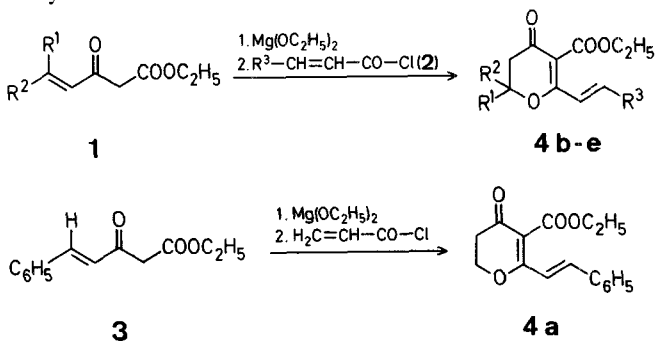
Synthesis of 3,5-Bis[alkenyl]-1-phenylpyrazoles and 3-Oxo-2-phenyl-6,7-dihydro-2*H*-pyrano[4,3-*c*]pyrazoles from 2,3-Dihydro-4-pyrone Derivatives

Bernard CHANTEGREL, Abdel-Ilah NADI, Suzanne GELIN

Laboratoire de Chimie Organique, Institut National des Sciences Appliquées, F-69621 Villeurbanne Cedex, France

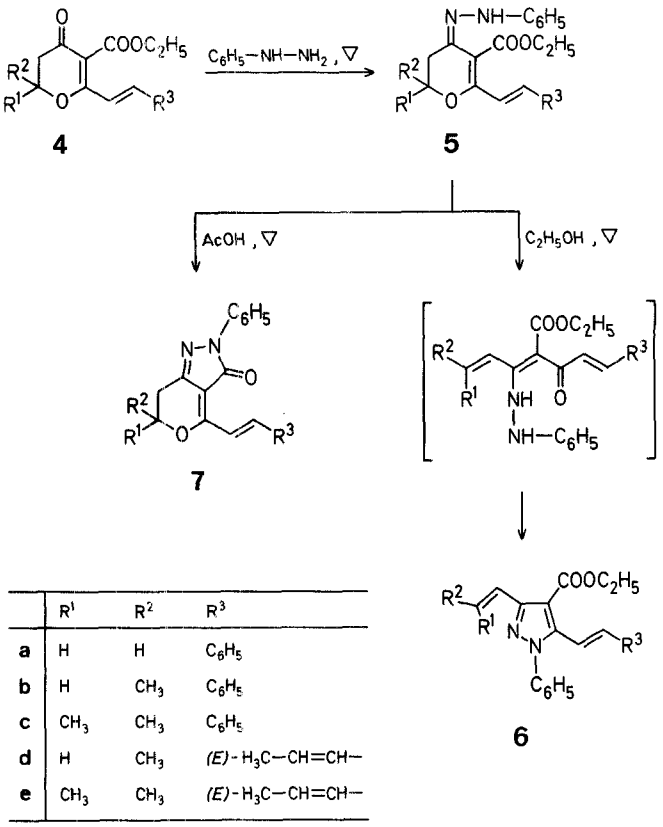
2,3-Dihydro-4-pyrones are potential sources of pyrazoles[1,2,3]. We describe here the utility of 5-ethoxycarbonyl-6-styryl- or -6-(1,3-pentadienyl)-2,3-dihydro-4-pyrones **4**, by their reaction with phenylhydrazine, to synthesize either 3,5-bis[alkenyl]-1-phenylpyrazoles **6** or 3-oxo-2-phenyl-6,7-dihydro-2*H*-pyrano[4,3-*c*]pyrazoles **7**.

Preparation of dihydropyrones **4** is accomplished as outlined in Scheme **A**, analogous to our method[4,5] for the synthesis of 4-oxo-4*H*-pyrans. Condensation of ethoxymagnesio-enolates of γ,δ-unsaturated β-keto esters **1** with cinnamoyl or sorbitoyl chloride **2** affords compounds **4b–e** in good yields. The ring unsubstituted dihydropyrone **4a** is synthesized by an alternative route starting from ethyl cinnamoylacetate **(3)** and acryloyl chloride. Substituted acryloyl chlorides like crotonyl chloride and β-methylcrotonyl chloride reacted with **3** to give **4b** and **4c** only in lower yield than the former route. The regioselective formation of 6-styryl- or 6-(1,3-pentadienyl)-2,3-dihydro-4-pyrones **4** is attributed to the reactivity differences of the double bond of the acyl groups of the open chain ethyl diacylacetate intermediate[5].



