# The Synthesis of Thienocycloheptenoindoles



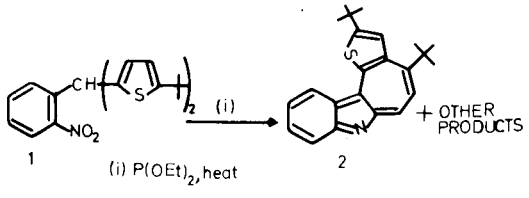
Belén Abarca [a], Rafael Ballesteros [a] and Gurnos Jones [b]

[a] Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, Valencia, Spain
[b] Department of Chemistry, University of Keele, Keele, Staffordshire, ST5 5BG, United KingdomReceived March 8, 1984

A synthesis of the methylthieno[3,2-*c*]cyclohepteno[*b*]indole **7** from 2-methylthieno[3,2-*b*]cycloheptanone **3** is described. Unsuccessful attempts to prepare the isomeric thienocycloheptenoindole system present in formula **2**, from the dihydrobenzothiophenone **8**, and from derivatives of 5-(2-thienyl)-4-oxopentanoic acid, **17** and **18**, and from *N*-benzylcycloheptindol-1-one **22** were unsuccessful. The preparation of 4,5-dihydro-2-phenyl-1-thienylmethyl-3*H*-pyridazin-3-one **20** and of the 5-aminopyrazole **21** are reported.

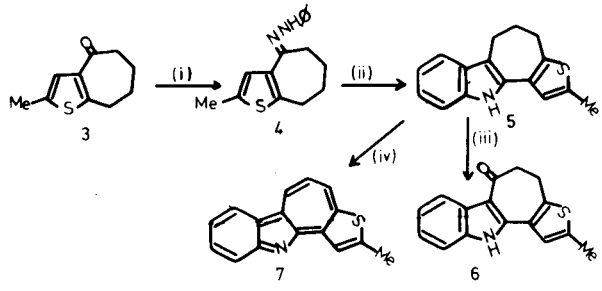
*J. Heterocyclic Chem.*, **21**, 1585 (1984).

One of us has reported the preparation of several new heterocyclic compounds by deoxygenation of *o*-nitrophenylbis(5-*t*-butyl-2-thienyl)methane **1** [1,2]. Of these, the most intriguing was deep blue; from its nmr spectrum it was assigned the tentative structure **2**. The non-alternant polycyclic structure was suggested [1] to account for the long wavelength absorption band. We describe here a successful synthesis of a representative **7** of the isomeric thienocycloheptenoindole system, and some unsuccessful attempts to obtain a simple example of the chromophore present in structure **2**.




Scheme I

We sought first to establish the properties of a related polycyclic system. The simplest approach was from the known [3,4] thiophene derivative **3**. The phenylhydrazone **4** was readily obtained and, when heated in glacial acetic acid, gave in good yield the indole **5**. The indole **5** was oxidized by DDQ in tetrahydrofuran to the ketone **6**. It was our intention originally to reduce the ketone and to dehydrate the resulting alcohol. However, the reported [5] dehydrogenation of a benzcycloheptindole by chloranil led us to try direct dehydrogenation of the tetrahydro derivate **5** by DDQ. In boiling benzene a 25% yield of the polycycle **7** was obtained. Compound **7** was a dark red solid; the maximum of longest wavelength was a broad band at 450-500 nm falling gradually toward 600 nm, compared with a much more intense band at 605 nm in compound **2**. The nmr spectrum showed signals at $\delta$ 2.55 (3H, s), 6.9 (1H, dd, J = 9 and 11 Hz, H5), 7.34 (1H, m, H8 or H9), 7.5-7.7 (2H, m), 7.95-8.05 (2H, m), and 8.19-8.25 (2H, m). For comparison compound **2** showed a singlet at $\delta$ 5.64, well upfield of any signal found for compound **7**.

