THE BASE-CATALYZED REARRANGEMENT OF N-ALKYL TRIPHENYLISOXAZOLIUM SALTS

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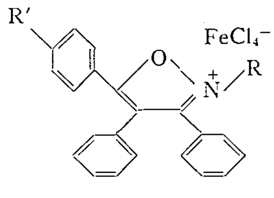
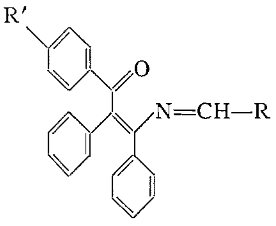
ABSTRACT

The action of base on trisubstituted N-alkyl isoxazolium salts, first described by Kohler and co-workers (1, 2), has been reinvestigated. On the basis of photochemical and spectroscopic studies it is concluded that the reaction of the N-methyl triphenylisoxazolium ion (I*a*) with aqueous sodium hydroxide leads to 4,5,6-triphenyl-2*H*-1,3-oxazine (III), a derivative of a heterocycle previously known only in benz-fused systems.

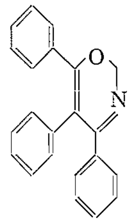
In 1928, Kohler and Blatt (1) described the action of alkali on N-methyl triphenylisoxazolium "ferric chloride double salt" (I*a*). Among the materials produced was one obtained most readily by shaking the isoxazolium salt with dilute aqueous alkali and ether for a few minutes and then separating and evaporating the ether layer. This they called the "anhydro compound" because of a presumed relation with some hydrated "pseudo bases". As possible representations of the "anhydro compound" they discussed structures II*a*, III, and IV, tentatively adopting II*a*; later Kohler and Richtmyer (2) considered II*a* as "definitely established". In the final communication of the series, Kohler and Bruce (3) described the preparation of an "anhydro compound" from the benzisoxazolium salt VI*c*, and assigned structure VII*c* to this compound.



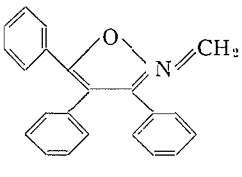
I*a*, R = CH_3; R' = H
I*b*, R = CH_2CH_3; R' = Br



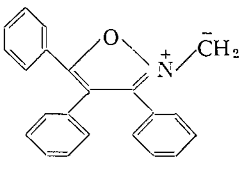
II*a*, R, R' = H
II*b*, R = CH_3; R' = Br



III



IV



V

Aliphatic Schiff bases are known to be reactive species readily undergoing polymerization and other addition reactions (4, 5). Those derived from formaldehyde are, in fact, apparently unstable under the usual conditions of their formation and only

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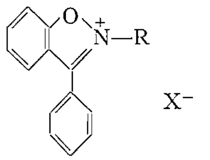
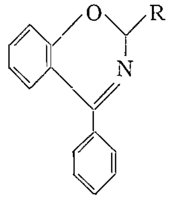


VI*a*, R = CH_3
VI*b*, R = $CH_2\phi$
VI*c*, R = CH_2CH_3



VII*a*, R = H
VIII*b*, R = ϕ
VII*c*, R = CH_3

hydrolysis or—in the absence of water—trimerization products have been isolated. It seemed to us that the comparative stability of the "anhydro compound" from the triphenylisoxazolium ferrichloride (I*a*) was not compatible with structure II*a* and, further, it was felt that the nature of this and the other "anhydro compounds" could be shown by the use of modern physical and chemical methods not available to Kohler and his co-workers.

Accordingly, we have prepared compounds I*a*, VI*a*, and VI*b* (as the ferric chloride or perchlorate salts) and obtained crystalline "anhydro compounds" by what is essentially Kohler's procedure. In Table I are listed the ultraviolet maxima, infrared peaks in the carbonyl region, and the chemical shifts of hydrogens attached to the non-aromatic carbon atoms; unless otherwise noted the n.m.r. peaks are singlets.

