The Hantzsch pyrrole synthesis[1]

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Ethyl esters of 2-alkyl- and 2,4-dialkylpyrrole-3-carboxylic acids are obtained generally by extensions of the Hantzsch synthesis, benzyl and *t*-butyl esters when the 2-alkyl group is methyl. Hemopyrrole is obtained from butanal and ethyl acetoacetate in three steps. Pyrroles bearing higher alkyl groups or carbobenzoxy groups are reductively alkylated like the corresponding methylpyrroles and carbethoxy derivatives; *t*-butyl esters do not survive.

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Introduction

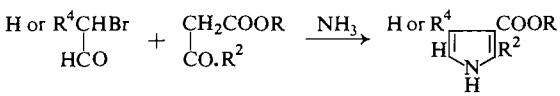
Numerous alkyl pyrroles were required to identify by gas–liquid partition chromatography (g.l.p.c.) those resulting from the reduction of porphyrins and their meso-alkyl derivatives cf. (1). Many of the pyrroles are now easily obtained (2) but the assembly suggested some deficiencies in the methods of pyrrole ring synthesis and a review of their possibilities.

The most generally useful pyrrole synthesis is that form of Knorr's which gives 2,4-dialkylpyrrole-3,5-dicarboxylic esters from two acylacetic esters, one of them nitrosated (3*a*); this will be referred to simply as the Knorr synthesis. Both alkyl groups are frequently desired but, if other than methyl, derive from less accessible acylacetates.

The other pyrrole ring syntheses (3*a*, 3*b*, 4), including other forms of Knorr's, are used when the above Knorr products are not appropriate intermediates, and in special, although important, cases. Their limitations are usually inherent: the intermediates may be less accessible (α-aminoketones), must be symmetrical to avoid ambiguity (1,3-diketones), or the products may be too specialized (2,5-dialkylpyrroles, *N*-substituted pyrroles).

As the Hantzsch pyrrole synthesis (3*a*) was an exception among these, having the formal generality of the Knorr synthesis, we questioned its apparent limitations. In it, ammonia and ethyl acetoacetate condensed with α-halo derivatives of acetaldehyde (5, 6) or of ketones (7, 8) giving 2-methyl-3-carbethoxypyrrole (the only generally useful product (6, 9)) or its 5-alkyl- and 4,5-dialkyl derivatives. The 5-position was thus an embarrassment: permanently blocked if alkylated or, if not, complicating the introduction of a 4-alkyl group. Further, the 2-methyl group seemed virtually obligatory for, when acylacetates other than methyl or ethyl acetoacetate had been used, the expected product was isolated in only one case: in 2% yield from oxalacetic ester, 2-chlorocyclohexanone and ammonia (10; cf. 5, 8, 11, 12). Apparently only eight or nine pyrroles had been made by the Hantzsch synthesis (contrast (3*a*)).

We find that neither of these limitations exists in principle, first because α-halo derivatives of aldehydes other than acetaldehyde may be used, and second because acylacetates other than methyl or ethyl acetoacetate may be used if, as in Hantzsch's original procedure (7), the crude products are purified by washing with both acid and alkali. Ethyl esters of 2-alkyl- and of 2,4-dialkylpyrrole-3-carboxylic acids are then obtained generally, benzyl and *t*-butyl esters, when the 2-alkyl group is methyl, eq. [1].

[1] 

Using chloroacetone, we also obtained the analogous ethyl and benzyl but not *t*-butyl esters of 2-alkyl-5-methylpyrrole-3-carboxylic acids. Aldehydes, however, are in all respects more appropriate components than the ketones used heretofore. Normal aldehydes to C_{12} are commercial products, they are halogenated unambiguously, and their halo-derivatives give both more useful pyrroles and higher yields than do halo-ketones.

