488. *Acetylenic Routes to Tropinone,* pseudo*Pelletierine, and Lobelanine.*

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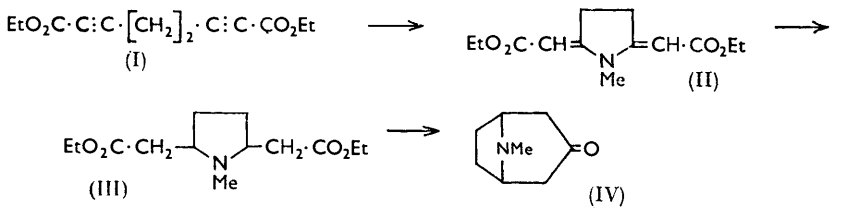
New syntheses of tropinone, *pseudo*pelletierine, and lobelanine have been achieved from hexa-1 : 5-diyne and hepta-1 : 6-diyne.

In spite of their considerable potential in the elaboration of heterocyclic systems acetylenic compounds have hitherto found little use in the synthesis of heterocyclic natural products. The present paper describes the application of triply bonded intermediates to the synthesis of some simple alkaloids.

Carboxylation of the bis-Grignard derivative from hexa-1 : 5-diyne,[1] followed by esterification, gave diethyl hexa-1 : 5-diyne-1 : 6-dicarboxylate (I), which with hot ethanolic methylamine gave a high yield of the pyrrolidine derivative (II) formed by the nucleophilic attack of one molecule of methylamine on the electron-depleted β-carbon atoms of



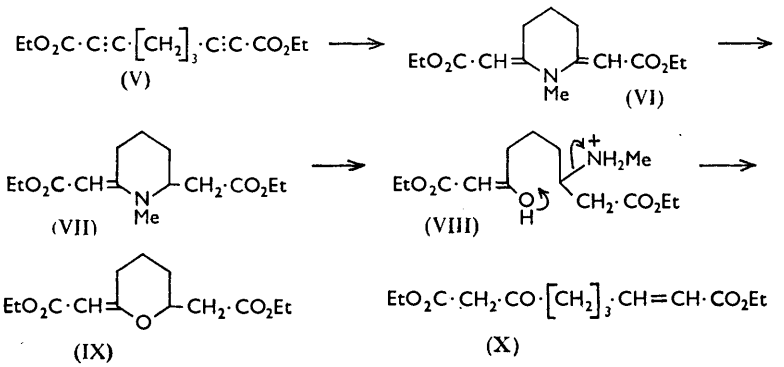
the two activated triple bonds. In view of the well-established *trans*-addition of nucleophilic agents to triple bonds [2] the product (II) very probably possesses the *trans-trans*-configuration about the double bonds (with respect to the carbon framework). The product (II) was crystalline and identical in m. p. with a substance previously obtained by Willstätter and Bommer [3] by the action of methylamine on diethyl 2 : 5-dioxohexane-1 : 6-dicarboxylate. This was regarded by the German workers as diethyl 1-methylpyrrole-2 : 5-diacetate. However, the spectral properties of the compound, especially its high-intensity ultraviolet absorption at 314 mμ, pointed conclusively to structure (II). This finding removes an apparent contradiction in the later literature where diethyl 1-methylpyrrole-2 : 5-diacetate, prepared by the action of ethyl diazoacetate on 1-methylpyrrole,[4] is described as a liquid; repetition of this process and spectral examination of the product confirmed this assignment.

Catalytic reduction of the ester (II) with platinic oxide in acetic acid readily gave the saturated pyrrolidine diester (III). Although the homogeneity of this product was not investigated the steric course of catalytic hydrogenation requires it to be predominantly the *cis*-isomer. Dieckmann cyclisation of the diester, followed by hydrolysis and decarboxylation, gave tropinone (IV). The dipiperonylidene derivative and the picrate showed no m. p. depression on admixture with authentic specimens.