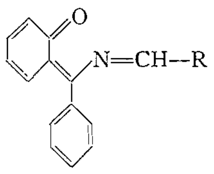
TABLE I
The "anhydro compounds" and model compounds: spectroscopic data

	ν_{max} (cm^{-1})	$\lambda\lambda_{max}$ (mμ) (ϵ, in parentheses)	δ (p.p.m.) from tetramethylsilane
"Anhydro compound" from I*a*	1626	239 (15,700) 338 (6,200)	5.58
"Anhydro compound" from VI*a*	1616	238 (10,900) 325 (1,700)	5.54
"Anhydro compound" from VI*b*	1610	240 (12,400) 329 (1,700)	6.39
Benzalaniline	1628	—	8.35
Benzophenone anil	1623	—	—
Benzyliminobenzophenone	1626	—	—
"Methanol adduct" (X)	1575, 1550	238 (9,300) 350 (12,500)	4.36*
Propyliminoacetaldehyde (XI)	1673	—	7.63†
2-Phenyl-2*H*-1,3-benzoxazin-4-one (XII)	—	—	6.22
Formaldehyde 2,4-dinitrophenylhydrazone	—	—	6.73, 7.12‡

*Doublet, *j* = 9 cycles/sec.
†Quartet, *j* = 4 cycles/sec.
‡*AB* quartet, *j* = 11 cycles/sec.

In addition to structures II*a*, VII*a*, and VII*b*, which correspond to Kohler's proposals, structures III, VIII*a*, and VIII*b* for these three "anhydro compounds" are a priori possible. Structure IV in which the nitrogen has 10 valence electrons is, of course, not possible and the related ylide (V) would be much too unstable to be isolated under these conditions.

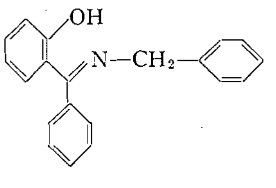
The single infrared maximum around 1620 cm^{-1} shown by each of the compounds is in accord with the cyclic structures III, VII*a*, and VII*b* being well within the range 1660–1480 cm^{-1} quoted by Bellamy (6) and similar to the C=N maxima of benzophenone anil (1623 cm^{-1}) and benzyliminobenzophenone (1626 cm^{-1}). The open-chain structures II*a*, VIII*a* and VIII*b*, on the other hand, would be expected to show two bands in this region.



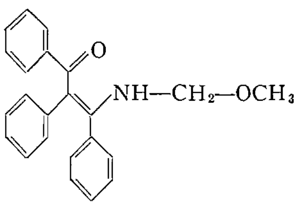
VIII*a*, R = H
VIII*b*, R = ϕ

The observation of only one band can be rationalized only by assuming that the carbonyl and azomethine absorptions coincide, an assumption that is extremely tenuous since the absorption occurs outside the normal range of carbonyl groups not involved in hydrogen bonding.

The ultraviolet data also agree well with the cyclic structures. The long wavelength bands of the "anhydro compounds" derived from the benzisoxazoles (at 325 and 329 mμ, respectively) are very close to that of benzylimino-*o*-hydroxybenzophenone (IX), which is found at 328 mμ. The close similarity between the ultraviolet spectra of the two "anhydro compounds" derived from the benzisoxazole also argues in favor of the cyclic structures. In the open-chain structure VIII*b*, the "new" phenyl group is conjugated with the main chromophoric system, which would be expected to result in distinct differences in the spectrum. The ultraviolet spectrum of the "methanol adduct" (X) (the formation of which is discussed below) is of interest in connection with the structure of the triphenyl "anhydro compound". The long wavelength of band X is found at *longer* wavelengths (by 12 mμ) than the corresponding band in the "anhydro compound". Though on the basis of the cyclic structure (III) for the "anhydro compound" this is unremarkable, on the basis of structure II*a* it would mean that the conjugation of another double bond with the chromophore of X yields a distinct hypsochromic shift.