Scheme **A**

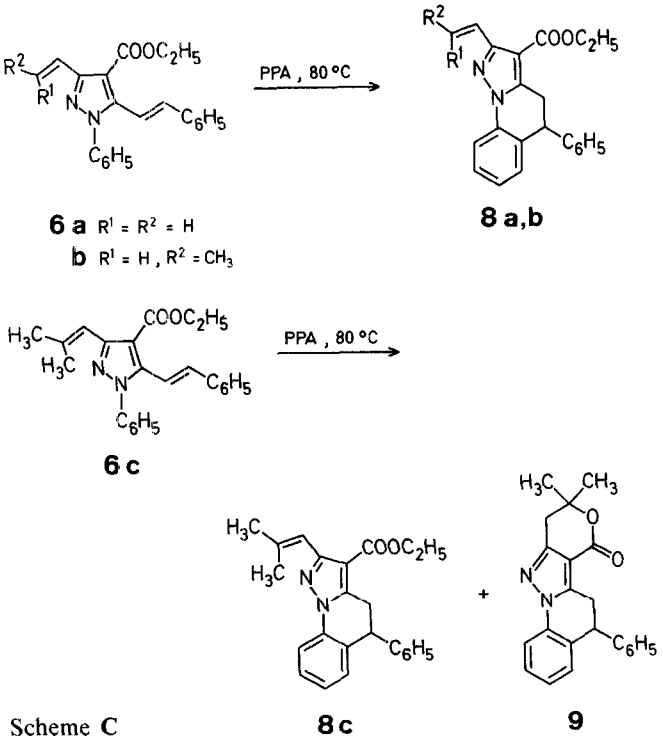
The nature of the reaction products obtained from phenylhydrazine and dihydropyrones **4** can be affected by varying the solvent used. The formation of new 3,5-bis[alkenyl]pyrazoles **6** is observed in ethanol, while the pyranopyrazoles **7** are obtained as major products (see experimental) in boiling acetic acid. The yields are strongly substituent dependent. In the case of **4e** ($R^1=R^2=CH_3$, $R^3=H_3C-CH=CH$), no appreciable amount of the pyrazole **6e** can be formed under conditions found satisfactory for its homologue **4d** ($R^1=H$, $R^2=CH_3$, $R^3=H_3C-CH=CH$).



	R^1	R^2	R^3
a	H	H	C_6H_5
b	H	CH_3	C_6H_5
c	CH_3	CH_3	C_6H_5
d	H	CH_3	*(E)*-$H_3C-CH=CH-$
e	CH_3	CH_3	*(E)*-$H_3C-CH=CH-$

Scheme **B**

The reaction proceeds by a nucleophilic attack at the C-4 carbon atom of the dihydropyrones **4** to give the phenylhydrazones **5** as intermediates, which rearrange with ring-opening of the dihydropyrones and recyclization to afford **6**, in ethanol. In acetic acid, the phenylhydrazones **5** resist ring opening and yield **7** (Scheme **B**).



Scheme **C**

The intermediate phenylhydrazones **5** have been isolated under mild conditions. When **5b** is heated in ethanol in the presence of a catalytic amount of phenylhydrazine, it gives **6b**, whereas **7b** is obtained in refluxing acetic acid. Chemical evidence for the structure **7** is provided by an alternative synthesis of **7c** and **7e**, recently reported from our laboratory[6].

The position of the *N*-phenyl group in compounds **6** is confirmed by the intramolecular cyclization of **6a** and **6b** to 2-alkenyl-3-ethoxycarbonyl-5-phenyl-4,5-dihydro-pyrazolo[1,5-*a*]quinoline **8a** and **8b** in polyphosphoric acid. Compound **6c** affords, under the same conditions, a mixture of **8c** and **9** (Scheme **C**). Besides the chemical transformations carried out to prove the structure of the compounds prepared, they have been also identified by their spectral and microanalytical data (Table).

