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# Acetylenic Carbamates as Potential Antitumour Agents

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## INTRODUCTION

A SERIES of acetylenic carbamates [1] showing experimental antitumour activity has been described and the main structural requirements defined [1, 2]. Significant inhibitory effects were seen only where both $R_1$ and $R_2$ were aryl groups, but substituents $R_3$ and $R_4$ could be varied widely without loss of activity. Derivatives of type (I) also displayed experimental antiviral activity [3, 4]. In a limited trial in human patients, compound (Ia) was effective in a case of giant follicular lymphoma, although other kinds of malignant disease did not respond [5].

In an extension of the American series, we have made a number of structural variants. The amino acid derivatives (Ib–d) were prepared from the corresponding *N*-carbonyl-DL-amino acid methyl esters (II a–c) and the acetylenic alcohol (IIIa), following the published method [1]. The diethoxyphosphinyl derivative (Ie) was made in a similar way. These reactions were carried out at room temperature in the presence of triethylamine (Ic, d, e), or with heating in the presence of sodium acetate (Ib). When *N*-carbonyl-DL-alanine methyl ester was heated with the alcohol (IIIa) and triethylamine, the oxazolidinone (IV) was the major product. That cyclization occurred under these conditions is not surprising [6], but structure (IV) is preferred to the alternative possibility (V) because the n.m.r. spectrum indicates the presence of two exocyclic methylene protons ($\tau$, 5·5, 5·8; $J$, 4Hz; cf. n.m.r. data for the methylene protons of 5,5-diphenyl-3-methyl-4-methyleneoxazolidinone [7]. Our structural assignment also supports an earlier view [8] regarding this type of ring closure.

Attempts to prepare carbamates carrying sugar residues by reaction of alcohol (IIIa) with appropriate protected isocyanates were unsuccessful [9].

The carbamates described thus far are o structure (I). We have in addition prepared two types of dicarbamates (VI and VII) by reaction of ethyl isocyanate with the corresponding diols (VIII and IX). The fluorinated derivatives were made because of the high potency of the *p*-fluoro compounds in the original series [1].

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## CHEMICAL SYNTHESIS

Melting points were determined on a Köfler block and are corrected; n.m.r. spectra were recorded on a 60 MHz Perkin–Elmer R-10 spectrometer; $CDCl_3$ was used as solvent and tetramethylsilane as internal standard. The chemical shifts are given in ppm on the $\tau$ scale and coupling constants ($J$) in Hz (Hertz). Gas–liquid chromatography (g.l.c.) was carried out on a Pye chromatograph (series 104, model 4), and Merck Kieselgel G was used in the thin-layer chromatography (t.l.c.).

1,1-*Diarylprop*-2-*yn*-1-*ols* (III)

The method of Hartzler [10] was used, starting from the appropriate diaryl ketone. It was advisable not to expose the liquid ammonia to the air for longer than was absolutely necessary, otherwise conversion was incomplete and the alcohol, contaminated with starting ketone (as shown by g.l.c.), was diffi-

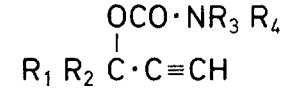
cult to crystallize. In such cases, the alcohol was obtained pure by repeating the synthetic procedure with the impure product.

*N-Carbonyl-DL-amino acid methyl esters* (II)

High yields (ca.90%) were obtained, following the method of Goldschmidt and Wick [11]. The alanine derivative (IIa) had b.p. 54°/5 mm; Schlögl [12] reported b.p. 82–84°/18 mm. The structures of the valine and methionine *derivatives* (IIb, c; b.p. 79°/10 mm and 114°/0·8 mm respectively) were confirmed by n.m.r. (IIb): OCNCH, 6·0 (doublet; $J$ 4·3); $OCH_3$, 6·2 (singlet); CH (in $Pr^i$), 7·7 (multiplet); $CH_3$ (in $Pr^i$) 8·95 (doublet; $J$ 7); 2nd $CH_3$ (in $Pr^i$), 9·05 (doublet; $J$ 7). (IIc): CH, 5·7 (multiplet); $OCH_3$ 6·2 (singlet); $SCH_2$ 7·4 (multiplet); $SCH_3$, 7·9 (singlet); $CH_2$ 7·9 (multiplet).

