Studies in the Synthesis of Camptothecin. An Efficient Synthesis of 2,3-Dihydro-1*H*-pyrrolo[3,4-*b*]quinoline

By **L. H. Zalkow,* J. B. Nabors, K. French,** and **S. C. Bisarya,** School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

An efficient regioselective synthesis of 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (3), a key intermediate in the synthesis of camptothecin, has been developed. The synthesis, which has been extended to a number of analogues, involves an acid-catalysed Friedländer condensation in the absence of a solvent. Base-catalysed condensation was shown to lead predominantly to the isomeric 2,3-dihydro-1*H*-pyrrolo[3,2-*b*]quinoline (10). The relative stabilities of the enols and enolates derived from *N*-acetyl-3-pyrrolidone and ethyl 3-oxopyrrolidine-1-carboxylate, intermediates in the synthesis of compounds (3) and (10), are discussed.

CAMPTOTHECIN (1), a novel pentacyclic alkaloid possessing anti-tumour activity, has been isolated from *Camptotheca acuminata, Nyssaceae*, and its structure has been determined by *X*-ray analysis of its iodoacetate (2).[1] As an essential part of our synthesis of camptothecin we required 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (3) and describe here a regioselective [2],† synthesis of this intermediate which has been scaled-up to kilogram quantities.‡ Since our preparation of compound (3), others [3] have reported its use in an approach to the

† The term regioselective was not originally defined to include reactions such as a aldol-type condensations. However, it appears to us that in aldol-type condensations involving unsymmetrical ketones such as (6) where enolization can occur in either of two directions to give two products [(9) or (11)] the terms regiospecific and regioselective are well suited to describe specificity in such reactions. In our case, we observe an enolate regioselective reaction [base-catalysed to give (11)] and an enol regioselective reaction [acid-catalysed to give (9)].

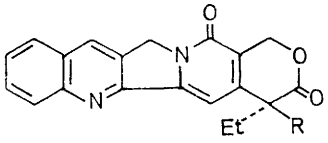
‡ Further details can be found in the Ph.D. dissertation of J. B. Nabors, jun., Georgia Institute of Technology. The scale-up was done by Starks Associates, Inc., 1280 Niagara St., Buffalo, New York.

[1] M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, 1966, **88**, 3888.

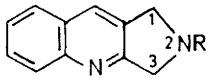
[2] A. Hassner, *J. Org. Chem.*, 1968, **33**, 2684.

[3] M. C. Wani, J. A. Kepler, J. B. Thompson, M. E. Wall, and S. G. Levine, *Chem. Comm.*, 1970, 404.

synthesis of camptothecin, but no experimental details for the preparation of compound (3) were provided, and the information [3] given indicates that the synthesis was not regioselective.

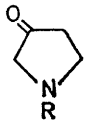


(1) R = OH
(2) R = O·CO·CH_2I



(3) R = H (7) R = Ac
(4) R = Me (9) R = CO_2Et

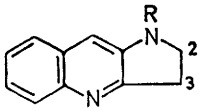
The synthesis of 2,3-dihydro-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline (4) by a base-catalysed Friedländer condensation of *N*-methyl-3-pyrrolidone with *o*-aminobenzaldehyde has been reported.[4] By analogy with earlier work we required as a precursor in the synthesis of compound (3), a 3-pyrrolidone such as (5) or (6)



(5) R = Ac
(6) R = CO_2Et

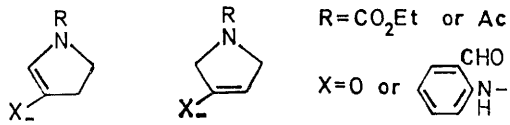
containing an *N*-substituent which could be readily removed.

N-Acetyl-3-pyrrolidone (5), prepared by a slight modification of the previously described [5] procedure, underwent a base-catalysed Friedländer condensation with *o*-aminobenzaldehyde to give, after chromatography, a crystalline product in low yield. This was identified an acetylpyrroloquinoline on the basis of its i.r. and mass spectra. However, the n.m.r. spectrum showed that it was not the desired 2-acetyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (7) but instead the isomeric 1-acetyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]quinoline (8): δ 2·38 (2H, t, *J* 8 Hz, 2-H_2) and 3·97 p.p.m. (2H, t, *J* 8 Hz, 3-H_2). A small amount of the desired isomer (7) was detected in the crude reaction mixture by g.l.c.