Ethyl (*E*)-3-oxo-4-hexenoate (**1**; $R^1=H$, $R^2=CH_3$)[7]; ethyl 5-methyl-3-oxo-4-hexenoate (**1**; $R^1=R^2=CH_3$)[8]; and ethyl (*E*)-3-oxo-5-phenyl-4-pentenoate **(3)**[9] are prepared as previously described.

5-Ethoxycarbonyl-6-styryl or -6-(1,3-pentadienyl)-2,3-dihydro-4-pyrones 4; General Procedure:

To a stirred suspension of magnesium ethoxide (5.7 g, 0.05 mol) in dry toluene (150 ml) is added the γ,δ-unsaturated β-keto ester **1** (or **3** in the case of **4a**) (0.05 mol). The mixture is stirred and heated to reflux for 2 h. After cooling to 0–5°C, the ethoxymagnesio-enolate is diluted with acetonitrile (100 ml) and a solution of the acyl chloride **2** (acryloyl chloride in the case of **4a**) (0.05 mol) in acetonitrile (50 ml) is added dropwise with efficient stirring. The mixture is allowed to stand at room temperature for 3 h and is then poured into 10% hydrochloric acid (200 ml). The organic layer is separated and the aqueous layer is extracted with ether (100 ml). The combined extracts are washed with a saturated sodium hydrogen carbonate solution (2 × 50 ml), water (2 × 50 ml), dried with sodium sulfate, and evaporated. The crude pyrone **4** is recrystallized from a suitable solvent or distilled under reduced pressure (Table). Analytical samples are obtained by chromatography on silica gel with ether as eluent.

5-Ethoxycarbonyl-6-styryl or -6-(1,3-pentadienyl)-4-phenylhydrazono-2,3-dihydro-4*H*-pyrans 5; General Procedure:

A mixture of the 5-ethoxycarbonyl-6-styryl or -6-(1,3-pentadienyl)-2,3-dihydro-4-pyrone **4** (0.01 mol) and phenylhydrazine (1.08 g, 0.01 mol)