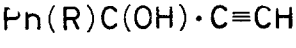
*Carbamates carrying amino acid-ester residues (Ib–d)*

The valine and methionine derivatives (Ic,d) were prepared by a procedure similar to method C of Dillard *et al.* [1]. For example, a mixture of 1,1-diphenylprop-2-yn-1-ol (IIIa; 0·6 g), *N*-carbonylmethionine methyl ester (3 g), triethylamine (1 ml), and alcohol-free chloroform (10 ml) was set aside at room temperature. The reaction was monitored by t.l.c. (ether–petrol, 1:1). After three days, no starting material was detectable. The residue from evaporation of the reaction mixture was chromatographed on Merck Kieselgel (0·05–0·2 mm particles), with ether–petrol (2:3) as eluant. Two successive crystallizations of the major product from benzene-cyclohexane gave the required *carbamate* (Id, 0·35 g; 30%), m.p. 89–90° (Found: C, 66·7; H, 5·9; N, 3·6; S, 8·2. $C_{22}H_{23}NO_4S$ requires C, 66·5; H, 5·8; N, 3·5; S, 8·1%), n.m.r.: $Ph_2C$, 2·7 (multiplet); NH, 4·4 (doublet; $J$ 8); NCH 5·6 (multiplet); $OCH_3$ 6·3 (singlet); C≡CH, 7·0 (singlet); $SCH_2$, 7·6 (multiplet); $SCH_3$, 8·0 (singlet); $CH_2$, 8·0 (multiplet). The *valine derivative* (Ic), made in a similar way, had m.p. 146–7° (benzene-cyclohexane; 75% yield) (Found: C, 72·2; H, 6·3; N, 3·8. $C_{22}H_{23}NO_4$ requires: C, 72·4; H, 6·3; N, 3·8%), n.m.r.: $Ph_2C$, 2·7 (multiplet); NH, 4·5 (doublet; $J$ 10); NCH, 5·7 (quartet; $J$ 10, 5); $OCH_3$, 6·3 (singlet); C=CH, 7·0 (singlet); CH, 7·9 (multiplet); $CH_3$ (in $Pr^i$), 9·1 (doublet; $J$ 7); 2nd $CH_3$ (in $Pr^i$), 9·15 (doublet; $J$ 7). The *alanine derivative* (Ib) was prepared in the same way as the *N*-ethyl derivative (Ij; see below). It had m.p. 130–131° (benzene-cyclohexane; 40% yield). (Found: C, 71·0; H, 5·6; N, 3·8. $C_{20}H_{19}NO_4$ requires C, 71·0; H, 6·0; N, 4·1%); n.m.r.: $Ph_2C$, 2·6 (multiplet); NH, 4·4 (doublet; $J$ 7); CH, 5·6 (quintet);

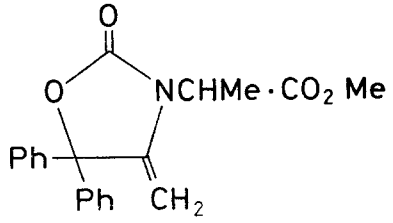


FORMULA (I). (a) – (j) $R_1$=Ph; (a) – (h) $R_2$=Ph; (a) $R_3$=H, $R_4$=cyclohexyl; (b) $R_3$=H, $R_4$=CHMe$CO_2$Me; (c) $R_3$=H, $R_4$=CH$Pr^i$$CO_2$Me; (d) $R_3$=H, $R_4$=CH($CH_2CH_2$SMe)$CO_2$Me; (e) $R_3$=H, $R_4$=$(EtO)_2PO$; (f) $R_3$=$R_4$=H; (g) $R_3$+$R_4$=$(CH_2)_5$; (h) $R_3$=H, $R_4$=Et; (i) $R_2$=*p*$FC_6H_4$, $R_3$=H, $R_4$=cyclohexyl; (j) $R_2$=*p*$ClC_6H_4$, $R_3$=H, $R_4$=Et.

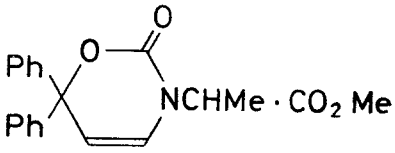
FORMULA (II). (a) R=Me; (b) R=$Pr^i$; (c) R=$CH_2CH_2$SMe.



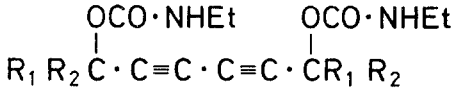
FORMULA (III). (a) R=Ph; (b) R=*p*$ClC_6H_4$ (c) R=*p*$FC_6H_4$.



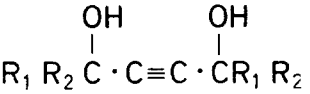
FORMULA (IV).



