High-yield Syntheses of Dilithio-derivatives of Furan, Thiophen, N-Methylpyrrole, 3-Methylfuran, and 3-Methylthiophen. Application of the Method to 2-Methylfuran, 2-Methylthiophen, 2,5-Dimethylfuran, 2,5-Dimethylthiophen, Benzo[b]furan, Benzo[b]thiophen, Pyrrole, and Indole

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Conditions are established for the preparation in yields approaching quantitative of 2,5-dilithio-furan and -thiophen. The effects of changes in reaction conditions on the rates of hydrogen–lithium exchange for furan and thiophen have been investigated and are discussed in detail. The appearance of a 2,4-dilithio-intermediate, peculiar to N-methyl-pyrrole, has been explored, and optimum conditions are presented for the syntheses of both 2,4- and 2,5-inter-mediates. 3-Methylfuran and 3-methylthiophen are similar to the parent heterocycles in their hydrogen–lithium exchange properties. The results of applying the procedure found to produce high yields of dilithio-products to a further eight heterocycles are described.

DIRECT synthesis of lithio-derivatives of aromatic heterocycles by proton abstraction with an alkyl-lithium has been known for some years.[1a,b] Early reports,[2,3] however, describe the production only of monolithio-species in low yields. Only for N-methylpyrrole has the direct formation of a (2,5-) dilithio-derivative been recorded,[4] though the intermediacy of 2,5-dilithiofuran is implied in one case.[5] The synthetic potential of dimetallo-heterocycles seems largely to have been ignored, perhaps because their preparation has in the past required halogen–organometal exchange in dihalogenated substrates, which are not readily accessible.[6]

Our preliminary work,[7] which involved a reinvestigation of the synthesis of 2,5-dilithio-N-methylpyrrole,

[1] (a) J. M. Mallan and R. L. Bebb, Chem. Rev., 1969, 69, 693; (b) B. J. Wakefield, 'The Chemistry of Organolithium Compounds,' Pergamon, Oxford, 1974.

[2] V. Ramanathan and R. Levine, J. Org. Chem., 1962, 27, 1216.

[3] R. A. Benkeser and R. B. Currie, J. Amer. Chem. Soc., 1948, 70, 1781.

[4] D. A. Shirley, B. H. Gross, and P. A. Roussel, J. Org. Chem., 1955, 20, 225.

[5] G. R. Ziegler and G. S. Hammond, J. Amer. Chem. Soc., 1968, 90, 513.

[6] I. T. Millar and H. Heaney, Quart. Rev., 1957, 11, 109.

[7] D. J. Chadwick, J.C.S. Chem. Comm., 1974, 790.

demonstrated that the 2,4-isomer is also formed and that under certain conditions it can be the predominant product. This anomalous result stimulated a general investigation into the factors controlling the extent and orientation of formation of lithio-derivatives of five-membered-ring heteroaromatic compounds. In addition, reports [8] of enhanced ionicity in solutions of n-butyl-lithium (Bu^{n}Li) containing $NNN'N'$-tetramethyl-ethylenediamine (TMEDA) encouraged us to examine its influence on such reactions. The effects of change in reaction conditions and amounts of reagents on the rates of production of, and orientations in lithio-derivatives of furan, thiophen, and N-methylpyrrole have therefore been studied in detail, and optimum conditions established for the production of dilithio-compounds. These, and sometimes other conditions, were then applied to pyrrole, 2- and 3-methylfuran, 2- and 3-methyl-thiophen, 2,5-dimethyl-furan and -thiophen, benzo[b]-furan and -thiophen, and indole.

The lithio-compounds were analysed by carboxylation and subsequent methylation giving mixtures of esters whose proportions were deduced from n.m.r. studies.