A similar procedure was tried with the homologous ester, diethyl hepta-1 : 6-diyne-1 : 7-dicarboxylate (V) (prepared from hepta-1 : 6-diyne) in order to obtain *pseudo*pelletierine. Ethanolic methylamine here gave a high yield of the expected piperidine derivative (VI). However, the next stage, involving catalytic hydrogenation, produced unexpected results. With ethanol as solvent, only one mol. of hydrogen was absorbed, and the product undoubtedly possessed the partially reduced structure (VII): no explanation of this is apparent. When more forcing conditions were used, with acetic acid as solvent, again the

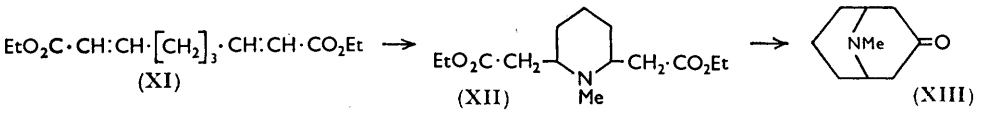
[1] Shaw and Whiting, *J.*, 1954, 3220.
[2] Truce and Simms, *J. Amer. Chem. Soc.*, 1956, **78**, 2757.
[3] Willstätter and Bommer, *Annalen*, 1921, **422**, 15.
[4] Rapoport, Christian, and Spencer, *J. Org. Chem.*, 1954, **18**, 842.

hydrogenation ceased after the absorption of one mol. of hydrogen, but this time the product was nitrogen-free, its properties being in accord with the hydropyran structure (IX). One of many plausible mechanisms for this replacement involves acid-catalysed hydrolysis of the initial product, the enamine (VII), to an open chain β-oxo-ester. Cyclisation of the protonated enolic form (VIII) of the latter with extrusion of methylamine then furnishes the product (IX). The close relation of (VII) and (IX) was confirmed by their producing with Brady's reagent the same 2 : 4-dinitrophenylhydrazone, that of the



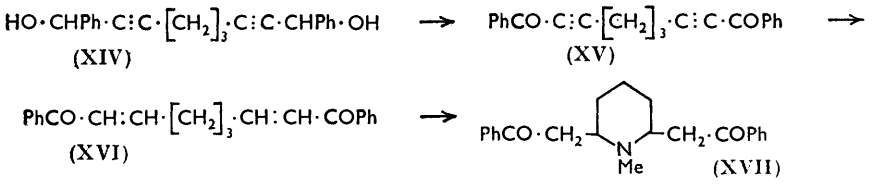
unsaturated oxodiester (X). The last compound may obviously be readily obtained from both the enamine (VII) and the enol ether (IX) by acid-catalysed hydrolysis of the ring followed by β-elimination involving loss of methylamine or water respectively. It is interesting that none of these difficulties attended the catalytic reduction of the closely similar pyrrolidine (II). One explanation for this may be that the latter compound was initially isomerised, under the influence of either the catalyst or the acetic acid used as solvent, to the corresponding 1-methylpyrrole, which then underwent hydrogenation to the saturated pyrrolidine (III) in the usual fashion.

Because of this unforeseen complication a modification was adopted. Partial catalytic hydrogenation of the diacetylenic diester (V) yielded the corresponding *cis-cis*-diethylenic



diester (XI). Addition of methylamine then furnished the required saturated piperidine (XII); Dieckmann cyclisation, hydrolysis, and decarboxylation gave *pseudo*pelletierine (XIII) identical with the naturally occurring alkaloid. This cyclisation indicated that the addition of methylamine to the *cis-cis*-diester had probably produced predominantly, if not entirely, the *cis*-disubstituted piperidine (XII).

Hepta-1 : 6-diyne was also used in a synthesis of lobelanine. The bis-Grignard complex with two mols. of benzaldehyde produced a mixture of the two diastereoisomeric diacetylene glycols of structure (XIV). Oxidation of this mixture by chromium trioxide gave the



crystalline diketone (XV) which was then converted into the *cis-cis*-diethylenic diketone (XVI) by partial catalytic hydrogenation. Addition of methylamine to the diketone

(XVI) again proceeded stereospecifically, to give as the sole isolable product the *cis*-piperidine (XVII) identical with lobelanine.

