ether-tetrahydrofuran and reaction conditions were chosen to approximate those found to be optimum for metalation in the naphthalene series: H. Gilman and S. Gray, *J. Org. Chem.*, **23**, 1476 (1958).

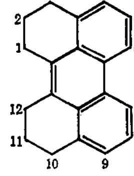
[4] 3-*n*-Hexylperylene (m.p. 141.8–142.6°) was prepared by Wolf-Kishner reduction of 3-*n*-hexanoylperylene. This ketone was secured by alternate syntheses: (a) Friedel-Crafts reaction of I and hexanoyl chloride (62.7%) and (b) the reaction of perylene-3-carbonyl chloride and di-*n*-pentylcadmium (55%).

[5] Details of this synthesis form a portion of the Ph.D. Thesis of H. E. Zieger, The Pennsylvania State University, Jan., 1961; *Dissertation Abstr.*, **22**(1) (1961).

[6] Ethylperylene was prepared from Ia by Friedel-Crafts acetylation (54%) and Wolf-Kishner reduction (95%).[5] The ultraviolet spectrum was obtained in cyclohexane.

[7] For 3-methylperylene see A. D. Campbell, R. S. Elder, and C. W. Emerson, *J. Chem. Soc.*, 3526 (1959).

[8] Only three monosubstituted perylenes are possible and the assumption[5] that was made is that 1,2,3,10,11,12-hexahydroperylene (i) furnished predominantly 5-acylhexahydroperylenes (61–63%) in Friedel-Crafts acylation. Because perylene derivatives secured from these ketones differed from their known 3-position isomers, they had to be either 1- or 2-derivatives of Ia



i

[9] N.m.r. spectra were obtained in carbon tetrachloride at 60 Mc./sec. Data for 2-ethylperylene and 2-*n*-hexylperylene were secured at the Central Research Laboratory of The Socony Mobil Oil Co., Inc., Princeton, N. J., under operating conditions similar to those for 1-*n*-butylperylene. Because of its low solubility, the spectrum of 3-*n*-hexylperylene was obtained in carbon disulfide.