[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES, U. S. VITAMIN AND PHARMACEUTICAL CORP.]

Reaction of *t*-Ethinyl Alcohols with Aryl Isocyanates

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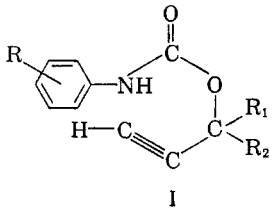
Reaction of *t*-ethinyl alcohols with aryl isocyanates gave 3-aryl-6,6-disubstituted 1,3-oxazine-2-ones, II and III, found to be inactive as anticonvulsants. In the instance of the synthesis of II, R = *m*-Cl, under lithium catalysis, evidence is presented which suggests that tri(*m*-chlorophenyl) isocyanurate is initially formed, followed by formation of the oxazine. When 3-hydroxypyridine was evaluated as the catalytic tertiary base for aryl isocyanate reactions, it was found that it readily formed 1:1 molar complexes with the isocyanates. These complexes have been characterized as betaines of the type IV.

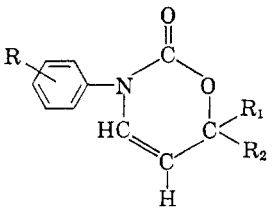
Inspection as anticonvulsants of a series of substituted phenylurethans[1] indicated heightened activity among *m*- and *p*-halo derivatives.

It was of interest to examine the corresponding carbanilates of the pharmacologically active ethinyl alcohols.[2-5] Such alcohols have been rendered more active by conversion to carbamate and allophanate derivatives.[6-9]

When 1-ethinylcyclohexanol or 3-methyl-1-pentyl-3-ol were treated under sodium acetate catalysis with the aryl isocyanates, there was obtained 1,3-oxazine-2-ones (II and III) which resulted from intramolecular cyclization of the anticipated carbanilate (I)



I



II, $R_1 = CH_3$; $R_2 = C_2H_5$
III, $R_1 + R_2 = -(CH_2)_5-$

The carbanilate structure was rejected on the basis of absence of the acetylenic hydrogen on titration,[10] the absence of an ultraviolet absorption spectrum typical of a substituted phenyl carbanilate,[1,11] and the absence of acetylene bands and —NH bands in the infrared spectrum. The oxazine structure was indicated by the ultraviolet spectra which suggests an out of plane *N*-phenyl ring on a cyclic structure[12] and evidence in the infrared[13] for a *cis* double bond, (II and III, R = *m*-chloro λ 7.15, 14.55; λ 7.10, 14.31) and —C—N—C—aromatic band (*ibid.* λ 7.52, 7.98; λ 7.78, 8.05). Additionally, other work[14,15] has indicated the reactivity under alkaline catalysis of amide groups with acetylene.

TABLE I

1,3-OXAZINE-2-ONES

R	M.P.[a]	Formula	Nitrogen, %[b] Calcd.	Found
		Derivatives of II		
o-Cl	93–94	$C_{13}H_{14}ClNO_2$	5.6	5.8
m-Cl[c]	84	$C_{13}H_{14}ClNO_2$	5.6	5.8
p-Cl	121–122	$C_{13}H_{14}ClNO_2$	5.6	5.6
p-Br	120–121	$C_{13}H_{14}BrNO_2$	4.7	4.6
		Derivatives of III		
o-Cl	172–173	$C_{15}H_{16}ClNO_2$	5.0	4.6
m-Cl[d,e]	140–141	$C_{15}H_{16}ClNO_2$		
p-Cl	174–176	$C_{15}H_{16}ClNO_2$	5.0	4.9
p-Br	174–177	$C_{15}H_{16}BrNO_2$	4.4	4.4

[a] Melting points are uncorrected, and were obtained after recrystallization from ethanol or isopropyl alcohol. No attempt was made to obtain maximum yields. [b] Analyses are by Weiler and Strauss, Oxford, England. [c] λ_{max} 240–248 (plateau) ε 2,800 (methanol). [d] *Anal.* Calcd.: C, 64.9; H, 5.8. Found: C, 64.8; H, 5.9. [e] λ_{max} 239–246 (plateau) ε 2800 (methanol).

The compounds, on testing in mice, failed to show anticonvulsant activity.

The reaction proceeded readily, with the electron-withdrawing R = halogen of the isocyanate pro-

(1) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6498 (1959).

(2) D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.*, **76**, 4446 (1954).

(3) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **77**, 4874 (1955).

(4) H. Gutman, O. Isler, G. Ryser, P. Zeller, and B. Pellmont, *Helv. Chim. Acta*, **42**, 719 (1959).

