2-(2-Naphthyl)benzo[*b*]thiophen. Part IV.[1] Further Aspects of Electrophilic Substitution, and Ring Closures to yield Pentacyclic Derivatives

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Electrophilic reagents attack 2-(2-naphthyl)benzo[*b*]thiophen at the free position on the thiophen ring, but there does not seem to be any strongly preferred position for further electrophilic substitution. Attempts to decarboxylate 2-(1-nitro-2-naphthyl)benzo[*b*]thiophen-3-carboxylic acid produced internal nucleophilic displacement of the nitro-group to yield a pentacyclic lactone. A pentacyclic ketone and a pentacyclic phenol have been prepared by Friedel–Crafts ring closures between the benzo[*b*]thiophen and naphthalene ring systems. A direct synthesis of the title compound is reported.

THESE researches were begun [2,3] when it seemed that 2-(2-naphthyl)benzo[*b*]thiophen (1) might become available on a large scale. Commercial considerations have not led to this result, and in a final paper we report some further findings which are worthy of record.

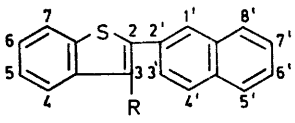
Nitration with a limited quantity of nitric acid gave [3] the 3-mononitro-compound (2), and further nitration of this, or treatment of the initial heterocycle with an excess of nitrating agent, gave a mixture of dinitro-compounds, m.p.s 183 and 232°. The material of m.p. 232° has been identified as the 3,8′-compound (12) by degradation and ultimate comparison with an authentic sample of methyl 8-nitro-2-naphthoate. It then seemed that the second product, m.p. 183°, could be either the

[1] Part III, A. H. Lamberton and J. E. Thorpe, *J. Chem. Soc.* (*C*), 1968, 2028.

[2] A. H. Lamberton and P. T. McGrail, *Chem. and Ind.*, 1961, 986.

[3] A. H. Lamberton and P. T. McGrail, *J. Chem. Soc.*, 1963, 1776.

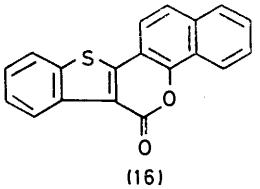
1',3- or the 3,5'-compound, since (*a*) the 3-bromo-derivative has been shown [1] to undergo nitration in the 1'-position, but (*b*) deactivation by the benzo[*b*]thienyl moiety could be expected to give the 3,5'- as a companion to the 3,8'-dinitro-compound. We sought to explore these possibilities by nitration of the acid (3), followed by decarboxylation and then, in parallel, nitration or bromination to give materials likely to have identical



(1) R = H
(2) R = NO_2
(3) R = CO_2H
(4) R = CO_2Me
(5) R = CHO
(6) R = CN
(7) R = Me
(8) R = CH_2OH
(9) R = CH:CH·CO_2H
(10) R = COCl
(11) R = CH_2·CO_2H

positions (3,*x'*) of substitution; these we felt would be usefully comparable with the dinitro-compounds, and with the known bromo-nitro-compound (13). This approach failed partly through practical difficulties in the nitration of the carboxylic acid, but could not in any case have been successful for an NO_2 group in the 1'-position, by reason of the rare but not unprecedented [4] nucleophilic substitution of the nitro-group by the carboxylate anion at the stage of attempted decarboxylation. The nitro-acid (14), prepared indirectly from (13), gave the pentacyclic lactone (16) in place of the desired mononitro-compound (15).

Nitration of the ester (4) gave mixtures from which one dinitro- and two mononitro-compounds were



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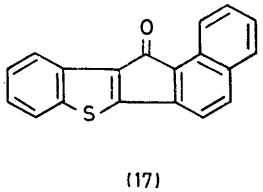

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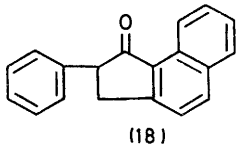

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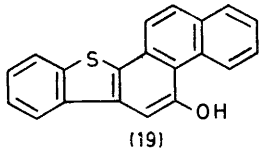
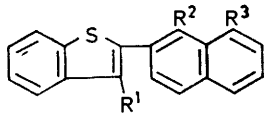


(19)

isolated, but only one of these three was fully characterised. Nitration of the formyl or cyano-derivative [(5) or (6)] likewise gave mixtures, and we conclude that, once the 3-position is occupied, there is no strongly preferred site for further electrophilic substitution.

