866. *Allenes. Part VIII.* A New Method for the Synthesis of Allenynes*

By C. S. L. Baker, Phyllis D. Landor, and S. R. Landor

1-Bromo- and 1-iodo-allenes are condensed in *NN*-dimethylformamide with terminal acetylenic compounds in the presence of cuprous ions and a suitable base (tributylamine for 3,3-dialkyl-1-bromoallenes, and ethylamine or t-butylamine for 3-monoalkyl-1-bromo- or -1-iodo-allenes) to give allenynes, which are purified by chromatography or distillation. Most of these synthetic allenynes show a high level of activity *in vitro* against mycobacterium tuberculosis.

The allenyne system, $>C{=}C{=}CH{-}C{\equiv}C{-}$, has been found to be an important structural feature of a number of mould metabolites.[1] Few methods are available for the synthesis of allenynes;[2] those described in the literature make use of two basic processes: prototropic rearrangement of a propynylic group to give an allene, first investigated by Jones and Whiting[3] and the reduction of suitably substituted acetylenes, as for instance the

$$-CH_2-C{\equiv}C- \rightleftharpoons -CH{=}C{=}CH-$$

conversion of enynols to allenic alcohols with lithium aluminium hydride[4] and the reduction of propynylic halides with a zinc–copper couple[5,6] or lithium aluminium hydride.[6] Except in simple cases, the prototropic rearrangement is difficult to stop at the allenyne stage whereas both reduction methods tend to give mixtures which are difficult to separate.[7]

The general method for the synthesis of allenynes described here[8] consists of coupling allenic halides with ethynyl compounds in the presence of cuprous ions and a suitable organic base.

$$RR'C{=}C{=}CHX + CH{\equiv}C{\cdot}[CH_2]_n{\cdot}R^2 \xrightarrow[\text{base}]{Cu^+} RR^1C{=}C{=}CH{-}C{\equiv}C{\cdot}[CH_2]_nR^2$$

Neither the simple allenynes nor the allenediynes prepared so far have shown any tendency to rearrange under the basic conditions used in their preparation.†

Altogether about eighty small-scale experiments were carried out in order to arrive at the best experimental conditions which are as follows: 1-iodo- and 1-bromo-3-monoalkylallenes give best yields and purest products by adding one equivalent of aqueous ethylamine or t-butylamine to one equivalent of cuprous chloride or bromide in *NN*-dimethylformamide followed by 1·1 equivalents of terminal acetylenic compound and one equivalent of halogenoallene. The mixture is stirred at 40—50° under nitrogen and then worked up.

* Part VII, C. S. L. Baker, P. D. Landor, and S. R. Landor, *J.*, preceding Paper,

† Application to the synthesis of the more sensitive two way conjugated system found in mycomycin where the allenic system acts as a block to conjugation will be a more stringent test.

[1] W. D. Celmer and A. Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 1870; J. D. Bu'Lock, E. R. H. Jones, and P. R. Leeming, *J.*, 1955, 4270; 1957, 1097; 1960, 2257; G. Bendz, *Arkiv Kemi*, 1959, **14**, 305.

[2] W. J. Gensler and J. Casella, *J. Amer. Chem. Soc.*, 1958, **80**, 1376; E. R. H. Jones, H. H. Lee, and M. C. Whiting, *J.*, 1960, 431; F. Bohlmann, P. Herbst, and H. Gleinig, *Chem. Ber.*, 1961, **94**, 948.

[3] G. Eglington, E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J.*, 1954, 3197.

[4] E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J.*, 1954, 1854.

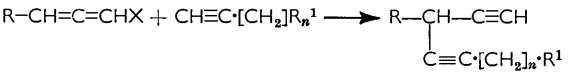
[5] Y. I. Ginzburg, *Zhur. obshchei Khim.*, 1940, **10**, 513.

