Addition Reactions of Heterocyclic Compounds. Part LXIV.[1] Indolizines from Reactions of Hex-3-yne-2,5-dione, But-3-yn-2-one, and Allenecarboxylic Esters with some Nitrogen-containing Heterocyclic Ylides

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Pyridinium methylides combine with hex-3-yne-2,5-dione, but-3-yn-2-one, methyl but-2-ynoate, methyl phenylacetylenecarboxylate, dimethyl penta-2,3-dienedioate, and ethyl 2-methylbuta-2,3-dienoate and 2-methylpenta-2,3-dienoate to give indolizines, identified from spectra.

DIETHYL and dimethyl acetylenedicarboxylate [2] and the much less investigated propiolic esters [3] give a wide variety of products with nitrogen-containing heterocycles and ylides,[4] and the reactions of but-3-yn-2-one with some pyridine derivatives have been reported.[5] Few other activated acetylenes and allenes have been examined in this connection and the present paper described some initial investigations.

Goldschmidt and Zoebelein [6] have reported the oxidation of hex-3-yne-2,5-diol to the 5-hydroxy-2-one (45%) and the 2,5-dione (1) (10%) by chromium trioxide

$$\underset{(1)}{MeCO{\cdot}C{\equiv}C{\cdot}COMe} \xrightarrow{ArNH_2} \underset{\substack{(2)\ Ar = Ph \\ (3)\ Ar = 4\text{-}NO_2C_6H_4}}{MeCO(ArNH)C{=}{=}CH{\cdot}COMe}$$

in aqueous sulphuric acid,[7] but we found their procedure satisfactory only for preparing a mixture (n.m.r. analysis) of the hydroxy-ketone (65%) and the diketone (10%). The hydroxy-ketone was obtained pure (n.m.r.) by distillation *in vacuo* from sufficient 4-nitroaniline to convert the diketone into the nitroanilino-derivative (3). None of the diketone was obtained from further oxidation of the hydroxy-ketone under the conditions recommended.[6] Only about half the oxidant had been consumed 4 h after its addition, but the amount of diketone isolable at this point or 20 h later was the same. The diketone was apparently oxidized to acetic acid at a rate comparable to that for its formation, and proved difficult to separate from unchanged hydroxy-ketone. Use of manganese dioxide as oxidant in an inert solvent [8] gave a maximum diketone : hydroxy-ketone ratio of 1 : 9 (n.m.r.), the diketone again being further oxidized. The least unsatisfactory but reproducible preparation of hex-3-yne-2,5-dione (10—18%) was the oxidation with chromic acid of a mixture of the diol and the hydroxy-ketone.

Hex-3-yne-2,5-dione is much more reactive than dimethyl acetylenedicarboxylate [9] towards aniline and 4-nitroaniline, for in methanol, which usually gives the *trans*-products, the addition giving compounds (2) and (3) is complete in 5 min at 10 °C.

Indolizines from ylides

Product	Ylide	Other reactant	Procedure	M.p. (°C)	Yield %
(9)	(4)	HC≡CE	A [a]	125—126	18
(10)	(4)	(1)	A	167—168	10
(10)	(7)	(1)	A [b,c]	162—168	7
(11)	(4)	HC≡CAc	A [b]	177—178	10
(12)	(5)	HC≡CE	B	153—154	35
(13)	(5)	(1)	B [a,d]	135—137	5
(14)	(5)	HC≡CAc	B	174—176 [e]	18
(15)	(5)	MeC≡CE	B	161	21
(16)	(5)	PhC≡CE	B	119—121	6
(17)	(6)	HC≡CE	C	161—163 [f]	3
(18)	(6)	HC≡CAc	C	141—144	2
(23)	(4)	(19)	A [a,g]	130—132	41
(24)	(4)	(20)	A [a,h,i]	101—103 [j]	20
(25)	(4)	(21)	A [a,h,i,k]	41—45	2
(26)	(5)	(19)	B [a]	127—129	26
(27)	(5)	(20)	B [l]	100.5—101.5 [m]	6
(29)	(28)	HC≡CE	A [a,b]	161—163	2
(30)	(28)	HC≡CE	A [b,n]	246—247	4
(31)	(28)	(1)	A [b]	216—217	7
(32)	(28)	HC≡CAc	A [a,b]	204—206	10
(33)	(28)	(19)	A [c,o]	141—145	10
(34)	(28)	(20)	A [a,i]	160—163	7
(35)	(28)	(21)	A [a,i]	90—91	4.5