Acetylation of the initial heterocycle was in our hands unfruitful, giving mixtures; but formylation with dichloromethyl butyl ether [5] gave the aldehyde (5) in excellent yield. This was characterised by oximation and dehydration to the known cyanide (6); it could be reduced to yield methyl (7) or hydroxymethyl (8) compounds and underwent a Knoevenagel reaction to give the *trans*-acrylic acid (9).

Ring closure by the reaction of tin(IV) chloride on the acid chloride (10) gave the ketone (17), identified by



(12) $R^1 = R^3 = NO_2$, $R^2 = H$
(13) $R^1 = Br$, $R^2 = NO_2$, $R^3 = H$
(14) $R^1 = CO_2H$, $R^2 = NO_2$, $R^3 = H$
(15) $R^1 = R^3 = H$, $R^2 = NO_2$

reductive desulphurisation to 2,3-dihydro-2-phenylbenz[*e*]inden-1-one (18). Arndt–Eistert treatment of the 3-carboxylic acid gave the homo-acid (11) which yielded, similarly, a phenolic derivative (19) of a ring system recently prepared [6] by photocyclisation. Structures (17) and (19) are based on the assumption that the C-1' and C-3 become members of the new ring; alternatives (*e.g.* C-3 and C-3') seem highly unlikely, though this (3,3') ring system has been produced by photocyclisation,[6] and by a diene synthesis from 1,4-naphthoquinone.[7]

Since 2-(2-naphthyl)benzo[*b*]thiophen will not be available as a commercial by-product, it seems worthwhile to report a practicable synthesis. The method of Murthy and Tilak [8] can be simplified in the earlier stages, but we were unable to improve the yield (13%) in the final stage of ring closure with rearrangement [β-naphthacyl phenyl sulphide ⟶ (1)]. A direct synthesis in reasonable yield has been achieved by the action of halogenonaphthalenes on 2-benzo[*b*]thienyllithium; this seems to involve a naphthyne intermediate, since α-chloronaphthalene could be used in place of the less accessible β-halogenonaphthalenes.

EXPERIMENTAL

N.m.r. spectra were determined with a Varian HA 100 spectrometer, i.r. spectra with a Perkin-Elmer Infracord 137 instrument, and mass spectra with an A.E.I. MS 12 spectrometer. The phrase 'worked up' implies washing, drying (Na_2SO_4), and evaporation (under reduced pressure) of solutions as required. Light petroleum was of b.p. 60—80° unless otherwise specified. Materials recorded as identical were proved to be so by m.p., mixed m.p., and comparison of i.r. spectra.

[4] D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 1962, 4579.
[5] A. Rieche, H. Gross, and E. Höft, *Chem. Ber.*, 1960, **93**, 88.
[6] A. Croisy, P. Jacquignon, and F. Perin, *J.C.S. Chem. Comm.*, 1975, 106.
[7] W. Davies and Q. N. Porter, *J. Chem. Soc.*, 1957, 4961.
[8] T. S. Murthy and B. D. Tilak, *J. Sci. Ind. Res., India*, 1960, **19B**, 395.

Preparation of the Dinitro-compounds.—A suspension of powdered 2-(2-naphthyl)benzo[*b*]thiophen (10 g) was stirred in acetic acid (50 ml) at 100 °C, and a mixture of fuming nitric acid (5 ml) with acetic acid (5 ml) was added dropwise over 1 h. After a further 3 h at 100 °C the solution was cooled to yield a solid (A), which was collected, recrystallised (AcOH), and washed successively with acetic acid, water, ethanol, and ether. The product, after further recrystallisations from acetic acid, yielded 3-*nitro*-2-(8-*nitro*-2-*naphthyl*)*benzo*[b]*thiophen* (3.9 g) as yellow needles, m.p. 232°; $\nu_{max.}$ (Nujol) 1 520 and 1 490 cm^{-1} (different NO_2 groups) (Found: C, 61.6; H, 2.9; N, 7.8; S, 9.0. $C_{18}H_{10}N_2O_4S$ requires C, 61.7; H, 2.9; N, 8.0; S, 9.2%).