(5) B. Brown, R. W. Schaffarzick, and R. H. Dreisbach, *J. Pharmacol. Exp. Therap.*, **115**, 230 (1955).

(6) E. E. Swanson, R. C. Anderson, and W. R. Gibson, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 40 (1956).

(7) A. H. Galley and P. Trotter, *Lancet*, **343** (Feb. 15, 1958).

(8) W. M. McLamore, S. Y. P'An, and A. Bavley, *J. Org. Chem.*, **20**, 1379 (1955).

(9) R. Preuss and R. Kopp, *Arzneimittel-Forsch*, **9**, 785 (1959).

(10) S. Siggia, *Quantitative Organic Analysis via Functional Groups*, John Wiley & Sons, Inc., New York, N. Y., 1949, p. 54.

(11) H. E. Ungnade, *J. Am. Chem. Soc.*, **76**, 5133 (1954). See in particular the relatively small steric effect associated with trimethylacetanilide.

(12) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6498 (1959).

(13) H. Gilman, *Organic Chemistry*, Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 143.

(14) A. Akiyoshi, T. Matsuda, and J. Murate, *J. Chem. Soc. Japan*, **56**, 440 (1953).

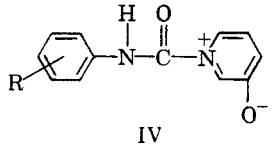
(15) M. F. Shostakovskii, F. P. Sidel'kovskaya, and M. G. Zelenskaya, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk.* 1457 (1957) [*Chem. Abstr.*, **52**, 7270f (1958)].

moting[16] reactivity by the difficulty realizable nucleophilic attack of the tertiary alcohol.[17] The linear ethinyl group as one of the substituents on the reactant tertiary carbinol[18] markedly reduces steric hindrance, and the driving force of oxazine cyclization, apparently also promotes the reaction.

The attempted preparation of II, R = *m*-chloro, failed. Under lithium alkoxide catalysis[17] at ambient temperature the reaction also failed and afforded instead tri(*m*-chlorophenyl) isocyanurate. At an elevated temperature the desired product was obtained. This would suggest dissociation of the trimer under the influence of heat with subsequent reaction to give the carbanilate which then cyclized to the oxazine. This was confirmed by isolation of *m*-chlorophenylurethan upon heating tri-(*m*-chlorophenyl) isocyanurate with ethanol under lithium catalysis.

Isocyanate dimers and trimers have been obtained from the aryl isocyanates under *N*-methylmorpholine catalysis,[19,20] pyridine-epichlorohydrin catalysis,[21] and amino-pyridine catalysis.[22] The —N—C—C—O— structural requirement[19-21] in catalysts of choice suggested evaluation of 3-hydroxypyridine in this reaction. In catalytic amounts, a product indicative of an equimolar complex of 3-hydroxypyridine and the isocyanate was obtained.

Equimolar condensation of 3-hydroxypyridine and aryl mono- or diisocyanates in acetonitrile, or in the absence of solvent, yielded crystalline compounds which gave strong ferric chloride tests and which have been formulated as betaines IV.[23]



IV

The *N* - (carbanilido) - 3 - oxypyridylbetaines are stable under ambient conditions, odorless and nonlachrymatory, and upon boiling with ethanol give the corresponding urethane. A similar condensation of 3-hydroxypyridine with phenyl isothiocyanate failed. When 3-hydroxypyridine was substituted for *N*-methylmorpholine under Kogon's conditions[19] phenyl isocyanate afforded the trimer, while *m*-chlorophenyl isocyanate gave the dimer.

The reaction of the aryl isocyanates with ethinyl alcohols is being explored further.

EXPERIMENTAL[24]

3-Aryl-6,6-disubstituted 1,3-oxazine-2-ones. These compounds were prepared by the same general procedure.

A mixture of 0.03 mole of the ethinyl alcohol and 0.03 mole of the appropriately substituted halophenyl isocyanate and 0.1 g. of anhydrous sodium acetate was heated on the steam bath for 4.5 hr. When cool, 30 ml. of ether (or chloroform) was added, the sodium acetate removed by filtration and the residue of product obtained on evaporation of the ether. The crude yields ranged from 28–94%. Under these conditions, II, R = *m*-chloro, was not obtained.