(8) R = Ac (11) R = CO_2Et
(10) R = H

We then attempted to synthesise ethyl 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline-2-carboxylate (9) *via* the intermediate (6).[6] Condensation of compound (6) with *o*-aminobenzaldehyde was extremely dependent on the conditions. Thus with *ca.* 1% ethanolic sodium hydroxide at room temperature an essentially quantitative conversion into a mixture of 2,3-dihydro-1*H*-pyrrolo[3,2-*b*]quinoline (10) (65%), the corresponding *N*-ethoxycarbonyl derivative (11) (20%), and ethyl 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline-2-carboxylate (9) (15%) was observed. In the presence of more concentrated base (*ca.* 12% ethanolic sodium hydroxide) complete conversion again occurred to give compounds (10) (81%) and (9) (19%). Thus, under basic conditions the condensations occurred predominantly to give the undesired heterocyclic nucleus; hydrolysis of the *N*-ethoxycarbonyl group occurred readily in the case of the ester (11) and was not observed for the ester (9). This difference was exploited to separate compounds (11) and (9). The preponderant formation of the [3,2-*b*]isomers (8) and (11) [or (10)] under alkaline conditions is indicative of the greater stability of the enolate (12) compared to (13).[7,*]



(12) (13)

When an acid catalyst was used in the Friedländer condensation a change in the ratio of isomers (9) and (11) was observed. A variety of acid catalysts in acetic acid gave, in general, nearly equal quantities of the esters (9) and (11), and in the absence of solvent the predominant product was always the isomer (9). The most satisfactory conditions for the synthesis of the ester (9) involved heating an intimate mixture of the ester (6), *o*-aminobenzaldehyde, and toluene-*p*-sulphonic acid in a molar ratio of 1 : 2 : 0·02 at 190—195° for 5 min under nitrogen. A quantitative conversion was obtained, and the ester (9) was isolated in 88% yield. The unwanted isomer (11) was hydrolysed under the alkaline conditions of the work-up to give the water-soluble potassium salt of compound (10), which was not soluble in chloroform. Thus, the isomers are cleanly separable without chromatography.

The increase in the amount of the ester (9) relative to (11) under acid-catalysed Friedländer conditions is consistent with the expected increased stability of the enol corresponding to (13) relative to the enolate.* An explanation for the increase in formation of compound (9) in the absence of acetic acid is that solvation of the enol corresponding to (12) is preferred to that of the enol from (13); thus the energy of the former is lowered relative to the latter. Under the acid-catalysed conditions, hydrolysis of the *N*-ethoxycarbonyl group never occurred, and compound (10) was not produced.

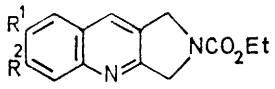
The free base, 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (3), was obtained either by alkaline hydrolysis or by heating with 48% hydrobromic acid to give the dihydrobromide, which on treatment with triethylamine was readily converted into compound (3). Owing to

* As previously pointed out,[7] an aldol-type condensation occurs at some stage in the overall Friedländer condensation, either before or during ring closure, and the direction of this condensation in unsymmetrical ketones is determined by the relative stabilities of the intermediate enolates (base-catalysed reactions) or enols (acid-catalysed reactions).

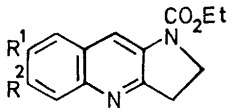
[4] G. Kempter and S. Hirschberg, *Chem. Ber.*, 1965, **98**, 419.
[5] Y-H. Wu, W. G. Lobeck, jun., and R. F. Feldkamp, *J. Medicin. Chem.*, 1962, **5**, 762.
[6] R. Kuhn and G. Osswald, *Chem. Ber.*, 1956, **89**, 1423.
[7] E. A. Fehnel, *J. Org. Chem.*, 1966, **31**, 2899.

the instability of the product, this conversion is preferred since the dihydrobromide can be stored indefinitely without decomposition and can be readily converted into compound (3) when desired.