The filtrates from the separation and first recrystallisation of the solid (A) were combined and reduced in volume by evaporation *in vacuo*; product (B) was then precipitated by the addition of water. Collection and crystallisation (ethanol) of (B) yielded 3-nitro-2-(*x*-nitro-2-naphthyl)-benzo[*b*]thiophen (2.5 g) as yellow prisms turning brown on exposure to light, m.p. 183°; $\nu_{max.}$ (Nujol) 1 515 and 1 500 cm^{-1} (different NO_2 groups) (Found: C, 61.7; H, 3.1; N, 8.0; S, 9.4%).

Nitration of 3-nitro-2-(2-naphthyl)benzo[*b*]thiophen gave, in similar fashion, the same pair of dinitro-compounds, which could also be separated by chromatography on alumina.

Identification of 3-*Nitro*-2-(8-*nitro*-2-*naphthyl*)*benzo*[b]*thiophen*.—Chromium trioxide (2.5 g) in 80% acetic acid (5 ml) was added dropwise to a hot solution of the dinitro-compound (0.5 g) in acetic acid (37 ml), and refluxing was

g) as creamy yellow rhombs, m.p. 250—252° (decomp.) (from acetic acid), $\nu_{max.}$ (Nujol) 1 675 (C=O) and 1 530 cm^{-1} (NO_2) (Found: C, 65.7; H, 3.2; N, 4.1. $C_{19}H_{11}NO_4S$ requires C, 65.3; H, 3.2; N, 4.0%).

The intermediate amide could be prepared by refluxing a solution of the nitro-cyanide (0.1 g) in acetic acid (5 ml) and sulphuric acid (85% w/w; 10 g) for 10 min and working up to give 2-(1-*nitro*-2-*naphthyl*)*benzo*[b]*thiophen*-3-*carboxamide* (0.03 g) as a yellow microcrystalline powder, m.p. 222° (decomp.) (from moist acetic acid); $\nu_{max.}$ (Nujol) 3 150 and 3 410 (NH), 1 670 (C=O), and 1 515 cm^{-1} (NO_2) (Found: C, 65.6; H, 3.5; N, 8.0; S, 9.4. $C_{19}H_{12}N_2O_3S$ requires C, 65.5; H, 3.5; N, 8.0; S, 9.2%).

Attempted Decarboxylation of the Nitro-acid (14), *leading to the Lactone* (16).—The acid (14) (0.1 g) was suspended in quinoline (2 ml) and heated for 1 h in an oil-bath at 180 °C. Cooling and acidification (2M-HCl) gave a precipitate which yielded [1]*benzothieno*[3,2-c]*naphtho*[2,1-e]*pyran*-6-*one* (0.03 g) as a bright yellow microcrystalline powder, m.p. 258—259° (from toluene); $\nu_{max.}$ (Nujol) 1 710 cm^{-1} (C=O) (Found: C, 75.6; H, 3.4%; M^+, 302. $C_{19}H_{10}O_2S$ requires C, 75.5; H, 3.3%; *M*, 302). Heating the nitro-acid alone (oil-bath at 270—290 °C) likewise produced the lactone; t.l.c. showed the cooled melt to contain both this and unchanged initial material. Elution with benzene from a silica gel column gave a fraction enriched in the lactone and this could be isolated, identical with the material previously prepared, by crystallisation of the enriched fraction from ethyl acetate.

Preparation of the Ester (4) *and of Sulphones from Com-*

N, 3.9; S, 8.8%). The position of nitration was identified by hydrolysis to the known nitro-acid (14).

Nitration under similar conditions but on a larger scale gave mixtures which were less easily separated. Preparative t.l.c. on silica (benzene) showed the above nitro-ester, m.p. 167°, to be still the major product, but accompanied by at least one distinct mononitro-ester, yellow needles, m.p. 180° (from benzene–light petroleum), $\nu_{max.}$ (Nujol) 1 700 (C=O) and 1 520 cm^{-1} (NO_2); M^+ 363 ($C_{20}H_{13}NO_4S$); and a dinitro-ester as a light yellow microcrystalline powder, m.p. 228° (from toluene), $\nu_{max.}$ (Nujol) 1 690 (C=O), 1 525, and 1 505 cm^{-1} (different NO_2 groups), M^+ 408 ($C_{20}H_{12}N_2O_6S$).