RESULTS AND DISCUSSION

(A) Lithiofurans.—The products from the reaction of furan with Bu^{n}Li after carboxylation and esterification are methyl furan-2-carboxylate (1), dimethyl furan-2,5-dicarboxylate (2), and (in small amounts) methyl 5-pentanoylfuran-2-carboxylate (3) (arising from the reaction of the lithium salt of furan-2,5-dicarboxylic acid with Bu^{n}Li; it is produced in the initial stages of the carboxylation before all of any excess of Bu^{n}Li has itself been carboxylated [9]).

(1)   (2)

(3)
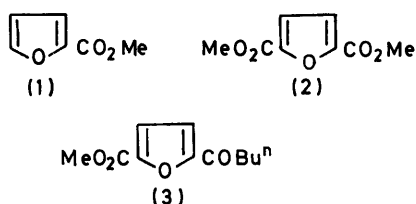
The following general conclusions may be drawn from the experiments listed in Table 1 (Experimental section). (1) The result of increasing the Bu^{n}Li : furan ratio from 1 : 1 to 2.5 : 1 is an increase in the proportion of dilithio-furan formed. (Further increase in the ratio produces anomalous results owing to the increased extent of polymer formation.) (2) When the reaction time is extended, the proportion of dilithio-intermediate is raised, though for reactions (x) and (xi) the effect is small and increased polymer formation reduces the total overall yield [cf. reactions (x) and (xi), and (v) and (vi) in Table 1]. (3) Increase in reaction temperature favours the dilithio-intermediate in all cases. (4) The presence of TMEDA accelerates the formation of lithiofurans so that, other things being equal, the ultimate yields of esters are raised. The effect of TMEDA on the ratio of products is, however, more complex. When the reaction

is carried out with an excess of Bu^{n}Li present, the proportion of dilithio-material is raised; in the absence of such an excess, the proportion is diminished. (5) If hexane is replaced by diethyl ether as solvent, higher proportions of mono-lithio-material result. (6) In no case is 2,4-dilithiofuran observed.

In addition to two irreversible reactions [(1) and (2) in Scheme 1], an equilibrium involving metal exchange between furan and its lithio-derivatives is possible [(3) in Scheme 1]. That 2,5-dithiofuran can indeed react with
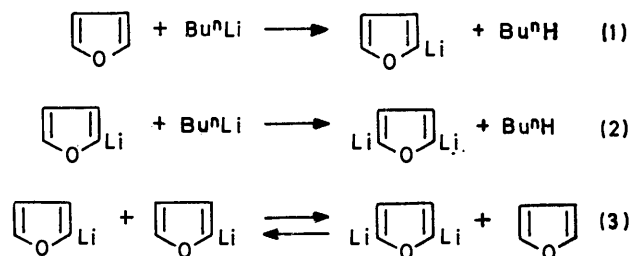
SCHEME 1

furan to give monolithiofuran is demonstrated by the results of the three parallel reactions of experiment (xx) (Table 1). Work-up of the 2.5 : 2.5 : 1 Bu^{n}Li–TMEDA–furan reaction after boiling the mixture under reflux for $\frac{1}{2}$ h gives (as expected from the previous results in Table 1) largely disubstituted product in high yield. A similar mixture, which after boiling has been left at room temperature for $\frac{1}{2}$ h, similarly gives mainly disubstituted product. However, a further mixture to which has been added, after boiling, a large excess of furan shows a large decrease in the absolute amount of disubstituted material present.

The need for a pathway [(3) in Scheme 1] whereby monolithiofuran may disproportionate is also implied by the temperature dependence noted in Table 1. A comparison of reactions (v) and (vii) shows that whereas at 25 °C monolithiofuran is in excess over dilithiofuran, the reverse is true for the reactions conducted at reflux temperature. Such behaviour is consistent with the existence of a route whereby monolithiofuran can revert to furan.