To test the applicability of the condensation to the synthesis of analogues of (9), the derivatives (16)—(19) were prepared and characterized. Compounds (20) and (21), analogues of (11) were also isolated and characterized. No attempt was made to determine the optimum conditions for the preparation of analogues (16)—(19).



(16) R^1 = Cl, R^2 = H
(17) R^1 = OMe, R^2 = H
(18) R^1 = H, R^2 = OMe
(19) R^1R^2 = O·CH_2·O



(20) R^1 = OMe, R^2 = H
(21) R^1 = H, R^2 = OMe

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 237B spectrophotometer for KBr pellets or liquid films. N.m.r. spectra were obtained with a Varian A60 spectrometer for $CDCl_3$ solutions with tetramethylsilane as internal standard. G.l.c. was performed using a F and M Biomedical Gas Chromatograph model 400 with a hydrogen flame detector equipped with glass columns [6 ft × ¼ in (o.d.)] of the specified coating material on Gas Chrom Q. Mass spectra were obtained with a Varian M66 mass spectrometer. U.v. spectra were recorded for methanolic solutions using a JASCO ORD/UV-5 spectrophotometer.

N-*Acetyl*-3-*pyrrolidone*.—*N*-Acetyl-3-pyrrolidone was prepared [5] by acid hydrolysis of ethyl *N*-acetyl-4-oxopyrrolidine-3-carboxylate, which was obtained in 43% yield by the reported method.[5] This yield was significantly improved (76%) by substitution of sodium metal for the sodium hydride previously employed. After distillation the product had b.p. 120—123° at 0·55 mmHg (lit.,[5] 126° at 0·6 mmHg); n_D^{30} 1·4912 (lit.,[5] 1·4978); $\nu_{max.}$ 1760 and 1650 cm^{-1}; δ (75°) 2·02 (3H, s), 2·65 (2H, t, *J* 7 Hz), and 3·63—4·20 p.p.m. (4H, m).

Reaction of N-*Acetyl*-3-*pyrrolidone with* o-*Aminobenzaldehyde*.—*N*-Acetyl-3-pyrrolidone (1·27 g), *o*-aminobenzaldehyde (1·21 g), ethanol (90 ml), and sodium hydroxide (10%; 5 ml) were stirred under nitrogen at room temperature for 45 h. The ethanol was evaporated, the residue distributed between ether and water, and the ether layer dried (Na_2SO_4) and concentrated to give a viscous yellow liquid (1·00 g), which was chromatographed on silica gel. 1-*Acetyl*-2,3-*dihydro*-1H-*pyrrolo*[3,2-b]-*quinoline* (8) (0·10 g, 5%), eluted in the ethanol–chloroform (1 : 3) fraction, had m.p. 125—127° (from ether); $\nu_{max.}$ 1665, 1610, and 1570 cm^{-1}; δ 2·25 (3H, s), 2·38 (2H, t, *J* 8 Hz), 3·97 (2H, t, *J* 8 Hz), and 7·32—8·07 p.p.m. (5H, m) [Found: C, 73·55; H, 5·65; N, 13·2%; *M* (mass spectrum), 212. $C_{13}H_{12}N_2O$ requires C, 73·55; H, 5·7; N, 13·2%; *M*, 212]. Compound (8) was also prepared from 2,3-dihydro-1*H*-pyrrolo[3,2-*b*]quinoline (10), obtained as described below, by acetylation with acetic anhydride.

G.l.c. (3% XE-60 column) and n.m.r. analysis of the crude product showed the presence of a small amount of the isomer (7), an authentic sample of which, obtained by acetylation of compound (3), had m.p. 208—210°, $\nu_{max.}$ 1625 cm^{-1}; δ 2·22 (3H, s), 4·95 (4H, s), and 7·30—8·17 p.p.m. (5H, m) (Found: C, 73·35; H, 5·7; N, 13·3. $C_{13}H_{12}N_2O$ requires C, 73·55; H, 5·7; N, 13·2%).

