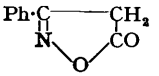
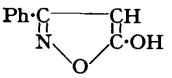
NOTES.

448. 3-*Phenyl*isooxazol-5-one.

By C. L. Angyal and R. J. W. Le Fèvre.

When (*J.*, 1949, 2812) the dipole moment of "3-phenyl*iso*oxazol-5-one" was reported as 4·9 D, it was realised that the chemical evidence cited in Beilstein's "Handbuch" (XXVII, 200; XVII, 1st Ergänzungsband, 278) suggested a possible tautomerism of (I) to (II)—or perhaps (III). The present note records some new experiments designed to investigate these possibilities.


(I)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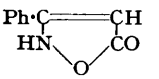

(III)

"Bromine titration," gave results corresponding to enol percentages of *ca.* 190, in other words the over-all reaction involved roughly twice the amount of bromine needed if (I) were 100% enolised. Further, the "4 : 4-dibromo-3-phenyl*iso*oxazol-5-one" described by A. Meyer (*Ann. Chim. Phys.*, 1914, **9**, 135, 252; *Compt. rend.*, 1913, **154**, 1511), although liberating 1 mol. of iodine from sodium iodide in neutral aqueous-alcoholic solution, released two in media acidified with hydrochloric acid. It was evident therefore that the conventional bromine addition technique applied to the parent phenyl*iso*oxazolone might be complicated by a multiplicity of reactions and could not provide with certainty the information desired.

Dipole moments were next determined of substances related in structure to (I) and (II), *viz.*, of 4 : 4-dimethyl-3-phenyl*iso*oxazol-5-one (Haller and Bauer, *Compt. rend.*, 1911, **152**, 553, 1146; *Ann. Chim. Phys.*, 1924, **10**, 278), 5-methoxy-3-phenyl*iso*oxazole (Oliveri-Mandala and Coppola, *Atti R. Accad. Lincei*, 1911, **20**, 248), and Meyer's dibromo-derivative (*loc. cit.*), the values being 5·0, 3·8, and 4·5 D, respectively. Unfortunately, these figures, even when the obvious implications are considered of the moments now measured of ethyl *iso*propyl and ethyl *iso*propenyl ethers (1·4 D and $1{\cdot}4_5$ D) and that (3·07 D) recorded by Tappi and Springer (*Gazzetta*, 1940, **70**, 190) for 3-phenyl*iso*oxazole, do not settle the question because it is impossible to show convincingly from them that the moment of structure (II) would be markedly different from that of structure (I). Accordingly evidence has been sought from infra-red spectroscopy, Nujol mulls of each substance being examined as a preliminary; the Figure shows the detail emerging between 1000 and 1800 cm.$^{-1}$, and Table 1 lists the maxima. The first two substances have high absorption at positions approaching those recorded (Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," van Nostrand, 1949) for carbonyl in oil suspensions of compounds such as 3-methyl-1-phenylpyrazol-5-one (1812 cm.$^{-1}$) and

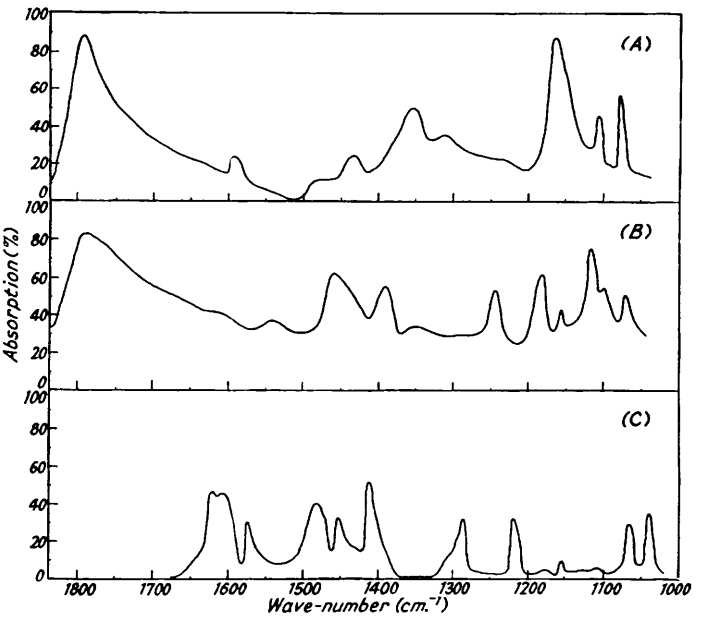
4-benzyl-2-phenyloxazol-5-one (1818 cm.$^{-1}$), and exceeding by 20—30 cm.$^{-1}$ those (1760—1770 cm.$^{-1}$) noted previously in the sydnones (Earl, Le Fèvre, Pulford, and Walsh, *J.*, 1951,

TABLE 1. *Absorption maxima (cm.$^{-1}$).*

" 3-Phenyl*iso*oxazol-5-one "	—	1078	—	1105	1162	—	*ca.* (1240)	1309	1350
Dimethyl derivative	—	1070	1097	1115	1155	1182	1244	—	1350
Methoxy derivative	1038	1066	—	(1107)	1155	(1175)	1218	1288	—
" 3-Phenyl*iso*oxazol-5-one "	—	1432	—	1486	—	1592	—	—	1792
Dimethyl derivative	1390	—	1459	—	1540	—	—	—	1788
Methoxy derivative	—	1412	1452	1482	—	1572	1602	1620	—

(Very weak absorptions shown by parentheses.)