Table. Compounds **4–9** prepared

Product No.	Yield [%]	m.p. [°C] (solvent) or b.p. [°C]/torr	Molecular formula[a] Lit. m.p. [°C]	I.R. ($CHCl_3$) $\nu_{C=O}$ [cm^{-1}]	U.V. (C_2H_5OH) λ_{max} [nm] (ε)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4a	63	89–90° (cyclohexane)	$C_{16}H_{16}O_4$ (272.3)	1675 1730	340 (23100)	1.40 (t, 3H, J=7 Hz); 2.70 (t, 2H, J=6 Hz); 4.40 (q, 2H, J=7 Hz); 4.65 (t, 2H, J=6 Hz); 7.10 (d, 1H, J=16 Hz); 7.3–7.7 (m, 6H)
4b	60	86–87° (methanol)	$C_{17}H_{18}O_4$ (286.3)	1670 1730	340 (27200)	1.39 (t, 3H, J=7 Hz); 1.57 (d, 3H, J=6 Hz); 2.57 (d, 2H, J=8 Hz); 4.39 (q, 2H, J=7 Hz); 4.67 (m, 1H); 7.07 (d, 1H, J=16 Hz); 7.3–7.7 (m, 6H)
4c	80	64–66° (C_2H_5OAc/hexane, 3:7)	$C_{18}H_{20}O_4$ (303.3)	1675 1730	340 (25800)	1.39 (t, 3H, J=7 Hz); 1.54 (s, 6H); 2.62 (s, 2H); 4.37 (q, 2H, J=7 Hz); 7.12 (d, 1H, J=16 Hz); 7.3–7.7 (m, 6H)
4d	57	165–170°/0.5	$C_{14}H_{18}O_4$ (250.3)	1670 1730	334 (21900)	1.34 (t, 3H, J=7 Hz); 1.51 (d, 3H, J=6 Hz); 1.8–2.0 (m, 3H); 2.52 (d, 2H, J=8 Hz); 4.32 (q, 2H, J=7 Hz); 4.62 (m, 1H); 5.9–6.7 (m, 3H); 6.9–7.7 (m, 1H)
4e	50	162–165°/0.5	$C_{15}H_{20}O_4$ (264.3)	1670 1730	334 (23500)	1.38 (t, 3H, J=7 Hz); 1.48 (s, 6H); 1.8–2.0 (m, 3H); 2.57 (s, 2H); 4.32 (q, 2H, J=7 Hz); 5.9–6.8 (m, 3H); 6.9–7.7 (m, 1H)
5a	57	155° (dec.) (acetonitrile)	$C_{22}H_{22}N_2O_3$ (362.4)	1730	302 (18400) 400 (31400)	1.45 (t, 3H, J=7 Hz); 2.66 (t, 2H, J=6 Hz); 4.32 (t, 2H, J=6 Hz); 4.50 (q, 2H, J=7 Hz); 6.6–7.6 (m, 13H)
5b	47	185° (dec.) (acetonitrile)	$C_{23}H_{24}N_2O_3$ (376.4)	1730	310 (16900) 382 (22400)	1.44 (t, 3H, J=7 Hz); 1.51 (d, 3H, J=6 Hz); 2.19 (dd, 1H, J=16 Hz, 11 Hz); 2.79 (dd, 1H, J=16 Hz, 3 Hz)[b]; 4.25 (m, 1H); 4.46 (q, 2H, J=7 Hz); 6.6–7.6 (m, 13H)
5c	18	181° (dec.) (acetonitrile)	$C_{24}H_{26}N_2O_3$ (390.4)	1730	302 (17700) 400 (30700)	1.43 (t, 3H, J=7 Hz); 1.46 (s, 6H); 2.52 (s, 2H); 4.47 (q, 2H, J=7 Hz); 6.7–7.6 (m, 13H)
5d	30	125° (dec.) (ethanol)	$C_{20}H_{24}N_2O_3$ (340.4)	1725	300 (19300) 384 (21000)	1.43 (t, 3H, J=7 Hz); 1.46 (d, 3H, J=7 Hz); 1.96 (d, 3H, J=5 Hz); 2.16 (dd, 1H, J=16 Hz, 11 Hz); 2.76 (dd, 1H, J=16 Hz, 3 Hz)[b]; 4.25 (m, 1H); 4.42 (q, 2H, J=7 Hz); 5.7–6.4 (m, 3H); 6.6–7.5 (m, 7H)
6a	72	74–75° (ethanol)	$C_{22}H_{20}N_2O_2$ (344.4)	1710	280 (15400) 260 (16300)	1.40 (t, 3H, J=7 Hz); 4.39 (q, 2H, J=7 Hz); 5.41 (dd, 1H, J=11 Hz, 2 Hz); 6.16 (dd, 1H, J=18 Hz, 2 Hz); 6.70 (d, 1H, J=16 Hz); 7.29 (dd, 1H, J=18 Hz, 11 Hz); 7.30 (s, 5H); 7.35 (d, 1H, J=16 Hz); 7.49 (s, 5H)
6b	66	111–112° (ethanol)	$C_{23}H_{22}N_2O_2$ (358.4)	1710	280 (15200) 265 (16200)	1.41 (t, 3H, J=7 Hz); 1.92 (d, 3H, J=5 Hz); 4.41 (q, 2H, J=7 Hz); 6.3–7.2 (m, 3H); 7.34 (s, 5H); 7.37 (d, 1H, J=16 Hz); 7.52 (s, 5H)
6c	37	142–143° (ethanol)	$C_{24}H_{24}N_2O_2$ (372.4)	1710	285 (16000) 268 (16600)	1.37 (t, 3H, J=7 Hz); 1.99 (s, 3H); 2.10 (s, 3H); 4.37 (q, 2H, J=7 Hz); 6.65 (m, 1H); 6.75 (d, 1H, J=16 Hz); 7.32 (s, 5H); 7.37 (d, 1H, J=16 Hz); 7.52 (s, 5H)
6d	47	91–92° (ethanol)	$C_{20}H_{22}N_2O_2$ (322.4)	1720	290 (18400) 250 (25600)	1.40 (t, 3H, J=7 Hz); 1.76 (d, 3H, J=6 Hz); 1.90 (d, 3H, J=5 Hz); 4.40 (q, 2H, J=7 Hz); 5.4–6.9 (m, 5H); 7.2–7.6 (m, 6H)
7a	50	181–182° (ethanol)	$C_{20}H_{16}N_2O_2$ (316.3)	1670	360 (33300) 246 (20100)	3.00 (t, 2H, J=6 Hz); 4.61 (t, 2H, J=6 Hz); 7.0–7.9 (m, 10H); 7.9–8.1 (m, 2H)

