J. Chem. Soc. (C), 1970

Cytotoxic Compounds. Part XI.¹ Enol Carbamates derived from α -Chloro- α -phenylacetophenone

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The sodium enolate of α -chloro- α -phenylacetophenone reacts with carbonyl chloride to form 2-chloro-1.2-diphenylvinyl chloroformate, which condenses with amines to give a series of 2-chloro-1.2-diphenylvinyl carbamates. The u.v. and i.r. spectra of these compounds are recorded.

An earlier paper ² described the preparation of enol acetates (II) from a series of α -aryl- α -halogenoacetophenones (I), and thus exemplified a method whereby a considerable reduction in the alkylating power (and consequently in the toxicity) of an α -halogeno-ketone could be achieved. Because of the favourable chemotherapeutic indices shown by certain nitrogen mustards which had been detoxicated by conversion into urethanes, such as (III) and (IV),^{1,3,4} there was a need to establish a synthetic route to enol urethanes of α -halogenoketones. Such compounds have never been described; ¹ Part X, L. N. Owen and R. Sridhar. J. Chem. Soc, (C), 1970,

¹ Part X, L. N. Owen and R. Sridhar. J. Chem. Soc. (C), 1970, 472.

² D. J. Cooper and L. N. Owen, J. Chem. Soc. (C), 1966, 533.
 ³ M. H. Benn, A. M. Creighton, L. N. Owen, and G. R. White, J. Chem. Soc., 1961, 2365.

indeed, only recently has an enol urethane of any kind been reported. Franko-Filipasic and Patarcity⁵ have obtained a few aliphatic and alicyclic compounds of the type (V) by direct interaction of a carbonyl compound with dimethylcarbamoyl chloride under drastic conditions (160°). Our first approach also involved this type of reagent, but in a reaction with the sodium enolate (VI)² of α -chloro- α -phenylacetophenone rather than with the free ketone. The result, however, was unpromising, and furthermore the monoarylcarbamoyl chlorides which would be required for the synthesis of

⁴ P. Hebborn, J. Theoret. Biol., 1968, 21, 449; T. J. Bardos,
Z. F. Chmielewicz, and P. Hebborn, Ann. New York Acad. Sci.,
1970, in the press.
⁵ B. R. Franko-Filipasic and R. Patarcity, Chem. and Ind.,

⁵ B. R. Franko-Filipasic and R. Patarcity, *Chem. and Ind.*, 1969, 166.

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some of the urethanes which we had in mind are not readily accessible. An alternative approach was there-



fore studied, in which an enol chloroformate could be condensed with an amine.

carbonyl chloride, but the product was not characterised and no proof of its structure was given; abortive attempts have been made (by Mr. P. J. Munday of this Department) to repeat this preparation. Vinyl chloroformate and propenyl chloroformate are reported to be formed by pyrolysis of the bischloroformates of ethylene glycol and propylene glycol respectively.⁷

Treatment of an ethereal suspension of the sodium enolate of α -chloro- α -phenylacetophenone with an excess of carbonyl chloride gave a product which could not be completely purified but which when distilled furnished an oil, showing strong i.r. absorption at 1775 cm.⁻¹, characteristic⁸ of the chloroformyl group. Weaker absorption at 1695 cm.⁻¹, and at other frequencies corresponding to absorptions in the spectrum of the parent ketone, indicated that some of the latter was still present. That the main component was the desired 2-chloro-1,2-diphenylvinyl chloroformate (VII) was shown by reaction of the distilled material with aniline. p-toluidine, N-methylaniline, and pyrrolidine, to give the crystalline urethanes, 2-chloro-1,2-diphenylvinyl N-phenyl- (VIII), N-p-tolyl- (IX), N-methyl-N-phenyl-(X), and N-tetramethylene-carbamate (XI) respectively. Reactions with methyl o-, m-, and p-aminobenzoate, which gave the N-(methoxycarbonylphenyl)carbamates (XII), (XIII), and (XIV), were carried out because of the biological advantages gained by the presence of the methoxycarbonylphenyl group in the nitrogen mustards (III) and (IV). 2-Chloro-1,2-diphenylvinyl N-p-(NNdi-2-chloroethylamino)phenylcarbamate (XV), a com-