2207). The absence of this feature in the third substance confirms that it is the *O*- and not the *N*-ether [*i.e.*, that it is derived from (II) and not from (III)]. Presumably bands due to the C=N linkage overlap those due to C=O and cause the broad absorption



(*A*) " 3-Phenyl*iso*oxazol-5-one."
(*B*) 4 : 4-Dimethyl-3-phenyl*iso*oxazol-5-one.
(*C*) 5-Methoxy-3-phenyl*iso*oxazole.

seen between 1800 and 1650 cm.$^{-1}$. Most of the remaining peaks can be attributed to C–H linkages, the phenyl group, etc.

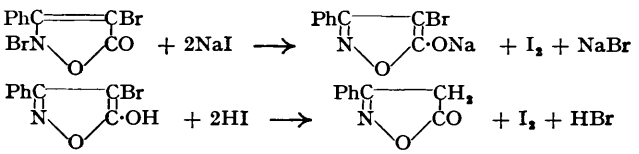
In the shorter-wave region, because Nujol has a broad absorption band at 2900—3000 cm.$^{-1}$, the spectrum of the parent compound was also run as a tetrachloroethylene mull and bands corresponding to phenyl (3075 cm.$^{-1}$) and methylene groups (2940 and 2985 cm.$^{-1}$) were identified. None of the substances showed signs of O–H or N–H bonds in the neighbourhood of 3 μ. A rejection of formulæ (II) and (III), while consistent with such lack of evidence, may not be safely concluded from it since the present observations were made on the crystalline solids—a state in which hydrogen bonding is often strongly developed among authentic hydroxyl-containing compounds, leading to a lowering of their O–H stretching frequencies from 3600 towards 3000 cm.$^{-1}$ and, in consequence, difficulty in distinguishing these from those due to C–H (compare, *e.g.*, various hydroxypyrimidines; Brownlie, *J.*, 1950, 3062; Short and Thompson, *J.*, 1952, 168).

Accordingly we sought to investigate the parent *iso*oxazolone around 3 μ as a solute.

Benzene—the solvent in which our dipole moment determinations (*J.*, 1949, 2812) had been made—was used (saturated solution). Between 2800 and 3800 cm.$^{-1}$ the spectrum of this solution was identical with that of benzene alone.

Again, no evidence of O–H could be seen. On the whole, therefore, we conclude that " 3-phenyl*iso*oxazol-5-one " is adequately represented by (I).

Finally we mention that the moment found for the dibromo-derivative of (I) would be equally explicable whether the two halogen atoms were both on $C_{(4)}$ of (I) or one each on $N_{(2)}$ and $C_{(4)}$ of (III)—this follows from elementary vectorial considerations since μ_{N-Br} is *ca.* zero (Theilacker and Fauser, *Annalen*, 1939, **539**, 103); however, the " bromine titration " observations already noted are more easily understood by a formula based on (III). The fact that the dibromo-derivative liberates iodine equivalent to one bromine atom from a neutral solution is a strong indication that one of the bromine atoms is attached to nitrogen. After the end-point is reached, the solution can be acidified and another mole of iodine liberated. At the same time a precipitate is formed which can be isolated and identified as the parent compound. The following equations are suggested for these reactions :



Experimental.—Substances. These were prepared by methods recorded in the literature, as follow : 3-phenyl*iso*oxazol-5-one, m. p. 151—152° (from alcohol), from ethyl benzoylacetate and hydroxylamine (Hantzsch, *Ber.*, 1891, **24**, 502); 5-methoxy-3-phenyl*iso*oxazole, m. p. 77—77·5° (from aqueous alcohol), from diazomethane and the preceding compound (Oliveri-Mandala and Coppola, *Atti R. Accad. Lincei*, 1911, **20**, I, 248); 4 : 4-dibromo-3-phenyl*iso*oxazol-5-one, m. p. 74—75° (from aqueous alcohol), from the parent by bromination in acetic acid (Meyer, *Ann. Chim. Phys.*, 1914, **9**, 135, 252); 4 : 4-dimethyl-3-phenyl*iso*oxazol-5-one, m. p. 69—70° (from aqueous alcohol), from ethyl dimethylbenzoylacetate and hydroxylamine (Haller and Bauer, *Compt. rend.*, 1911, **152**, 553, 1146; *Ann. Chim. Phys.*, 1924, **10**, 278); ethyl *iso*propenyl ether, b. p. 57—61°, from acetone diethyl acetal by treatment with phosphoric oxide in quinoline (Claisen, *Ber.*, 1898, **31**, 1019).