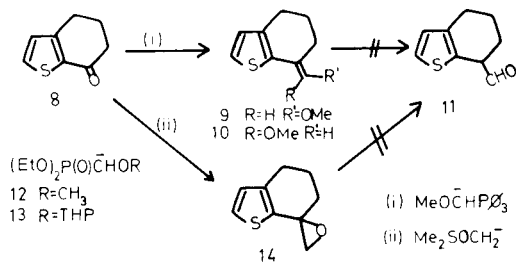



(i) ØNHNH$_2$ (ii) AcOH, heat (iii) DDQ, THF (iv) DDQ, $C_6H_6$, boil

Scheme II

Our attempts to prepare the isomeric polycyclic system suggested for compound **2** have been less successful. One approach, from 3-(2-thienyl)indoles has been reported elsewhere [6]. In the knowledge that cyclohexanecarboxaldehyde phenylhydrazone undergoes cyclization and rearrangement to cycloheptindole under Fischer indole synthesis conditions [7], we attempted to prepare the aldehyde **11**. The known ketone **8** [8] was treated with methoxymethylenetriphenylphosphorane [9]. The reaction was very slow and after 72 hours gave a mixture which appeared from the nmr spectrum to contain a low percentage of the mixed enol ethers **9** and **10**, but these could neither be purified, nor converted into aldehyde **11**. No reaction was observed between the ketone **8** and the Wittig-Horner reagents **12** [10] or **13** [11], indicating again the very low carbonyl activity of the ketone **8**. With dimethylsulphoxonium methylide the ketone gave, in 11% yield, the oxirane **14** identified by nmr spectroscopy, notably by the singlet at $\delta$ 2.5 ($OCH_2$). The low yield and the instability of the product prohibited any further pursuit of this route.

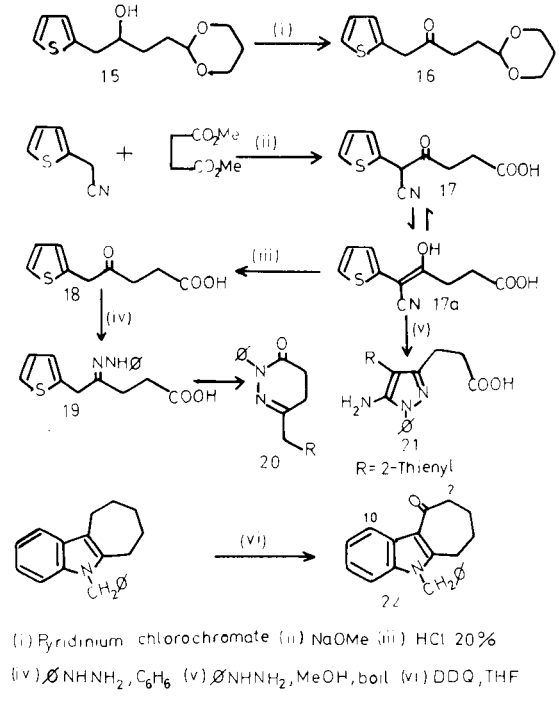
Other ketones which could, by a Fischer indole procedure, be precursors for a synthesis of the polycyclic system present in compound **2**, are **16** and **18**. Reaction between 2-thienylacetaldehyde and the Grignard reagent from 2-(2-bromoethyl)-1,3-dioxane gave alcohol **15** which, without purification, was oxidised by pyridinium chlorochromate to ketone **16**. All attempts to convert the ketone **16** into an



Scheme III

ester of acid **18**, by using *N*-bromosuccinimide [12] were unsuccessful, giving complex mixtures, so an alternative route to acid **18** was adopted. Cagniant *et al.* [13] have reported the condensation of 2-thienylacetonitrile with dialkyl oxalates. A similar condensation between 2-thienylacetonitrile and dimethyl succinate gave, not the expected ester, but the cyanoketoacid **17**; the yield was 27%, but recovery of substantial amounts of 2-thienylacetonitrile implied a conversion of 70%. The acid **17** was observed to be predominantly enolic **17a** from the nmr spectra. A number of acid conditions were tried to achieve the hydrolysis and subsequent decarboxylation of compound **17**, but the best gave only a 14% yield of the γ-ketoacid **18**, much polymer being always formed. Attempts at basic hydrolysis gave only 2-carboxymethylthiophene. The ketoacid **18** reacted with phenylhydrazine to give a phenylhydrazone **19** in good yield. Attempts to form an indole using boiling acetic acid gave instead the dihydropyridazin-3-one **20**. Such cyclizations of γ-ketoacid phenylhydrazones are commonly observed [14] and in our case indole formation does not compete.