IX

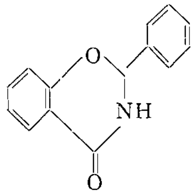


X

Though the nuclear magnetic resonance spectra of comparatively few model systems have been reported, again the cyclic structures are much more satisfactory for their interpretation than the acyclic. Protons bonded to an azomethine carbon evidently absorb at rather low field. Aliphatic aldoximes have been found at 6.3–7.0 p.p.m. (7), aliphatic aldehyde semicarbazones at 7.4–7.8 p.p.m. (8), and aliphatic aldehyde 2,4-dinitrophenylhydrazones at 6.8–7.2 p.p.m. (8). We have found that the azomethine proton of propyliminoacetaldehyde (XI) absorbs at 7.63 p.p.m and the corresponding protons of formaldehyde 2,4-dinitrophenylhydrazone at 6.73 and 7.12 p.p.m. The methylene protons of the "anhydro compounds" derived from the N-methyl isoxazolium salts (I*a* and VI*a*), however, are found at 5.58 and 5.54 p.p.m. The corresponding methine proton of the "anhydro compound" from the N-benzyl isoxazolium salt (VI*b*) absorbs at 6.39 p.p.m.; the azomethine proton of benzalaniline absorbs at 8.35 p.p.m.; the methine proton of the model compound XII (9) on the other hand is found at 6.22 p.p.m.

$CH_3CH{=}NCH_2CH_2CH_3$

XI



XII

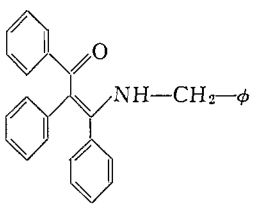
It is evident that the n.m.r., infrared, and ultraviolet data individually agree—on the basis of expectations derived from the study of model systems—far better with the cyclic structures III, VII*a*, and VII*b* for the "anhydro compounds" than with the open-chain structures II, VIII*a*, and VIII*b*. In addition the data show a measure of agreement with one another which, independent of the model systems, strongly supports the same conclusion. The C=N bands in the infrared are in the same region, the ultraviolet spectra of the two benz-fused compounds are very similar, and the chemical shift of the methylene protons of the two "anhydro compounds" derived from N-methyl isoxazolium salts are virtually identical; the shift to lower field accompanying the replacement of one proton by a phenyl group is as expected.

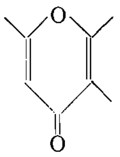
Following the conclusions from the physical data just discussed and anticipating those of the discussion of the chemical reactions of the compounds, we shall, for simplicity, describe the reactions in terms of the cyclic structures III, VII*a*, and VII*b*, and shall refer to the compounds by the corresponding names.

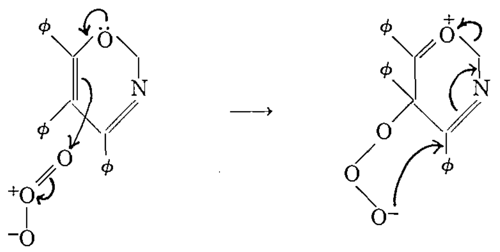
Kohler and Blatt (1) reported that the triphenyloxazine (III), on being refluxed with methanol for an hour, was converted to a "methanol adduct" to which he ascribed structure X. We have prepared this compound and have measured its infrared, ultraviolet, and n.m.r. spectra, which, coupled with Kohler's observation that the "methanol adduct" (like the oxazine (III) itself) hydrolyzes readily to dibenzoylphenylmethane, comprise good support for the structure (X) proposed by Kohler. The formation of X from the "anhydro compound" is readily rationalized on the basis of the oxazine structure (III) by assuming that under the conditions of the reaction the oxazine (III) is reversibly converted into the open-chain compound (II*a*); such a transformation is, formally at least, merely a variant on the familiar ring–chain tautomerism of oxazolidines, tetrahydrooxazines, and similar compounds.

Kohler and Blatt also reported (1) that the oxazine (III) reacts with phenyl magnesium bromide, giving the vinylamine XIII. Again this reaction probably proceeds via an open-chain intermediate, though it is likely that the ring opening is accelerated by complexing with the metal. The action of Grignard reagents on carbinolamine ethers to yield products derived from the corresponding Schiff bases has been frequently observed (10).