Preparation and Identification of the Aldehyde (5).—Titanium tetrachloride (5 ml) was added to a stirred suspension of 2-(2-naphthyl)benzo[*b*]thiophen (1 g) in carbon disulphide (25 ml) at 0 °C, and dichloromethyl butyl ether [5] (1 g) was then added dropwise. The mixture was stirred for 2 h at room temperature, then the complex was decomposed with 2M-HCl, and organic material extracted with chloroform. The extract was worked up to give a mixture separable by chromatography on a silica gel column. Elution with carbon tetrachloride gave a fraction enriched in the initial heterocycle; subsequent elution with 95% ethanol, followed by chloroform, gave a fraction enriched in the aldehyde. Crystallisation of the latter fraction yielded 2-(2-*naphthyl*)*benzo*[b]*thiophen*-3-*carbaldehyde* (0.93 g) as cream-coloured needles, m.p. 146—147° (from propan-2-ol); $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1} (C=O); τ($CDCl_3$) −0.10 (1 H, s, CHO) (Found: C, 79.4; H, 4.1. $C_{19}H_{12}OS$ requires C, 79.1; H, 4.2%).

Attempts to oxidise the aldehyde smoothly to the corresponding carboxylic acid were unsuccessful, and the structure was determined as follows. The aldehyde (1 g) was refluxed for 1.5 h with hydroxylamine hydrochloride (1 g) in ethanol (10 ml) and pyridine (1 ml), and worked up to yield the anti-*oxime* (0.80 g) as rhombs, m.p. 156° (from methanol) (Found: C, 75.3; H, 4.6; N, 4.3. $C_{19}H_{13}NOS$ requires C, 75.2; H, 4.3; N, 4.6%). The oxime (0.2 g) was refluxed for 1 h with acetic acid (2 ml) and acetic anhydride (2 ml), and treated with water (5 ml). The precipitate was collected, dissolved in chloroform, and worked up to yield a mixture separable by chromatography on a silica gel column: elution with carbon tetrachloride–benzene (50 : 50 v/v) gave a fraction which was crystallised from toluene–light petroleum to yield 2-(2-naphthyl)benzo[*b*]thiophen-3-carbonitrile (0.06 g), identical with authentic material.[3]

Derivatives of the Aldehyde (5).—A mixture of the aldehyde (0.5 g) with potassium hydroxide (0.24 g), diethylene glycol (1 ml), and hydrazine hydrate (90%; 0.2 ml) was heated in an oil-bath (Huang-Minlon conditions) and set aside overnight. Addition of benzene gave a yellow precipitate, which finally yielded the *azine* (0.06 g) as yellow felted needles, m.p. 305—306° (from dimethylformamide); $\nu_{max.}$ (Nujol) 1 605 cm^{-1} (C=N) (Found: C, 79.5; H, 4.4; N, 4.9; S, 11.4%; M^+, 572. $C_{38}H_{24}N_2S_2$ requires C, 79.7; H, 4.2; N, 4.9; S, 11.2%; *M*, 572). Acidification of the benzene filtrate (conc. HCl) gave a further precipitate which, together with a chloroform extract of the residual aluminium hydride (0.1 g) in boiling ether (10 ml), and refluxing was continued for 1.5 h. Cooling, treatment with ethyl acetate, removal of insoluble salts by filtration, and work-up of the filtrate gave 3-*hydroxymethyl*-2-(2-*naphthyl*)-*benzo*[b]*thiophen* (0.03 g) as plates, m.p. 126—127° (from benzene–light petroleum) (Found: C, 78.3; H, 5.0; S, 10.8. $C_{19}H_{14}OS$ requires C, 78.6; H, 4.9; S, 11.0%).