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TABLE 1

Pyrroles by the Hantzsch synthesis

Components	Yield (%)	Code	Product: Substituents 2	3	4	5	Melting point (°C)	Melting point lit. (°C)	Anal. Calcd. (Found) C	H	N
Chloroacetone and											
ethyl acetoacetate	50 (7)	1.1	Me	COOEt		Me					
methyl acetoacetate	25 (8)	1.2	Me	COOMe		Me					
t-butyl acetoacetate	0										
benzyl acetoacetate	8	1.3	Me	$COOCH_2C_6H_5$		Me	89–91		73.34 (73.48)	6.59 (6.67)	6.11 (6.09)
ethyl propionylacetate	9	1.4	Et	COOEt		Me	55–57		66.27 (66.45)	8.34 (8.27)	7.73 (7.70)
ethyl butyrylacetate	2	1.5	$CH_2CH_2CH_3$	COOEt		Me	73–75		67.66 (67.47)	8.78 (8.61)	7.17 (7.38)
MeCHBrCOEt and ethyl acetoacetate	7	2.1	Me	COOEt	Me	Et	107.5–108	106–107 (15, 2)	67.66 (67.53)	8.78 (8.86)	7.17 (7.23)
$ClCH_2CHCl(OEt)$ and ethyl acetoacetate	40 (5)	5.1	Me	COOEt							
$BrCH_2CHBr(OAc)$ and											
ethyl acetoacetate	45 (6)	5.1	Me	COOEt							
t-butyl acetoacetate	36	5.2	Me	$COOCMe_3$			112–114		66.27 (66.13)	8.34 (8.42)	7.73 (7.65)
benzyl acetoacetate	12	5.3	Me	$COOCH_2C_6H_5$			57–59		72.54 (72.64)	6.09 (6.16)	6.51 (6.61)
ethyl propionylacetate	29	5.4	Et	COOEt			<20		64.65 (64.39)	7.84 (7.71)	8.38 (8.14)
ethyl butyrylacetate	20	5.5	$CH_2CH_2CH_3$	COOEt			33–35		66.27 (66.10)	8.34 (8.32)	7.73 (7.65)
EtCHClCHO and ethyl acetoacetate	30	6.1	Me	COOEt	Et		77–79				
EtCHBrCHBr(OAc) and											
ethyl acetoacetate	40	6.1	Me	COOEt	Et		77–79				
EtCHBrCHO and											
ethyl acetoacetate	45	6.1	Me	COOEt	Et		77–79		66.27 (66.12)	8.34 (8.21)	7.73 (7.86)
t-butyl acetoacetate	32	6.2	Me	$COOCMe_3$	Et		73–75		68.86 (68.68)	9.15 (9.01)	6.67 (6.83)
benzyl acetoacetate	25	6.3	Me	$COOCH_2C_6H_5$	Et		63–65		74.05 (74.16)	7.07 (7.24)	5.76 (5.57)
ethyl propionylacetate	15	6.4	Et	COOEt	Et		43–45		67.66 (67.84)	8.78 (8.86)	7.17 (7.26)
ethyl butyrylacetate	16	6.5	$CH_2CH_2CH_3$	COOEt	Et		56–58		68.86 (68.76)	9.15 (9.20)	6.69 (6.61)
$CH_3(CH_2)_4CHBrCHBr(OAc)$ and											
ethyl acetoacetate	45	6.6	Me	COOEt	$(CH_2)_4CH_3$		69–71		69.92 (69.86)	9.48 (9.61)	6.27 (6.31)
$CH_3(CH_2)_4CHBrCHO$ and											
ethyl acetoacetate	55	6.6	Me	COOEt	$(CH_2)_4CH_3$		69–71				
ethyl propionylacetate	49	6.7	Et	COOEt	$(CH_2)_4CH_3$		52–53		70.85 (70.85)	9.77 (9.61)	5.90 (5.75)

It will be noted that the principal limitation on the related pyrrole synthesis of Feist could not be avoided in this way for 2,5-dimethyl-3-carbethoxypyrrole resulted when β-aminocrotonic ester was condensed with either hydroxyacetone or lactaldehyde in hot acetic acid (13).

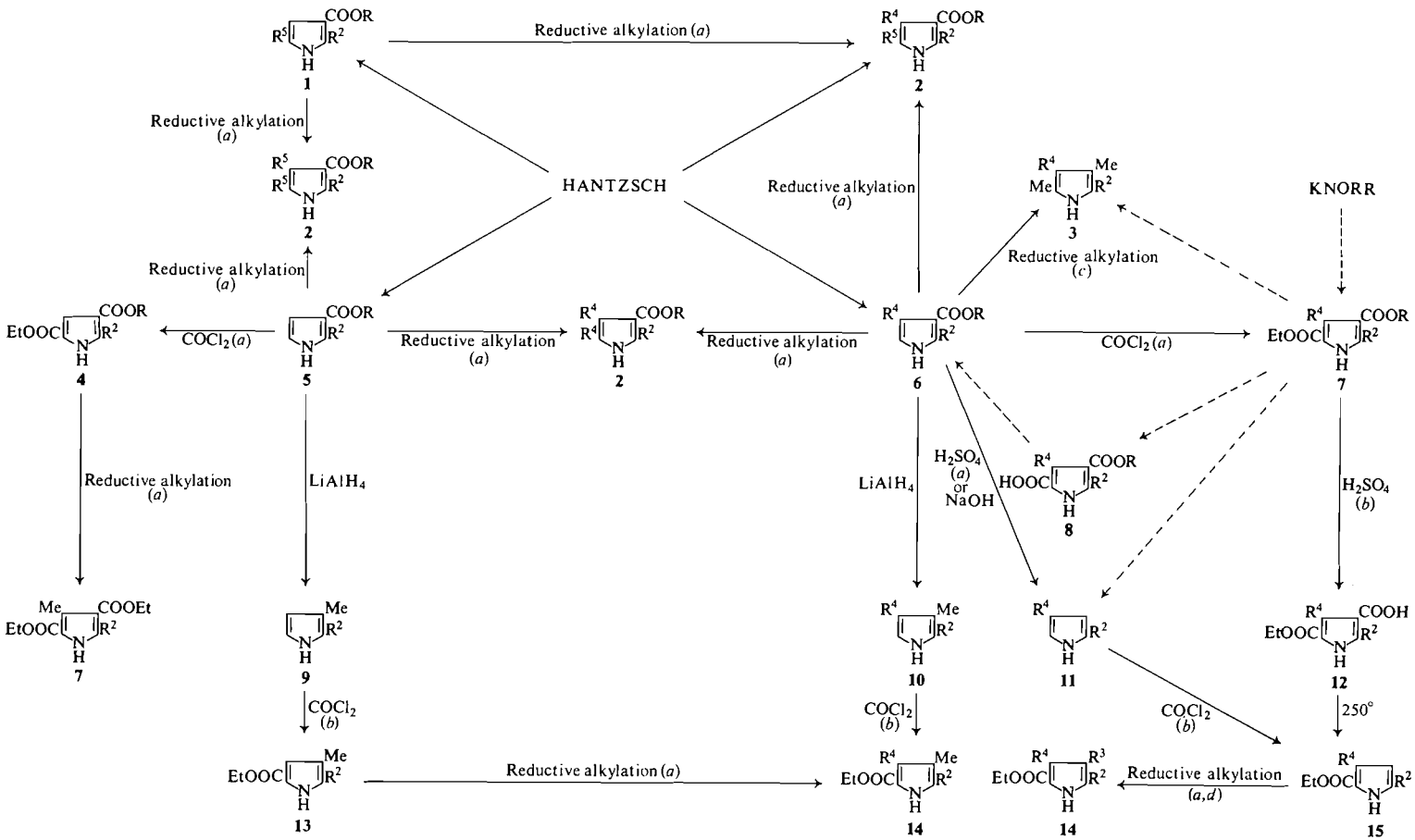
Table 1[3] shows some products of conventional Hantzsch syntheses, 1.1, 1.2, 2.1, and 5.1 and those now obtained by the above extensions, using one mole of each organic component under uniform conditions. Particularly when the yields were low, these conditions were not ideal, for when the mixtures were refluxed for 1 h after the spontaneous reaction was over, the yield of 6.5 was 24% instead of 16% although that of 6.1 (45%) was unchanged (cf. (8)). Also, the cheaper component should presumably be in excess.