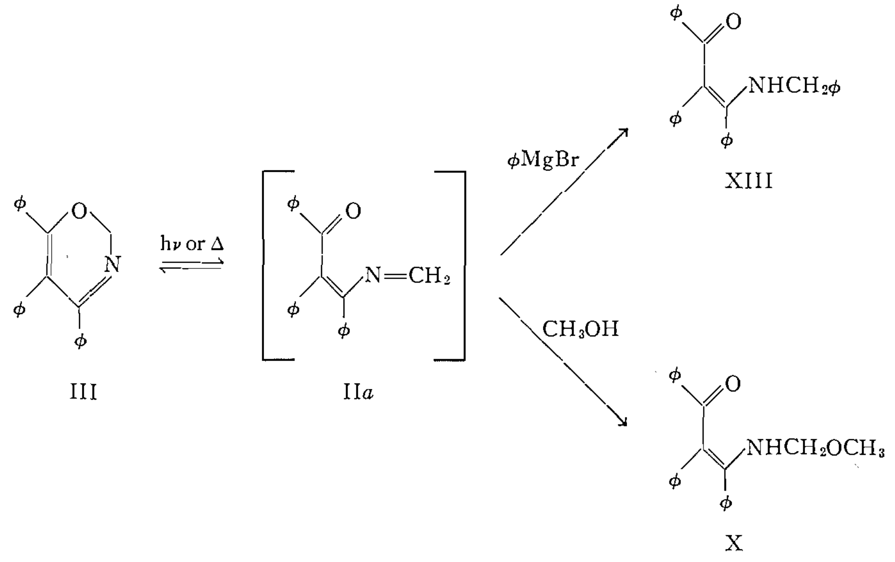
Kohler and co-workers (1, 2) described the action of ozone on the triphenyl "anhydro compounds"; most notably, ozonolysis of the "anhydro compound" from I*b* (in ethyl bromide solution at room temperature) gave *p*-bromobenzil and benzamide. They considered that the results of these experiments established the open-chain structures (II*a* and II*b*) for these compounds. It has already been shown, however, that structure II*a* for the "anhydro compound" derived from I*a* is far from satisfactory in explaining the spectroscopic data, and since ozone is a highly reactive species which may yield so-called abnormal products by a number of different mechanisms (11, 12), it is much more reasonable to propose that the root of the apparent anomaly lies with the ozonolysis rather than the physical data. The double bond in III bears an oxygen and a carbon–nitrogen double bond; it is notable that a formally similar system in 2,3,6-trimethyl-4-pyrone (XIV) leads to "abnormal" ozonolysis products, methylglyoxal and biacetyl (13). The process XV → XVI (or its one-step equivalent) illustrates a possible mode of ozone addition which would yield abnormal cleavage products. It is, of course, also conceivable that the ozone is reacting with the small equilibrium concentration of the open-chain tautomer under the conditions of the reaction.