Dipole moment determinations. These have been made by customary methods (cf. *J.*, 1948, 1949; 1949, 333). Essential data are given in Tables 2 and 3 under headings explained in

TABLE 2. *Dielectric constant and density measurements.*

	5-*Methoxy*-3-*phenyl*isooxazole				4 : 4-*Dimethyl*-3-*phenyl*isooxazol-5-one		
10^5w_2	0	533	1068	1638	245	436·4	563·2
ε_{25}	2·2725	2·3205	2·3706	2·4247	2·3059	2·3335	2·3578
d_4^{25}	0·87378	0·87502	0·87634	0·87773	0·87435	0·87476	0·87515

	4 : 4-*Dibromo*-3-*phenyl*isooxazol-5-one				*Ethyl* isopropyl ether				
10^5w_2	0	674	844	1235	1182·4	1680·6	2043·7	2531·5	2795·6
ε_{30}	2·2628	2·3090	2·3201	2·3476	2·2866	2·2982	2·3044	2·3149	2·3203
d_4^{30}	0·86718	0·86998	0·87126	0·87284	0·86524	0·86433	0·86377	0·86297	0·86258

	Ethyl isopropenyl ether						
10^5w_2	979·8	1431·2	2352·7	2861·2	3675·7	3809·8	4108·6
ε_{30}	2·2870	2·2966	2·3200	2·3305	2·3537	2·3556	2·3642
d_4^{30}	0·86607	0·86549	0·86428	0·86386	0·86284	0·86281	0·86253

TABLE 3. *Calculation of results.*

Solute	M_2	Mean $\alpha\varepsilon_1$	Mean β	$_\infty P_2$	R_2	μ (D)
5-Methoxy-3-phenyl*iso*oxazole	175·2	9·16	0·272	345	45 *	$3·8_3$
4 : 4-Dimethyl-3-phenyl*iso*oxazol-5-one	189·2	14·0	$0·262_5$	546	50 *	$4·9_3$
4 : 4-Dibromo-3-phenyl*iso*oxazol-5-one	318·8	6·84	0·525	467	56 *	$4·4_6$
Ethyl *iso*propyl ether	88·1	2·05	−0·192	70·3	31·5 †	$1·3_9$
Ethyl *iso*propenyl ether	86·1	2·43	$-0·134_5$	73·2	31 ‡	$1·4_5$

* Calc. from R_2 = 40·5 c.c. for phenyl*iso*oxazolone (*J.*, 1949, 2812).
† Mean between values for Et_2O and Pr^i_2O (cf. *J.*, 1952, 1643).
‡ Previous R_2 minus $2R_H$, plus $R_{\text{double bond}}$.

Trans. Faraday Soc., 1950, **46**, 1, except that subscripts 1 and 2 here refer respectively to the solvent and solute (this is the reverse of the convention formerly adopted; cf. *J.*, 1952, 1932).

Infra-red spectra. These were taken on a Perkin-Elmer spectrometer model 12-C, calibration being effected by means of the curves shown by Oetjen, Kao, and Randall (*Rev. Sci. Instr.*, 1942, **13**, 515) for ammonia gas or atmospheric carbon dioxide and water vapour.

The authors acknowledge with gratitude the help of Mr. R. L. Werner with the infra-red spectra.

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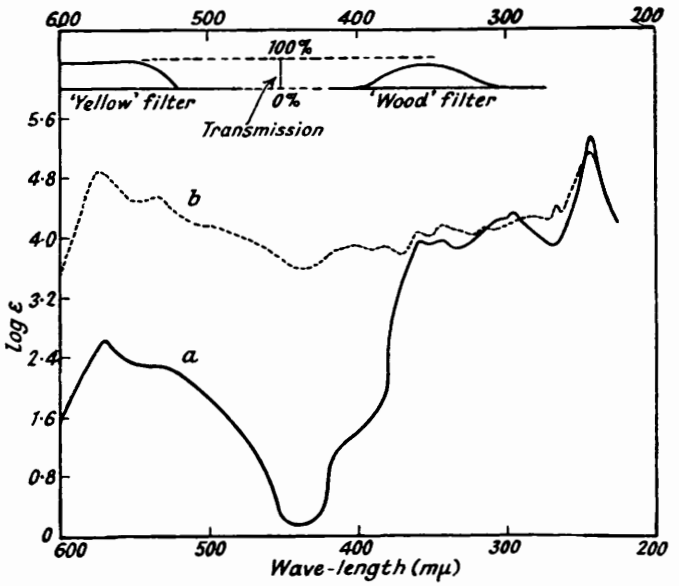
449. *Reversible Appearance and Disappearance of Coloured Modifications of Some Compounds as a Result of Irradiation at Low Temperatures.*

By YEHUDA HIRSHBERG, EPHRAIM H. FREI, and ERNST FISCHER.

THE reversible formation of coloured modifications of some compounds in solution, as a result of ultra-violet irradiation at low temperatures, was first described by Hirshberg for dianthronylidene and related compounds (Hirshberg, *Compt. rend.*, 1950, **231**, 903; cf. Hirshberg and Fischer, *J.*, 1953, 629), and for some spirans (Fischer and Hirshberg, *J.*, 1952, 4522). In these experiments the rate of the spontaneous reversion of the coloured

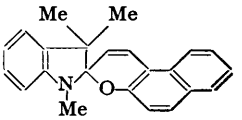
Absorption spectrum of (I) *at* 173° K (a) *before and* (b) *after ultra-violet irradiation.*



to the colourless modifications was measured at a series of temperatures, and Arrhenius parameters of the reversion reaction were estimated. We have now found that the reversion to the colourless form can also be brought about by irradiation with light corresponding to the absorption maximum of the coloured modification in the visible region.