To choose between equivalent halo-aldehydes and derivatives, all were first condensed with ethyl acetoacetate and ammonia. Neither 2-bromo-1,1-diethoxybutane nor 1,2-dibromo-1-ethoxybutane gave pyrroles whether or not the mixtures were heated. The best yields (45–55%) were obtained using 1,2-dibromoethyl acetate, 2-bromobutanal, and 2-bromoheptanal. These three, also obtained directly and more easily than their alternatives, were then used with other acylacetates. The yields were then more various (12–49%) and no pyrroles were obtained using benzyl propionylacetate, ethyl pivalylacetate, 2,4-pentanedione, nor the sodium salt of oxalacetic ester or of ethyl acetopyruvate. Chloroacetone (except when used with ethyl acetoacetate) and 2-bromo-3-pentanone both gave lower yields of pyrroles than did the three preferred halo-aldehyde derivatives (Table 1); similarly, the yield of the pyrrole from 3-chloro-2-butanone and ethyl acetoacetate was only 26% (8).

Scheme 1 represents the Hantzsch products (1, 2, 5, 6), related Knorr products (7), the more useful pyrroles derived from these (9, 10, 11, 14), and some reactions connecting them. As specified in Table 2 we have carried out many of these reactions on the Hantzsch products to confirm the structures of the new ones of types 1 and 6, to provide a basis for comparing the Hantzsch products 5 and 6 with the Knorr products 7 as intermediates, and to further define the scope of reductive alkylation. These reactions were carried out under standardized conditions and the only failures encountered are discussed below.

Discussions of the Hantzsch synthesis have emphasized that pyrroles are formed from halo-ketones as in eq. [1] (R^5 for H on 5) rather than with R^4 and R^5 interchanged, and all our products were formulated accordingly. The only evidence in support of this was that 2,5-dimethyl-3-carbethoxypyrrole, 1.1, was obtained from chloroacetone, ethyl acetoacetate, and ammonia (7). In the 2,4-dimethyl-3-carbethoxyfuran formed concurrently, R^4 and R^5 were interchanged (11). The only other evidence was that ethyl β-bromolevulinate, ethyl acetoacetate, and ammonia give the diethyl ester of 2,4-dimethyl-3-carboxypyrrole-5-acetic acid, a pyrrole in which R^4 and R^5 are interchanged (14). In view of this, all the doubtful structures of new Hantzsch products (types 1, 2, and 6) were confirmed, and eq. [1] evidently does represent the products from uncomplicated halo-aldehydes and -ketones. The pyrrole 2.1 was known (15, 2); although it is confused in the literature with its isomer 2.14 of the same m.p. (15, 3*c*), their mixture m.p. is depressed. The remainder, of types 1 and 6, were systematically related to products of the Knorr synthesis, 7, including the new 7.7. With two exceptions, 6.6 and 6.7, ethyl and benzyl esters 6 were authenticated by conversion to Knorr products, 7 (Scheme 1). Pyrroles 1 and 6 with R and R^2 in common were then related through 2. When two pyrroles, 6, differed only in R^4 (6.1 and 6.6, or 6.4 and 6.7), only one was confirmed through 7 for both could be related to the same 1 through a pyrrole of type 2. Less systematically, the structure of 6.1 also follows from its conversion to the known pyrroles 2.14, 3.1, 10.1, 15.1, 14.4 and 14.5, and that of 6.4 from its conversion to 14.2. To avoid a Knorr synthesis, the structure of the *t*-butyl ester 6.2 was confirmed by reducing it to 10.1 which was identified as the solid 14.4, a known pyrrole also obtained from the corresponding ethyl and benzyl esters, 6.1 and 6.3. Similarly, although without the structural significance, the ethyl and benzyl esters 5 were related to 6 and, except in one instance, to 1 through pyrroles of type 2. The *t*-butyl ester 5.2 could not be reductively alkylated, but it was reduced like the corresponding ethyl and benzyl esters, 5.1 and 5.3, to 9.1 which was identified as the solid 13.1.