The poor yield in the acid treatment of compound **17** led us to attempt to prepare a phenylhydrazone directly from it. The product, of molecular formula $C_{10}H_{15}N_3O_2S$, was, from it spectral data, the aminopyrazole **21**. There are, again, examples of the formation of 5-aminopyrazole from β-ketonitriles and arylhydrazines [15,16]. Our final attempts to prepare the polycyclic system present in structure **2** started from *N*-benzylcyclohept[*b*]indol-1-one (**22**). This compound was obtained in variable yield by the method of Oikawa and Yonemitsu [17] by oxidising the cycloheptindole with DDQ in tetrahydrofuran. Since the authors gave no nmr evidence for the site of oxidation and the ketone **22** is the only suitable precursor we established the structure by addition of europium shift reagent to the solution used for the nmr spectrum. Downfield shifts occurred in a multiplet originally at δ 8.4-8.7 (1H, H10) and in one multiplet (4H) originally at δ 2.5-3.0; in the latter case a two proton multiplet (H2) moved. No substantial change occurred in the benzyl singlet at δ 5.18 and hence oxidation at C5 is excluded. Unfortunately, all attempts to generate and to alkylate the enolate of compound **22** failed, as did attempts to form an enamine, so that the thiophene ring could not be constructed. Consideration of the spectral data of compound **7** had meanwhile thrown doubt on the structure **2** advanced for the nitrene insertion product, so no further attempts have been made to synthesize the thienocycloheptoindoles.



Scheme IV

## EXPERIMENTAL

Melting points were determined on a Kofler hot stage, and are uncorrected. The uv-visible spectra were determined for solutions in 95% ethanol, and the nmr spectra for solutions in deuteriochloroform, unless otherwise stated. Separations were on columns of alumina (Woelm) of activity IV, on silica, or on preparative plates, 40 × 20 cm, of silica (Merck $PF_{254}$).

5,6,7,8-Tetrahydro-2-methylcyclohepta[*b*]thiophen-4-one (**3**).

This compound was prepared as described by Cagniant and Cagniant [3,4]. The phenylhydrazone **4** was prepared from ketone **3** (2.2 g) and phenylhydrazine (1.35 g) in boiling benzene (10 ml) (4 hours) in 60% yield. It was recrystallized from absolute ethanol, mp 89-91°; nmr: δ 1.7-2.0 (4H, m, H6 and 7), 2.4 (3H, s), 2.5-3.0 (4H, two overlapping triplets, H5 and H8), 6.6-7.3 (6H, m); ir: ν max 3460 $cm^{-1}$; ms: 270 ($M^+$).

*Anal.* Calcd. for $C_{16}H_{18}N_2S \cdot C_2H_5OH$: N, 8.86. Found: N, 8.85. The C and H analyses were variable, the compound rapidly turning brown in air.

1,9,10,11-Tetrahydro-2-methylthieno[3,2-*c*]cyclohepteno[*b*]indole (**5**).

A solution of the phenylhydrazone **4** (1 g) in glacial acetic acid (30 ml) was boiled (7 hours). The solvent was evaporated *in vacuo*, and the residue shaken with aqueous sodium bicarbonate and dichloromethane. The organic layer was dried, evaporated and the residue chromatographed on alumina (50 g, IV). Elution with petroleum (60-80° bp)/benzene (9:1) gave almost pure indole **5**, (0.8 g, 85%), recrystallized from cyclohexane, mp 127-127.5°; nmr: δ 2.05-2.25 (2H, m, H10), 2.45 (3H, s), 3.0-3.17 (4H, two overlapping t, H9 and H11), 6.83 (1H, s, H3), 7.0-7.4 (4H, m, H5-H8), 8.0

(1H, br, NH); ir (Nujol): ν max 3440 $cm^{-1}$.

*Anal.* Calcd. for $C_{16}H_{15}NS$: C, 75.85; H, 6.00; N, 5.55. Found: C, 75.9; H, 6.0; N, 5.55.

The same yield could be obtained on a larger scale if the crude phenylhydrazone was immediately dissolved in glacial acetic acid and indolised as above.

10,11-Dihydro-2-methylthieno[3,2-*c*]-4*H*-cyclohepteno[*b*]indol-9-one (**6**).

A solution of DDQ (4.54 g) in tetrahydrofuran (40 ml) was added dropwise to a cooled (0°) solution of indole **5** (2.53 g) in tetrahydrofuran (100 ml) and water (10 ml). An intense colour developed as the DDQ was added, which slowly disappeared. The mixture was stirred (1 hour) then evaporated. The residue was extracted by ethyl acetate, and the ethyl acetate solution percolated through alumina (500 g, IV) to give almost pure ketone **6** (2.3 g, 86%). Recrystallized from acetone or ethyl acetate, mp > 240°; nmr: δ 2.2 (3H, s), 2.9 (4H, s, H10 and H11), 7.0-7.1 (2H, m), 7.3-5.25 (2H, m), 8.16-8.25 (1H, m, H8); ir ν max (Nujol): 3300, 1605, 1580 $cm^{-1}$.