Ethyl 3-*Oxopyrrolidine*-1-*carboxylate* (6).—This compound, prepared as previously described [7] had b.p. 118—120° at 0·8 mmHg (lit.,[7] 122—123° at 12 mmHg); $\nu_{max.}$ 1760 and 1710 cm^{-1}; δ 1·28 (3H, t, *J* 7 Hz), 2·58 (2H, t, *J* 7 Hz), 3·58—3·97 (4H, m), and 4·18 p.p.m. (q, 2H, *J* 7 Hz).

Reaction of Ester (6) *with* o-*Aminobenzaldehyde*.—(a) *Mild base catalysed*. The ester (6) (1·57 g), *o*-aminobenzaldehyde (1·21 g), absolute ethanol (90 ml), and sodium hydroxide (10%; 5 ml) were stirred under nitrogen for 24 h at room temperature. The ethanol was evaporated, the residue distributed between ether and water, and the ether layer dried (Na_2SO_4) and concentrated to yield a viscous, yellow material (0·85 g). The water layer was concentrated to yield crude 2,3-*dihydro*-1H-*pyrrolo*[3,2-b]-*quinoline* (10) (1·10 g, 65%), m.p. 139—141° (from benzene); $\nu_{max.}$ 3205, 1625, and 1575 cm^{-1}; δ 3·00—3·85 (4H, m), 4·18 (1H, s), 6·73 (1H, s), and 7·20—7·95 p.p.m. (4H, m) [Found: C, 77·5; H, 5·95; N, 16·35%; *M* (mass spectrum), 170. $C_{11}H_{10}N_2$ requires C, 77·65; H, 5·9; N, 16·45%; *M*, 170]. Chromatography of the ether extract on silica gel gave *ethyl* 2,3-*dihydro*-1H-*pyrrolo*[3,4-b]*quinoline*-2-*carboxylate* (9), (0·36 g, 15%) m.p. 134—135°; $\nu_{max.}$ 1700, 1625, and 1570 cm^{-1}; δ 1·35 (3H, t, *J* 7 Hz), 4·28 (2H, q, *J* 7 Hz), 4·83 (4H, s), and 7·50—8·17 p.p.m. (5H, m); $\lambda_{max.}$ 207, 229, 293, 299, 305, and 312 nm (log ε 4·37, 4·16, 3·72, 3·85, and 3·80) [Found: C, 69·4; H, 6·05; N, 11·45%; *M* (mass spectrum), 242. $C_{14}H_{14}N_2O_2$ requires C, 69·4; H, 5·85; N, 11·6%; *M*, 242]; and ethyl 2,3-*dihydro*-1H-*pyrrolo*[3,2-b]*quinoline*-1-*carboxylate* (11), (0·48 g, 20%), m.p. 80—81°; $\nu_{max.}$ 1705, 1615, and 1575 cm^{-1}; δ 1·38 (3H, t, *J* 7 Hz), 3·30 (2H, t, *J* 9 Hz), 4·21 (2H, t, *J* 9 Hz), 4·37 (2H, q, *J* 7 Hz), and 7·33—8·25 p.p.m. (5H, m) [Found: C, 69·35; H, 5·95; N, 11·4%; *M* (mass spectrum), 242] in the ethanol-chloroform (1 : 3) eluate. Compounds (9)—(11) were readily separable on a 3% XE-60 column at 230° (helium flow rate 100 ml min^{-1}; retention times 3·7 (9), 3·2 (11), and 0·7 min (10).

(b) *Strong base catalysed*. The ester (6) (13·0 g), *o*-aminobenzaldehyde (10·0 g), absolute ethanol (160 ml), and sodium hydroxide (85%; 28 ml) were stirred under nitrogen for 18 h; ethanol was removed, and the residue was distributed between chloroform (400 ml) and water (400 ml). The chloroform layer was dried (Na_2SO_4) and concentrated to yield the ester (9), (4·2 g, 18%) as a brown solid. The aqueous layer was adjusted to pH 8 with conc. hydrochloric acid, then again extracted with chloroform. The organic layer was dried and concentrated to yield compound (10), (13·4 g, 79%).