[6] N. J. Bailey and C. R. Pfeifer, *J. Org. Chem*, 1955, **20**, 1337; T. L. Jacobs, E. G. Teach, and D. Weiss, *J. Amer. Chem. Soc.*, 1955, **77**, 6254; T. L. Jacobs and R. D. Wilcox, *ibid.*, 1964, **86**, 2240.

[7] S. R. Landor and E. S. Pepper, unpublished work.

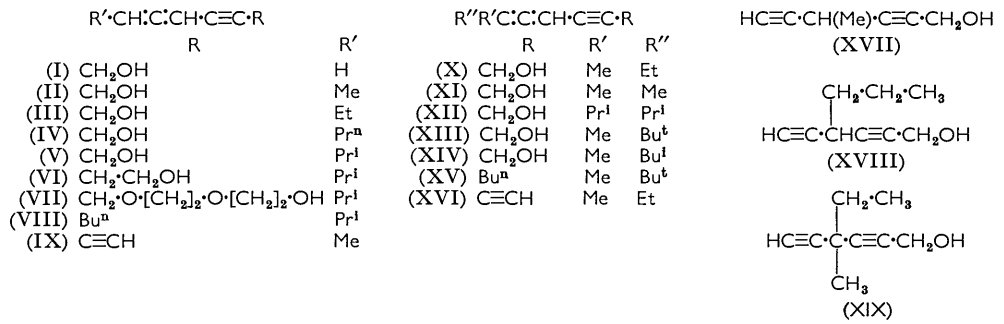
[8] C. S. L. Baker, P. D. Landor, and S. R. Landor, *Proc. Chem. Soc.*, 1963, 340.

Any terminal acetylenic by-products, produced by some coupling occurring at position 3 of the allenic halide,

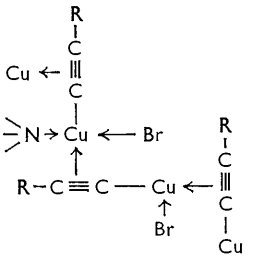


are best removed by washing with ammoniacal silver nitrate and the products are then about 90% pure. Further purification either by chromatography or distillation *in vacuo* can only be achieved at the price of considerable losses by oxidative attack and polymerisation. The products are readily identified by infrared and ultraviolet spectra and gas–liquid chromatography (g.l.c.).

A similar procedure is used for 3,3-dialkyl-1-bromoallenes except that tributylamine is used instead of ethylamine for best yields. Generally less than 10% of terminal acetylenic by-product is formed. Cuprous bromide gave a 20% better yield than cuprous chloride under the same conditions while cuprous iodide, cuprous acetylide, and catalytic quantities of cuprous bromide or chloride gave only low yields. *NN*-Dimethylformamide was a better solvent for the reaction than methanol, tetrahydrofuran, water, or diglyme. The reaction is slow at room temperature and this results in some decomposition of the product in the reaction mixture. Somewhat surprisingly it was found that the larger the 3-alkyl substituent on the halogenoallene the higher the yield and this can be ascribed to the stabilising effect of bulky groups on both the bromoallenes and the allenynes.[9]

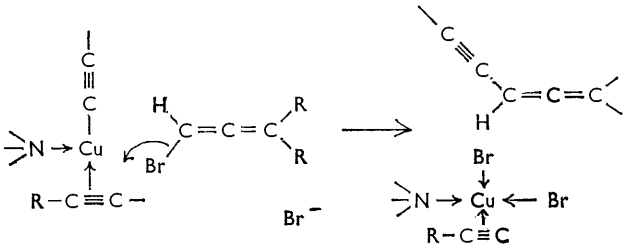


Blake, Calvin, and Coates [10] regard the yellow alkyl- and aryl-ethylnylcopper complexes as co-ordination polymers in which there is substantial back-co-ordination from the filled metal *d*-orbital to the antibonding orbital of at least two acetylene groups bound to the metal. They report that these co-ordination polymers are apparently unaffected by bases such as pyridine and triethylamine. We have shown here that the cuprous acetylide complex prepared in the absence of base did not give any coupled product on subsequent addition of allenic bromide and base. It must be assumed, therefore, that the function of the base is not just the removal of hydrogen bromide but that it is an essential part of the co-ordination complex, which might be represented as