3-(m-Chlorophenyl)-6-ethyl-6-methyl-1,3-oxazine-2-one. A mixture of 6 g. (0.06 mole) of 3-methyl-1-pentyne-3-ol, 9.2 g. (0.06 mole) of *m*-chlorophenyl isocyanate and 0.07 g. of lithium, on standing, afforded an exothermic reaction followed by the appearance of a white solid. The reaction mixture was heated at 125° and a vigorous reaction accompanied by solution of the white solid and browning of the reaction mixture occurred. When cool, 150 ml. of chloroform was added, and the solution filtered. The oily residue, upon removal of the chloroform, and solution in 10 ml. of isopropyl alcohol and standing gave 3.6 g. (23%) of product, m.p. 79–83°, which on recrystallization (isopropyl alcohol) gave 2.4 g. (15.9%) m.p. 84°.

When the above reaction was interrupted at the appearance of the white solid, and conducted in the absence of heat, the formed white solid separated to give 2.2 g. (36.6%) of tri(*m*-chlorophenyl) isocyanurate, m.p. 253°, recrystallized (acetone-methanol), m.p. 256°. The compound so isolated did not depress the melting point of this trimer prepared by established procedures.[19]

Tri(m-chlorophenyl) isocyanurate. A mixture of 15.3 g. (0.1 mole) of *m*-chlorophenyl isocyanate, 0.8 ml. of ethanol, and 0.3 ml. of *N*-methylmorpholine was heated at 125° for 4 hr. When cool, there was obtained after filtration and trituration with benzene, 10.5 g. (68.6%) of product, m.p. 256° not raised after recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{12}Cl_3N_3O_3$: N, 9.1. Found: N, 9.3.

In a similar manner, triphenyl isocyanurate was prepared, m.p. 285–286° (ethanol); (reported,[21] m.p. 285°).

m-Chlorophenylurethane. A mixture of 2 g. (0.004 mole) of tri(*m*-chlorophenyl) isocyanurate, 0.6 g. (0.012 mole) of ethanol and 0.02 g. of lithium was heated at 120° for 3 hr. When cool, the precipitated unchanged trimer was separated and the filtrate distilled to give 1.1 g. of product, b.p. 95° (0.05 mm.).

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.1; H, 5.0; N, 7.0. Found: C, 54.4; H, 5.1; N, 6.7.

m-Chlorophenyl isocyanate dimer. The compound was prepared from 5 g. of *m*-chlorophenyl isocyanate and 0.5 ml. of triethylamine[25] to give 3.4 g. (68%); recrystallization (ethanol) gave 2.4 g. (48%) of dimer, m.p. 227–230°.[26]

Anal. Calcd. for $C_{14}H_8Cl_2N_2O_2$: C, 54.7; H, 2.6; N, 9.1. Found: C, 55.0; H, 2.7; N, 9.1.

Phenyl isocyanate dimer was prepared by using pyridine[27] as a catalyst, m.p. 176°.

Reaction of 3-hydroxypyridine plus ethanol with phenyl isocyanate, following Kogon's procedure,[19] gave the trimer of phenyl isocyanate, m.p. 285–286°, not depressing the melting point of authentic trimer.

(16) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Revs.*, **57**, 47 (1957).

(17) W. J. Bailey and J. R. Griffith, American Chemical Society Cleveland Meeting, 1960, Abstr., p. 12-O.

(18) D. N. Robertson, *J. Org. Chem.*, **25**, 931 (1960) has noted facile reaction of ethinyl tertiary carbinols with dihydropyran.

(19) I. C. Kogon, *J. Am. Chem. Soc.*, **78**, 4911 (1956).

(20) R. Tsuzuki, K. Ichikawa, and M. Kase, *J. Org. Chem.*, **25**, 1009 (1960).

(21) J. I. Jones and N. G. Savill, *J. Chem. Soc.*, 4392 (1957).

(22) Imperial Chem. Ind. Ltd., Ger. Patent, **1,081,895** (1960).

(23) S. L. Shapiro, K. Weinberg, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 5140 (1959).

(24) Descriptive data shown in the Table are not reproduced in the Experimental section.

(25) J. M. Lyons and R. H. Thomson, *J. Chem. Soc.*, 1971 (1950).

(26) L. C. Raiford and H. B. Freyermuth, *J. Org. Chem.*, **8**, 230 (1943), reported m.p. 153–154°.

(27) C. J. Brown, *J. Chem. Soc.*, 2931 (1955), reported m.p. 176°.

Under similar conditions, the use of *m*-chlorophenyl isocyanate gave the dimer, m.p. 227–229° (ethanol), not depressing the melting point of dimer prepared by an authentic procedure.

N-(Carbanilido)-3-oxypyridyl betaines, IV. These compounds were obtained by heating an equimolar mixture of the aryl isocyanate and 3-hydroxypyridine in a bath maintained at 195° for 0.5 hr. When cool, the reaction product was recrystallized (acetonitrile).