Experimental

Hexa-1 : 5-*diyne*-1 : 6-*dicarboxylic Acid*.—Hexa-1 : 5-diyne [5] (7·8 g.) in dry ether (25 ml.) was added to a solution of ethylmagnesium bromide [from magnesium (6 g.)] in ether (200 ml.) and refluxed for 2 hr. The cooled mixture was kept in an autoclave with an excess of solid carbon dioxide at room temperature for several days. The complex was then decomposed with 2N-sulphuric acid, and the dicarboxylic acid (7·8 g., 47%), m. p. 182—187°, isolated in the usual manner.

Treatment of the crude diacid (11 g.) with 10% v/v ethanolic sulphuric acid (150 ml.) at room temperature for 5 days gave *diethyl hexa*-1 : 5-*diyne*-1 : 6-*dicarboxylate* (I) (12 g., 82%), b. p. 147—150°/0·5 mm., n_D^{22} 1·4807 (Found: C, 64·9; H, 6·35. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%).

2 : 5-*Di*(*ethoxycarbonylmethylene*)-1-*methylpyrrolidine* (II).—Diethyl hexa-1 : 5-diyne-1 : 6-dicarboxylate (11·7 g.) was heated under reflux with dry ethanolic methylamine (25% solution; 60 ml.) for 8 hr. Concentration to small bulk and cooling induced crystallisation of the almost pure *pyrrolidine* (10·8 g.). Recrystallisation from ethanol gave elongated plates (9·4 g., 71%), m. p. 161·5—163·5° (lit.,[3] m. p. 163—164°), $\lambda_{max.}$ (in chloroform) 314 mμ (ε 55,500) (Found: C, 61·6; H, 7·2; N, 5·5. $C_{13}H_{19}O_4N$ requires C, 61·6; H, 7·55; N, 5·55%). The infrared spectrum (in carbon tetrachloride) showed a strong absorption band at 1710 cm.$^{-1}$ (conjugated ester-carbonyl). The isomeric diethyl 1-methylpyrrole-2 : 5-diacetate was obtained [4] in low yield as a viscous yellow oil, b. p. 124—130°/0·1 mm., n_D^{22} 1·4940. The ultraviolet absorption (in ethanol) resembled closely that of 1-methylpyrrole, showing only rising end-absorption; in the infrared region the expected unconjugated ester-carbonyl absorption occurred at 1726 cm.$^{-1}$ (in carbon tetrachloride).

2 : 5-*Di*(*ethoxycarbonylmethyl*)-1-*methylpyrrolidine* (III).—The pyrrolidine (II) (2·53 g.) in presence of platinic oxide (350 mg.) in glacial acetic acid (15 ml.) at atmospheric pressure required 3 hr. for complete hydrogenation. The bulk of the solvent was removed under reduced pressure, and the residue basified with 2N-sodium hydroxide. Isolation with ether gave the saturated ester (2·1 g., 84%), b. p. 138—140°/2 mm., n_D^{26} 1·4533 (lit.,[3] n_D^{15} 1·4597) (Found: C, 60·6; H, 8·3; N, 5·45. Calc. for $C_{13}H_{23}O_4N$: C, 60·7; H, 9·0; N, 5·45%).

Tropinone.—A suspension of potassium *tert*.-butoxide in xylene (25 ml.) was prepared by dissolving potassium (1·3 g.) in dry *tert*.-butyl alcohol (12 ml.) in a three-necked flask equipped with stirrer, dropping funnel, and short fractionating column (10 cm.) carrying a partial take-off distillation head. The excess of alcohol was removed through the column as the xylene azeotrope. When the refractive index of this distillate reached that of pure xylene, the diester (III) (3·22 g.) in xylene (15 ml.) was added to the stirred suspension, and refluxing continued for 7 hr. The ethanol–xylene azeotrope formed during cyclisation was distilled off until the refractive index of pure xylene was again attained. The mixture was cooled, and the xylene removed under reduced pressure. The solid residue gave a positive ferric chloride test. This product was heated under reflux with 4N-hydrochloric acid (60 ml.) for 1 hr. The solution was reduced in volume to *ca.* 20 ml., basified with solid sodium carbonate, and continuously extracted with ether for 4 hr. Removal of ether from the dried extracts afforded a brown semisolid material (0·47 g.); sublimation of a portion of this product in a high vacuum gave almost pure tropinone, m. p. 40—42° undepressed on admixture with an authentic sample. A portion of the crude tropinone (100 mg.) was warmed with piperonaldehyde (300 mg.) in ethanol (4 ml.) and potassium hydroxide (250 mg.) in water (1 ml.). The resultant solid was filtered off, dried, and recrystallised from ethyl acetate to give yellow needles of dipiperonylidene-tropinone, m. p. and mixed m. p. 212—213°. From aqueous acetone, the tropinone gave a picrate as needles (from water), m. p. and mixed m. p. 210—211° (decomp.).