(c) *Sulphuric acid catalysed in acetic acid*. The ester (6) (1·57 g), *o*-aminobenzaldehyde (1·21 g), acetic acid (10 ml), and conc. sulphuric acid (3 drops) were heated on a steam bath for 1 h, cooled, then poured into an ice-cold solution of conc. ammonium hydroxide (15 ml) in water (40 ml). A brown oil separated and was extracted with chloroform. The extract was dried (Na_2SO_4) and concentrated to yield a light brown oil (2·75 g), which was chromatographed on silica gel. Elution with ethanol–chloroform (1 : 3) gave the esters (9) (0·70 g, 29%) and (11) (0·87 g, 36%) and unchanged starting material (0·52 g, 33%).

(d) *Toluene*-p-*sulphonic acid catalysed*. The ester (6)

(3·14 g), *o*-aminobenzaldehyde (4·80 g), and toluene-*p*-sulphonic acid (1·00 g) were mixed, then heated at 190—195° for 5 min under nitrogen. The mixture was cooled rapidly by dropwise addition of chloroform. G.l.c. analysis of the mixture (3% XE-60, 230°) showed esters (9) (90%) and (11) (10%). Evaporation of the chloroform gave a solid which was dissolved in ethanol (80 ml), then sodium hydroxide (85%; 14 ml) was added, and the mixture was stirred at room temperature for 18 h. The ethanol was removed, and the residue was partitioned between water (200 ml) and chloroform (200 ml). The water layer was neutralized by dropwise addition of conc. hydrochloric acid; the oil which separated was extracted with chloroform and on drying and concentration it gave compound (10) (0·24 g, 7%). The chloroform layer from the earlier extraction was dried and concentrated to yield a residue. Extraction of the residue with cyclohexane gave the ester (9) (4·26 g, 88%).

2,3-*Dihydro*-1H-*pyrrolo*[3,4-b]*quinoline* (3).—(a) *Alkaline hydrolysis*. The ester (9) (121 mg), absolute ethanol (5 ml), sodium hydroxide (350 mg), and water (0·4 ml) were refluxed overnight under nitrogen, then cooled, poured into cold water (40 ml), and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated to yield the product as a buff solid. Crystallization gave material (71 mg, 82%), m.p. 101—103° (from ether); $\nu_{max.}$ 3250, 1660, and 1553 cm^{-1}; δ 2·70 (1H, s, disappears on addition of D_2O), 4·29 (4H, s), and 7·30—8·10 p.p.m. (5H, m) [*M* (mass spectrum), 170. Calc. for $C_{11}H_{10}N_2$: *M*, 170]. G.l.c. analysis (3% XE-60, 230°) showed a single compound. The compound was unstable at room temperature in the presence of air.

(b) *Acid hydrolysis*. The ester (9) (12·1 g) was added to freshly distilled 48% hydrobromic acid (100 ml), and the solution was heated under nitrogen for 24 h. Cooling and washing with ethanol gave 2,3-*dihydro*-1H-*pyrrolo*-[3,4-b]*quinoline dihydrobromide* as golden needles (15·6 g, 93%), m.p. 240—250° (decomp.); $\nu_{max.}$ 3250, 1620, and 1560 cm^{-1} (Found: C, 40·2; H, 3·75; Br, 47·9; N, 8·25. $C_{11}H_{12}Br_2N_2$ requires C, 39·8; H, 3·65; Br, 48·15; N, 8·45%). The free base was obtained by treatment of the salt with aqueous triethylamine followed by extraction with methylene chloride.