[a] Chromatographed on alumina (elution with toluene) prior to recrystallization. [b] Not refluxed. [c] Chromatographed on alumina with 1 : 1 toluene–chloroform prior to recrystallization. [d] The solution in dimethylformamide was diluted with water and extracted with chloroform; the chloroform was removed *in vacuo*. [e] Lit., m.p. 175°, from an alternative synthesis (N. J. Leonard, K. Conrow, and R. W. Fulmer, *J. Org. Chem.*, 1957, **22**, 1445). [f] Lit., m.p. 161—162°, from an alternative synthesis (C. A. Henrick, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1967, **20**, 2467. [g] Refluxed for 2 h. [h] Refluxed in dioxan. [i] Refluxed for 24 h. [j] Lit., m.p. 115—116°, from an alternative synthesis (I. Dainis, *Austral. J. Chem.*, 1972, **25**, 1025). [k] Final purification by vacuum distillation; b.p. 105—115° at 0.1 mmHg. [l] Left at room temperature for 24 h. [m] Lit., m.p. 99—100°, from an alternative synthesis (I. Dainis, *Austral. J. Chem.*, 1972, **25**, 1003). [n] Eluted from alumina with chloroform. [o] Refluxed for 4 h.

Heterocyclic ylides combine with activated acetylenes to give dihydroindolizines (8), which usually undergo aromatization to indolizines [10] (Scheme 1); hex-3-yne-2,5-dione, but-3-yn-2-one, methyl propiolate, methyl but-2-ynoate, and methyl phenylacetylenecarboxylate follow this pattern with the ylides (4)—(6), and (28). In the case of the ylide (7) and hex-3-yne-2,5-dione the

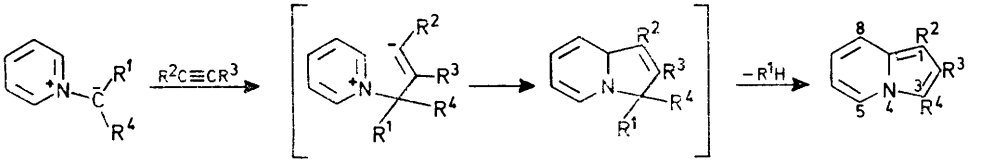
[1] Part LXIII, P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin, and J. R. Carruthers, *J.C.S. Perkin I*, 1976, 1269.
[2] R. M. Acheson, *Adv. Heterocyclic Chem.*, 1963, **1**, 125, and earlier papers in the present series.
[3] R. M. Acheson and J. Woollard, *J.C.S. Perkin I*, 1975, 740.
[4] H. Ogura and K. Kikuchi, *J. Org. Chem.*, 1972, **37**, 2679; S. R. Challand, S. F. Gait, M. J. Rance, C. W. Rees, and R. C. Storr, *J.C.S. Perkin I*, 1975, 26 and papers quoted therein; K. T. Potts, D. R. Choudhury, and T. R. Westby, *J. Org. Chem.*, 1976, **41**, 187.
[5] R. M. Acheson and J. Woollard, *J.C.S. Perkin I*, 1975, 446.
[6] S. Goldschmidt and A. Zoebelein, *Chem. Ber.*, 1961, **94**, 169.
[7] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.
[8] I. Bell, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1958, 1313.
[9] N. D. Heindel, T. A. Brodof, and J. E. Kogelschatz, *J. Heterocyclic Chem.*, 1966, **3**, 222.
[10] T. Kutsuma, K. Fujiyama, Y. Sekine, and Y. Kobayashi, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1558; *cf.* N. Basketter and A. O. Plunkett, *Chem. Comm.*, 1971, 1578.

ester group was eliminated yielding the indolizine (10). Qualitatively the reactivity of the acetylenes towards the ylide (5) decreased in the order hex-3-yne-2,5-dione, dimethyl acetylenedicarboxylate, but-3-yn-2-one, and methyl propiolate, and no indolizine was formed from 5-hydroxyhex-3-yn-2-one.

Attempts to prepare ethyl 2-methylbuta-2,3-dienoate (20) by treating 4,5-dimethylpyrazol-3-one with thallium(III) nitrate, as outlined in a preliminary communication,[11] resulted in a mixture of products, which

twelve constituents were present. However the allenes (19)—(21) combined with the ylides (4), (5), and (28), as shown in Schemes 2 and 3, to give indolizines. The mesomeric carbanion (Scheme 2) cyclises from the atom bearing the most electronegative group which is subsequently eliminated.