XIII


XIV

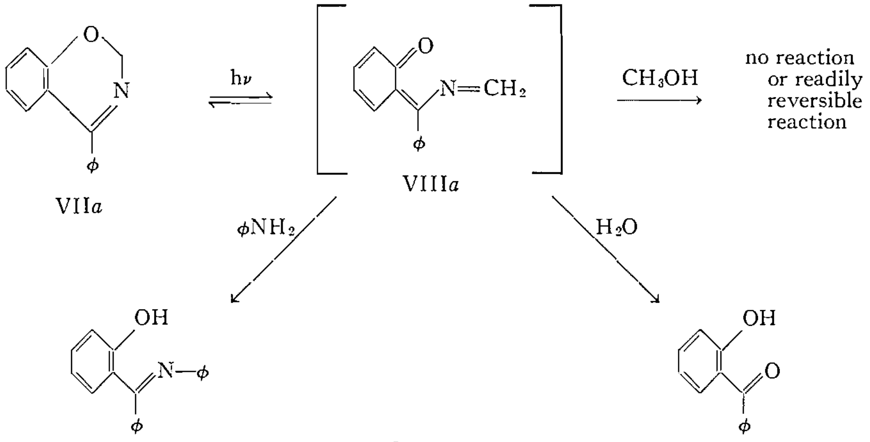

XV XVI

To provide further information about the nature of the "anhydro compounds" we have investigated some photochemical reactions of these compounds. Barton (14) has recently suggested that it is a general property of any ring of $2n$ members containing $(n-1)$ conjugated double bonds, when irradiated with light of the appropriate wavelength, to form an open-chain compound having n conjugated double bonds. It would be expected then that ultraviolet irradiation of III would yield II*a* and that if formation of the methanol adduct takes place via II*a*, the reaction might be accelerated by ultraviolet irradiation. We have, in fact, found that irradiation of a solution of the oxazine (III) in methanol at −60° leads to complete conversion to the methanol adduct (X) within 2 hours. The thermal reaction, which takes place rapidly in refluxing methanol and slowly at room temperature, is completely suppressed at −60°. These results are in accord with Scheme 1.



Scheme 1

Irradiation of VII*a* and VII*b* would also be expected to yield the open-chain species VIII*a* and VIII*b*, respectively, though since the ring opening disrupts the aromatic system, it would be anticipated that these compounds would cyclize very readily, giving back starting materials. When a solution of VII*a* in dry methanol was irradiated, only starting material was isolated. When irradiated in methanol–ether (reagent grades) *o*-hydroxybenzophenone was obtained. Irradiation in dry methanol in the presence of aniline yielded the anil of *o*-hydroxybenzophenone. Without irradiation no reaction was observed either after refluxing with methanol–ether or on standing in the methanol–aniline mixture. These results agree with Scheme 2, analogous to Scheme 1.

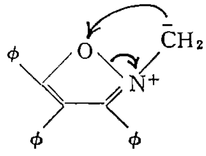


SCHEME 2

In addition to allowing ready rationalization and correct prediction of the thermal and photochemical addition reactions, the oxazine structures predict that the triphenyl compound (III) should be more reactive than the benz-fused compounds (VII*a* and VII*b*). On the other hand, reactions involving additions to structures VIII*a* and VIII*b* would lead to aromatic systems and hence should proceed more readily than the corresponding reactions with II*a*. The observed order of reactivity is that predicted on the basis of the oxazine structures III, VII*a*, and VII*b*.

From this study of the spectroscopic properties and a number of chemical reactions of Kohler's "anhydro compounds", we conclude that they are best represented by the oxazine structures III, VII*a*, and VII*b*. It appears that a "bare" (i.e. not fused to a benzene ring) 2*H*-1,3-oxazine, though a simple heterocyclic system, has not been reported previously; the "anhydro compound" (III) is evidently the first example of this type of heterocycle.

As reasonable mechanisms for the formation of the oxazine we suggest that an ylide (V), formed by abstraction of a proton by base, may either rearrange as indicated by the arrows in structure XVII (a process which is formally analogous to the Stevens rearrangement) or, alternatively, the ring of the ylide (V) may open to form II*a*, which then equilibrates with III.



XVII

EXPERIMENTAL

Infrared and nuclear magnetic resonance spectra were determined in dilute carbon tetrachloride solution using, respectively, a Beckman IR-7 grating spectrophotometer equipped with sodium chloride optics, and a Varian DP-60 spectrometer. Chemical shifts are reported in parts per million from internal tetramethylsilane. Ultraviolet spectra were determined in cyclohexane solution using a Beckman DK-1 instrument. Petroleum ether refers to the fraction of b.p. 35–60°. Melting points were determined on a Kofler block and are uncorrected.

*4,5,6-Triphenyl-2*H*-1,3-oxazine (III)*

This compound was prepared from N-methyl triphenylisoxazolium ferrichloride (I*a*) (m.p. 161–162°) as described by Kohler and Blatt (1) and melted at 140–141°; reported m.p. 140–141° (1).