Experimental.—When a solution of 1 : 3 : 3-trimethylindoline-2-*spiro*-6′-(2′ : 3′-β-naphthopyran) (I) in an ethanol–methanol mixture at 173° K is irradiated with light in the 365-mμ region (from a mercury arc and a Wood's filter; transmission about 66% of the 365-mμ group and 10% of the 313-mμ group), an intense mauve colour is produced (Figure). At this temper-

ature both the coloured and the colourless modification are stable. (Extrapolation of the kinetic data to 173° K gives a half-life time of about 6 weeks for the spontaneous decay of colour at this temperature.)



(I)

Irradiation of the coloured solution with light from a 300-w incandescent lamp passed through a " yellow " filter (transmission 80—90% between 800 and 540 mμ and none below 500 mμ) results in a steady decrease in intensity of colour. The cycle of colour formation by ultra-violet irradiation and its eradication by " yellow " irradiation can be repeated many times.

Similar observations were made on solutions of (I) in non-polar solvents.

Work is now in progress on other compounds showing indications of similar behaviour.

We acknowledge our indebtedness to Dr. Gabriel Stein, who suggested the irradiation in the visible region independently of one of us (E. H. F.).

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[*Received, February* 19*th*, 1953.]

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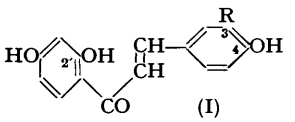
450. *The Isolation of* 2′ : 4 : 4′-*Trihydroxychalkone from Yellow Varieties of* Dahlia variabilis.

By E. C. BATE-SMITH and T. SWAIN.

PRICE (*J.*, 1939, 1017) isolated the chalkone butein (I ; R = OH) from selected genotypes of yellow varieties of *Dahlia variabilis* and concluded that this compound was primarily responsible for the colour in all yellow dahlias. In 1949 one of us (E. C. B.-S.) noted that both unhydrolysed and hydrolysed extracts of petals of yellow dahlias, when separated on paper chromatograms in butanol–acetic acid–water (4 : 1 : 5), showed the presence, in addition to butein (R_F 0·78), of a faster-running aglycone (R_F 0·87) which gave an orange colour with caustic alkali. On the basis of its R_M value (Bate-Smith and Westall, *Biochem. Biophys. Acta*, 1950, **4**, 427) and the interrelations of the other flavonoid compounds in *Dahlia variabilis* (Lawrence and Scott-Moncrieff, *J. Genetics*, 1935, **30**, 155) it was presumed to be 2′ : 4 : 4′-trihydroxychalkone (I ; R = H).



(I)

In the present work this constituent was separated from butein in the hydrolysed extracts of the yellow dahlia " Pius IX " on columns of " Magnesol " (cf. Ice and Wender, *Arch. Biochem. Biophys.*, 1952, **38**, 185). The compound and its triacetate did not depress the melting points of synthetic 2′ : 4 : 4′-trihydroxychalkone and its triacetate respectively (Nadkarni and Wheeler, *J.*, 1938, 1320). Degradation on a micro-scale of both the natural and the synthetic chalkones with potassium hydroxide and examination of the products by paper chromatography (Lindstedt and Misiorny, *Acta Chem. Scand.*, 1951, **5**, 1) gave resacetophenone and *p*-hydroxybenzoic acid. The compound from " Pius IX " had similar R_F values to synthetic (I ; R = H) on paper chromatograms in several solvent systems (Table 1). Further the spectra of the compound in ethanolic M/500-sodium ethoxide (Mansfield, Swain, and Nordström, *Nature*, in the press) and 0·17% alcoholic

aluminium chloride solution (cf. Gage and Wender, *Proc. Oklahoma Acad. Sci.*, 1949, **30**, 145; *Chem. Abs.*, 1952, **46**, 3463*a*), and of the acetate in ethanol and 0·17% aluminium chloride solution were indistinguishable from those of the synthetic chalkone (I; R = H) and its acetate respectively in the same solvents (Table 2).