[3]In Table 1 and Table 2 the units figure in the code identifies the pyrrole type, as defined in Scheme 1, and the decimal numbers distinguish individual pyrroles within it.



SCHEME 1

TABLE 2

Pyrroles from Hantzsch products

Starting pyrrole	Method	Code	Substituents 2	3	4	5	Yield (%)	Melting point (°C)	Melting point lit. (°C)	Anal. Calcd. (Found) C	H	N
		1.2	Me	COOMe		Me						
1.2	Reductive alkylation (*a*)	2.2	Me	COOMe	Me	Me	63	124–126		64.65 (64.80)	7.84 (7.98)	8.38 (8.21)
1.2	Reductive alkylation (*a*)	2.3	Me	COOMe	Et	Me	45	142–144		66.27 (66.09)	8.34 (8.22)	7.73 (7.58)
		1.3	Me	$COOCH_2C_6H_5$		Me						
1.3	Reductive alkylation (*a*)	2.4	Me	$COOCH_2C_6H_5$	Me	Me	65	86–88		74.05 (73.92)	7.04 (7.16)	5.76 (5.61)
1.3	Reductive alkylation (*a*)	2.5	Me	$COOCH_2C_6H_5$	Et	Me	20	90–91		74.68 (74.81)	7.44 (7.43)	5.44 (5.33)
		1.4	Et	COOEt		Me						
1.4	Reductive alkylation (*a*)	2.6	Et	COOEt	Me	Me	76	99–101		67.66 (67.56)	8.78 (8.70)	7.17 (7.35)
1.4	Reductive alkylation (*a*)	2.7	Et	COOEt	Et	Me	45	119–121		68.86 (68.99)	9.15 (9.32)	6.67 (6.70)
1.4	Reductive alkylation (*a*)	2.8	Et	COOEt	$(CH_2)_4CH_3$	Me	40	74–76	Below	—	—	—
		1.5	$CH_2CH_2CH_3$	COOEt		Me						
1.5	Reductive alkylation (*a*)	2.9	$CH_2CH_2CH_3$	COOEt	Et	Me	38	111–113		69.92 (70.16)	9.48 (9.55)	6.27 (6.38)
		5.2	Me	$COOCMe_3$								
5.2	$COCl_2$ (*a*)	4.1	Me	$COOCMe_3$		COOEt	86	166–167		61.64 (61.47)	7.56 (7.39)	5.53 (5.39)
5.2	$LiAlH_4$	9.1	Me	Me			60		(3*d*, 9)	75.74 (75.82)	9.54 (9.69)	14.72 (14.88)
9.1	$COCl_2$ (*b*)	13.1	Me	Me		COOEt	67	113–115	114 (3*e*)			
		5.3	Me	$COOCH_2C_6H_5$								
5.3	Reductive alkylation (*a*)	2.4	Me	$COOCH_2C_6H_5$	Me	Me	46	86–88	Above	74.05 (74.22)	7.04 (7.10)	5.76 (5.68)
5.3	Reductive alkylation (*a*)	2.10	Me	$COOCH_2C_6H_5$	Et	Et	11	103–105		75.24 (75.42)	7.80 (7.96)	5.16 (5.29)
5.3	$COCl_2$ (*a*)	4.2	Me	$COOCH_2C_6H_5$		COOEt	78	154–156		66.88 (67.03)	5.96 (6.08)	4.88 (5.07)
5.3	$LiAlH_4$	9.1	Me	Me			77		Above	75.74 (75.88)	9.54 (9.67)	14.72 (14.83)
9.1	$COCl_2$ (*b*)	13.1	Me	Me		COOEt	63	113–115	Above			
		5.4	Et	COOEt								
5.4	Reductive alkylation (*a*)	2.6	Et	COOEt	Me	Me	67	99–101	Above	67.66 (67.88)	8.78 (8.53)	7.17 (7.29)
5.4	Reductive alkylation (*a*)	2.11	Et	COOEt	Et	Et	31	105–107		69.92 (69.79)	9.48 (9.63)	6.27 (6.45)
5.4	$COCl_2$ (*a*)	4.3	Et	COOEt		COOEt	89	116–118		60.24 (60.41)	7.16 (7.30)	5.85 (5.69)