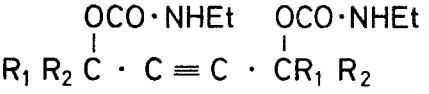
FORMULA (V).



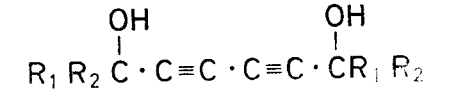
FORMULA (VI). (a) $R_1$=R=$_2$Ph; (b) $R_1$=Ph, $R_2$=*p*$FC_6H_4$.



FORMULA (VII). (a) $R_1$=$R_2$=Ph; (b) $R_1$=Ph, $R_2$=*p*$FC_6H_4$.



FORMULA (VIII). (a) $R_1$=$R_2$=Ph; (b) $R_1$=Ph, $R_2$=*p*$FC_6H_4$.



FORMULA (IX). (a) $R_1$=$R_2$=Ph; (b) $R_1$=Ph, $R_2$=*p*$FC_6H_4$.

*Table* 1. *Dicarbamates*

| Compound | M.p. (°C) | Yield (%) | Formula | Found C | Found H | Found F | Found N | Requires C | Requires H | Requires F | Requires N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VIa | 152–154* | 60 | $C_{34}H_{32}N_2O_4$ | 76·4 | 6·1 | — | 5·2 | 76·7 | 6·0 | — | 5·3 |
| VIb | 127–128* | 65 | $C_{34}H_{30}F_2N_2O_4$ | 72·2 | 4·9 | 6·3 | 5·0 | 71·9 | 5·3 | 6·7 | 4·9 |
| VIIa | 232–233† | 90 | $C_{36}H_{32}N_2O_4$ | 77·2 | 5·7 | — | 4·9 | 77·7 | 5·8 | — | 5·0 |
| VIIb | 219–220* | 60 | $C_{36}H_{30}F_2N_2O_4$ | 72·9 | 5·0 | 6·7 | 4·7 | 73·0 | 5·1 | 6·4 | 4·7 |

*From benzene.
†From ethyl acetate.

$OCH_3$, 6·3 (singlet); C≡CH, 7·0 (singlet); $CH_3$, 8·6 (doublet; $J$ 7).

N-(*Diethoxyphosphinyl*)-1,1-*diphenylprop*-2-*ynyl carbamate* (*Ic*)

This carbamate was prepared from diethylphosphinyl isocyanate [13] by the method used for the preparation of the valine and methionine compounds (see above). The *product* (60%) had m.p. 129–130° (benzene–petrol). (Found: C, 61·8; H, 5·8; N, 3·7; P, 8·2 $C_{20}H_{22}NO_5P$ requires C, 62·0; H, 5·7; N, 3·6; P, 8·0%); n.m.r.: $Ph_2C$, 2·7 (multiplet); NH, 2·2 (doublet); $OCH_2$, 5·9 (quintet); C≡CH, 7·0 (singlet); $CH_3$, 8·75 (triplet).

N-*Ethyl*-1-(4-*chlorophenyl*)-1-*phenylprop*-2-*ynyl carbamate* (Ij)

The procedure was essentially that of Shapiro *et al.* [6]. A mixture of the corresponding alcohol (IIIb; 4·0 g), ethyl isocyanate (1·5 g) and anhydrous sodium acetate (0·1 g) was heated on a steam bath for 5 hr. Ether (30 ml) was added to the cooled mixture. Evaporation of the filtrate gave an oil which, on two successive crystallizations from ethyl acetate–petrol, gave the *carbamate* (1·9 g; 38%), m.p. 116° (Found: C, 68·8; H, 5·1; Cl, 11·2; N, 4·3. $C_{18}H_{16}ClNO_2$ requires: C, 69·0; H, 5·1; Cl, 11·3; N, 4·5%); n.m.r.: $Ph_2C$, 2·7 (multiplet); NH, 5·0 (triplet); $CH_2$, 6·8 (quintet); C≡CH, 7·0 (singlet); $CH_3$, 8·9 (triplet).