The n.m.r. spectrum of the solution obtained when equivalent amounts of the ylide (28) and dimethyl penta-2,3-dienedioate were stirred for 18 h in acetonitrile showed resonances for two OCH_3 groups (τ 6.23 and



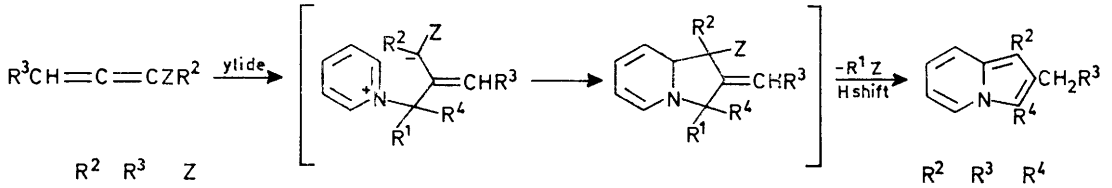
	R^1	R^4
(4)	CN	CN
(5)	H	Ac
(6)	H	COPh
(7)	E	CN

(8)

	R^2	R^3	R^4
(9)	E	H	CN
(10)	Ac	Ac	CN
(11)	Ac	H	CN
(12)	E	H	Ac
(13)	Ac	Ac	Ac
(14)	Ac	H	Ac
(15)	E	Me	Ac
(16)	E	Ph	Ac
(17)	E	H	COPh
(18)	Ac	H	COPh

E = CO_2Me (throughout)

SCHEME 1



	R^2	R^3	Z
(19)	H	E	E
(20)	Me	H	CO_2Et
(21)	Me	Me	CO_2Et

(22)

	R^2	R^3	R^4
(23)	E	E	CN
(24)	Me	H	CN
(25)	Me	Me	CN
(26)	E	E	Ac
(27)	Me	H	Ac

SCHEME 2

was difficult to purify. Bestmann and Hartung's synthesis[12] gave pure samples of (20) and its 4-methyl derivative (21) readily, and in 44 and 48% yield, respectively. Dimethyl penta-2,3-dienedioate (19) was obtained (14% yield) as described by Craig and Moyle,[13] but with methanol as reaction solvent, since the use of ethanol, as reported, gave a mixture of ethyl and methyl esters.

Ethyl 2-methylbuta-2,3-dienoate and dimethyl penta-2,3-dienedioate reacted with pyridine, its 2-amino and 4-methyl derivatives, isoquinoline, and 1-methylimidazole under various conditions to give complex mixtures containing much polymer. T.l.c. showed that up to

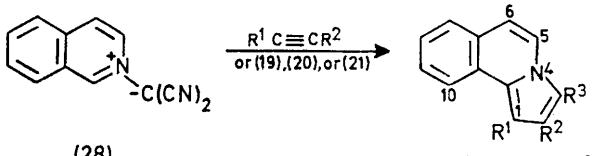
6.55), four aromatic protons (2.65—3.5), one other proton (3.38, d, J 1.5 Hz), and two AB systems. One of these [τ 3.60 (d) and 3.42 (d) (J 7.5 Hz)] corresponded to the 3- and 4-hydrogen atoms of the original isoquinoline, and the other was at higher field [4.82 (d) and 5.13br (d) (J 6.5)]. Double-resonance experiments showed that the proton resonating at τ 5.13 was also coupled to the proton resonating at τ 3.38. These data are consistent with the presence of an intermediate [*cf.* (22)], but all attempts at isolation by crystallisation or the formation of derivatives with picric acid or methyl iodide gave no crystalline materials. Column chromatography gave only the corresponding indolizine (33).

[11] E. C. Taylor, R. L. Robey, and A. McKillop, *J. Org. Chem.*, 1972, **37**, 2797.

[12] H. J. Bestmann and H. Hartung, *Chem. Ber.*, 1966, **99**, 1198.

[13] J. C. Craig and M. Moyle, *J. Chem. Soc.*, 1963, 5356.

The structures of the indolizines (9)—(18) and (23)—(27) follow from their n.m.r. spectra and the fact that ester groups at positions 1 and 3 deshield the 8- and 5-protons by *ca.* 1.0 and 1.6 p.p.m., respectively.[14] The spectra of compounds (10), (11), and (13)—(18) show



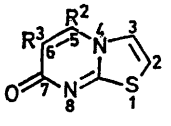
(28)