3-Phenyl-1,2-benzisoxazole

The following procedure was found to be more satisfactory than that of Kohler and Richtmyer (2). *o*-Chlorobenzophenone oxime (15) (4.42 g) was dissolved in a mixture of 50% aqueous potassium hydroxide solution (30 ml) and ethylene glycol monomethyl ether (10 ml). The solution was refluxed and after about 1 hour had separated into two phases. After being heated for a further 6 hours, the mixture was cooled, yielding a crystalline product. Recrystallization from methanol gave 3.1 g (80%) of material melting at 82–83°.

N-Methyl-3-phenyl-1,2-benzisoxazolium Ferrichloride (VIa)

3-Phenyl-1,2-benzisoxazole (3.3 g) was added to freshly distilled dimethyl sulphate (15 ml) and heated at 125° for 24 hours. The solution was cooled and treated with 6 *N* hydrochloric acid. Ferric chloride solution (2 parts $FeCl_3$ to 1 part water) was added until the yellow salt precipitated; yield 6.25 g (90%); m.p. 117–119°. Calculated for $C_{12}H_{12}ONFeCl_4$: C, 41.22%; H, 2.97%; N, 3.35%. Found: C, 41.36%; H, 3.12%; N, 3.43%.

*3-Phenyl-2*H*-1,3-benzoxazine (VIIa)*

N-Methyl-3-phenyl-1,2-benzisoxazolium ferrichloride (5.25 g) was shaken for 15 minutes with ether (15 ml) and a 5% aqueous solution of sodium hydroxide (15 ml). The ether layer was washed with water, dried over anhydrous sodium sulphate, and evaporated, yielding a yellow oil (1.35 g, 50%). Addition of a solution of picric acid in ether gave a dimorphous yellow picrate, m.p. 103–104° (from methylene chloride – ether) and 158–160° (from glacial acetic acid). A solution of the picrate in methylene chloride was poured onto a column of basic alumina (Woelm, grade I); on elution with benzene a white solid was obtained which recrystallized from ether – petroleum ether as white needles, m.p. 49–50°. The infrared spectra of the crystalline and crude oily materials were virtually identical. Calculated for $C_{14}H_{11}ON$: C, 80.37%; H, 5.30%; N, 6.81%. Found: C, 80.64%; H, 5.28%; N, 6.69%.

N-Benzyl-3-phenyl-1,2-benzisoxazolium Perchlorate (VIb)

3-Phenyl-1,2-benzisoxazole (440 mg) was dissolved in benzyl chloride (3 ml), and a saturated solution of silver perchlorate (500 mg) in ether added. A white precipitate formed immediately, which was filtered off and triturated with methylene chloride. The mixture was filtered (to remove the silver chloride) and the filtrate evaporated to about 2 ml. Addition of ether gave white crystals (275 mg, 30%) which, after four recrystallizations from methylene chloride – ether, melted at 164–165°. Calculated for $C_{20}H_{16}O_5NCl$: C, 62.26%; H, 4.18%; N, 3.63%. Found: C, 61.86%; H, 4.26%; N, 3.41%.

*2,4-Diphenyl-2*H*-1,3-benzoxazine (VIIb)*

The perchlorate (VI*b*) (145 mg) was dissolved in methanol (5 ml) and a 5% aqueous sodium hydroxide solution (15 ml) added with stirring during 15 minutes. On work-up a crystalline material (89 mg, 84%) was obtained which recrystallized from methylene chloride – petroleum ether as white needles melting at 97–99°. Calculated for $C_{20}H_{15}ON$: C, 84.18%; H, 5.30%; N, 4.91%. Found: C, 83.87%; H, 4.90%; N, 5.19%.