A mixture of the aldehyde (0.5 g), malonic acid (0.4 g), pyridine (2 ml), and morpholine (0.1 ml) was heated for 1 h on a steam-bath, refluxed for 5 min, cooled, and poured into dilute hydrochloric acid. The resultant precipitate was collected, and unchanged initial aldehyde (*ca.* 0.14 g) extracted by refluxing for 10 min with benzene (20 ml). The residual material was collected from the hot benzene and crystallised to give (E)-3-{2-(2-*naphthyl*)-3-*benzo*[b]-*thienyl*}*acrylic acid* (0.18 g), as cream-coloured plates, m.p. 246—247° (from propan-1-ol); $\nu_{max.}$ (Nujol) 1 675 cm^{-1} (C=O); τ [$(CD_3)_2SO$] 3.40 (1 H, d, *J* 16 Hz, $=CH\cdot CO_2$) (Found: C, 76.2; H, 4.6; S, 9.8. $C_{21}H_{14}O_2S$ requires C, 76.3; H, 4.3; S, 9.7%). The n.m.r. doublet from the inner CH of the double bond was masked by the aromatic proton signals.

Preparation and Identification of the Ketone (17).—2-(2-Naphthyl)benzo[*b*]thiophen-3-carboxylic acid [3] (2.0 g) in benzene (60 ml) was converted into the acid chloride by treatment (mild warming for 1.25 h, and final reflux for 5 min) with phosphorus pentachloride (3.5 g). The resultant solution was cooled nearly to crystallisation of the benzene, tin(IV) chloride (14 ml) in benzene (14 ml) was added, and the mixture was set aside for 0.25 h at the same temperature (ice–water cooling). The complex was then destroyed with a little ice, concentrated hydrochloric acid (50 ml), and a few drops of ether to give a crimson organic layer which was separated, filtered, and worked up to yield *naphtho*[2′,1′:3,4]*cyclopenta*[1,2-b][1]*benzothiophen*-12-*one* (0.60 g) as golden needles, m.p. 198—199° (from propan-1-ol); $\nu_{max.}$($CHCl_3$) 1 695 cm^{-1} (C=O); τ ($CDCl_3$) 1.23 (1 H, d, *J* 8.5 Hz with additional fine splitting) and 1.88—2.92 (9 H, m) (Found: C, 79.7; H, 3.8; S, 11.2%; M^+, 286. $C_{19}H_{10}OS$ requires C, 79.7; H, 3.5; S, 11.2%; *M*, 286). Acidification of the sodium hydroxide wash of the crimson organic solution gave the initial 3-carboxylic acid (crude, 0.6 g).

A solution of the ketone (17) (0.4 g) in ethanol (30 ml) was refluxed with Raney nickel (*ca.* 20 g of alloy ⟶ type [12] W-2) for 0.25 h. Removal of the nickel, evaporation, and crystallisation alternately from light petroleum (b.p. 80—100°) and 95% ethanol gave 2,3-dihydro-2-phenylbenz[*e*]-inden-1-one (0.21 g) as needles, m.p. 118°, identical with material prepared by an independent synthesis; $\nu_{max.}$(KBr) 1 690 cm^{-1} (C=O), τ ($CDCl_3$) 1.81—2.95 (11 H, m, ArH) and 5.95—6.87 (3 H, m) (Found: C, 88.6; H, 5.4%; M^+, 258. Calc. for $C_{19}H_{14}O$: C, 88.4; H, 5.5%; *M*, 258). Datta and Bardhan [13] prepared this compound from β-2-naphthyl-α-phenylpropionic acid by formation of the acid chloride and Friedel–Crafts condensation. Our comparison sample, prepared from the same acid in the same way except for the use of tin(IV) chloride in place of aluminium chloride,

chloride (2.0 g), then more thionyl chloride (1.3 g) was added and refluxing was continued for 1.2 h. Evaporation under reduced pressure left an oil, converted by addition of ether (10 ml) into a suspension of the crude (solid) acid chloride (10). This suspension was added to ethereal diazomethane [obtained [10] from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (10 g)] at 0 °C, and the mixture was set aside at room temperature for 3.25 h. Evaporation and crystallisation from benzene–light petroleum (1 : 2 v/v) (charcoal) gave the *diazo-ketone* (10; CHN_2 in place of Cl) (1.75 g) as pale yellow needles, m.p. 119—120° (decomp.); $\nu_{max.}$($CHCl_3$) 3 000 (C–H), 2 100 ($-\overset{+}{N}\equiv N$), and 1 600 cm^{-1} (C=O) (Found: C, 73.5; H, 4.0; N, 8.5. $C_{20}H_{12}N_2OS$ requires C, 73.1; H, 3.7; N, 8.5%).