	R¹	R²	R³
(29)	E	H	CN
(30)	E	H	$CONH_2$
(31)	Ac	Ac	CN
(32)	Ac	H	CN
(33)	E	CH_2E	CN
(34)	Me	Me	CN
(35)	Me	Et	CN

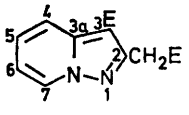
SCHEME 3

that the deshielding by ketone carbonyl groups, *ca.* 1.3 and 2.0 p.p.m., respectively, is a little greater than that of ester carbonyls. The low-field signal for the 10-proton, observed for (32) and for the other 1-carbonyl-substituted benzo[*g*]indolizines, is absent in the spectrum of (31); this must be due to the 1-carbonyl group being twisted from the deshielding orientation by the 2-substituent. The C=O vibrations for carbonyl substituents directly attached to the indolizine ring show in all cases a shift to lower frequencies, indicating the importance of charged resonance forms which have been discussed before in connection with the u.v. spectra of these types of compound.[14]

With 2-aminothiazole, the allenes (19) and (20) gave the thiazolo[3,2-*a*]pyrimidin-7-ones (36) and (37), respectively. These structures are preferred to those of the 5-one isomers because of the similarities to the n.m.r. spectra of known thiazolo[3,2-*a*]pyrimidin-7-ones, but not to those of the corresponding 5-ones.[15] This result shows that the allenes, like methyl propiolate, attack the thiazole at the heterocyclic nitrogen atom.



(36) R^2=CH_2E, R^3=H
(37) R^2=R^3=Me



(38)

The pyrazolopyridine (38) was obtained from the allene (19) and the ylide derived from 1-aminopyridinium iodide.

† For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

[14] R. M. Acheson and D. A. Robinson, *J. Chem. Soc.* (*C*), 1968, 1633.

EXPERIMENTAL

The instruments used have been described previously.[16] Except for the examples given, n.m.r., u.v., i.r., and mass spectra and analytical data for the new compounds are available as Supplementary Publication No. SUP 21821 (10 pp.).†

General Procedures for the Preparation of Indolizines (*Table* 1).—(*A*) The ylides (4),[17] (7),[18] and (28) [17] (5 mmol) and the acetylene or allene (7.5 mmol) were refluxed in toluene (15 ml) for 1 h. Solvent was removed *in vacuo* and the residue recrystallized from methanol to give the indolizine.

(*B*) Sodium hydride (10 mmol) was added with stirring to 1-acetonylpyridinium chloride (10 mmol) in dry ($MgSO_4$) dimethylformamide (25 ml) and the mixture was left 10 min. The acetylene or allene (15 mmol) was added and after 1 h the solvent was removed *in vacuo*. Extraction of the residue with boiling methanol gave the indolizine, *e.g.* 1,2,3-*triacetylindolizine* (13), τ (100 MHz; $CDCl_3$) 0.00 (5-H), 2.95 (6-H), 2.50 (7-H), 1.90 (8-H), and 7.30, 7.40, and 7.55 (3 Me), $J_{5,6}$ 6, $J_{6,7}$ 7, $J_{7,8}$ 9 Hz; $\nu_{max.}$ (Nujol) 3 110w, 1 700s, 1 625s, 1 540w, and 1 500s cm^{-1}; $\lambda_{max.}$ (MeOH) 206 (ε 12 800), 229 (25 500), 252 (39 600), 284infl (10 200), 292 (12 800), 319 (20 400), 338 (30 700), and 350 nm (46 300).

(*C*) Sodium carbonate (47 mmol) was added with stirring to phenacylpyridinium bromide (35 mmol) in water (5 ml) and the solution was extracted with chloroform. After evaporation to 5 ml, toluene (15 ml) and the acetylene or allene (30 mmol) were added with stirring. After 20 h, the solvent was removed *in vacuo*. Chromatography of the residue on alumina (elution with toluene) gave the indolizine, which was recrystallized from methanol.

Hex-3-yne-2,5-dione.—Chromium trioxide (100 g) in concentrated sulphuric acid (90 ml) and water (550 ml) was added with vigorous stirring over 2 h to hex-3-yne-2,5-diol (28 g) and 5-hydroxyhex-3-yn-2-one (28 g) in acetone (400 ml) at −5 to 0 °C. After 1 h, water (150 ml) was added and the solution extracted with ether. The extract was washed (aq. $NaHCO_3$), dried ($MgSO_4$), and distilled to give crude hex-3-yne-2,5-dione (3—6 g), b.p. 50° (bath) at 0.15 mmHg (lit.,[6] 26—38° at 0.1 mmHg) and 5-hydroxyhex-3-yn-2-one (b.p. 50—75° at 0.2 mmHg) (23 g).

Hex-3-yne-2,5-dione gave complex mixtures with 3,5-dimethylpyridine, isoquinoline, benz-imidazole, -oxazole, and -thiazole, and 1,2-dihydro-1-phenylpyridine.