5,5-*Diphenyl*-3-(1-*methoxycarbonylethyl*)-4-*methyleneoxazolidin*-2-*one* (IV)

The method of preparation resembled that of the valine and methionine derivatives (Ic, d), but toluene, not chloroform, was used as solvent. *N*-carbonyl-DL-alanine methyl ester (prepared *in situ*) and diphenylprop-2-ynol were heated under reflux for 5 hr. Evaporation gave an oil which crystallized from ethyl acetate–petrol, giving the *oxazolidinone*, m.p. 96°, in high yield. (Found: C, 70·8; H, 5·65; N, 4·2. $C_{20}H_{19}NO_4$ requires: C, 71·0; H, 5·95; N, 4·1%); n.m.r.: $Ph_2C$, 2·6 (multiplet); NCH, 5·2 (quartet); $C{=}CH_2$, 5·5, 5·8 (quartet; $J$ 6); $OCH_3$, 6·3 (singlet); C–$CH_3$, 8·4 (doublet; $J$ 8).

1,1,4,4-*Tetra-arylbut*-2-*yne*-1,4-*diols* (VIII)

The method of Beumel and Harris [14] was used. The fluorinated *diol* (VIIIb), m.p. 160–161° (benzene–petrol), was thus prepared from *p*-fluorobenzophenone in 65% yield. (Found: C, 78·6; H, 5·0; F, 9·0. $C_{28}H_{20}F_2O_2$ requires: C, 78·9; H, 4·7; F, 8·9%).

1,1,6,6-*Tetra-arylhexa*-2,4-*diyne*-1,6-*diols* (IX)

The procedure of Chodkiewicz [15] was used. The fluorinated *diol* (IXb), m.p. 96–7° (benzene–petrol), was prepared in 70% yield from the acetylenic alcohol (IIIc). (Found: C, 80·1; H, 4·7; F, 8·7. $C_{30}H_{20}F_2O_2$ requires: C, 80·0; H, 4·4; F, 8·4%).

*Dicarbamates* (VI, VII)

The reaction between the appropriate diol and ethyl isocyanate in the presence of triethylamine was carried out at room temperature as in the preparation of the amino acid derivatives (Ic, d). Data are given in Table 1.

## PHARMACOLOGICAL METHODS

The plasma cell tumour assay method resembled that described previously [16]. Balb/C- mice (male or female, but not mixed in any one test; tumour growth rate tended to be greater in the females) were implanted with the ADJ/PC6A plasma cell tumour subcutaneously by trocar. The animals were not treated until the tumours were well established and readily palpable (17–28 days after transplantation; tumour mass ca.1 g). Compounds were injected intraperitoneally as single doses in arachis oil or arachis oil–acetone (9: 1). Groups of three mice were used for each dose level and the untreated tumour control groups each comprised 11 animals. Ten or 11 days

*Table 2. Antitumour potency and toxicity of a series of acetylenic carbamates and of an oxazolidinone*

| Compound | Dose (mg/kg) | PC6 tumour inhibition (%)* | Mortality | LD50 (mg/kg) | ID90 (mg/kg) | Therapeutic index |
|---|---|---|---|---|---|---|
| Ia† | 3·3 | 13 | 0/3 | 68 | 23 | 3 |
| | 10 | 60 | 0/3 | | | |
| | 30 | 100 | 0/3 | | | |
| | 90 | 100 | 2/3 | | | |
| | 180 | — | 3/3 | | | |
| Ib | 3·3 | −7 | 0/3 | >90 | — | — |
| | 10 | 12 | 0/3 | | | |
| | 30 | 89 | 0/3 | | | |
| | 90 | 58 | 1/3 | | | |
| Ic | 10 | −16 | 0/3 | >320 | 140 | >2 |
| | 20 | −50 | 0/3 | | | |
| | 40 | 9 | 0/3 | | | |
| | 80 | 70 | 0/3 | | | |
| | 160 | 100 | 0/3 | | | |
| | 320 | 100 | 1/3 | | | |
| Id | 10 | −14 | 0/3 | 113 | — | — |
| | 20 | −39 | 0/3 | | | |
| | 40 | −4 | 0/3 | | | |
| | 80 | 27 | 0/3 | | | |
| | 160 | — | 3/3 | | | |
| Ie | 5 | 15 | 0/3 | 23 | — | — |
| | 10 | −4 | 0/3 | | | |
| | 20 | −6 | 1/3 | | | |
| | 40 | — | 3/3 | | | |
| If† | 6·6 | 48 | 0/3 | 52 | 26 | 2 |
| | 10 | 8 | 0/3 | | | |
| | 30 | 100 | 0/3 | | | |
| | 90 | | 3/3 | | | |
| Ig† | 6·6 | −24 | 0/3 | 128 | 68 | 2 |
| | 10 | 43 | 0/3 | | | |
| | 30 | 62 | 0/3 | | | |
| | 90 | 100 | 0/3 | | | |
| | 180 | — | 3/3 | | | |
| Ih† | 10 | −20 | 0/3 | 135 | 25 | 5 |
| | 20 | 25 | 0/3 | | | |
| | 40 | 100 | 0/3 | | | |
| | 80 | 100 | 0/3 | | | |
| | 160 | 100 | 2/3 | | | |
| | 320 | — | 3/3 | | | |
| Ii† | 22 | 67 | 0/3 | 38 | — | — |
| | 66 | — | 3/3 | | | |
| Ij | 10 | 0 | 0/3 | 170 | 45 | 4 |
| | 30 | 60 | 0/3 | | | |
| | 60–120 | 100 | 0/3 | | | |
| | 240 | — | 3/3 | | | |
| IV | 81 | −55 | 0/3 | >243 | — | — |
| | 243 | 7 | 0/3 | | | |
| VIa | 80 | 27 | 0/3 | >1280 | — | — |
| | 160 | 34 | 0/3 | | | |
| | 320 | 25 | 0/3 | | | |
| | 640 | —‡ | 0/3 | | | |
| | 1280 | —‡ | 0/3 | | | |