*Anal.* Calcd. for $C_{16}H_{13}NOS$: C, 71.9; H, 4.9; N, 5.25. Found: C, 71.35; H,4.65; N, 5.0.

2-Methylthieno[3,2-*c*]cycloheptenо[*b*]indole (**7**).

DDQ (2.4 g) was added to a hot solution of the tetrahydro derivative **5** (1.23 g), giving an immediate chocolate brown precipitate. The mixture was boiled (6 hours). The benzene solution was cooled, filtered, and the filtrate extracted by sodium hydroxide, and then by 2 *N* hydrochloric acid. The orange acid solution was basified and extracted by dichloromethane to give a purple solution. The solution was dried (magnesium sulfate) filtered, and evaporated. Recrystallization from cyclohexane gave the polycycle **7**, mp 137-138° (0.3 g, 25%); nmr: δ 2.55 (3H, s), 6.8-7.0 (1H, dd, J = 9 and 11 Hz, H10), 7.25-7.4 (1H, m), 7.25-7.4 (2H, m), 7.57-7.75 (2H, m), and 7.95-8.25 (2H, m); uv λ max (cyclohexane): 255 (4.23), 265 (4.24), 305 (4.44), 325 (4.49), 354 (4.20), 400 (4.08), 410 (4.17) nm; λ max (ethanol): very similar, with a broad band centered at 500 nm (3.19); ms: 249 ($M^+$).

*Anal.* Calcd. for $C_{16}H_{11}NS$: C, 77.05; H, 4.45; N, 5.6. Found: C, 76.7; H, 4.45; N, 5.8.

Reactions With 4,5-Dihydro-6*H*-benzo[*b*]thiophen-7-one (**8**).

(a).

In the best of a number of conditions tried, a solution of methoxymethyltriphenylphosphonium chloride in ether was treated with the equivalent amount of *n*-butyllithium and stirred (1 hour, room temperature). Benzothiophen-7-one (**8**) was added slowly at room temperature. After 72 hours, the mixture was hydrolysed, the organic material showing nmr signals at δ1.6-1.8 (m), 2.3-2.8 (m), 3.5 (s), 3.6 (s) and 6.65-7.2 (m). All attempts at purification caused decomposition.

(b).

A solution of dimethylsulphoxonium methylide was prepared from trimethylsulphoxonium iodide (1.51 g) and sodium hydride (0.205 g) in dry DMSO (7 ml) at 80°. The ketone **8** (1 g) in DMSO (2 ml) was added at ambient temperature and the mixture stirred (8 days). Addition of water, ether extraction, and plc purification of the ethereal extract gave one band from which the oxirane **14** was obtained (12 mg, 11%) as an oil; nmr: δ 1.1-1.8 (4H, m), 2.5 (2H, s, $OCH_2$), 2.55-2.9 (2H, m), 6.65 (1H, d, J = 5 Hz), and 7.1 (1H, d, J = 5 Hz).

2-[4-(2-Thienyl)butan-3-on-1-yl]-1,3-dioxan (**16**).

A solution of 2-thienylacetaldehyde [18] (3.2 g) in tetrahydrofuran (10 ml) was added to a stirred solution of the Grignard reagent from 2-(2-bromoethyl)-1,2-dioxan (4.87 g) and magnesium (0.6 g) in dry THF (10 ml), at room temperature. After further stirring (2.5 hours) the mixture was hydrolysed with aqueous ammonium chloride, extracted with ether, and the ethereal extracts dried (sodium sulfate) and evaporated, giving 9.8 g of crude product. This crude product was dissolved in dry dichloromethane (20 ml) and added to a suspension of pyridinium chlorochromate (13.04 g) and sodium acetate (0.29 g) also in dichloromethane (34 ml). After stirring for 2 hours at room temperature ether was added and insoluble material was removed by decantation. Further washing with ether and decantation was followed by filtration through silica, evaporation, and chromatography on silica using ether/hexane (1:2) as eluent. The butanonyl dioxane **16** (1.3 g, 21%) was obtained as a yellow oil; nmr: δ 1.1 (1H, m, 5e'), 1.45-3.0 (5H, m), 2.45-3.7 (6H, m), 4.35 (1H, t, H2, J = 6 Hz), 6.7 (1H, m), 6.9 (1H, m) and 7.4 (1H, m): ms: 240 ($M^+$); ir (carbon tetrachloride): ν max 1715, 1550, 1150 $cm^{-1}$.