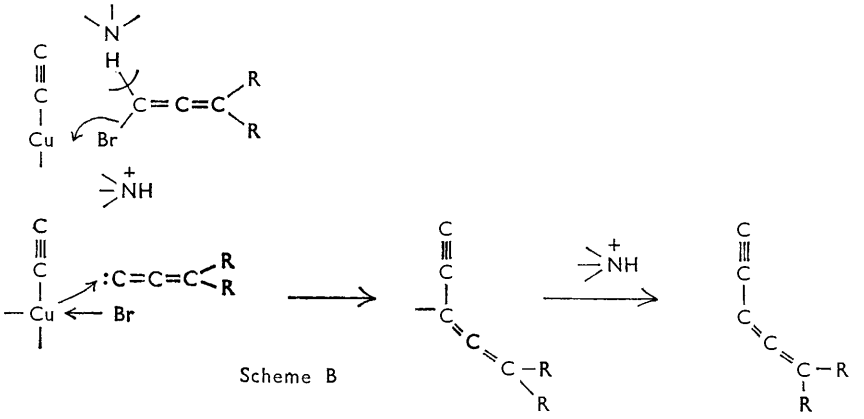
[9] F. Bohlmann, *Chem. Ber.*, 1953, **86**, 657.
[10] D. Blake, G. Calvin, and G. E. Coates, *Proc. Chem. Soc.*, 1959, 396.

A plausible mechanism for the coupling is shown.



Scheme A

and this can be visualised either without (Scheme A), or with prior proton elimination from the allene (Scheme B),



Scheme B

The reaction is formally if not mechanistically analogous to the coupling of a bromoacetylene and a terminal acetylenic compound to give unsymmetrically substituted diacetylenes.[11] Since completion of this work Stephens and Castro [12] have described the preparation of diarylacetylenes from aryl iodides and cuprous acetylide in refluxing pyridine.

Naturally occurring allenyne compounds such as marasin or mycomycin show a limited spectrum of antibiotic activity of which the activity against mycobacterium tuberculosis is most marked. This activity is apparently destroyed when the allenic group is changed to other unsaturated groups such as acetylene or diene by alkaline isomerisation. Our synthetic allenynes were tested for antibiotic activity as part of a programme relating structure to antibiotic activity. A number show a high level of activity *in vitro* against mycobacterium tuberculosis.

Experimental

Allenic iodides were prepared by the action of triphenyl phosphite methiodide on acetylenic carbinols [13] and allenic bromides by reacting hydrobromic acid in the presence of a cuprous bromide–copper catalyst with acetylenic carbinols.[14] Reactions were carried out under an atmosphere of oxygen-free nitrogen and the allenynes stored in high dilution in methanol or pentane at −40°. Multiple runs (to establish the best reaction conditions) were carried out on a 0·025-mole scale in six test tubes (25 ml.) attached to ground-glass joints joined to a circular glass tube with a slow stream of nitrogen passing through. Ammoniacal silver nitrate refers to a 10% aqueous silver nitrate solution to which 0·880 ammonia had been added until the

[11] W. Chodkiewicz, *Ann. Chim.* (*France*), 1957, **2**, 819.
[12] R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313.
[13] Part VII, *J.*, 1965, 4348.
[14] D. K. Black, S. R. Landor, A. N. Patel, and P. F. Whiter, *Tetrahedron Letters*, 1963, 483.

precipitate first formed redissolved. Ether was removed under reduced pressure and finally at 2·0 mm. for several hours using a rotary evaporator. Ultraviolet (in ethanol) and infrared spectra were determined immediately on distilled or chromatographed samples and analytical