Hepta-1 : 6-*diyne*.—1 : 3-Dibromopropane (300 g.) in dry ether (200 ml.) was added to a solution of sodium acetylide [from sodium (100 g.) in liquid ammonia (2 l.)] with vigorous stirring, a slow stream of purified acetylene being maintained through the mixture throughout the addition. After 90 minutes' further stirring the ammonia was allowed to evaporate and the

[5] Raphael and Sondheimer, *J.*, 1950, 120.

residue treated with water and ether. The ethereal layer was separated, washed with dilute sulphuric acid, saturated aqueous sodium carbonate, and water, and dried ($MgSO_4$). The ether was removed through a Dufton column (30 cm.), and the residual oil fractionated, to give the hydrocarbon (40—52%), b. p. 108—112°/760 mm., n_D^{20} 1·4428—1·4460 (lit.,[6] b. p. 111·5°/760 mm., n_D^{20} 1·4423).

Hepta-1 : 6-*diyne*-1 : 7-*dicarboxylic Acid* (V).—Hepta-1 : 6-diyne (6·9 g.) in dry ether (25 ml.) was added, with stirring, to a solution in 1 : 1 ether–benzene (250 ml.) of ethylmagnesium bromide [from magnesium (4·5 g.)]. After 90 minutes' heating under reflux the resulting complex was treated with carbon dioxide under pressure as in the above cognate preparation. Isolation in the usual manner gave *hepta*-1 : 6-*diyne*-1 : 7-*dicarboxylic acid* (6·8 g., 49%) which crystallised from benzene in plates, m. p. 98·5—100° (Found: C, 59·7; H, 4·35. $C_9H_8O_4$ requires C, 60·0; H, 4·4%).

The esters were prepared as described above from the diacid and alcoholic sulphuric acid (10% v/v; 15 ml. per g. of acid). *Dimethyl hepta*-1 : 6-*diyne*-1 : 7-*dicarboxylate* had b. p. 132°/0·1 mm., n_D^{17} 1·4890 (Found: C, 63·2; H, 5·8. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·75%). The *diethyl ester* had b. p. 148°/0·06 mm., n_D^{22} 1·4805 (Found: C, 65·9; H, 6·85. $C_{13}H_{16}O_4$ requires C, 66·05; H, 6·85%).

2 : 6-*Di*(*ethoxycarbonylmethylene*)-1-*methylpiperidine* (VI).—The preceding diethyl ester (4·72 g.) was refluxed for 3 hr. with excess of 10% ethanolic methylamine (30 ml.) and ethanol (20 ml.). The residual oil, after removal of the excess of amine and ethanol, was distilled in a short-path apparatus to furnish the *piperidine* (VI) (83—90% yield depending on scale of distillation), b. p. 170—174°/0·06 mm., n_D^{25} 1·5680, $\lambda_{max.}$ (in chloroform) 322 mμ (ε 21,100) (Found: C, 63·0; H, 7·95; N, 5·80. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·25%).

2-*Ethoxycarbonylmethyl*-6-*ethoxycarbonylmethylenetetrahydropyran* (IX).—When the piperidine (VI) (1·34 g.) in glacial acetic acid (10 ml.) was hydrogenated in the presence of platinic oxide (200 mg.) absorption of hydrogen ceased after 40 min. (uptake, 118 ml. at 17°/758 mm.; complete reduction required 231 mol.). The solvent was neutralised with solid sodium carbonate, water was added, and the *tetrahydropyran* isolated with ether as an oil, b. p. 118°/0·02 mm., n_D^{25} 1·4731, $\lambda_{max.}$ (in chloroform) 256 mμ (ε 4750) (Found: C, 60·4; H, 8·0. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·85%). Treatment with Brady's reagent afforded the 2 : 4-*dinitrophenylhydrazone* of diethyl 6-oxohept-1-ene-1 : 7-dicarboxylate (X) as yellow needles (from ethanol), m. p. 111·5—113° (Found: C, 52·4; H, 5·2; N, 13·2. $C_{19}H_{24}O_8N_4$ requires C, 52·3; H, 5·55; N, 12·85%).