*Table 2 continued*

| Compound | Dose (mg/kg) | PC6 tumour inhibition (%)* | Mortality | $LD_{50}$ (mg/kg) | $ID_{90}$ (mg/kg) | Therapeutic index |
|---|---|---|---|---|---|---|
| VIb | 73 | −16 | 0/3 | | | |
| | 145 | −17 | 0/3 | | | |
| | 290 | −32 | 0/3 | >1160 | — | — |
| | 580 | −13 | 0/3 | | | |
| | 1160 | −22 | 0/3 | | | |
| VIIa | 100 | −2 | 0/3 | | | |
| | 300 | 40 | 0/3 | >900 | — | — |
| | 900 | −38 | 0/3 | | | |
| VIIb | 100 | −11 | 0/3 | | | |
| | 300 | −32 | 0/3 | >900 | — | — |
| | 900 | 13 | 0/3 | | | |

*Values of less than 40 are not considered significant. Negative values indicate that the mean tumour weight exceeded that of the controls.
†Dillard *et al.* [1].
‡Visual examination of tumours only; no apparent inhibition.

after drug treatment, the mice were killed, and the tumours dissected out and weighed. The $LD_{50}$ and $ID_{90}$ (dose giving 90% tumour inhibition) were determined graphically; the therapeutic index is defined in this work as $LD_{50}/ID_{90}$.

The L1210-mouse leukaemia screening test followed the standard procedure at this Institute [17]. Briefly, C57/DBA2 F1 hybrids were inoculated subcutaneously with standard titres of leukaemic spleen cells. Five daily doses of the compounds in arachis oil were given intraperitoneally, treatment beginning 24 hr after tumour inoculation. Groups of 5 mice were used for each dose level, and methotrexate-treated controls were included to check the sensitivity of the tumour. The three dose levels used for each of the three carbamates tested (Ia, f, g) were based on preliminary chronic-toxicity determinations (10 daily doses). Drug activity was assessed by the increase, if any, in average survival time over that of the control mice, which die on average 11 days after tumour inoculation under the conditions used in these laboratories.

## RESULTS AND DISCUSSION

Dillard and co-workers [1, 2] used leukaemia C1498 and the plasma cell tumour X5563 in mice, with a multiple dose regimen, to evaluate their carbamates. Neither of these tumours is maintained at this Institute. It was found, however, that the established ADJ/PC6A plasma cell tumour in mice responded to single doses of each of 5 representative compounds (Ia, f–i) reported by the American group as tumour-inhibitory. On the other hand, multiple daily doses of compounds (Ia), (If) and (Ig), each tested at three dose levels up to the toxic range, failed to increase the average survival time of mice previously inoculated with L1210 leukaemia; the chronic $LD_{50}$ values in random-bred female mice for carbamates (Ia), (If) and (Ig) were 56, 35 and 56 mg/kg/day × 10 respectively. The PC6 tumour system was therefore used to compare the activities of the compounds described here. The detailed results are set out in Table 2.

Four compounds (Ia, f–h) from the earlier series [1] caused complete tumour regression at tolerated doses. The fifth carbamate (Ii) of this group was not fully assessed, but it is clear that the *p*-fluoro group imparts no therapeutic advantage in the PC6 test system. In the same way, the *N*-ethyl carbamate (Ih) and its *p*-chloro analogue (Ij) were approximately equal in potency. These two compounds showed the (for this series) relatively high therapeutic indices of 5 and 4 respectively.