TABLE 1. R_F *Values and colour reactions of the chalkones, their acetates, and degradation products.*

		R_F in					
			$BuOH–H_2O$		$EtOAc–H_2O$		
No.		$BuOH–AcOH–H_2O$	plain paper	borate paper	plain paper	borate paper	$COMe_2–H_2O$ 1 : 3 *
1	Natural chalkone	0·87	0·86	0·83	0·93	0·93	0·08
2	2′ : 4 : 4′-Trihydroxychalkone	0·87	0·86	0·83	0·93	0·93	0·08
3	Butein	0·78	0·80	0·02	0·87	0·03	0·03
4	Natural chalkone acetate	0·91	0·88	—	—	—	0·95
5	2′ : 4 : 4′-Trihydroxychalkone triacetate	0·91	0·88	—	—	—	0·95
6	Degradation product from natural chalkone	—	0·75	0·10	—	—	—
		—	0·89	0·86	—	—	—
7	Degradation product from 2′ : 4 : 4′-trihydroxychalkone	—	0·73	0·11	—	—	—
		—	0·88	0·86	—	—	—
8	*p*-Hydroxybenzoic acid	—	0·74	0·12	—	—	—
9	Resacetophenone	—	0·89	0·86	—	—	—

	Colour reactions				
		Fluorescence in :			
No.	$FeCl_3$ soln.	u.-v. light	u.-v. light + NH_3 vapour	NaOH	Diazotised † *p*-nitroaniline + Na_2CO_3
1	Brown	Brown	Golden yellow	Deep yellow	—
2	Brown	Brown	Golden yellow	Deep yellow	—
3	Green-brown	Orange	Reddish-orange	Orange	—
4	—	Dull violet	Faint yellow	Yellow	—
5	—	Dull violet	Faint yellow	Yellow	—
6	—	—	—	—	Red
	—	Green	Brown	—	Brown
7	—	—	—	—	Red
	—	Green	Brown	—	Brown
8	—	—	—	—	Red
9	—	Green	Brown	—	Brown

* Somewhat variable results. † Swain (*loc. cit.*).

TABLE 2. $\lambda_{max.}$ (mμ) *of the chalkones and their acetates in various solvents.*

	Ethanol		M/500-NaOEt		0·17% $AlCl_3$–EtOH	
Compound	Band I	Band II	Band I	Band II	Band I	Band II
Natural chalkone	370	240	440 *	245 *	422 *	236 *
2′ : 4 : 4′-Trihydroxychalkone	370	242	440 *	252 *	422 *	236 *
Butein	382	262	447	281	445	(324) †
Neutral chalkone acetate	312	—	—	—	312	—
2′ : 4 : 4′ Trihydroxychalkone acetate	312	—	—	—	312	—

* These spectra have a number of small inflections.
† This peak appears to be related to an inflection at 318 mμ in EtOH.

2′ : 4 : 4′-Trihydroxychalkone has not previously been isolated from natural sources. Its occurrence with butein is interesting since flavones and anthocyanins are linked biosynthetically (Lawrence and Scott-Moncrieff, *loc. cit.*) and gives further weight to the view that these compounds are formed from a common precursor (Robinson, *Nature*, 1936, **137**, 172).

Experimental.—Isolation of 2′ : 4 : 4′-trihydroxychalkone from "Pius IX." The white tips were removed from the ray florets and the remainder (112 g.) covered with alcohol (400 ml.) and disintegrated in a Waring blender, the pulp was re-extracted with alcohol (2 × 200 ml.), and

the combined extract taken to dryness *in vacuo*, yielding a dark orange, sticky solid (5·3 g.). [Attempts to free this from sugars on IRC-50 carboxylic acid ion-exchange resin (Gage *et al.*, *Science*, 1951, **113**, 422) were abandoned since the adsorptive capacity of the resin for the chalkones was too small.] The solid was hydrolysed with hydrochloric acid in 50% ethanol (100 ml.), diluted, neutralised to pH 4 (NaOH), and extracted with ethyl acetate. Removal of the solvent gave a dark brown sticky solid (1·26 g.) which showed the presence of butein, 2′ : 2 : 4′-trihydroxychalkone, and traces of glycosidic material as well as of free sugars (mainly glucose) on a paper chromatogram. The solid was dissolved in dry acetone, absorbed on acid-washed " Magnesol " (a synthetic magnesium silicate, Westvaco Chemical Division, South Charleston, W. Va.), and eluted with acetone, giving a fraction (0·65 g.) consisting of chalkones and a little sugar. This was applied to a column of unwashed " Magnesol–Celite 545 " (4 : 1) and developed with dry acetone, giving a fast running band of crude 2′ : 4 : 4′-trihydroxychalkone, and sugars only (0·31 g.). Recrystallisation from water and then dilute alcohol gave yellow crystals, m. p. 199·5—200·5° (Found : C, 65·3, 65·6, 66·0; H, 5·0, 5·1, 5·6. Calc. for $C_{15}H_{12}O_4,H_2O$: C, 65·7; H, 5·1%) (Nadkarni and Wheeler, *loc. cit.*, state that 2′ : 4 : 4′-trihydroxychalkone forms a monohydrate, m. p. 202—204°). The acetate separated from alcohol as colourless needles, m. p. 119·5—120° (Found : C, 65·6; H, 4·8. Calc. for $C_{21}H_{18}O_7$: C, 65·9; H, 4·7%).

Synthetic 2′ : 4 : 4′-trihydroxychalkone. The procedure described by Nadkarni and Wheeler (*loc. cit.*) gave an impure product. The method was improved by neutralisation to pH 8 only, extraction with ethyl acetate, and washing with saturated sodium sulphite solution and water. Removal of the solvent and extraction of the solid with benzene left almost pure chalkone. It recrystallised from aqueous alcohol as light orange-yellow rhombs, m. p. 202—203° alone or mixed with the natural product (Found : C, 65·9; H, 5·1%). The acetate had m. p. 120—120·5° alone or mixed with the acetate of the natural product (Found : C, 65·8; H, 4·9%).