The data of Table 1 indicate that the effect of change of solvent from hexane to ether is a pronounced acceleration in the formation of monolithiofuran, and in this sense is reminiscent of the effect of addition of TMEDA to 1 : 1 mixtures of furan and Bu^{n}Li. Both ether and TMEDA are expected to enhance the degree of ionic character of carbon–lithium bonds through complexing with lithium, thereby making Bu^{n}Li more reactive in proton abstraction: acceleration in the formation of monolithiofuran is then to be expected. That the rate of the subsequent conversion to dilithiofuran shows by

[8] A. W. Langer, jun., Trans. New York Acad. Sci., 1965, 27, 741; ' Polyamine-chelated Alkali Metal Compounds,' ed. A. W. Langer, jun., A.C.S., Washington, 1974; G. E. Coates, M. L. H. Green, and K. Wade, ' Organometallic Compounds,' Methuen, London, 1967.

[9] I. L. Finar, ' Organic Chemistry,' Longmans, London, 1967.

comparison little sensitivity to solvent change may be a consequence of this increased ionicity in ether making a further proton abstraction from a species in which there must already be substantial negative charge on carbon more difficult. The situation is, however, complex: degree of aggregation of various species, solvation effects, and relative solubilities may all influence the outcome.

When Bu^nLi is present in excess over furan, acceleration of the reactions by any means (increase in the concentration of Bu^nLi, raising of the reaction temperature, or introduction of TMEDA) results in increased proportions of dilithiofuran. A similar result is observed if the reaction time is increased.

Ramanathan and Levine [2] did not isolate products derived from dilithiofuran. Repetition of their reaction [(xviii) in Table 1] shows that in addition to a 66% yield of monosubstituted material (77% reported), a 19% yield of disubstituted product also results.

(B) *Lithiothiophens*.—The products obtained after reaction and work-up as for furan [Table 2 (Experimental section)] are methyl thiophen-2-carboxylate (4) and dimethyl thiophen-2,5-dicarboxylate (5). The trends

(4)   (5)
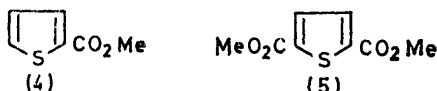
noted for furan are again evident. No 2,4-dilithio-intermediate was observed.

Comparison of the results for furan and thiophen reveals two major differences between reactions carried out under similar conditions. (1) With hexane as solvent, the *total* amount of lithio-derivatives formed is significantly less for thiophen than for furan except where conditions lead to appreciable polymerisation of the furan, though in the presence of TMEDA yields approach quantitative in both cases. With ether as solvent the differences between comparable reactions are slight. (2) With hexane as solvent, the proportions of *dilithio*-intermediate are greater for thiophen than for furan.

Mallan and Bebb [1a] quote the results of a competitive reaction [10] between furan and thiophen (in ether solvent) for an insufficient quantity of Bu^nLi. The conclusion that thiophen reacts more rapidly than furan is regarded as ' unexpected ' in the light of a comparison between dibenzofuran and dibenzothiophen, the former reacting more rapidly. The apparent contradiction between this observation and (1) above prompted us to study two such competitive reactions with *hexane* as solvent [Table 3 (Experimental section)]. The data of Table 3 demonstrate that, in accord with conclusion (1), in the absence of TMEDA with hexane as solvent, furan reacts more rapidly with Bu^nLi than does thiophen. However, in the presence of TMEDA, the rate of reaction of thiophen increases relative to and indeed exceeds that of furan. (This effect was not discerned in the experiments of Tables 1 and 2 because yields tend to be quantitative in both cases in the presence of TMEDA.) Thiophen

reacts more rapidly than furan under conditions which favour the ionisation of the C–Li bonds (ether as solvent and/or TMEDA present). This is in accord with general experience of the relative stability of sulphur ylides in comparison with the oxygen analogues, if one assumes that negative charge is being developed on the heterocyclic rings in the transition states leading to the mono-lithio-derivatives. However, the magnitude of orbital repulsion effects in the heterocyclic α-anions must be substantially different from that in essentially sp^3-hybridised ylides. There is every reason to suppose, nonetheless, that these effects will work in the same direction in both cases and indeed will be magnified in the heterocycles where the sp^2 orbital containing the lone pair of the heteroatom and that of the adjacent negative charge are close. In apolar conditions (hexane as solvent; TMEDA absent) where ionisation of the C–Li bond is not encouraged, thiophen reacts less rapidly than furan with Bu^nLi. This may be a consequence of the superior ability of oxygen to interact synergically with lithium (which is a σ donor and π acceptor) as compared with sulphur: the p orbitals are a better size for overlap and its greater electronegativity enhances the inductive effect. The more ionic the C–Li bond becomes, the less is this synergesis realisable.