Table. (Continued)

Product No.	Yield [%]	m.p. [°C] (solvent) or b.p. [°C]/torr	Molecular formula[a] Lit. m.p. [°C]	I.R. ($CHCl_3$) $\nu_{C=O}$ [cm^{-1}]	U.V. (C_2H_5OH) λ_{max} [nm] (ε)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
7b	45	187–188° (ethanol)	$C_{21}H_{18}N_2O_2$ (330.3)	1670	360 (33300) 246 (20300)	1.62 (d, 3H, J=6 Hz); 2.5–3.1 (m, 2H)[b]; 4.62 (m, 1H); 7.0–7.9 (m, 10H); 7.9–8.1 (m, 2H)
7c	43	167–168° (ethanol)	167–168°[6]	1670	360 (31000) 246 (18900)	1.58 (s, 6H); 2.90 (s, 2H); 7.2–7.9 (m, 10H); 7.9–8.1 (m, 2H)
7d	68	164–165° (ethanol)	$C_{18}H_{18}N_2O_2$ (294.3)	1670	350 (34700) 254 (17100)	1.59 (d, 3H, J=6 Hz); 1.92 (d, 3H, J=5 Hz); 2.5–3.1 (m, 2H)[b]; 4.59 (m, 1H); 5.9–6.6 (m, 2H); 6.9–7.7 (m, 5H); 7.8–8.2 (m, 2H)
7e	65	136–137° (ethanol)	136–137°[6]	1670	350 (31000) 254 (15300)	1.55 (s, 6H); 1.92 (d, 3H, J=5 Hz); 2.85 (s, 2H); 6.2–6.5 (m, 2H); 7.1–7.6 (m, 5H); 7.9–8.1 (m, 2H)
8a	80	114–115° (acetonitrile)	$C_{22}H_{20}N_2O_2$ (344.4)	1700	280 (13700) 264 (11800)	1.34 (t, 3H, J=7 Hz); 3.3–3.9 (m, 2H)[b]; 4.1–4.4 (m, 3H); 5.46 (dd, 1H, J=11 Hz, 2 Hz); 6.30 (dd, 1H, J=18 Hz, 2 Hz); 6.9–7.5 (m, 9H); 8.0–8.2 (m, 1H)
8b	77	129–130° (ethanol)	$C_{23}H_{22}N_2O_2$ (358.4)	1700	290 (14800) 270 (13400)	1.32 (t, 3H, J=7 Hz); 1.95 (d, 3H, J=5 Hz); 3.3–3.9 (m, 2H)[b]; 4.1–4.5 (m, 3H); 6.7–7.6 (m, 10H); 8.0–8.2 (m, 1H)
8c	15	126–127° (ethanol)	$C_{24}H_{24}N_2O_2$ (372.4)	1700	286 (15500) 270 (15500)	1.32 (t, 3H, J=7 Hz); 2.01 (s, 3H); 2.22 (s, 3H); 3.3–3.9 (m, 2H)[c]; 4.1–4.5 (m, 3H); 6.78 (s, 1H); 6.9–7.7 (m, 8H); 7.9–8.1 (m, 1H)
9	76	167–168° (ethanol)	$C_{22}H_{20}N_2O_2$ (344.4)	1720	278 (14300)	1.51 (s, 3H); 1.55 (s, 3H); 3.04 (s, 2H); 3.3–3.9 (m, 2H)[b]; 6.9–7.6 (m, 8H); 7.9–8.1 (m, 1H)

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.24, N ±0.24.

[b] AB part of ABX system.

in ethanol (25 ml, or 10 ml in the case of **4d**) is refluxed for 20 min (or 10 min in the case of **4a**). The mixture is then allowed to stand at room temperature for 1 h and cooled to 0–5°C. The precipitated product is isolated by suction and washed with ether (20 ml); the product is pure by T.L.C. analysis on silica gel (PF 254) using hexane/ethyl acetate (4:1) as eluent. Analytical samples are obtained by recrystallization from a suitable solvent (Table). Attempts to isolate the phenylhydrazone of **4e** in appreciable yield failed.