2-Chloro-	1,2-dip	henylvinyl	carbamates
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Prop			Found (%)					Required (%)			
ompound	method	M.p.	б	н	N	Cì	Formula	c	Н	N	Cì
(VIII)	Α	154—158°	71.7	4.5	4.0		C ₂₁ H ₁₆ ClNO ₂	71.8	4.6	4 ·0	
` (IX)	Α	151	72.9	$5 \cdot 1$		9.5	$C_{22}H_{18}CINO_2$	$72 \cdot 6$	5.0		9.8
`(X)	Α	113 - 115	72.5	4.8		10.0	$C_{22}H_{18}CINO_2$	72.6	5.0		9.8
(XI)	Α	143 - 145	69.9	5.5	4.0	10.8	C ₁₉ H ₁₈ ClNO ₂	69·9	5.5	4∙3	10.8
(XII)	в	127-129	67.7	4.5	3.4	8.7	C ₂₃ H ₁₈ ClNO ₄	67.7	4.5	3.4	8.7
(XIII)	В	198200	67.9	4.4	3.3	8.8	C ₂₃ H ₁₈ ClNO ₄	67.7	4.5	$3 \cdot 4$	8.7
XIV)	в	186 - 188	67.5	4.5	3.2	8.6	C ₂₃ H ₁₈ ClNO ₄	67.7	4.5	3.4	8.7
`(XV)	С	158 - 160	60.6	4 ·6	$5 \cdot 5$		$C_{25}H_{23}Cl_3N_2O_2$	60.7	4.7	5.7	

Absorption spectra

$\nu_{\rm max}$ (CHCl ₃) in cm. ⁻¹								
Compound	NH	Amide I	Ester	C=C	Amide II	λ_{max} .	(EtOH) in nm. (log ε)
(VIII)	3420	1745			1535	$212 (4 \cdot 29)$	233 (4·50)	273 (4.06)
`(IX)	3410	1740		1620	1540	212 (4·32)	235 (4·45)	276 (4·05)
`(X)		1720		1630		210(4.38)	227 (4·34)	275 (3.97)
(XI)		1720		1635		210(4.18)	223 (4·21)	276 (3.96)
(XII)	3300	1745	1690		1540	225 (4·61)	247 (4·29)	292(4.01)
(XIII)	3420	1750	1715	1610	1540	226 (4·62)		271 (4.16)
(XIV)	3450	1755	1705		1535	2 10 (4·46)		270 (4·55)
(XV)	3400	1745			1535	210(4.22)	224 (4.01)	270 (4.23)

Enol chloroformates themselves are almost unknown. Matsuzak⁶ claimed to have prepared 1-methylvinyl chloroformate by interaction of acetone and liquid

⁶ M. P. Matsuzak, J. Amer. Chem. Soc., 1934, **56**, 2007. ⁷ F. E. Kung, U.S.P. 2,377,085/1943 (Chem. Abs., 1945, **39**, 3792). pound containing a deactivated nitrogen mustard unit as well as the deactivated α -halogeno-ketone, was prepared by condensation of the chloroformate with NNbis-(2-chloroethyl)-*p*-phenylenediamine.

⁸ J. L. Hales, J. I. Jones, and W. Kynaston, J. Chem. Soc., 1957, 618.

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The u.v. and i.r. spectra of the urethanes are recorded in the Table. The analogous enol acetates ² all showed absorption in the range 1620—1645 cm.⁻¹ (C=C stretching), but in some of the urethanes this was so weak that it could not be identified with certainty.

From a condensation between the chloroformate (VII) and the methyl ester of DL-phenylalanine the only pure material to be isolated was a halogen-free product identified as NN-carbonylbis(phenylalanine methyl ester) (XVI); the m.p. did not agree with that previously recorded,⁹ but the difference is probably due to stereo-isomerism, since the compound can exist in a *meso* and and in a racemic form. Glycine methyl ester also failed to give a urethane, and in this case a small amount of bis-(2-chloro-1,2-diphenylvinyl) carbonate (XVII) was separated from the reaction mixture. It may have been formed during distillation of the crude chloroformate; phenyl chloroformate is known to undergo disproportionation into diphenyl carbonate and carbonyl chloride when heated.¹⁰