TABLE 1

Allenynes prepared by method A from the iodides R'·CH:C:CHI

R'	Iodide (g.)	Acetylenic cpd. (g.)	Amine (g.)	CuCl (g.)	DMF (ml.)	Crude product	Purity (%)	Yield (%)	Method of washing
H	16·6	Prop-2-ynol (6·2)	7·3	9·9	40	(I)	100 [a]	45	(*b*)
Me	72	,, (25)	29·2	39·6	250	(II)	90 [b]	40	(*b*)
Me	9·0	,, (3·6)	3·6	4·9	20 [c]	(II) + (XVII)	(47 : 53) [d]	68	(*a*)
Et	10·8	,, (3·4)	4·4	5·9	20	(III)	75 [b]	57	(*b*)
Pr^n	10·4	,, (3·6)	3·6	4·9	40	(IV)	50 [e]	37	(*b*)
Pr^i	52	,, (15·4)	20·0	27·2	250	(V)	85	49	(*b*)
Pr^i	11·0	But-3-ynol (3·5)	4·9 [f]	0·1	25 [g]	(VI)	—	36	(*a*)
Pr^i	10·4	Diethylene glycol mono-prop-2-ynyl ether (8·0)	3·6	4·9	20	(VII)	—	16	(*a*)
Pr^i	20·8	Hex-1-yne (9·0)	8·0	10·9	20	(VIII)	80	62	(*b*)
Me	36·0	Diacetylene (13·0)	14·6	19·8	100 [h]	(IX)	—	15	(*a*)

[a] G.l.c. (120°) and u.v. spectroscopy. [b] G.l.c. (150°) and u.v. spectroscopy. [c] After being heated the mixture was set aside at room temperature for ½ hr. [d] G.l.c. (150°). Acetylation (pyridine–acetic anhydride) at room temperature for 24 hr., dilution with ether, washing three times with dilute hydrochloric acid then sodium hydrogen carbonate, and drying ($MgSO_4$) gave a mixture of acetates, $\nu_{max.}$ 3280 (≡CH) and 1940 cm.$^{-1}$ (C:C:C). Hydrogenation (H_2/Pt) in ether gave a mixture of saturated alcohols with different carbon skeletons (2 peaks on g.l.c. at 100°). Washing of the mixture with ammoniacal silver nitrate in methanol gave the pure allenyne free from diyne (i.r. spectroscopy and g.l.c. at 150°). [e] U.v. spectroscopy. [f] Ethylamine (14 ml. of 35% aqueous solution). [g] Exothermic reaction, mixture heated up to 40°. [h] Hydroxylamine hydrochloride, amine, and cuprous chloride were added to the diacetylene in DMF at 0° followed by addition of allenic chloride. After removal of ether, the product distilled at 1·5 mm. into a cold-trap and the residue exploded.

TABLE 2

Allenynes prepared by method B from the bromides R'R''C:C:CHBr

R'	R''	Bromide (g.)	Acetylenic cpd. (g.)	Amine (moles)	CuBr (g.)	DMF (ml.)	Crude product	Yield (%)	Method of isolation
Pr^n	H	32·2	Prop-2-ynol (12·3)	0·20 [a]	28·8	80	(IV) [b]	51	(*a*)
Pr^n	H	12·0	,, (4·5)	0·075 [a]	10·8	30	(IV) + (XVIII) [c]	59	(*a*) [d]
Me	H	21·3	,, (10·0)	0·16 [a]	22·9	65	(II)	13	(*b*)
Et	H	20·6	,, (8·6)	0·14 [a]	20·0	55	(III) [e]	31	(*b*)
Pr^i	H	12·1	,, (4·6)	0·075 [a]	10·8	30	(V) [f]	44	(*a*)
Et	Me	32·2	,, (12·3)	0·20 [g]	28·8	80	(X)	51	(*a*)
Et	Me	8·0	,, (3·0)	0·05 [g]	7·2	20	(X) + (XIX) [h]	63	(*a*) [d]
Me	Me	14·7	,, (6·2)	0·10 [g]	14·4	40	(XI)	33	(*a*)
Pr^i	Pr^i	20·3	,, (6·2)	0·10 [g]	14·4	40	(XII) [i]	62	(*a*)
Bu^t	Me	18·9	,, (6·2)	0·10 [g]	14·4	40	(XIII) [j]	62	(*a*)
Bu^i	Me	18·9	,, (6·2)	0·10 [g]	14·4	40	(XIV) [k]	65	(*a*)
Bu^t	Me	12·3	Hex-1-yne (5·9)	0·065 [g]	9·4	25	(XV) [l]	82	(*b*)
Et	Me	32·2	Diacetylene (13·6)	0·20 [g]	28·8	40	(XVI)	25	— [m]