2-*Ethoxycarbonylmethyl*-6-*ethoxycarbonylmethylene*-1-*methylpiperidine* (VII).—When shaken with 10% palladium–charcoal (500 mg.) in ethanol (10 ml.) the piperidine (VI) (880 mg.) absorbed only one mol. of hydrogen. Filtration, removal of solvent, and distillation gave the *piperidine* (VII), b. p. 133—139°/0·05 mm., n_D^{25} 1·5072, $\lambda_{max.}$ (in chloroform) 302 mμ (ε 10,000) (Found: C, 62·5; H, 8·5; N, 5·1. $C_{14}H_{23}O_4N$ requires C, 62·4; H, 8·6; N, 5·2%). By treatment with Brady's reagent the product gave the 2 : 4-dinitrophenylhydrazone of the oxo-diester (X) undepressed by the corresponding derivative prepared as in the preceding experiment.

Diethyl Hepta-1 : 6-*diene*-1 : 7-*dicarboxylate* (XI).—Diethyl hepta-1 : 6-diyne-1 : 7-dicarboxylate (18 g.) in ethanol (50 ml.) was hydrogenated in the presence of Lindlar's catalyst (5·0 g.) until 2 mol. of hydrogen had been absorbed. Filtration, evaporation, and distillation gave the cis-cis-*diester*, b. p. 104—106°/0·04 mm., n_D^{25} 1·4675 (Found: C, 65·3; H, 8·15. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·35%).

2 : 6-*Di*(*ethoxycarbonyl*)-1-*methylpiperidine* (XII).—The diester (XI) (9·3 g.) was refluxed for 9 hr. with 5% ethanolic methylamine (60 ml.). After removal of the excess of methylamine and alcohol, fractional distillation of the residue gave 2 : 6-*di*(*ethoxycarbonyl*)-1-*methylpiperidine* (9·2 g., 87%), b. p. 117—120°/0·05 mm., n_D^{25} 1·4642 (Found: C, 62·1; H, 9·1; N, 4·95. $C_{14}H_{25}O_4N$ requires C, 61·95; H, 9·3; N, 5·15%).

pseudo*Pelletierine* (XIII).—The three-necked flask fitted with stirrer, gas-inlet tube, dropping funnel, and partial take-off distillation head described above was charged with " atomised " sodium (600 mg.) in *p*-cymene (4 ml.). The ester (XII) (6·95 g.) in *p*-cymene (8 ml.) was added and the mixture held at 158—160° (oil-bath) in nitrogen for 15 min. with concomitant removal by fractional distillation of the ethanol formed. The cooled mixture was treated with water, the organic phase separated, and the aqueous layer acidified with 50% sulphuric acid and refluxed for 90 min. The cooled solution was basified with 40% potassium hydroxide solution,

[6] Henne and Greenlee, *J. Amer. Chem. Soc.*, 1945, **67**, 484.

saturated with potassium carbonate, and continuously extracted with ether. Drying ($MgSO_4$) and distillation of the residual oil (after removal of the ether) gave an unsharply melting mixture of *pseudo*pelletierine and its hydrate (0·7 g.). By treatment with a concentrated acetone solution of picric acid, *pseudo*pelletierine picrate was obtained in yellow prisms, m. p. and mixed m. p. 258—260° (decomp.). The dipiperonylidene derivative, prepared as above, had m. p. and mixed m. p. 228—230°.