X = O or S
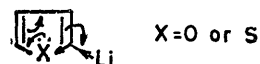
Benkeser and Currie [3] report only a monosubstituted product from the reaction of thiophen with Bu^nLi, in unspecified yield. Repetition of their reaction [(x) in Table 2] gave a 53% yield of monosubstituted product and an 8% yield of disubstituted material.

(C) *Lithio-N-methylpyrroles*.—The products of reaction and work-up as before are methyl N-methylpyrrole-2-carboxylate (6), dimethyl N-methylpyrrole-2,5-dicarboxylate (7), and dimethyl N-methylpyrrole-2,4-dicarboxylate (8). The following general points emerge from the

(6)   (7)

(8)
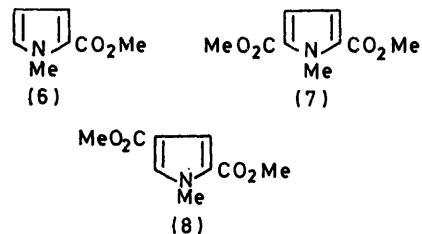
data of Table 4 (Experimental section). (1) The presence of TMEDA again exerts a profound enhancing effect on the rates of hydrogen–lithium exchange. (2) Heating reaction mixtures in the presence of TMEDA leads to mainly the 2,5-dilithio-intermediate. (3) The results of experiment (vii) (Table 4) imply that any attempt to effect conversion into the monolithio-intermediate by using short reaction times at room

[10] Y. L. Gol'dfarb and Y. L. Danyushevskii, *J. Gen. Chem.* (*U.S.S.R.*), 1961, **31**, 3410.

temperature (whatever the ratio of Bu^{n}Li to N-methyl-pyrrole) is doomed to failure owing to low conversion of starting material into products; neither would acceleration of the reaction by heating be satisfactory since

TABLE 1

Reactions with furan

An asterisk implies no precipitate formed during reaction; solvent 1 is hexane, 2 is ether; the presence (in 1 : 1 molar ratio with Bu^{n}Li) or absence of TMEDA is denoted by a tick ($\sqrt{}$) or cross ($\times$); mole % yields are based on the initial amount of furan present

Reaction no.	Temp. (°C or R = reflux)	Time (h)	Solvent	Bu^{n}Li : furan (n : 1)	TMEDA	Yields (mole %) Monoester [a]	Diester [a]	Total
(i) *	25	0.5	1	1	$\times$	13	9	22
(ii)	R	0.5	1	1	$\times$	17	14	31
(iii) *	25	0.5	1	1	$\sqrt{}$	76	0	76
(iv)	R	0.5	1	1	$\sqrt{}$	70	15	85
(v) *	25	0.5	1	2	$\times$	10	4	14
(vi)	25	16	1	2	$\times$	25	17	42
(vii)	R	0.5	1	2	$\times$	19	31	50
(viii)	R	0.5	1	2	$\sqrt{}$	30	55	85
(ix)	R	0.5	1	2.5	$\times$	14	86	100
(x)	R	0.5	1	2.5	$\sqrt{}$	9	91	100
(xi)	R	3	1	2.5	$\sqrt{}$	5	57	62
(xii) *	−40	3	1	4.5	$\times$	0	0	0
(xiii) *	−5	3	1	4.5	$\times$	<1	0	<1
(xiv) *,[b]	25	16	1	4.5	$\times$	28	14	42
(xv) [d]	R	16	1	4.5	$\times$	0	0	0
(xvi)	25	0.5	1	4.5	$\sqrt{}$	45	55	100
(xvii)	25	0.5	2	1	$\sqrt{}$	98	0	98
(xviii)	R	4	2	1	$\times$	66	19	85
(xix)	R	0.5	2	2.5	$\sqrt{}$	33	55	88
(xxa)	R	0.5	1	2.5	$\sqrt{}$	8	92	100
(xxb)[c] {then	R / 25	0.5 / 0.5	1	2.5 } / ca. 0.13}	$\sqrt{}$	113	36	149 [e]
(xxc) {then	R / 25	0.5 / 0.5	1	2.5} / 2.5}	$\sqrt{}$	7	93	100