[a] Ethylamine, added as a 70% aqueous solution. [b] G.l.c. showed a major peak (*t*, 14 min.) and a minor peak (*t*, 4 min.). [c] G.l.c. (150°) showed 50% allenyne (*t*, 18 min.) and 50% diyne (*t*, 10 min.). Distillation at 75—80°/1·3 × 10^{-2} mm. gave no separation. Hydrogenation of the distilled mixture (H_2/Pt) in ether gave a mixture of saturated alcohols with different carbon skeletons (i.r. spectroscopy and g.l.c.). Acetylation (acetic anhydride–pyridine) at room temperature for 48 hr., dilution with ether washing with dilute hydrochloric acid, sodium hydrogen carbonate, and water, and drying ($MgSO_4$) gave a mixture of acetates, $\nu_{max.}$ 3250 (≡CH) and 1950 cm.$^{-1}$ (C:C:C). [d] Silver nitrate washing omitted. [e] G.l.c. (150°, N_2 1·4 l./hr.) showed a major peak (*t*, 16 min.) and a minor peak (<2%) (*t*, 4 min.). [f] G.l.c. (152°) showed a major peak (80%) (*t*, 12 min.) and a minor peak (20%) (*t*, 25 min.). [g] Tri-n-butylamine, added directly. [h] G.l.c. (150°, N_2 1·6 l./hr.) showed 90% allenyne (*t*, 16 min.) and 10% diyne (*t*, 7 min.). [i] 50—60° for 10 hr. G.l.c. (152°) showed one peak (*t*, 24 min.). [j] 50—60° for 6 hr. G.l.c. (150°) showed one peak (*t*, 32 min.). [k] 40—50° for 6 hr. G.l.c. (152°) showed a major peak (*t*, 22 min.) and a minor peak (<1%) (*t*, 5 min.). [l] 50—60° for 6 hr. G.l.c. (150°) showed a major peak (*t*, 3 min.) and a minor peak (<2%) (*t*, 15 min.). [m] Diacetylene added in 40 ml. DMF to the other reagents at 0°, giving a red precipitate followed by addition of allenic bromide. The mixture was stirred at 40—50° for 1½ hr. and addition of potassium cyanide solution then gave a black precipitate insoluble in an excess of potassium cyanide. After filtration, ether was added to the solution, the aqueous was layer extracted with ether, and the combined extracts were washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and evaporated.