A solution of the diazo-ketone (1.5 g) in dioxan (15 ml) was added dropwise to a hot solution of sodium thiosulphate (1.5 g) and anhydrous sodium carbonate (2.0 g) in water (30 ml) containing freshly precipitated silver oxide [from silver nitrate (5 g)], and heating (steam-bath) was continued for 18 h. After cooling and filtration, the filtrate was acidified (2M-hydrochloric acid) and extracted with ether to give, on work-up, {2-(2-*naphthyl*)-3-*benzo*[b]-*thienyl*}*acetic acid* (1.0 g) as yellowish brown needles, m.p. 176—177° (crystallisation by dissolution in hot benzene, and addition of 2 volumes of cold light petroleum); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1} (C=O), τ (Me_2CO) 1.61—2.59 (11 H, m, ArH) and 5.94 (2 H, s, CH_2) (Found: C, 75.2; H, 4.1; S, 10.3. $C_{20}H_{14}O_2S$ requires C, 75.4; H, 4.4; S, 10.1%). {2-(2-Naphthyl)-3-benzo[*b*]thienyl}acetic acid (0.2 g) was converted into the acid chloride and cyclised essentially as described for the ketone (17) except for the use of sodium hydrogen carbonate in place of sodium hydroxide in the washing procedures, to yield *benzo*[b]*phenanthro*[2,1-d]-*thiophen-5-ol* (0.08 g) as cream-coloured felted needles from toluene (charcoal), m.p. *ca.* 250° on rapid heating (on normal heating darkened from 200 °C onwards without visible liquefaction under 350 °C); $\nu_{max.}$ (Nujol) 3 550 cm^{-1} (OH) (no carbonyl peak) (Found: C, 80.2; H, 4.1; S, 10.4%; M^+, 300. $C_{20}H_{12}OS$ requires C, 80.0; H, 4.0; S, 10.7%; *M*, 300). The phenolic nature of the material was confirmed by insolubility in aqueous sodium hydrogen carbonate, but slow dissolution in warm 2M-sodium hydroxide to give a solution from which it could be recovered by acidification. Treatment of the phenol (74 mg) in tetrahydrofuran with ethereal diazomethane gave a product which was purified by chromatography (silica gel column; elution successively with carbon tetrachloride and benzene) to yield (from benzene eluate) *5-methoxybenzo*[b]-*phenanthro*[2,1-d]*thiophen* (23 mg) as pale cream needles, m.p. 162—163° (from hexane) (Found: C, 79.3; H, 4.7; S, 10.4%; M^+, 314. $C_{21}H_{14}OS$ requires C, 80.2; H, 4.5; S, 10.2%; *M*, 314).

Synthesis of 2-(2-*Naphthyl*)*benzo*[b]*thiophen*.—A solution of benzo[*b*]thiophen (4 g) in ether (15 ml) was refluxed and stirred in anhydrous conditions under argon for 0.5 h with n-butyl-lithium in hexane (15% w/w; 20 ml). A solution of the halogenonaphthalene in ether (12 ml) was then added, followed by piperidine (0.3 ml) in ether (12 ml). The resultant orange solution was refluxed and stirred under argon for 4—6 h, with the addition of two further portions of piperidine (0.3 ml) in ether (12 ml) after *ca.* one-third and two-thirds of the refluxing period. The mixture was then cooled, set aside overnight, and poured into 0.25M-hydrochloric acid (160 ml). The resultant precipitate was collected, washed, dried, and crystallised from benzene to give 2-(2-naphthyl)benzo[*b*]thiophen, identical with authentic material, in the following yields: from 2-fluoronaphthalene (2.9 g) after 4.7 h reflux, 1.80 g (35%); from 1-chloronaphthalene (3.2 g) after 3.75 h reflux, 0.98 g (19%); from 2-chloronaphthalene (3.2 g) after 6.25 h reflux, 1.67 g (33%).

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