[a] A. P. Dunlop and F. N. Peters, ' The Furans,' Reinhold, New York, 1953.   [b] In this reaction, the esters were accompanied by methyl 5-pentanoylfuran-2-carboxylate (7 mole %) (see text).   [c] In this reaction, a four-molar excess of furan over the original amount used was added after the ½ h boiling and the mixture was then left at 25 °C for a further ½ h.   [d] This reaction was accompanied by polymer formation.   [e] For consistency, the yields in this reaction are given as mole % of the *initial* amount of furan present.   That the total yield exceeds 100% merely reflects the continued reaction between the excess of furan added and Bu^{n}Li at 25 °C during 0.5 h.
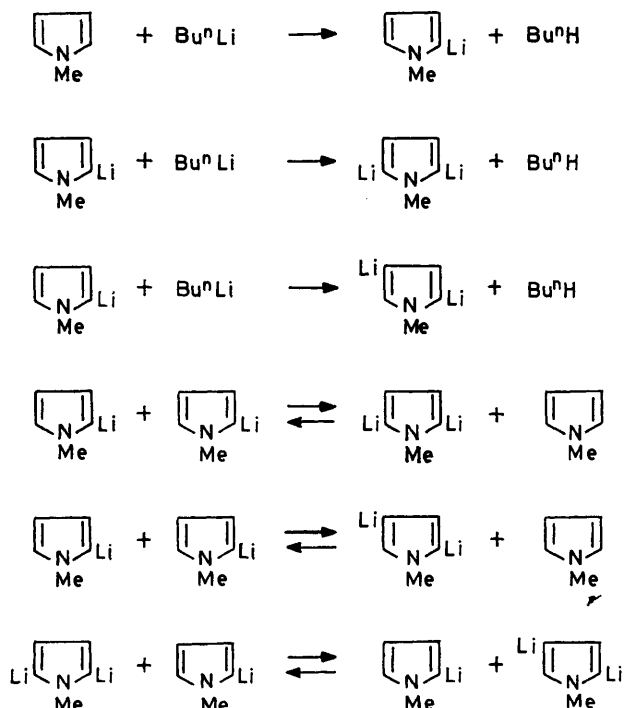
SCHEME 2

even a 1 : 1 Bu^{n}Li–N-methylpyrrole mixture then gives mixtures of lithio-intermediates [experiments (iv) and (v) in Table 4]. The utility of TMEDA in this context is clear from the 100% yield of monolithio-material obtained in experiment (i), even though a 2.5 : 1 ratio of Bu^{n}Li to N-methylpyrrole was present (presumably a 1 : 1 ratio would suffice [11]). The absence of dilithio-material in this experiment is one manifestation of an apparently general reduced tendency of N-methylpyrrole to undergo hydrogen–lithium exchange in comparison with furan and thiophen: this may reflect an increased inability of the heteroatom to sustain adjacent negative charge. (4) The results of experiment (iv) (TMEDA absent) demonstrate that the quantities of both dilithio-species increase with time, but that after a certain point the concentration of the 2,4-dilithio-intermediate increases at the expense of the 2,5-compound: the initial rate of production of the former is, however, much less than that of the latter. Although the experiments carried out in the presence of TMEDA show high conversion of starting materials into products, the 2,5-isomer is always favoured almost to the exclusion of the 2,4-compound. The possible system of reactions (Scheme 2) contains irreversible and potentially reversible

[11] N. Gjøs and S. Gronowitz, *Acta Chem. Scand.*, 1971, **25**, 2596.