Paper chromatography. The chromatograms were run as described by Swain (*Biochem. J.*, 1953, **53**, 200) but without strict temperature control. The results are shown in Table 1.

Micro-degradation. The chalkone (*ca.* 0·5 mg.) and a few drops of water and potassium hydroxide (*ca.* 0·1 g.) were heated until the initial dark orange colour disappeared (1—2 min.), diluted with water, acidified, and extracted with ether (0·5 ml.). It was run on paper chromatograms and the results are shown in Table 1.

Spectra. The spectra in ethanolic 0·002M-sodium ethoxide were plotted as described by Mansfield *et al.* (*loc. cit.*). The spectra in 0·17% alcoholic aluminium chloride were plotted after dilution of the original ethanolic solution (2·5 ml.) with 1% alcoholic aluminium chloride solution (0·5 ml.).

We thank the Westvaco Chemical Division, W. Va., U.S.A., for a gift of Magnesol. This paper forms part of the programme of the Food Investigation Board of the Department of Scientific and Industrial Research.

LOW TEMPERATURE RESEARCH STATION, CAMBRIDGE. [*Received, March 3rd*, 1953.]

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451. *The Acid-catalysed Hydrolysis of Benzoyl Fluoride.*

By C. W. L. BEVAN and R. F. HUDSON.

THE hydrolysis of benzoyl chlorides has been studied extensively and in no case has acid catalysis of these reactions been demonstrated (Olivier and Berger, *Rec. Trav. chim.*, 1927, **46**, 609; Hudson *et al.*, *J.*, 1950, 1729, 3529). Recently, it has been shown that in the hydrolysis of benzyl fluorides (Bernstein and Miller, *J. Amer. Chem. Soc.*, 1948, **70**, 3602) and of aliphatic fluorides (Chapman and Levy, *J.*, 1952, 1675) there is in many cases considerable acid catalysis. It therefore appeared of interest to examine the corresponding reactions of benzoyl fluoride.

The hydrolyses were carried out in aqueous acetone and a summary of the results is given in Table 1. Values of the pseudo-unimolecular constant k_1 were obtained by using 0·05N-hydrochloric acid in each case, and the catalytic hydrolysis constant, k_H, was calculated from the assumed relation, $k_1 = k_0 + k_H[HCl]$.

The rate constants k_0 and k_1 were calculated from the general expression for a first-order process, and in no case were significant deviations observed (cf. Table 2).

TABLE 1. *Solvolytic and catalytic rate constants at* 30°.

Concn. of H_2O vol. %	Concn. of H_2O moles/l.	$100k_0$, min.$^{-1}$	$100k_1$, min.$^{-1}$	$100k_H$, l. mole^{-1} min.$^{-1}$	Concn. of H_2O vol. %	Concn. of H_2O moles/l.	$100k_0$, min.$^{-1}$	$100k_1$, min.$^{-1}$	$100k_H$, l. mole^{-1} min.$^{-1}$
9·1	5·06	0·0034	0·0273	0·475	40·0	22·2	0·218	0·288	1·4
15·0	8·33	0·0136	0·0241	0·57	50·0	27·8	0·475	—	—
30·0	16·7	0·0928	—	—	70·0	38·9	2·18	2·33	3
37·5	20·83	0·170	—	—					

TABLE 2. *Determination of rate constants* (k_0, *in min.*$^{-1}$).

Benzoyl fluoride in 50% aqueous acetone at 30·0°; [C_6H_5·COF] expressed in ml. of 0·1057N-$Th(NO_3)_4$ per 5-ml. sample.

t (min.)	0	31	48	60	73	92	108	122	141	
[C_6H_5·COF]	2·17	1·85	1·69	1·61	1·52	1·40	1·29	1·18	1·07	
10^3k_0	—	4·67	4·85	4·73	4·68	4·60	4·70	4·87	4·91	Mean 4·75

The effect of solvent is shown in Fig. 1, from which it is observed that the rate of solvolysis is proportional to the cube of the water content, expressed as moles/l. of solvent, except in the most aqueous solutions. This effect is greater than for the S_N2

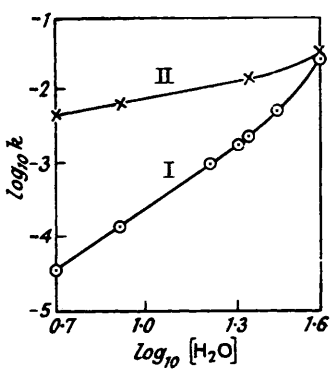


FIG. 1. *Relation between velocity constant at* 30° *and water content of the medium expressed as mole/l.*

(I) *Solvolysis.*
(II) *Catalysis.*

hydrolysis of simple alkyl halides, and is probably determined by the greater solvation around the partially ionised fluorine atom in the transition state than around corresponding chlorides and bromides. The acid catalysis is seen to be much less dependent on water concentration, as shown by the values of k_H in Table 1. The rate increase is approximately proportional to the water content of the medium (Fig. 1).