TABLE 3

Properties of allenynes

No.	Allenynes	$\nu_{max.}$ (cm.$^{-1}$) (OH)	(C≡C)	(C=C=C)	(HC=C=C)	$\lambda_{max.}$ (mμ)	(ε)
1	Hexa-4,5-dien-2-ynol (I)	3400s	2200w	1930s	850s	221	(3650)
2	*Hepta*-4,5-*dien*-2-*ynol* (II)	3400s	2200m	1940m	860sh	220	(11,800)
3	6-Methylhepta-4,5-dien-2-ynol (XI)	3400vs	2220s	1950s	790vs	221	(16,300)
4	Octa-2,3-dien-5,7-diyne (IX)	3300m [a]	2200w	1940m	855m		[b]
5	Octa-4,5-dien-2-ynol (III)	3400vs	2220m	1940s	870vs	220	(12,800)
6	6-*Methylocta*-4,5-*dien*-2-*ynol* (X)	3400s	2220m	1950m	800m	220	(14,400)
7	7-*Methylocta*-4,5-*dien*-2-*ynol* (V)	3400s	2200m	1940s	865s	220	(13,700)
8	6,7,7-*Trimethylocta*-4,5-*dien*-2-*ynol* (XIII)	3300vs	2220m	1950m	790s	221	(16,800)
9	6-*Isopropyl*-7-*methylocta*-4,5-*dien*-2-*ynol* (XII)	3400vs	2220m	1940m	790s	222	(18,300)
10	1-[2-(2-Hydroxyethoxy)ethoxy]-7-methylocta-4,5-dien-2-yne (VII)	3400s	2200w	1940m	865m	218	(11,500)
11	*Nona*-4,5-*dien*-2-*ynol* (IV)	3400vs	2220m	1950vs	875, 855s	220	(15,800)
12	6,8-Dimethylnona-4,5-dien-2-ynol (XIV)	3400vs	2220w	1950m	790s	221	(12,400)
13	8-Methylnona-5,6-dien-3-ynol (VI)	3400s	2200w	1940s	865s	220	(16,000)
14	3-Methylnona-3,4-dien-5,8-diyne (XVI)	3300s [a]	2200m	1940m	800w		[c]
15	2-*Methylundeca*-3,4-*dien*-6-*yne* (VIII)	[d]	2200w	1930m	865s		[e]
16	2,2,3-Trimethylundeca-3,4-dien-6-yne (XV)		2210vw	1940m	790vs	222	(15,100)

w, weak; m, medium; s, strong.

No.	Purified by	B. p./mm.	Yield (%)	Found (%) C	H	Formula	Required (%) C	H
2	Distillation [f]	46—48°/1·93 × 10^{-2}		77·4	7·4	C_7H_8O	77·7	7·4
3	Distillation [g]	58—61/1 × 10^{-3}	12					
4	Chromatography [h]							
5	Distillation [g]	60—63/0·03	12					
6	Distillation [g,i]	60—65/1·93 × 10^{-2} [j]	17	79·7	9·1	$C_9H_{12}O$	79·4	8·9
7	Distillation	54/8·60 × 10^{-3}		81·4	7·9	$C_9H_{12}O$	79·4	8·9
8	Distillation [g]	77—80/7 × 10^{-3}	43	81·0	9·7	$C_{11}H_{16}O$	80·5	9·8
9	Distillation [g]	65—67/3 × 10^{-3}	23	81·6	9·9	$C_{12}H_{18}O$	81·0	10·1
11	Distillation [g]	64/0·02	10	80·6	8·8	$C_9H_{12}O$	79·4	8·9
12	Distillation [g]	72—75/2·6 × 10^{-2}	25					
13	Chromatography [k]		12					
14	Chromatography [k,l]							
15	Distillation [m]	48—52/3·44 × 10^{-2}		88·5	11·1	$C_{12}H_{18}$	88·9	11·1
16	Distillation [g]	58—61/0·15	42					

[a] (C≡CH). [b] $\lambda_{max.}$ 210, 237·5, 249, 263, 278·5 mμ (ε 60,600, 11,800, 13,200, 14,600, 11,200). [c] λ_{max} 204, 210, 237·5, 249·5, 263, 278·5, 291, 310 mμ (ε 30,800, 38,800, 12,300, 13,400,13, 700, 11,600, 7300, 6400). [d] Also $\nu_{max.}$ 1600 and 920w cm.$^{-1}$ (conj. C=C). [e] $\lambda_{max.}$ 221, 268, 282 mμ (ε 10,500, 2800, 2200). [f] Hydrogenation of the distilled material (H_2/Pt in ether at atmospheric pressure) gave n-heptanol, identified by its i.r. spectrum and by preparation of the phenylurethane, m. p. and mixed m. p. 62—63° (from light petroleum). [g] Large polymeric residue. [h] In pentane. [i] In presence of hydroquinone. [j] G.l.c. (152°, N, 1·9 l./hr.) showed one peak (*t*, 13 min.). [k] In light petroleum (b. p. 40—60°). [l] Also purified by evaporative distillation at 8 × 10^{-3} mm. and warming to 45°. [m] G.l.c. (143°) showed the presence of ~10% 1,3-dienyne.