*Irradiation of 4,5,6-triphenyl-2*H*-1,3-oxazine*

4,5,6-Triphenyl-2*H*-1,3-oxazine (III) (50 mg) was dissolved in a mixture of ether (20 ml) and methanol (2 ml). The solution was divided into two equal portions and each half placed in a glass-stoppered, 50-ml round-bottomed Pyrex flask. One flask was wrapped carefully with aluminum foil to allow as little light as possible to reach the inside, the other flask was not wrapped. The flasks were immersed in cold methanol contained in a stainless steel beaker cooled in a dry ice – methanol bath. The temperature of the methanol surrounding the reaction flasks was kept at $-60\pm5°$ during the experiment. A Hanovia C-H-3 ultraviolet lamp was placed in a Pyrex test tube and immersed in the methanol bath so that the light source was the same distance (ca. 2 cm) from each flask. After 90 minutes' irradiation both samples were removed from the bath and the solvent removed *in vacuo*. The infrared spectrum of the crude irradiated material indicated that it consisted largely of the "methanol adduct" (X); recrystallization gave X (17 mg), identified by comparison of the melting point and infrared spectrum with that of an authentic sample obtained by Kohler and Blatt's procedure (1). The infrared spectrum of the crude material from the shielded sample indicated it to be almost pure starting material, which, after recrystallization, was identified as III by melting point and infrared spectrum.

In a second experiment ultraviolet spectroscopy showed that the irradiated sample was converted to the methanol adduct in less than 2 hours and that no significant change took place with the shielded sample in 6 hours.

*Irradiation of 4-phenyl-2*H*-1,3-benzoxazine (VIIa)*

(a) In Methanol–Ether

4-Phenyl-2*H*-1,3-benzoxazine (450 mg) was dissolved in a mixture of ether (Mallinckrodt anhydrous, 85 ml) and methanol (Fisher Spectranalyzed, 85 ml), and the solution irradiated for 10 hours in a quartz immersion apparatus (16) using a Hanovia C-H-3 lamp. The solvent was evaporated and the material soluble in ether chromatographed on silica gel. Elution with petroleum ether – benzene (20:1) gave a yellow oil (200 mg), identified by its infrared and n.m.r. spectra as *o*-hydroxybenzophenone.

(b) In Dry Methanol

When the irradiation was carried out under the same conditions as in (*a*) but using as solvent methanol carefully dried by the magnesium methoxide procedure, only starting material was obtained.

(c) In Methanol–Aniline

4-Phenyl-2*H*-1,3-benzoxazine (450 mg) and freshly distilled aniline (1 ml) were dissolved in methanol dried by the magnesium methoxide procedure (170 ml), and the solution irradiated in the immersion apparatus. After about 10 minutes the solution began to redden and within ½ hour was a dark red. The irradiation was continued for 10 hours. The solvent was then evaporated and the residue triturated with methylene chloride. The methylene chloride solution was filtered through a silica gel column and the solvent evaporated, leaving yellow needles (205 mg), identified by melting point, mixed melting point, and infrared spectrum as the anil of *o*-hydroxybenzophenone (17). The proton magnetic resonance spectrum of the anil showed a singlet (due to hydrogen-bonded O—H) at 13.80 p.p.m. and a broad absorption at 6.7 to 7.3 p.p.m. due to the aromatic hydrogens.

*Treatment of 4-Phenyl-2*H*-1,3-benzoxazine (VIIa) with Methanol–Ether*

4-Phenyl-2*H*-1,3-benzoxazine (25 mg) was dissolved in a mixture of methanol (Fisher Spectranalyzed, 5 ml) and ether (Mallinckrodt anhydrous, 5 ml), and the solution refluxed for 12 hours. The solvent was evaporated; the infrared spectrum of the residue showed it to be unchanged starting material.

*Treatment of 4-Phenyl-2*H*-1,3-benzoxazine (VIIa) with Methanol–Aniline*

Aniline (0.2 ml) was added to a solution of 4-phenyl-2*H*-1,3-benzoxazine (10 mg) in dry methanol (15 ml), and the solution allowed to stand at room temperature for 16 hours. The infrared spectrum of the product showed it to be unchanged starting material.

ACKNOWLEDGMENTS

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