These results, together with those of Bernstein and Miller, show that the hydrolyses of benzyl fluoride and benzoyl fluoride are catalysed by acids to a similar extent. It is known that the corresponding chlorides hydrolyse by very similar mechanisms, so the tendency for the halide atom to ionise is of the same order in the two cases. It is logical therefore to assume that acid affects the hydrolysis of benzoyl and benzyl fluorides in the same way, *i.e.*, in the electrophilic removal of the fluoride ion.

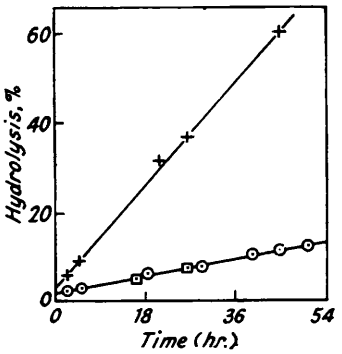
The rate of the solvolysis increases rapidly with water concentration, showing that the pseudo-ionic transition state is highly solvated by water molecules in a similar way to the benzoyl chlorides. On the other hand, the rate of the catalysed reaction increases relatively slowly with increase in water content, indicating that water does not participate in the solvation, and the reaction is probably an example of electrophilic catalysis in nucleophilic substitution (cf. Hughes, Ingold, *et al.*, *J.*, 1940, 925).

Finally, the rate figures given in Fig. 2 show that lithium chloride causes no increase in rate, so the catalysis is due to H^+ ions alone and, as in the case of the chloride, no salt effect can be detected.

Experimental.—Preparation of benzoyl fluoride. Ammonium fluoride (70 g.), dried by azeotropic distillation with carbon tetrachloride, was added to acetone (250 ml.) which had been dried by refluxing it with potassium carbonate followed by distillation. Benzoyl chloride (110 ml.) was added slowly to the stirred mixture in an apparatus protected from atmospheric moisture, and the reagents were refluxed for 2 hr. on a water-bath. On cooling, the salt was rapidly filtered off and after removal of the acetone the benzoyl fluoride was distilled at reduced pressure

FIG. 2.

\+ *In presence of* 0·05N-HCl.
⊙ *Pure solvent.*
⊡ *In presence of* 0·10N-LiCl.



and a middle fraction collected (b. p. 55°/18 mm.) (quantitative hydrolysis gave F, 15·2. Calc. for C_6H_5·COF : F, 15·4%).

Rate measurement. This was done by titration of the liberated fluoride ion with thorium nitrate, sodium alizarinsulphonate being used as indicator. In a typical experiment 100 ml. of the solvent (made up by volume from pure dry acetone and distilled water) contained in a "Polythene" vessel were placed in the thermostat for an hour, after which 0·3 ml. of benzoyl fluoride was added, and the vessel rapidly shaken. 5-Ml. portions were withdrawn at appropriate intervals and added to 1 ml. of chloroacetic–chloroacetate buffer and 1 ml. of the indicator (0·1%). Infinity readings were obtained as the mean of a number of aliquots which had been at the thermostat temperature for at least ten times the half life.

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452. *Steroids. Part XLVI.* Synthesis of* 11β*-Hydroxytestosterone and* 11*-Ketotestosterone.*

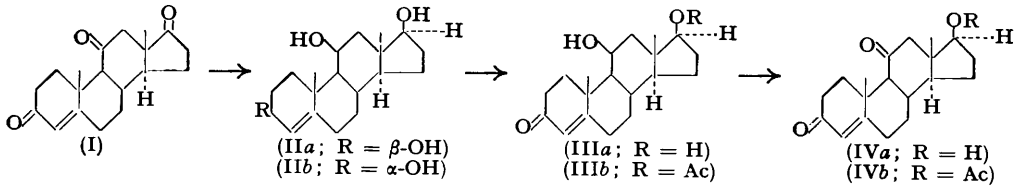
By O. MANCERA, G. ROSENKRANZ, and F. SONDHEIMER.

IN view of the remarkable pharmaceutical properties of 17α : 21-dihydroxypregn-4-ene-3 : 11 : 20-trione (cortisone, Kendall's Compound E) and 11β : 17α : 21-trihydroxypregn-4-ene-3 : 20-dione (hydrocortisone, Kendall's Compound F), it became of interest to make available for biological testing other and simpler 11-keto- and 11β-hydroxy-hormone analogues. We now report the synthesis of 11β : 17β-dihydroxyandrost-4-en-3-one (11β-

* Part XLV, Djerassi, Mancera, Romo, and Rosenkranz, *J. Amer. Chem. Soc.*, in the press.

hydroxytestosterone) (III*a*) and 17β-hydroxyandrost-4-ene-3 : 11-dione (11-ketotestosterone) (IV*a*) * from androst-4-ene-3 : 11 : 17-trione (adrenosterone) (I).

