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SYNTHESIS OF HETEROBICYCLIC COMPOUNDS

Part III.—Formation of 2H-1,3-Benzoxazine-2H-(3H)-dione

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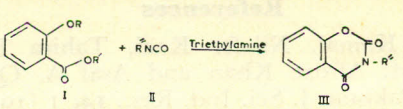
The vigorous reaction between phenyl isocyanate and methyl salicylate in the presence of triethylamine, has been reinvestigated and found not to yield diphenylurea or *N*-phenylurethan as hitherto claimed. The reaction is general for *o*-hydroxybenzoic acid or esters, and isocyanates (PhNCO), and it yields 3-substituted derivative of 2H,1,3-benzo-oxazine-2,4-(3H)-dione. The mechanism of the reaction is discussed.

In the literature[1] it is stated that phenyl isocyanate and methyl salicylate react in the presence of triethylamine to form *N*-phenylurethane (IV) at 65°C. Higher temperature promotes the formation of *N*,*N*-diphenylurea. The formation of this urea from phenyl isocyanate is not possible without water. A reinvestigation of the reaction under the same anhydrous conditions showed that neither products were formed.

The reaction was exothermic and affords a crystalline compound III, $C_{14}H_9NO_3$, m.p. 246°C, which did not resemble diphenylurea at all. The compound was neutral. Under mild alkaline conditions it afforded salicylanilide and mild HCl treatment in methanol gave methyl salicylate and aniline hydrochloride. Thus the behaviour of the compound resembled that of benzoxazine (III, R″=Ph) already known[2] and with which it was found to be identical (mixed m.p. and IR spectrum). The overall reaction is written below:



I II III

The reaction of phenyl isocyanate and other *o*-hydroxybenzoic esters (I R′=H, R=Et) was also examined. The results are tabulated in Table 1.

Phenyl isocyanate and *o*-hydroxybenzoic esters react together to form compound III without a catalyst, but the time of reaction is very long, the yields are very poor (Table 1), and the temperature required for the completion of the reaction is high. Benzoxazine (III) was also formed when aspirin or aspirin chloride were heated with phenyl isocyanate at 240°C, while acetic acid, acetic acid and hydrogen chloride were expelled respectively. Again the yield was low and the reaction mixture was very unclean to work with. Methyl salicylate and ethyl salicylate, when refluxed with phenyl isocyanate in toluene, gave neither urethene nor oxazine, but crystalline compounds of m.p. 105°C and 146°C respectively.

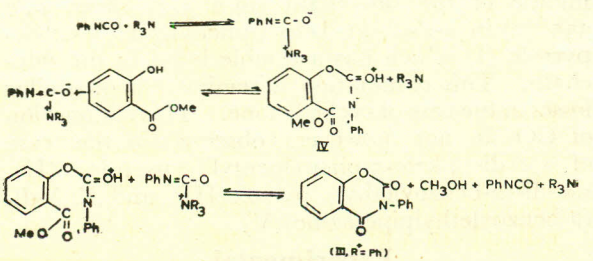
TABLE 1.—FORMATION OF BENZOOXAZINE III FROM PHENYL ISOCYANATE (II) AND *o*-HYDROXYBENZOIC ESTERS (I).

Hydroxybenzoic esters (I) R′	R	Catalyst	Time hr	Temp °C	Yield %
CH_3-	H	Triethylamine	1	Room temp	92
C_2H_5-	H	,,	1	,,	90
CH_3-	H	—	24	240	24
C_2H_5-	—	—	24	240	10
C_3H_7-	H	—	24	240	11
C_4H_9-	H	—	24	240	67
CH_3-	CONHPh	Triethylamine	1	60	96
C_2H_5-	,,	,,	1	60	90
H	CH_3CO	—	1	Room temp	60
I,OR′=Cl	CH_3CO	—	—	—	—
H	H	—	1	Room temp	41

The nature of these two products is being studied and will be reported later.