1 : 9-*Diphenylnona*-2 : 7-*diyne*-1 : 9-*diol* (XIV).—The bisbromomagnesium complex of hepta-1 : 6-diyne (13·8 g.) was prepared in the usual manner from ethylmagnesium bromide [from magnesium (8·0 g.)] in 1 : 1 dry ether–benzene (400 ml.), then cooled and treated with excess of redistilled benzaldehyde (36 g.). The mixture was heated under reflux for 30 min. and the complex then decomposed with saturated aqueous ammonium chloride (200 ml.). The organic phase was isolated, washed with saturated aqueous sodium carbonate, dried ($MgSO_4$), and evaporated. After removal of the benzaldehyde and other low-boiling materials the mixture of diastereoisomers of 1 : 9-diphenylnona-2 : 7-diyne-1 : 9-diols distilled at 180—190°/10^{-4} mm., as a yellow syrup, n_D^{25} 1·586 (Found: C, 82·6; H, 6·50. Calc. for $C_{21}H_{20}O$: C, 82·8; H, 6·6%).

1 : 9-*Diphenylnona*-2 : 7-*diyne*-1 : 9-*dione* (XV).—The above glycol (7·48 g.) in acetone (15 ml.) was treated with a solution of chromium trioxide (3·4 g.) in water (10 ml.) containing concentrated sulphuric acid (2·85 ml.) during 20 min. at 0°. After a further 2 hours' stirring at room temperature water (100 ml.) was added and the product isolated by ether-extraction. Removal of solvent and crystallisation from methanol gave the *diketone* (5·2 g., 69%) as plates, m. p. 59—60°, $\lambda_{max.}$ (in chloroform) 264 mμ (ε 2860) (Found: C, 83·9; H, 5·35. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·35%). The *mono*-2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange platelets, m. p. 138—140° (Found: C, 66·9; H, 3·95; N, 11·9. $C_{27}H_{20}O_5N_4$ requires C, 67·4; H, 3·63; N, 11·7%), $\lambda_{max.}$ (in chloroform) 384 and 262 mμ (ε 32,400 and 30,500 respectively).

cis-cis-1 : 9-*Diphenylnona*-2 : 7-*diene*-1 : 9-*dione* (XVI).—The acetylenic diketone (6 g.) was partially hydrogenated in benzene (60 ml.) with Lindlar's catalyst (2·4 g.), the uptake being discontinued when 2 mols. of hydrogen had been absorbed (944 ml. at 18°/769 mm.). Filtration and removal of benzene gave the cis-cis-*diketone*, b. p. 184°/10^{-4} mm., n_D^{25} 1·589, $\lambda_{max.}$ (in chloroform) 248 mμ (ε 22,600) (Found: C, 82·4; H, 6·70. $C_{21}H_{20}O_2$ requires C, 82·8; H, 6·60%), $\nu_{max.}$ 691 cm.$^{-1}$. Complete hydrogenation of the diyne afforded 1 : 9-diphenylnonan-1 : 9-dione which crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 52—54° (lit.,[7] m. p. 56—57°).

Lobelanine (XVII).—A solution of the above diketone (6·48 g.) in ethanol (10 ml.) was treated dropwise with a solution of methylamine (0·62 g.) in ethanol (25 ml.) during 1 hr. After a further 2 hours' stirring, the ethanol was removed under a vacuum, leaving crude lobelanine as a brown syrup. When a solution of this product in ethanol (10 ml.) was saturated with dry hydrogen chloride lobelanine hydrochloride (2·05 g., 27%) was obtained as a cream-coloured solid, m. p. 196° (decomp.) (lit.,[8] m. p. 198°) (Found: C, 70·7; H, 6·6; N, 4·1. Calc. for $C_{22}H_{26}O_2NCl$: C, 71·05; H, 7·05; N, 3·75%). The free base was regenerated by shaking the hydrochloride (1·3 g.) with saturated aqueous sodium carbonate (10 ml.) and benzene (5 ml.). The benzene phase afforded lobelanine, plates [from light petroleum (b. p. 60—80°)], m. p. 97—98° (lit.,[8] m. p. 94—95°) (Found: C, 78·6; H, 7·4; N, 4·0. Calc. for $C_{22}H_{25}O_2N$: C, 78·8; H, 7·5; N, 4·2%).

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[7] Wieland and Dragendorff, *Annalen*, 1929, **473**, 83.
[8] Schöpf and Lehmann, *ibid.*, 1935, **518**, 1.