EXPERIMENTAL

All reactions were carried out in anhydrous solvents

2-Chloro-1,2-diphenylvinyl Chloroformate.—Sodium hydride (1.45 g.) was added to a mixture of dry methanol (0.95 g.) and ether (50 c.c.). When the evolution of hydrogen ceased, a solution of α -chloro- α -phenylaceto-phenone ¹¹ (6.8 g.) in dry ether (30 c.c.) was added. After 30 min. the resulting orange-coloured suspension was added dropwise, with stirring, to liquid carbonyl chloride (4 c.c.) at 0°; the colour was instantly discharged. Sodium chloride was filtered off and the solution was concentrated under reduced pressure. The residue was then distilled to give the crude chloroformate (5.0 g.), b.p. 140—146°/1 mm., ν_{max} (CHCl₃) 1775vs and 1695 (ketonic impurity) cm.⁻¹. A similar result was obtained by use of a solution of carbonyl chloride in toluene instead of the liquid reagent.

2-Chloro-1,2-diphenylvinyl Carbamates (see Table).— Method A. A solution of aniline (0.55 g.) in ether (5 c.c.)was added dropwise to a stirred solution of crude 2-chloro-1,2-diphenylvinyl chloroformate (0.9 g.) in ether (5 c.c.); after 1 hr., aniline hydrochloride (which had been immediately precipitated) was filtered off and the filtrate was

- ⁹ H. Giesemann and D. Braun, J. prakt. Chem., 1959, 8, 39.
- ¹⁰ S. T. Bowden, J. Chem. Soc., 1939, 310.

washed successively with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water. Evaporation of the dried solution then gave an oil which solidified on trituration with petroleum (b.p. $40-60^{\circ}$). Four recrystallisations from petroleum (b.p. $100-120^{\circ}$) gave 2-chloro-1,2-diphenylvinyl N-phenylcarbamate (VIII) (0.3 g.).

Method B. A mixture of the chloroformate (1.0 g.), methyl o-aminobenzoate (0.5 g.), pyridine (0.6 g.), and benzene (10 c.c.) was stirred for 2 hr. and then washed and worked up as in method A. The oily product was purified by chromatography on silica, with chloroform-petroleum (b.p. 40-60°) (7:3) as eluant, to yield a solid. Recrystallisation from petroleum (b.p. 100-120°) then gave 2chloro-1,2-diphenylvinyl N-(o-methoxycarbonylphenyl)carbamate (XII) (0.6 g.). For the m- and the p-isomer, chromatography was not necessary; the crude product readily solidified.

Method C. A mixture of the chloroformate (3.0 g.), NNbis-(2-chloroethyl)-p-phenylenediamine hydrochloride 12 (2.7 g.), pyridine (1.6 g.), and ether (30 c.c.) was stirred for 2 hr. and then washed as in method A. Evaporation of the dried solution gave a grey solid, which after recrystallisation from petroleum (b.p. 100–120°) (charcoal) had m.p. 133–139°. Chromatography on alumina, with chloroform as eluant, followed by further recrystallisation from petroleum, furnished 2-chloro-1,2-diphenylvinyl N-p-(bis-2chloroethylamino)phenylcarbamate (XV) as needles (1.1 g.).

NN-Carbonylbis(phenylalanine methyl ester) (XVI).— When a mixture of the chloroformate (1.5 g.), DL-phenylalanine methyl ester (1.0 g.), triethylamine (1.4 g.), and ether (40 c.c.) was worked up according to method A, the solid product gave prisms (0.7 g.) of the urea, m.p. 131° [from benzene-light petroleum (b.p. 100—120°)], v_{max} . 3440, 1738, and 1678 cm.⁻¹ (Found: C, 65.5; H, 6.2; N, 7.2. Calc. for C₂₁H₂₄N₂O₅: C, 65.6; H, 6.3; N, 7.3%) (lit.,⁹ m.p. 163—164°; possibly a stereoisomer).

Bis-(2-chloro-1,2-diphenyl)vinyl Carbonate (XVII).—A similar reaction between the chloroformate and glycine methyl ester gave an oil from which a solid (0·1 g.) separated after several weeks. This was the carbonate, m.p. 154° (Found: C, 71·1; H, 4·0. $C_{29}H_{20}Cl_2O_3$ requires C, 71·4; H, 4·1%).

We thank Imperial Chemical Industries (India) Ltd. for a scholarship (to R. S.).

[9/1638 Received, September 22nd, 1969]

- ¹¹ A. M. Ward, Org. Synth., 1943, Coll. Vol. II, 159.
- ¹² J. L. Everett and W. C. J. Ross, J. Chem. Soc., 1949, 1972.