Mechanism

The formation of compound III seems to involve two main steps, firstly, urethane formation and secondly, cyclisation of the urethane. Both of the steps are catalysed by a base–isocyanate complex. It appears that the second step of the reaction is as fast as the first step, because urethane of methyl salicylate could not be isolated in spite of several attempts.



In support of the above scheme, which was first advanced by Daker *et al.*[3] for the formation of urethane and which was later supported with further evidence by Flynn[4] it was found that the *N*-phenyl-urethane of methyl salicylate and ethyl salicylate, when heated in the base like triethylamine and PhNCO, cyclised to give compound III. Triethylamine or dil NaOH alone did not effect the cyclisation of urethane IV which suggested that the formation of oxazine (III R=Ph) also depended on a base–isocyanate complex and not on the removal of a proton by triethylamine alone from urethane IV.

Experimental

Formation of 3-*Phenyl*-2H,1,3-*Benzoxazine*-2,4-(3H) *dione* (*III R″=Ph*)

Methyl salicylate (7.6 g, 0.05 mole), phenyl isocyanate (5.95 g, 0.05 mole) and triethylamine (0.5 ml) were mixed in a round bottom flask (250 ml). The reaction was exothermic and the contents became yellow after ½ hr. It was kept as such at room temperature for 2 hr, when crystalline 3-phenyl-2H,1,3-benzoxazine-2, 4(3H)-dione (11 g, 92%) separated, which on recrystallisation from benzene melted at 246–247°C and showed no depression with an authentic sample prepared by the method of Crum *et al.*[2] (Found: C, 70.7; H, 4.0; N, 5.8%. Calc. for $C_{14}H_9NO_3$: C, 70.3; H, 3.8; N, 5.9%.)

Similar treatment of ethyl salicylate (4.15 g, 0.025 mole) and phenyl isocyanate (2.975 g, 0.025 mole) in the presence of triethylamine (0.5 ml) gave compound III (R″=Ph) (5.4 g, 90.0%), m.p. 246°C, undepressed by an authentic sample.

Methyl salicylate (15.2 g, 0.1 mole) and phenyl isocyanate (5.95 g, 0.05 mole) were heated at 200°C for 30 hr. The mixture after removal of the reactants under reduced pressure solidified and was cooled. Trituration of the solid with ether gave 3-phenyl-2H, 1,3-benzoxazine-2, 4(3H) dione (5.8 g, 24%), m.p. 246°C, undepressed by an authentic sample. Similarly, compound III (R″=Ph) was obtained from other esters of salicylic acid and phenyl isocyanate and the results are given below:

TABLE 2.—FORMATION OF OXAZINES FROM ESTERS OF SALICYLIC ACID (0.1 MOLE) AND PHENYL ISOCYANATE (0.05 MOLE, 5.95 G) WITHOUT CATALYST (TIME OF REACTION 24 HR).

Esters	Temp	Oxazine g	Yield %
Ethyl (16.6 g)	210°	2.4	10
Propyl (18.0 g)	220°	2.7	11.3
n-Butyl (19.4 g)	240°	1.6	6.7

Formation of N-*phenylurethan of Methyl Salicylate*

Phenyl isocyanate (5.95 g, 0.05 mole) and methyl salicylate (7.6 g, 0.05 mole) were mixed together at room temperature and were diluted with diethyl ether (100 ml). To this solution, 1 ml triethylamine was added. As reaction was exothermic, the reaction mixture was cooled.* It was kept as such for 1 hr and then diluted with petroleum ether (60–80°C). It gave a solid (6 g, 44.4%) (m.p. 114°C) which on purification by recrystallisation with benzene and petroleum ether (1:1) gave m.p. 120°C, lit.[1,6] m.p. 119–120°C, 117°C. (Found: C, 66.8; H, 4.9% N, 5.2%. Calc. for $C_{15}H_{13}NO_4$ C, 66.4; H, 4.8; N, 5.2%.)