3-*Anilinohex-3-ene-2,5-dione* (2).—Hex-3-yne-2,5-dione (0.5 g) in methanol (5 ml) was added with stirring to aniline (0.43 g) in methanol (5 ml) cooled in ice–water. After 1 h, distillation gave the *ketone* (2) (0.7 g) as a golden liquid, b.p. 120—130° at 0.25 mmHg.

3-(4-*Nitroanilino*)*hex-3-ene-2,5-dione* (3).—Hex-3-yne-2,5-dione (1 g) in methanol (5 ml) was added with stirring to 4-nitroaniline (1.2 g) in methanol (10 ml) cooled in ice–water. After 5 min, the *ketone* (3) (1.4 g) was filtered off, golden needles (from methanol), m.p. 117—118°.

Methyl 7-*Oxo*-7H-*thiazolo*[3,2-a]*pyrimidine-5-acetate* (36).—Dimethyl penta-2,3-dienedioate (1.56 g, 10 mmol) was

[15] H. Reimlinger, *Chem. Ber.*, 1971, **104**, 2232.
[16] R. M. Acheson, J. M. F. Gagan, and D. R. Robinson, *J. Chem. Soc.* (*C*), 1968, 362.
[17] W. J. Linn, O. W. Webster, and R. E. Benson, *J. Amer. Chem. Soc.*, 1965, **87**, 3651.
[18] C. Leonte and I. Zugrăvescu, *Tetrahedron Letters*, 1972, **20**, 2027.

added to 2-aminothiazole (1.0 g, 10 mmol) in acetonitrile (15 ml). After stirring at room temperature for 18 h, *methyl 7-oxo-7H-thiazolo*[3,2-a]*pyrimidine-5-acetate* was filtered off as a yellow solid, m.p. 170° (1.1 g, 49%) (from methanol), giving off-white crystals, m.p. 169—173°; τ [$(CD_3)_2SO$] 2.23 (2-H), 2.73 (3-H), 3.82 (6-H), 5.92 (5-CH_2), and 6.46 (OMe), $J_{2.3}$ 5, τ ($CF_3{\cdot}CO_2H$) 1.78 (2-H), 2.12 (3-H), 2.77 (6-H), 5.58 (5-CH_2), and 6.10 (OMe), $J_{2.3}$ 4.5; $\nu_{max.}$ (Nujol) 3 120w, 1 725s, 1 640s, 1 610s, 1 580s, and 1 560s cm^{-1}; $\lambda_{max.}$ (MeOH) 217.5 (ε 23 600), 228infl (19 800), and 276br nm (15 900).

5,6-*Dimethylthiazolo*[3,2-a]*pyrimidin-7-one* (37).—Ethyl 2-methylbuta-2,3-dienoate (1.26 g) was added to a solution of 2-aminothiazole (1.0 g) in acetonitrile (25 ml). The mixture was stirred at room temperature for 4 days and refluxed for 24 h. After cooling, 5,6-*dimethylthiazolo*[3,2-a]*pyrimidin-7-one* was filtered off, crystals (from methanol) (950 mg, 53%), m.p. 260—262°.

Methyl 3-Methoxycarbonylpyrazolo[2,3-a]*pyridine-2-acetate* (38).—1-Aminopyridinium iodide [19] (1.0 g) in dimethylformamide (10 ml) was stirred with anhydrous potassium carbonate (0.7 g) for 30 min at room temperature. Dimethyl penta-2,3-dienedioate (1.0 g) was added dropwise to the solution and the mixture was stirred for 48 h at room temperature. Water (50 ml) was added and the material extracted into chloroform (4 × 50 ml) was chromatographed on alumina. Elution with toluene gave *methyl 3-methoxycarbonylpyrazolo*[2,3-a]*pyridine-2-acetate*, white needles (from methanol) (100 mg), m.p. 95—96°, τ ($CDCl_3$) 1.91 (4-H), 2.62 (5-H), 3.11 (6-H), 1.54 (7-H), 5.88 (2-CH_2), and 6.13 and 6.29 (2 Me), $J_{4.5}$ 9, $J_{4.6}$ 1.5, $J_{5.6}$ 7, $J_{5.7}$ 1, $J_{6.7}$ 6 Hz; $\nu_{max.}$ (Nujol) 1 735s, 1 730s, 1 695s, 1 635s, 1 517s, and 1 500s cm^{-1}; $\lambda_{max.}$ (MeOH) 220.5infl (ε 48 700), 223.5 (5 700), 225.5infl (32 000), 242 (24 700), 247.5 (25 200), 303br (25 600), and 324infl mn (6 100).

[5/2425 *Received*, 12*th December*, 1975]

[19] R. Gösl and A. Meuwsen, *Chem. Ber.*, 1959, **92**, 2521.