TABLE 2

Reactions with thiophen

The conventions of Table 1 are used

Reaction no.	Temp. (°C or R = reflux)	Time (h)	Solvent	Bu^{n}Li : thiophen (n : 1)	TMEDA	Monoester [a]	Diester [b]	Total
(i)	R	0.5	1	1	×	0	12	12
(ii)	R	0.5	1	1	√	42	30	72
(iii)	25	0.5	1	2	×	0	0	0
(iv)	R	0.5	1	2	×	0	28	28
(v)	25	0.5	1	2	√	29	71	100
(vi)	R	0.5	1	2	√	0	100	100
(vii)	R	0.5	1	2.5	√	0	100	100
(viii)	R	16	1	4.5	×	0	97	97
(ix)	25	0.5	2	1	√	93	7	100
(x)	{ R then 25	3 16 }	2	1	×	53	8	61
(xi)	R	0.5	2	2.5	√	39	46	85

Yields (mole %)

[a] ' Dictionary of Organic Compounds,' ed. I. Heilbron and H. Bunbury, Eyre and Spottiswoode, London, 1965.　[b] H. D. Hartough, ' Thiophen and its Derivatives,' Wiley, New York, 1952.

TABLE 3

Competition between furan and thiophen for an insufficient quantity of Bu^{n}Li in the absence or presence of TMEDA

Solvent is hexane; reaction time 0.5 h; temperature that of the refluxing solvent; molar ratio of reactants (furan : thiophen : Bu^{n}Li) 1 : 1 : 0.67; where appropriate Bu^{n}Li : TMEDA ratio is 1 : 1; the conventions of Table 1 are used

Yields (mole %)

Reaction no. [a]	TMEDA	Furan 2-ester (1)	Furan 2,5-diester (2)	Thiophen 2-ester (4)	Thiophen 2,5-diester (5)
(i)	×	11.9	18.3	7.8	4.6
(ii)	√	16.7	8.2	33.4	0

[a] In all these reactions, all the Bu^{n}Li was consumed.

important, as noted previously in the discussion of the results obtained with furan. Whether the results obtained here arise from the operation of predominantly thermodynamic or kinetic influences is impossible to deduce without a far more extensive study of the individual steps involved in Scheme 2.

In a comparison of the results obtained for N-methylpyrrole with those for furan and thiophen, perhaps the most striking observation is the appearance of the 2,4-dilithio-compound. This may again be a reflection of nitrogen's reduced ability to sustain adjacent negative charge as compared with oxygen and sulphur.

For the remaining ten substrates, only those reaction conditions expected on the basis of the above experience

TABLE 4

Reactions with N-methylpyrrole

The conventions of Table 1 are used

Reaction no.	Temp. (°C or R = reflux)	Time (h)	Solvent	Bu^{n}Li : Substrate (n : 1)	TMEDA	Monoester [b]	2,4 [c]	2,5 [b]	Total
(i) *	25	0.5	1	2.5	√	100	0	0	100
(ii)	R	0.5	1	2.5	√	41	7	50	98
(iii) [d]	R	0.5	1	4.5	√	26	2	62	90
(iv)	R	3	1	1	×	8	16	11	35
(v)	R	16	1	1	×	13	8	8	29
(vi)	R	120	1	4.5	×	4	40	2	46
(vii) *,a	R	0.5	1	4.5	×	0.4	0.1	1.1	1.6
(vii)	R	1	1	ca. 4.5	×	0.9	0.6	1.1	2.6
(vii)	R	2	1	ca. 4.5	×	1.1	0.8	1.5	3.4
(vii)	R	4	1	ca. 4.5	×	1.8	3.6	2.7	8.1
(vii)	R	8	1	ca. 4.5	×	1.7	8.3	4.2	14.2
(vii)	R	24	1	ca. 4.5	×	{ 1.7 2.2	19.7 26.4	3.2 4.8	24.6 33.4 }