samples sealed at once under nitrogen for immediate analysis. Alumina used for chromatography was Peter Spence grade " H " deactivated with 10% of 10% acetic acid. G.l.c. was carried out, at various temperatures, on silicone oil with a N_2 flow-rate of 2 l./hr., unless otherwise stated.

Preparation of Allenynes.—The allenynes (Table 3) were prepared by the following general methods.

Method A (Table 1). t-Butylamine was added to a vigorously stirred mixture of cuprous chloride and a crystal of hydroxylamine hydrochloride in *NN*-dimethylformamide (DMF). The acetylenic compound was run in, giving a coloured copper complex, and the mixture stirred for 5 min. The iodo-allene was added and the mixture stirred at 40° for 2 hr. The copper complex was decomposed with aqueous potassium cyanide and the product isolated with ether, washed with either (*a*) dilute hydrochloric acid (4 times) or (*b*) dilute hydrochloric acid (4 times) then ammoniacal silver nitrate and dried ($MgSO_4$). The crude product was isolated by removal of the solvent.

Method B (Table 2). The amine was added to a slurry of cuprous bromide in DMF. The

acetylenic compound was added, giving a copper complex. The allene was added, the mixture stirred at 40—50° for 2 hr., and saturated potassium cyanide added until a clear solution was obtained. This was extracted with ether and the extract was washed with dilute hydrochloric acid then distilled water. The product was isolated by either (*a*) shaking the extract with ammoniacal silver nitrate, filtering, washing the ethereal layer with distilled water, drying ($MgSO_4$), and evaporating, or (*b*) evaporating the extract, dissolving the residue in methanol and then proceeding as in (*a*).

The experimental conditions used in the preparation of compounds (II), (IV), and (X) were achieved after carrying out a series of small-scale experiments (30, 15, and 32, respectively) in which temperature (0—70°), solvent (methanol, methanol–water, and dimethylformamide), time (2 hr. to overnight), base (ethylamine, tributylamine, t-butylamine, and tetramethylene diamine), and type of copper catalyst (cuprous chloride or cuprous bromide—catalytic or equivalent) were varied.

Result of Biological Testing

Altogether sixteen compounds were tested *in vitro* against *M. tuberculosis* (human strain, H37 RV) and two were found to be highly active, 7-methylocta-4,5-dien-2-yn-1-ol and nona-4,5-dien-2-yn-1-ol, almost completely suppressing growth for 11 days at a concentration of 0·5 p.p.m.; four were found to be inactive, and the rest had a fair level of activity. In an attempt to increase the solubility of 7-methylocta-4,5-dien-2-yn-1-ol in water a diethyleneoxy-group was attached to the allenyne system,

$$(CH_3)_2CH{\cdot}CH{=}C{=}CHI + CH{\equiv}C{-}CH_2(OCH_2CH_2)_2OH \longrightarrow (CH_3)_2CH{-}CH{=}C{=}CH{-}C{\equiv}C{-}CH_2{-}(O\,CH_2CH_2)_2OH$$

Surprisingly, the minimum inhibitory concentration increased from 0·78 γ/ml. to 25 γ/ml. Further, substituting $-C{\equiv}C{-}CH_2CH_2OH$ (analogous to marasin) for $-C{\equiv}C{-}CH_2OH$ again increased the M.I.C. from 5 γ/ml. to 720 γ/ml. (when $R{=}CH_3$). The simple analogue of marasin, $CH{\equiv}C{-}CH{=}C{=}CH{-}CH_2CH_2OH$, was inactive.[7]

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