Substituted Pyrroloquinoline Analogues (16)—(21).—The substituted pyrroloquinolines (16)—(21) were prepared by a modification of the toluene-*p*-sulphonic acid procedure, from the appropriately substituted aminobenzaldehyde. In these reactions the selective hydrolysis step was omitted to allow isolation of the analogues, where possible. The compounds were purified by column chromatography on silica gel and had the following properties. *Ethyl* 7-*chloro*-2,3-*dihydro*-1H-*pyrrolo*[3,4-b]*quinoline*-2-*carboxylate* (16) (26%), m.p. 173—175°; $\nu_{max.}$ 1685 and 1600 cm^{-1}; δ 1·32 (3H, t, *J* 6 Hz), 4·29 (2H, q, *J* 6 Hz), 4·82 (4H, s), and 7·47—8·10 p.p.m. (4H, m); $\lambda_{max.}$ 310, 318, and 325 nm (log ε 3·74, 3·68, and 3·89) (Found: C, 60·9; H, 4·9; Cl, 12·75; N, 9·95. $C_{14}H_{13}ClN_2O_2$ requires C, 60·75; H, 4·75; Cl, 12·8; N, 10·15%). *Ethyl* 2,3-*dihydro*-7-*methoxy*-1H-*pyrrolo*[3,4-b]*quinoline*-2-*carboxylate* (17) (15%), m.p. 218—220°, $\nu_{max.}$ 1680 and 1625 cm^{-1}; δ 1·50 (3H, t, *J* 7 Hz), 3·90 (3H, s), 4·25 (2H, q, *J* 7 Hz) 4·80 (4H, s), and 7·00—8·00 p.p.m. (4H, m); $\lambda_{max.}$ 335 nm (log 3·93) (Found: C, 66·0; H, 6·0; N, 10·25. $C_{15}H_{16}N_2O_3$ requires C, 66·2; H, 5·9; N, 10·3%). *Ethyl* 2,3-*dihydro*-6-*methoxy*-1H-*pyrrolo*[3,4-b]*quinoline*-2-*carboxylate* (18) (31%) m.p. 174—176°; $\nu_{max.}$ 1700 and 1615 cm^{-1}; δ 1·35 (3H, t, *J* 7 Hz), 4·27 (2H, q, *J* 7 Hz), 4·75 (4H, s), and 7·00—9·00 p.p.m. (4H, m); $\lambda_{max.}$ 330 nm (log ε 4·07) (Found: C, 66·05; H, 6·0; N, 10·35%). *Ethyl* 2,3-*dihydro*-6,7-*methylenedioxy*-1H-*pyrrolo*[3,4-b]*quinoline*-2-*carboxylate* (19) (13%), m.p. 257—259°; $\nu_{max.}$ 1700 and 1630 cm^{-1}; δ 1·30 (3H, t, *J* 7 Hz), 4·20 (2H, q, *J* 7 Hz), 4·80 (4H, s), 6·10 (2H, s), and 7·10—8·00 p.p.m. (4H, m); $\lambda_{max.}$ 324 and 347 nm (log ε 4·18 and 4·40) (Found: C, 62·85; H, 5·1; N, 9·75. $C_{15}H_{14}N_2O_4$ requires C, 62·95; H, 4·95; N, 9·95%). *Ethyl* 2,3-*dihydro*-7-*methoxy*-1H-*pyrrolo*[2,3-b]*quinoline*-1-*carboxylate* (20) (6%) m.p. 142—144°; $\lambda_{max.}$ 1700 and 1615 cm^{-1}; δ (C_6D_6) 1·25 (3H, t, *J* 7 Hz), 3·00 (3H, t, *J* 8 Hz), 3·75 (2H, t, *J* 8 Hz), 4·20 (2H, q, *J* 7 Hz), and 7·10—8·00 p.p.m. (4H, m); $\lambda_{max.}$ 250 and 329 nm (log ε 4·81 and 4·18) (Found: C, 66·05; H, 6·0; N, 10·15%). *Ethyl* 2,3-*dihydro*-6-*methoxy*-1H-*pyrrolo*[2,3-b]*quinoline*-1-*carboxylate* (21) (9%), m.p. 153—155°; $\nu_{max.}$ 1695 and 1620 cm^{-1}; δ 1·38 (2H, t, *J* 8 Hz), 4·32 (2H, q, *J* 7 Hz), and 7·50—8·10 p.p.m. (4H, m); $\lambda_{max.}$ 270, 346, and 355 nm (log ε 4·08, 3·98, and 4·00) (Found: C, 66·05; H, 6·15; N, 10·15%).

We thank Chemotherapy, National Cancer Institute, National Institutes of Health for financial support, Mr. G. Harrison for assistance in the preparation of compound (9) and Dr. P. Torline for the preparation of compound (7).

[1/076 *Received, January 18th*, 1971]