4.3	Reductive alkylation (*a*)	7.1	Et	COOEt	Me	COOEt	80	114–116	116 (3*f*)	61.64 (61.81)	7.56 (7.72)	5.53 (5.35)
5.4	$LiAlH_4$	9.2	Et	Me			70		(3*g*, 16)	77.01 (77.11)	10.16 (10.03)	12.83 (12.88)
9.2	$COCl_2$ (*b*)	13.2	Et	Me		COOEt	87	75–77	79 (16)	66.27 (66.11)	8.34 (8.45)	7.73 (7.81)
13.2	Reductive alkylation (*a*)	14.1	Et	Me	Me	COOEt	63	75–76	78 (17)	67.66 (67.56)	8.78 (8.81)	7.17 (7.33)
13.2	Reductive alkylation (*a*)	14.2	Et	Me	Et	COOEt	42	60–62	62–63 (18)	68.86 (68.68)	9.15 (9.25)	6.69 (6.74)
		5.5	$CH_2CH_2CH_3$	COOEt								
5.5	Reductive alkylation (*a*)	2.12	$CH_2CH_2CH_3$	COOEt	Me	Me	67	80–82	82–83 (19)	68.86 (69.02)	9.15 (9.31)	6.69 (6.51)
5.5	Reductive alkylation (*a*)	2.13	$CH_2CH_2CH_3$	COOEt	Et	Et	43	94–96		70.85 (71.03)	9.77 (9.67)	5.90 (5.74)
5.5	$COCl_2$ (*a*)	4.4	$CH_2CH_2CH_3$	COOEt		COOEt	75	112–114		61.64 (61.48)	7.56 (7.37)	5.53 (5.40)
4.4	Reductive alkylation (*a*)	7.2	$CH_2CH_2CH_3$	COOEt	Me	COOEt	72	116–117		62.90 (63.07)	7.92 (8.04)	5.24 (5.12)
5.5	$LiAlH_4$	9.3	$CH_2CH_2CH_3$	Me			78			77.99 (77.84)	10.64 (10.78)	11.37 (11.44)
9.3	$COCl_2$ (*b*)	13.3	$CH_2CH_2CH_3$	Me		COOEt	82	64–66		67.66 (67.77)	8.78 (8.75)	7.17 (7.29)
13.3	Reductive alkylation (*a*)	14.3	$CH_2CH_2CH_3$	Me	Me	COOEt	84	79–81		68.86 (69.03)	9.15 (8.98)	6.69 (6.69)
		6.1	Me	COOEt	Et							
6.1	Reductive alkylation (*a*)	2.14	Me	COOEt	Et	Me	76	105–107	105–107 (2)	67.66 (67.55)	8.78 (8.83)	7.17 (7.28)
6.1	Reductive alkylation (*a*)	2.15	Me	COOEt	Et	Et	52	105–107	104–106 (1)	68.86 (68.68)	9.15 (9.29)	6.67 (6.81)
6.1	Reductive alkylation (*c*)	3.1	Me	Me	Et	Me	48	62–65	69 (3*h*)	78.77 (78.63)	11.02 (11.30)	10.21 (10.30)
6.1	$COCl_2$ (*a*)	7.3	Me	COOEt	Et	COOEt	77	112–114	115 (3*f*)	61.64 (61.76)	7.56 (7.59)	5.53 (5.39)
6.1	$LiAlH_4$	10.1	Me	Me	Et		75		(3*i*)	77.99 (78.17)	10.64 (10.49)	11.37 (11.23)
6.1	NaOH	11.1	Me		Et		60		(3*j*)	77.01 (77.19)	10.16 (10.04)	12.83 (12.95)
6.1	H_2SO_4	11.1	Me		Et		70		Above			
11.1	$COCl_2$ (*b*)	15.1	Me		Et	COOEt	76	83–85	86 (3*k*)	66.27 (66.15)	8.34 (8.23)	7.73 (7.58)
10.1	$COCl_2$ (*b*)	14.4	Me	Me	Et	COOEt	70	95–97	97 (3*l*)	67.66 (67.60)	8.78 (8.76)	7.17 (7.13)
15.1	Reductive alkylation (*a*)	14.4	Me	Me	Et	COOEt	70	95–97	Above			
15.1	Reductive alkylation (*d*)	14.5	Me	Et	Et	COOEt	41	72–74	75 (3*m*)	68.86 (68.70)	9.14 (9.15)	6.67 (6.51)

TABLE 2 (*concluded*)