Similar treatment of ethyl salicylate with phenol isocyanate in equimolar ratio gave *N*-phenylurethan, which on recrystallisation melted at 100°C, lit.[6] m.p. 98–100°C. (Found: C, 67.8; H, 5.2; N, 5.2%. Calc. for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.2; N, 4.9%.)

Formation of 3-*Phenyl*-2-*H*,1,3-*benzoxazine*-2,4 (3*H*)-*dione from* N-*Phenylurethane of Methyl Salicylate*

The urethane (0.271 g, 0.001 mole) was added to phenyl isocyanate (0.11 g, 0.001 mole) and triethylamine mixture (0.2 ml) in a pear-shaped flask (25 ml) under anhydrous conditions. The mixture was heated mildly on water bath until the solution became clear. The coloured thick melt solidified on cooling and was triturated with petroleum ether. The oxazine (III R″=Ph) weighed 0.23 g (96%) and, on recrystallisation melted at 246°C, undepressed by an authentic sample. The IR of the product was also exactly similar to that of an authentic sample.

Similar treatment of the *N*-phenylurethane of ethylsalicylate yielded 3-phenylbenzooxazine (III R″=Ph) in 90% yield.

Preparation of 3-*Phenyl*-2*H*, 1,3-*benzoxazine*-2,4(3H)-*dione*

From Aspirin Chloride.—Aspirin chloride (3.97 g 0.02 mole) and phenyl isocyanate (2.4 g, 0.02 mole) were refluxed for 3 hr in an oil bath. The mixture was washed with dry ether to remove the unreacted isocyanate. The residue was dissolved in benzene and the solution on concentration deposited colourless needles of compound III (R″=Ph), 50 mg, m.p. 246°C, undepressed by an authentic sample.

From Aspirin.—Aspirin (9.0 g, 0.05 mole) and phenyl isocyanate (11.9 g, 0.1 mole) were refluxed for 3 hr. On triturating the reaction mixture with dry ether, a powder (7.5 g, 63.0%) was obtained which after recrystallisation from benzene melted at 246°C, undepressed by an authentic sample.

Form Salicylic Acid.—Salicylic acid (13.8 g, 0.1 mole) and phenyl isocyanate (23.8 g, 0.2

mole) were heated at 180°C on oil bath, while being protected from moisture. After about an hour the mixture became solid. The solid was triturated with benzene and filtered, the solid weighed 17.0 g, m.p. 216°C, which on fractional crystallisation from benzene gave two solids. The first fraction weighed 7.0 g (41%) and had m.p. 246°C and identical in all respects with 3-phenyl-2H,1,3-benzoxazine-2,4(3H) dione. The second crystalline solid (10 g), m.p. 239°C was identical with *N,N'*-diphenylurea. (Found: N, 13.03 Calc. for $C_{13}H_{12}N_2O$: N, 13.2%.)

Treatment of the Product (III R″=Ph) with Methanolic Potash

3-Phenyloxazine (III R″=Ph) (0.25 g) and methanolic potash (2.5 ml, 10%) were heated on water bath until dissolution of the solid took place. It was cooled and acidified with 2N HCl and the liquid evaporated. An oil was obtained, which was identified by its b.p. as methyl salicylate. (Found: C, 63.2, H, 4.3%. Calc. for $C_8H_7O_3$: C, 63.5; H, 4.6%.)

A solid, m.p. 200°C, was obtained which was identified as aniline hydrochloride. (Found: N, 10.5%. Calc. for C_6H_8NCl: N, 10.8%).

Treatment of Compound III (R″=Ph) with Aq. Potash

Compound III (R″=Ph) (0.25 g) and KOH (3 ml, 10%) were heated mildly until the solution became clear. It was cooled and acidified with 2N HCl. Evolution of CO_2 was observed and a crystalline product was obtained, which melted at 135°C, and was found to be identical with salicyl anilide. (Found: C, 73.0; H, 5.0; N, 6.1%. Calc. for $C_{13}H_{11}NO_2$. C, 73.2; H, 5.1; N, 6.5%).

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