4-Ethoxycarbonyl-1-phenyl-3,5-bis[alkenyl]pyrazoles 6; General Procedure:

A mixture of the 4-pyrone **4** (0.01 mol) and phenylhydrazine (1.62 g, 0.015 mol) in ethanol (60 ml) is refluxed for the appropriate time [4 h **(4a)**, 8 h **(4b)**, 16 h **(4c–e)**]. The solvent is then evaporated and the residue is dissolved in dichloromethane (50 ml). The organic phase is washed with 10% hydrochloric acid (2 × 20 ml), water (2 × 20 ml), dried with sodium sulfate, and then evaporated under reduced pressure to give the crude pyrazoles **6a–e**, which are further purified by column chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent.

In the case of **4e**, the corresponding 3,5-bis[alkenyl]-1-phenylpyrazole **6e** ($R^1=R^2=CH_3$) is identified only by its ^{1}H-N.M.R. spectrum; yield: ~10%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.41 (t, 3H, J=7 Hz); 1.77 (d, 3H, J=6 Hz); 1.96 (s, 3H); 2.06 (s, 3H); 4.31 (q, 2H, J=7 Hz); 5.4–7.0 (m, 4H); 7.2–7.6 ppm (m, 6H).

4-Ethoxycarbonyl-1-phenyl-3-(1-propenyl)-5-styrylpyrazole (6b) from 5b:

A mixture of **5b** (1.88 g, 5 mmol) and a small amount of phenylhydrazine (0.5 g) in ethanol (40 ml) is refluxed for 8 h. The mixture is then worked up as described above to give **6b**; yield: 1.4 g (78%).

3-Oxo-2-phenyl-6,7-dihydro-2*H*-pyrano[4,3-c]pyrazoles 7; General Procedure:

A mixture of the 4-pyrone **4** (0.01 mol) and phenylhydrazine (1.08 g; 0.01 mol) in acetic acid (100 ml) is refluxed for 1 h. The mixture is then evaporated under reduced pressure and the residue is dissolved in dichloromethane (50 ml). The organic phase is successively washed with 5% sodium hydrogen carbonate solution (2 × 10 ml), water (2 × 10 ml), dried with sodium sulfate, concentrated to ~5 ml, and chromatographed through a column (40 mm × 20 cm) of silica gel (110 g) using dichloromethane as eluent to give first **6** as the minor product and then the major product **7** as red crystals. Analytical samples of **7** are obtained by recrystallization from ethanol.

Product	Fraction collected [ml]	Yield [g]	Yield [%]
6a	300→ 475	0.15	4
7a	525→1315	1.60	50
6b	250→ 550	0.90	25
7b	600→1300	1.50	45
6c	250→ 550	0.10	3
7c	600→1300	1.50	43
6d	450→ 750	0.40	12
7d	800→1200	2.00	68
6e	300→ 400	0.20	6
7e	450→1050	2.00	65

6-Methyl-3-oxo-2-phenyl-4-styryl-6,7-dihydro-2*H*-pyrano[4,3-c]pyrazole (7b) from 5b:

A solution of **5b** (3 g, 8 mmol) in acetic acid (95 ml) is refluxed for 1 h. The mixture is then worked up as described above to give, after column chromatography, **6b**; yield: 1.1 g (38%) and **7b**; yield: 1.28 g (48%).

5-Phenyl-4,5-dihydropyrazolo[1,5-a]quinoline Derivatives 8a–c and 9; General Procedure:

A mixture of pyrazole **6** (2 g) in polyphosphoric acid (20 ml) is heated with stirring at 80 °C for 3 h. The mixture is then poured into ice/water (200 g) and extracted with chloroform (3 × 50 ml). The combined extracts are washed with water (20 ml), dried with sodium sulfate, and rotary evaporated to give crude **8a, b**, or a mixture of **8c** and **9** in the case of the pyrazole **6c**. Separation of **8c** and **9** is performed by column chromatography on silica gel (110 g) using hexane/ethyl acetate 1:1 as eluent; **8c** is first eluted [fraction 150–270 ml; yield: 300 mg (15%)] and then **9** [fraction 320–620 ml; yield: 1.4 g (76%)].

Received: May 26, 1983

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