Starting pyrrole	Method	Code	Substituents 2	3	4	5	Yield (%)	Melting point (°C)	Melting point lit. (°C)	Anal. Calcd. (Found) C	H	N
		6.2	Me	$COOCMe_3$	Et							
6.2	$COCl_2$ (*a*)	7.4	Me	$COOCMe_3$	Et	COOEt	86	91–93		64.03 (63.91)	8.24 (8.41)	4.98 (5.10)
6.2	$LiAlH_4$	10.1	Me	Me	Et		55		Above	77.99 (77.80)	10.64 (10.49)	11.37 (11.53)
10.1	$COCl_2$ (*b*)	14.4	Me	Me	Et	COOEt	68	95–97	Above			
		6.3	Me	$COOCH_2C_6H_5$	Et							
6.3	Reductive alkylation (*a*)	2.5	Me	$COOCH_2C_6H_5$	Et	Me	83	89–91	Above	74.68 (74.51)	7.44 (7.35)	5.44 (5.26)
6.3	Reductive alkylation (*a*)	2.10	Me	$COOCH_2C_6H_5$	Et	Et	34	104–106	Above	75.24 (75.42)	7.80 (7.69)	5.16 (5.37)
6.3	$COCl_2$ (*a*)	7.5	Me	$COOCH_2C_6H_5$	Et	COOEt	86	126–128	127–129 (18)	68.55 (68.41)	6.71 (6.80)	4.44 (4.28)
6.3	$LiAlH_4$	10.1	Me	Me	Et		65		Above	77.99 (78.10)	10.64 (10.25)	11.37 (11.21)
10.1	$COCl_2$ (*b*)	14.4	Me	Me	Et	COOEt	71	95–97	Above			
		6.4	Et	COOEt	Et							
6.4	Reductive alkylation (*a*)	2.7	Et	COOEt	Et	Me	80	119–121	Above	68.86 (68.88)	9.15 (9.32)	6.67 (6.76)
6.4	Reductive alkylation (*a*)	2.11	Et	COOEt	Et	Et	35	105–107	Above	69.92 (70.10)	9.48 (9.32)	6.27 (6.41)
6.4	$COCl_2$ (*a*)	7.6	Et	COOEt	Et	COOEt	72	94–96	97 (3*n*)	62.90 (63.07)	7.92 (7.76)	5.24 (5.36)
6.4	$LiAlH_4$	10.2	Et	Me	Et		79		(3*o*)	78.77 (78.83)	11.02 (11.16)	10.21 (10.55)
10.2	$COCl_2$ (*b*)	14.2	Et	Me	Et	COOEt	67	63–65	Above	68.86 (69.03)	9.15 (9.32)	6.67 (6.69)
		6.5	$CH_2CH_2CH_3$	COOEt	Et							
6.5	Reductive alkylation (*a*)	2.9	$CH_2CH_2CH_3$	COOEt	Et	Me	87	111–113	Above	69.92 (70.03)	9.48 (9.60)	6.27 (6.23)
6.5	Reductive alkylation (*a*)	2.13	$CH_2CH_2CH_3$	COOEt	Et	Et	42	94–96	Above	70.85 (70.93)	9.77 (9.89)	5.90 (5.78)
6.5	$COCl_2$ (*a*)	7.7	$CH_2CH_2CH_3$	COOEt	Et	COOEt	80	84–86	See Experimental	64.03 (64.19)	8.24 (8.42)	4.98 (5.11)
		6.6	Me	COOEt	$(CH_2)_4CH_3$							
6.6	Reductive alkylation (*a*)	2.16	Me	COOEt	$(CH_2)_4CH_3$	Me	70	77–79	78–79 (2)	70.85 (70.68)	9.77 (9.60)	5.90 (6.02)
6.6	Reductive alkylation (*a*)	2.17	Me	COOEt	$(CH_2)_4CH_3$	Et	68	60–61		71.67 (71.85)	10.03 (9.91)	5.57 (5.66)
6.6	Reductive alkylation (*c*)	3.2	Me	Me	$(CH_2)_4CH_3$	Me	45			80.38 (80.31)	11.81 (11.65)	7.81 (7.88)
6.6	$LiAlH_4$	10.3	Me	Me	$(CH_2)_4CH_3$		74			79.94 (80.11)	11.59 (11.43)	8.48 (8.49)
6.6	$COCl_2$ (*a*)	7.8	Me	COOEt	$(CH_2)_4CH_3$	COOEt	75	83–85		65.06 (65.04)	8.53 (8.46)	4.74 (4.69)
7.8	H_2SO_4 (*b*)	12.1	Me	COOH	$(CH_2)_4CH_3$	COOEt	71	224		62.90 (62.79)	7.92 (7.84)	5.24 (5.11)
12.1	250°	15.2	Me		$(CH_2)_4CH_3$	COOEt	45	64–66		69.92 (69.88)	9.48 (9.48)	6.27 (6.39)
15.2	Reductive alkylation (*a*)	14.6	Me	Me	$(CH_2)_4CH_3$	COOEt	74	83–85		70.85 (71.02)	9.77 (9.69)	5.90 (6.01)
10.3	$COCl_2$ (*b*)	14.6	Me	Me	$(CH_2)_4CH_3$	COOEt	67	83–85	Above			
		6.7	Et	COOEt	$(CH_2)_4CH_3$							
6.7	Reductive alkylation (*a*)	2.8	Et	COOEt	$(CH_2)_4CH_3$	Me	70	74–76	Above	71.67 (71.71)	10.03 (10.06)	5.57 (5.70)