*Anal.* Calcd. for $C_{12}H_{16}O_3S$: C, 60.0; H, 6.6. Found: C, 60.25; H, 6.35.

5-Cyano-4-oxo-5-(2-thienyl)pentanoic Acid (**17**).

To a solution of sodium (7.44 g) in absolute methanol (200 ml) at 35°, was added, with stirring, 2-thienylacetonitrile (20 g) over 1 hour. The mixture was boiled for 1 hour, then dimethyl succinate (23.76 g) was added dropwise over 1 hour at 70°. Boiling was continued for 1.5 hours after addition. The cooled mixture was treated with water (700 ml) and extracted with ether (4 × 100 ml). The ether extracts were dried and evaporated to give almost pure 2-thienylacetonitrile (12.22 g). The aqueous phase (*p*H 14) was acidified with 7% hydrochloric acid (160 ml), extracted with ether, and the ether extracts dried (sodium sulfate) and evaporated. The crude product (22.85 g) was again dissolved in ether and decolourized by charcoal. Filtration and evaporation of the ether left a residue which was crystallized from chloroform to give the cyano acid **17**, mp 108-110° (10 g, 70% on unrecovered thienoacetonitrile); nmr ($d_6$-acetone): δ 2.75-3.11 (4H, m), 7.02 (1H, dd, J = 5 and 3.6 Hz, H4), 7.17 (1H, dd, J = 3.6 and 1 Hz, H3), 7.36 (1H, dd, J = 5 and 1 Hz, H5), 8.17 (2H, s); $^{13}C$ nmr: δ 29.6 (t, C3'), 31.2 (t, C2'), 84.1 (s, C5'), 118.8 (s, C6'), 122.8 (d, C5), 124.7 (d, C3), 125.8 (d, C4), 134.4 (s, C2), 166.9 (s, C4'), 172.3 (s, C1), off-resonance multiplicities in parenthesis; ir ν max (potassium bromide): 2240, 1700, 1630, 1400, 1200 $cm^{-1}$; ms: 223 ($M^+$), 224 (M + 1), 225 (M + 2).

*Anal.* Calcd. for $C_{10}H_9NO_3S$: C, 53.8; H, 4.05; N, 6.3. Found: C, 53.7; H, 4.0; N, 6.25.

4-Oxo-5-(2-thienyl)pentanoic Acid (**18**).

A mixture of cyanoacid **17** (5 g) and 20% hydrochloric acid (75 ml) was boiled (6 hours). Dilution of the cooled solution was followed by extraction with dichloromethane. The organic extracts were dried (sodium sulfate), evaporated, and the residual ketoacid **18** (0.55 g, 14%) recrystallized from cyclohexane, mp 68°; nmr: δ 2.7 (4H, overlapping triplets), 3.9 (2H, s), 6.8-7.0 (2H, m), 7.2 (1H, dd, J = 5 and 1 Hz); ms: 198 (21%), 199 (4%), 200 (1%) ($M^+$); ir ν max (potassium bromide): 1710-1700 $cm^{-1}$.

*Anal.* Calcd. for $C_9H_{10}O_3S$: C, 54.5; H, 5.05. Found: C, 54.3; H, 4.8.

4,5-Dihydro-2-phenyl-6-(2-thienylmethyl)-2*H*-pyridazin-3-one (**20**).

(a).

The ketoacid **18** (0.4 g) and phenylhydrazine (0.215 g) were dissolved in benzene (50 ml) and boiled (2 hours) with a fitted Dean-Stark trap. Evaporation of the solvent gave a solid (0.56 g), (96%) characterised spectroscopically as the phenylhydrazone **19**.

(b).

The crude solid was dissolved in glacial acetic acid (7 ml) and the solution was boiled (4.5 hours). After further standing (12 hours) the solution was diluted with water (100 ml), neutralised by solid sodium bicarbonate, extracted with benzene, and the organic phase dried (sodium sulfate) and evaporated. The yellow residue was purified by plc (eluent, chloroform) to give tetrahydropyridazinone **20** (0.35 g, 67%); nmr: δ 2.55 (4H, s), 3.85 (2H, s), 6.8-7.0 (2H, m), 7.1-7.5 (6H, m); $^{13}C$ nmr: δ 23.8 (t), 27.25 (t), 36.4 (t), 124.3 (d), 124.9 (d), 125.6 (d), 126.2 (d), 126.8 (d), 127.8 (d), 137.8 (s), 140.65 (s), 155.35 (s) and 164.45 (s); ir ν max (carbon tetrachloride): 1660, 1600 $cm^{-1}$; ms: 270 (84), 271 (16), 272 (8).