The compounds were of analytical purity, and were obtained as follows: R (melting point) respectively: H (135–136°); *o*-CH_3 (81–84°); *m*-CH_3 (120–121°); *p*-CH_3 (153–155°); *o*-Cl (103–104°); *m*-Cl (159–160°); *p*-Cl (196–197°); *p*-Br (203–208°); *o*-CH_3O (83–84°); *p*-CH_3O (134–135°); bisbetaine from 4,4′-diisocyanate-3,3′-bitolyl (128–132°).

One gram of IV, R = H, was boiled in 20 ml. of ethanol, the ethanol removed to a residual volume of 5 ml., and upon addition of 5 ml. of water and 1.7 ml. of 3*N* hydrochloric acid, *N*-phenylurethane was isolated, m.p. 49–50° (hexane), not depressing the melting point of authentic *N*-phenylurethane, mixed m.p. 49–50°.

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[CONTRIBUTION FROM THE ROHM & HAAS CO.]

The Vinylation of Glycerol

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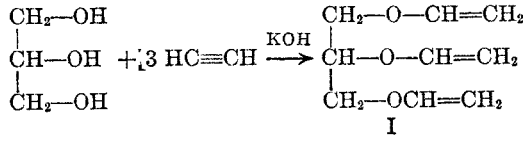
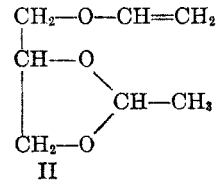
The base-catalyzed vinylation of glycerol in a batch process afforded predominantly 2-methyl-4-vinyloxymethyl-1,3-dioxolane (II) together with 5–12% of 1,2,3-trivinyloxypropane (I). When the reaction was stopped before completion, the precursor of II, 4-hydroxymethyl-2-methyl-1,3-dioxolane (III) was isolated in 30% yield. These results contradict earlier reports[1–3] concerning the course of the reaction. By means of a continuous condensed-phase coil reactor under pressures much above those generally employed in batch experiments, the conversion of glycerol to the trivinyl ether I was increased to 50%; the major by-product was the dioxolane II.

The trivinyl ether of glycerol, 1,2,3-trivinyloxypropane (I), was disclosed first by Favorskii and Shostakovskii in a general survey of the vinylation reaction.[1] Later publications by Shostakovskii and Gracheva[2,3] described the base-catalyzed vinylation of glycerol in greater detail. They reported that I was obtained in 90% yield by the treatment of glycerol with acetylene at 10–12 atmospheres initial pressure in the presence of powdered potassium hydroxide at 170–190°.

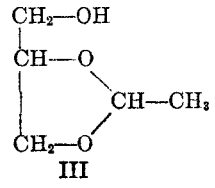


I

Our attempts to reproduce these results were consistently unsuccessful. It was observed that when glycerol was heated with acetylene under 13–35 atmospheres for seven to twenty-nine hours in the presence of a catalytic quantity of sodium glyceroxide or powdered potassium hydroxide, the major product, isolated in 33–66% yield, was 2-methyl-4-vinyloxymethyl-1,3-dioxolane (II). In addition, only small amounts (5–12%) of the trivinyl ether I were produced. The precursor of II, 4-hydroxymethyl-2-methyl-1,3-dioxolane (III), was



II



III

obtained in 30% yield by limiting the vinylation time to two hours.

The structure II was established by hydrogenation, followed by mild acid hydrolysis and periodate analysis for 1,2-glycol. Similarly, the structure III was confirmed by periodate analysis of the hydrolyzate of the methyl ether of III. The periodate analyses for vicinal hydroxyl functions eliminate the isomeric 1,3-dioxane structures as possible alternatives for II and III. The analytical and hydrogenation data left little doubt as to the structure of I. The infrared spectra of I, II, and III were entirely consistent with their assigned structures.

In contrast to these findings, it has been reported[2,3] that partial vinylation afforded, in addition of I, the 1-mono and 1,3-divinyl ethers of glycerol; cyclic acetals were not observed as primary reaction products. A comparison of the published data for I[1,2] with the physical constants summarized in Table I suggests that the product

(1) A. E. Favorskii and M. F. Shostakovskii, *J. Gen. Chem. U.S.S.R.*, **13**, 1 (1943).

(2) M. F. Shostakovskii and E. P. Gracheva, *J. Gen. Chem. U.S.S.R.*, **19**, 1250 (1949).

(3) M. F. Shostakovskii and E. P. Gracheva, *Akad. Nauk. S.S.S.R. Inst. Org. Khim. Sintezy Org. Soedinenii Sbornik*, I, 144 (1950); *Chem. Abstr.*, **47**, 8002 (1953).