We had used methylpyrroles and their carbethoxy derivatives to determine sets of conditions suitable for the reductive alkylation of representative types of pyrroles, and the limitations of these methods (2). The alkylations now carried out (Scheme 1 and Table 2) now show that the generalizations made then are equally applicable to pyrroles bearing higher alkyl groups, and to their carbethoxy or carbobenzoxy derivatives. The only exception was the dicarboxylic ester 4.2 which was too insoluble to be methylated at room temperature, and its carbobenzoxy group was displaced by a methyl group at 45° (see Experimental). The *t*-butyl esters, however, did not survive at room temperature. In detail, the ethyl esters 1.4, 4.3, 4.4, 5.4, 5.5, 6.1, 6.4, 6.5, 6.6, 6.7, 13.2, 13.3, 15.1, 15.2 were methylated, 1.4, 1.5, 5.4, 5.5, 6.1, 6.4, 6.5, 6.6, 13.2, 15.1 were ethylated, and 1.4 was converted into its *n*-pentyl derivative; like their lower homologue (2), 4.3 and 4.4 were not ethylated. The benzyl esters 1.3, 5.3, and 6.3 were both methylated and ethylated; the methylation of 4.2 is discussed above and its ethylation, like that of 4.3 and 4.4 was not to be expected. At 100°, when no difficulty was expected as carbalkoxy groups are replaced, both 6.1 and 6.6 were completely *C*-methylated.

In conclusion, the Hantzsch synthesis and the Knorr synthesis in its various forms have the same formal generality but that of the latter is more fully realized, particularly because 4-acetic and 4-propionic acids are obtained directly, the choice of acylacetates providing the 2- and 3-substituents is wider, and 1,3-diketones may replace acylacetates. The Hantzsch synthesis has advantages when its use permits a commercial aldehyde (halogenated) to replace a higher acylacetate (nitrosated), and also when 4-free pyrroles are required or when the final products are to be 3-methyl derivatives. Thus the 2-alkyl- and 2,4-dialkyl-3-methylpyrroles 9.2, 9.3, 10.1 (hemopyrrole), 10.2, 10.3 are now obtained (as was 2,3-dimethylpyrrole, 9.1 (9)) in three steps from aldehydes and acylacetates, hemopyrrole (12%) from butanal and ethyl acetoacetate.[4] The Hantzsch synthesis also provides attractive routes to 14 (R^3 = Me): 10.1, 10.2, 10.3 → 14.4, 14.2, 14.6 respectively, 13.2 → 14.1 and 14.2, or 13.3 → 14.3. More generally, 14 (R^3 = Me) was obtained through 6.1 → 11.1 → 15.1 → 14.4 and 14.5, or 6.6 → 7.8 → 12.1 → 15.2 → 14.6.

It was necessary to clear up confusion over the m.p. of 2,3-dimethyl-5-carbethoxypyrrole, 13.1 (16, 4). Fischer and Fink applied their "modified Knorr" synthesis (eq. [2*b*]) to 3-formyl-2-butanone and identified the product, m.p. 128°, as 13.1. They concluded, without further evidence, that the lower m.p., 114° (3*e*), of earlier preparations was due to the presence of some of the *N*-carbethoxypyrrole. The *N*-carbethoxy derivative may contaminate products from pyrrylmagnesium halides and ethyl chloroformate (3*a*), and its presence here would reflect on the purity of all the products we obtained by the phosgene method. We found,[5] however, that Fischer and Fink's product is a mixture of 13.1, m.p. 114–116°, with 10–30% of 2,3,4-trimethyl-5-carbethoxypyrrole, m.p. 126–129°, into which it was resolved by preparative g.l.p.c.; conversely, mixtures of these two pyrroles had the same nuclear magnetic resonance (n.m.r.) spectrum and m.p. (128–130°) as the product of Fischer and Fink. Evidently, Knorr syntheses with 1,3-dicarbonyl compounds can take a third course (eq. [2*c*]) (possibly six if the dicarbonyl compound is unsymmetrical) which was foreshadowed by the equivalence of acetylacetone and its oxymethylene derivative in the normal Knorr synthesis (eq. [2*a*]) (16).

Experimental

Melting points are corrected. The assigned structures were consistent with the n.m.r. spectra. Pyrroles gave negative Beilstein tests for halogen and positive Ehrlich reactions. Those encountered more than once had identical n.m.r. spectra and their mixture m.p.'s were not depressed.

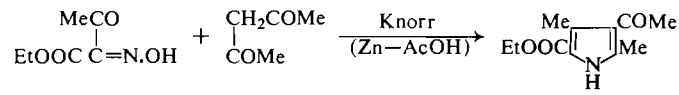
The following were obtained by methods in the literature: *t*-butyl acetoacetate (20), benzyl acetoacetate (21), ethyl and benzyl propionylacetate, ethyl butyrylacetate (18), 2-bromo-3-pentanone (22), 1,2-dibromo-1-ethoxybutane (23), 2-chlorobutanal (24), 2-bromobutanal and 2-bromoheptanal (25), and 1,2-dibromo-1-acetoxyheptane (26). 2-Bromo-1,1-diethoxybutane, $b.p._{20}$ 86–88°, and 1,2-dibromo-1-acetoxybutane were obtained like the corresponding pentane (27) and heptane (26) respectively. Hydriodic acid (d = 1.94) and 50% hypophosphorous acid were used.