Of the amino acid derivatives, only the valine compound (Ic) caused complete regression at a non-lethal dose, but the therapeutic index was unremarkable. The alanine derivative (Ib) gave a degree of inhibition, but neither the methionine analogue (Id) nor the phosphinyl derivative (Ie) affected the PC6 tumour at tolerated doses.

Compounds (IV), (VI) and (VII) were apparently devoid of activity, but toxic dose levels were not established. The lack of activity of the oxazolidinone (IV) is not surprising, because cyclized compounds exa-

mined by Shapiro and others [6] and now believed (see Introduction) to be oxazolidinones analogous to compound (IV), showed no anticonvulsant activity; in this they differed from the corresponding open chain acetylenic carbamates (I:$R_1$ and $R_2$=alkyl).

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## SUMMARY

*A number of acetylenic mono- and dicarbamates has been prepared. Activity against the ADJ/PC6A plasma cell mouse tumour was seen only among the monocarbamates. Three of the active derivatives were separately tested against the L1210 leukaemia in mice but failed to increase the average survival time. A related oxazolidinone did not inhibit the plasma cell tumour.*

## REFERENCES

1. R. D. Dillard, G. Poore, D. R. Cassady and N. R. Easton, Acetylenic carbamates. A new class of potential oncolytic agents. *J. med. pharm. Chem.* **10,** 40 (1967).
2. R. D. Dillard, G. A. Poore, N. R. Easton, M. J. Sweeney and W. R. Gibson, Acetylenic carbamates. III. The N-cycloaliphatic derivatives. *J. med. pharm. Chem.* **11,** 1155 (1968).
3. D. C. DeLong, R. D. Dillard, N. R. Easton, F. Streightoff, W. S. Boniece and C. E. Redman, *In vivo* antiviral chemotherapy. III. Anti-influenza action of 1,1-diaryl-2-propynyl carbamates. *Antimicrob. Agents & Chemother.* 1966, 509 (1967).
4. D. C. DeLong, L. A. Baker, R. D. Dillard and N. R. Easton, Inhibition and regression of Friend leukaemia virus-induced splenomegaly. *Antimicrob. Agents & Chemother.* 1967, 654 (1968).
5. J. G. Armstrong, R. W. Dyke, P. J. Fouts and C. J. Jansen, A series of carbamate compounds. II. In *Cancer Chemotherapy*, Japanese Cancer Association Gann Monogr. 2, p. 269 (1967).
6. S. L. Shapiro, V. Bandurco and L. Freedman, Reaction of *t*-ethinyl alcohols with aryl isocyanates. *J. org. Chem.* **26,** 3710 (1961).
7. R. D. Dillard, D. R. Cassady and N. R. Easton, Acetylenic carbamates. II. Reactions of 1,1-diaryl-2-propynyl carbamates with acids and bases. *J. med. pharm. Chem.* **10,** 1180 (1967).
8. N. R. Easton, D. R. Cassady and R. D. Dillard, Reactions of acetylenes. I. *t*-ethynyl alcohol with isocyanates. *J. org. Chem.* **27,** 2927 (1962).
9. E. M. Bessell and J. H. Westwood, In preparation.
10. H. D. Hartzler, Carbenes from derivatives of ethynylcarbinols. The synthesis of alkenylidenecyclo-propanes. *J. Am. chem. Soc.* **83,** 4990 (1961).
11. S. Goldschmidt and M. Wick. Über Peptidsynthesen. I. *Ann. Chim.* **575,** 217 (1952).
12. K. Schlögl, Über β-Isocyanatfettsaureester und einige ihrer Reaktionsprodukte. *Mh. Chem.* **89,** 61 (1958).
13. A. V. Kirsanov and M. S. Marenets, Esters of Methane-phosphoric acids. (In Russian.) *Zh. obshch. Khim.* **29,** 2256 (1959).
14. O. F. Beumel and R. F. Harris, The reaction of lithium acetylide-ethylenediamine with ketones. *J. org. Chem.* **29,** 1872 (1964).
15. W. Chodkiewicz, Contribution à la synthèse des composés acétyléniques. *Ann. Chim.* **2,** 819 (1957).
16. R. Wade, M. E. Whisson and M. Szekerke, Some serum protein nitrogen mustard complexes with high chemotherapeutic selectivity. *Nature, Lond.* **215,** 1303 (1967).
17. B. C. V. Mitchley and F. J. C. Roe, In preparation.