*Anal.* Calcd. for $C_{15}H_{14}N_2OS$: C, 66.65; H, 5.2; N, 10.35. Found: C, 66.6; H, 5.2; N, 10.3.

5-Amino-3-(2-carboxyethyl)-1-phenyl-4-(2-thienyl)pyrazole (**21**).

A solution of the cyanoacid **17** (1 g) and phenylhydrazine (0.48 g) in ab-

solute methanol was boiled 6 hours. Evaporation of the solvent and chromatography of the residue on a silica column (chloroform eluent) gave a pink coloured solid (0.76 g) and when crystallised from aqueous methanol gave the pyrazole **21**, mp 160-161°; nmr (DMSO-$d_6$): δ 2.85 (2H, t), 2.56 (2H, t), 5.21 (2H, s, exch deuterium oxide), 7.02-7.17 (2H, m), 7.35-7.62 (7H, m); $^{13}$C nmr: δ 22.5 (t, $CH_2$), 33.6 (t, $CH_2$), 96.7 (s, pyrazole C4), 122.8 (d, thienyl C5), 123.5 (d), 124.0 (d), 126.1 (d), 127.2 (d), 128.8 (d), 133.9 (s, thienyl C2), 138.4 (s), 143.6 (s, pyrazole C3), 148.2 (s, pyrazole C5), 173.3 (s, $CO_2H$); ir: ν max 3400, 3320, 1700-1710, 1610, 1600, 1560, 1505, 1200 $cm^{-1}$; uv: λ max 250 nm (log 10, ε 6200).

*Anal.* Calcd. for $C_{16}H_{15}N_3O_2S$: C, 61.3; H, 4.8; N, 13.4. Found: C, 61.1; H, 4.75; N, 13.5.

## REFERENCES AND NOTES

[1] G. Jones, C. Keates, I. Kladko and P. M. Radley, *Tetrahedron Letters*, 1445 (1979).

[2] P. C. Hayes, G. Jones, C. Keates, I. Kladko and P. M. Radley, *J. Chem. Res., (S)*, 288 (1980); *(M)*, 3519 (1980).

[3] P. Cagniant and D. Cagniant, *Bull. Soc. Chim. France*, 680 (1955).

[4] G. Jones, R. K. Jones and M. J. Robinson, *J. Chem. Soc., Perkin Trans. I*, 968 (1973).

[5] W. Treibs, R. Steinert and W. Kirchhoff, *Ann. Chem.*, **581**, 54 (1953).

[6] B. Abarca, R. Ballesteros and G. Jones, *Ann. Quim.*, **79C**, 23 (1983).

[7] G. Jones and T. S. Stevens, *J. Chem. Soc.*, 2344 (1953).

[8] J. P. Conjat, P. Cagniant, D. Cagniant and M. Mirjolet, *Tetrahedron Letters*, 2885 (1975).

[9] G. Wittig and E. Knauss, *Angew. Chem.*, **71**, 127 (1959).

[10] M. Green, *J. Chem. Soc.*, 1324 (1963).

[11] A. F. Kluge and I. S. Cloudsdale, *J. Org. Chem.*, **44**, 4847 (1979).

[12] R. N. Carde, P. C. Hayes, G. Jones and C. J. Cliff, *J. Chem. Soc., Perkin Trans. I*, 1132 (1981).

[13] P. Cagniant and D. Cagniant, *C. R. Hebd. Seances Acad. Sci.*, **229**, 1150 (1949); D. Cagniant and G. Merle, *ibid.*, **264C**, 112 (1967).

[14] N. N. Suvorov and V. S. Murasheva, *Zh. Obshch. Khim.*, **30**, 3112 (1960); *Chem. Abstr.*, **55**, 17620 (1961).

[15] L. C. Behr, R. Fusco and C. H. Jarboe, "Pyrazoles, Pyrazolines, Indazoles and Condensed Rings", Interscience, New York, 1967, p 1.

[16] H. R. Snyder, Jr., *J. Heterocyclic Chem.*, **12**, 1303 (1975).

[17] Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **42**, 1213 (1977).

[18] E. Winterfeldt, *Chem. Ber.*, **96**, 3349 (1963).