Adrenosterone (I) on reduction with lithium aluminium hydride yielded a mixture of, essentially, androst-4-ene-3β : 11β : 17β-triol (II*a*) and -3α : 11β : 17β-triol (II*b*) (for the stereochemistry of lithium aluminium hydride reduction of Δ^4-3-ketones 11-ketones, and 17-ketones see, *inter al.*, Dauben, Micheli, and Eastham, *J. Amer. Chem. Soc.*, 1952, **74**, 3852; Sarett, Feurer, and Folkers, *ibid.*, 1951, **73**, 1777; Rosenkranz, Kaufmann, and Romo, *ibid.*, 1949, **71**, 3689, respectively), which was oxidised directly with manganese dioxide in chloroform at room temperature. Only the allylic alcohol function was attacked under these conditions, and 11β-hydroxytestosterone (III*a*), further characterised as the 17-monoacetate (III*b*), was isolated in 62% overall yield. This transformation is analogous to that of androst-4-ene-3 : 17-dione to testosterone described recently (Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62).



11-Ketotestosterone (IV*a*) was prepared simply and in excellent yield from the monoacetate (III*b*) by oxidation and subsequent hydrolysis.

Experimental.—Rotations were determined in chloroform, and ultra-violet absorption spectra in 95% ethanol solution.

Manganese dioxide. Concentrated aqueous potassium permanganate was added to a stirred aqueous manganese sulphate solution kept at 90°, until a slight excess was present (pink coloration of the supernatant liquid). Stirring at 90° was continued for a further 15 min. The oxide was collected by filtration, washed well with hot water, then with methanol and ether, and dried at 120—130° to constant weight. It could be kept for several months in a well-stoppered bottle without loss in activity.

11β : 17β-*Dihydroxyandrost-4-en-3-one* (11β-*hydroxytestosterone*) (III*a*). A solution of adrenosterone (350 mg.; m. p. 213—215°) in dry tetrahydrofuran (30 c.c.) was added dropwise to lithium aluminium hydride (300 mg.) dissolved in tetrahydrofuran (20 c.c.), and the mixture was heated under reflux for 30 min. The excess of reagent was decomposed by ethyl acetate, and a saturated aqueous sodium sulphate solution then added (until the precipitate began to adhere to the sides of the flask), followed by solid sodium sulphate (5 g.). The precipitated salts were removed and washed with tetrahydrofuran, and the filtrate was evaporated to dryness. The amorphous residue (350 mg.), dissolved in dry chloroform (35 c.c.), was shaken with manganese dioxide (3·5 g.) for 65 hr. at room temperature (*ca.* 20°). The oxide was removed and washed well with hot chloroform. Evaporation, chromatographic purification of the residue on alumina, and crystallisation of the fractions eluted with chloroform from acetone–hexane then furnished the 11β : 17β-*dihydroxy*-compound (220 mg., 62%), m. p. 228—232°. Further crystallisation yielded a sample, m. p. 232—234°, $[\alpha]_D^{20}$ +155° (Found : C, 74·85; H, 9·45. $C_{19}H_{28}O_3$ requires C, 74·95; H, 9·25%). Light absorption : Max. 2420 Å, ε = 16,600.

Acetylation (pyridine–acetic anhydride, room temp., 16 hr.) furnished the 17-*acetate* (III*b*), plates (from ether–hexane), m. p. 149—150°, $[\alpha]_D^{20}$ +123° (Found : C, 72·9; H, 8·85. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·75%).

17β-*Hydroxyandrost-4-ene-3* : 11-*dione* (11-*ketotestosterone*) (IV*a*). 11β-Hydroxytestosterone 17-acetate (100 mg.) in glacial acetic acid (3 c.c.) was oxidised with chromium trioxide (50 mg.) in 80% aqueous acetic acid (1 c.c.) for 30 min. at room temperature. Crystallisation of the product from acetone–hexane yielded the 17-*acetate* (91 mg., 92%) of (IV*a*) as long needles, m. p. 162—163°, $[\alpha]_D^{20}$ +170° (Found : C, 73·2; H, 8·5. $C_{21}H_{28}O_4$ requires C, 73·25; H, 8·2%).

This product was hydrolysed by refluxing it for 30 min. with potassium carbonate in aqueous

* While this manuscript was in preparation, independent and different syntheses of (IV*a*) were reported by Herzog, Jevnik, Perlman, Nobile, and Hershberg (*J. Amer. Chem. Soc.*, 1953, **75**, 266).

methanol. The resulting keto-alcohol, produced in nearly quantitative yield, crystallised from acetone–hexane as felted needles, m. p. 183—184°, $[\alpha]_D^{20}$ +210° (Found : C, 75·6; H, 8·7. Calc. for $C_{19}H_{26}O_3$: C, 75·45; H, 8·65%). Light absorption : Max. 2380 Å, $\varepsilon = 16{,}200$ {Herzog *et al.* (*loc. cit.*) give m. p. 181—182·4°, $[\alpha]_D^{25}$ +178° (in $COMe_2$); light absorption : Max. 2380 Å, $\varepsilon = 14{,}400$}.

Thanks are offered to Srta. Paquita Revaque for the ultra-violet light absorption data and to Srta. Amparo Barba for the microanalyses.

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