Yields (mole %) — Diesters

[a] In this reaction, 2 ml samples were removed from the reaction medium at the time intervals shown, and worked up in the usual way. The duplicate figures for the 24 h experiment are for a sample and for the residue; the differences reflect the difficulties in sampling a heterogeneous mixture.　[b] Ref. 4.　[c] Ref. 7.　[d] Increase of reaction time to 1 h affords a 90% yield of 2,5-diester.

steps. The effect of TMEDA may arise either from a reversal in the relative thermodynamic stabilities of the dilithio-compounds or from acceleration to varying degrees of the various steps of Scheme 2 (or from a combination of both effects): other factors may also be

to lead to dilithio-intermediates were used. Results are summarised in Table 5 and require no discussion.

EXPERIMENTAL

Tables 1—5 summarise the experimental results; full details are available in a Thesis.[12] General procedures

[12] C. Willbe, Part II Thesis, Oxford, 1975.

TABLE 5

Distribution of products from attempted syntheses of dilithio-derivatives of heterocycles; solvent hexane, reaction temperature that of refluxing solvent; reaction time 0.5 h; TMEDA present in an equimolar proportion to $Bu^n Li$; yields in parentheses are for $Bu^n Li$: substrate 4.5 : 1, otherwise 2.5 : 1; references are given to known compounds (the rest are new)

Products (R = $CO_2 Me$)

Substrate	Products
pyrrole (N–H)	(9) 80% (68%) [e]; (10) 4% (3%) [e]; (11) R 4% (3%) [e]; (12) 2% (3%) [e]
Me–furan	(13) 62% [e]
Me–furan	(14) 66% (77%); (15) 18% (14%) [f]; (16) 4% (9%)
Me–thiophen	(17) 95% [g]; (18) 3% [h]
Me–thiophen [a]	(19) 100% (100%)
Me–furan–Me [b]	(20) 20%
Me–thiophen–Me [c]	(21) 39% (49%); (22) 19% (37%) [i]; (23) 5% (12%)
benzofuran [d]	(?) R ; (?) R
benzothiophen	(24) 55% [g]; (25) 12%
indole (N–H)	(26) 93% [j]

[a] Cf. S. Gronowitz, P. Moses, A. B. Hörnfeldt, and R. Hakansson, Arkiv. Kemi, 1961, 17, 165; V. Ramanathan and R. Levine, J. Org. Chem., 1962, 27, 1667 ($Bu^n Li$: substrate 1 : 1). [b] At least three other esters (20%) were also formed. [c] Cf. A. J. Clarke, S. McNamara, and O. Meth-Cohn, Tetrahedron Letters, 1974, 2373; and the queries of S. Gronowitz and T. Frejd, Acta Chem. Scand. B, 1975, 29, 818. [d] Identified spectroscopically as components of inseparable mixtures. [e] 'Dictionary of Organic Compounds,' ed. I. Heilbron and H. Bunbury, Eyre and Spottiswoode, London, 1965. [f] A. P. Dunlop and F. N. Peters, ' The Furans,' Reinhold, New York, 1953. [g] H. D. Hartough, ' Thiophen and its Derivatives,' Wiley, New York, 1952. [h] R. G. Jones, J. Amer. Chem. Soc., 1955, 77, 4069. [i] G. N. Jean and F. F. Nord, J. Org. Chem., 1955, 20, 1363. [j] A. G. Anastassiou, R. L. Elliott, and A. Lichtenfeld, Tetrahedron Letters, 1972, 4569.

(preparation of heterocyclic lithio-derivatives, carboxylic acids, and methyl esters) and physical data for new com- pounds are available as Supplementary Publication No. SUP 21974 (6 pp.).†