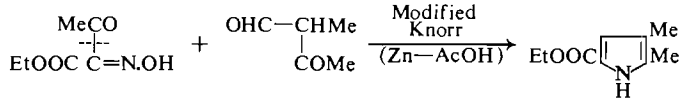
Standard (not Optimal) Conditions for the Hantzsch Syntheses in Table 1

Aqueous ammonia (50 ml of 28%, 50 ml of water) was added to the acylacetate and halo-compound (0.1 mole of each) and the mixture was stirred for 2 h while the tem-

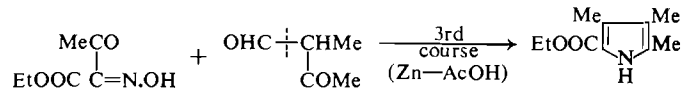
[4]The bromine required costs six times as much as these cabalistic starting materials.

[5]With D. T. Krajcarski.

[2a] 

[2b] 

13.1

[2c] 

perature rose to about 60° then fell. Next day the product was extracted into ether and the extract was washed with 10% NaOH, with water, with 5% HCl, and again with water. Ether was removed from the dried (Na_2SO_4) extract *in vacuo*. The products 1.3, 1.4, 2.1, 5.2, 5.3, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7 crystallized from the residues after a few hours at room temperature and 1.5 crystallized at 0°. These were recrystallized from ether–pentane and then, if necessary, decolorized by sublimation (ca. 90°, 0.5 mm). In the case of 5.4 and 5.5, the distilled residues crystallized at 0°; 5.4 was then drained on cold tile and redistilled, 5.5 was recrystallized from pentane.

Standard Conditions for the Reactions Detailed in Table 2 as Designated There and in Scheme 1

$LiAlH_4$. 3-Methylpyrroles from 3-Carbethoxypyrroles: 9 and 10 from 5 and 6 cf. (9)

A solution of the pyrrole (0.01 mole) in 20 ml of dry tetrahydrofurane was dropped into a stirred solution of $LiAlH_4$ (0.8 g) in 20 ml of tetrahydrofurane over 1/2 h. The solution was then refluxed for 18 h, cooled, and ordinary ether (20 ml) added followed by enough 10% NaOH (ca. 100 ml) to redissolve the initial precipitate. The mixture was extracted with ether, the dried (Na_2SO_4) extract was evaporated (rotary), and the residue was distilled at ca. 90° (10 mm).

$COCl_2$. 5-Carbethoxypyrroles

(a) From 3-Carbethoxypyrroles: 4 and 7 from 5 and 6

A solution of the pyrrole (0.01 mole) in 25 ml of toluene and 1.2 g of dimethylaniline was cooled in an ice–salt bath and stirred while a solution of phosgene (1 g) in toluene (10 ml) was dropped in over 15 min. After standing overnight, the mixture was refluxed for 2 h. Absolute ethanol (10 ml) containing dimethylaniline (1.2 g) was then dropped in at room temperature and the mixture stirred and heated for 1 h. Toluene was removed at room temperature *in vacuo* (rotary), and the residue poured into dilute hydrochloric acid (10 ml concentrated and 100 ml water). The solid which separated was crystallized from ether–pentane.

(b) From Purely Alkyl Pyrroles, cf. (6): 13, 14, and 15.1 from 9, 10, and 11.1

The pyrrole (0.01 mole), in dry ether (25 ml) and dimethylaniline, was treated as in (*a*) but without any heating.

Reductive Alkylation cf. (1, 2)

(a) Using Hydriodic Acid at Room Temperature: 2 from *1, 5, or 6; 7(R^4 = Me, R = Et) from 4(R = Et); 14 from 13; 14(R^3 = Me) from 15*

The pyrrole (0.004 mole) in acetic acid (10 ml), hydriodic acid (10 ml), hypophosphorous acid (2 ml), and the aldehyde (1*x* – 5*x* theory) were stirred for 2 h at room temperature. The solution was poured into 200 ml of water, the mixture made alkaline with ammonia, and the precipitate was recrystallized from ether – *n*-pentane.

(b) Using Hydriodic Acid at 45°, with Loss of Benzyloxycarbonyl Groups: 2,3,4-Trimethyl-5-carbethoxypyrrole from 2-Methyl-3-benzyloxycarbonyl-5-carbethoxypyrrole, 4.2, or from its 4-Methyl Derivative (28)

The pyrrole (0.574 g) in acetic acid (10 ml), hydriodic acid (5 ml), and hypophosphorous acid (1 ml) was stirred for 2 h at 45° with 0.3 g of paraformaldehyde. The product (75%), m.p. 127–129°, was isolated as under (*a*) above.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.44; H, 8.51; N, 7.57.

(c) Using Hydriodic Acid at 100°, with the Loss of Carbethoxy Groups: 3 from 6

The pyrrole (0.01 mole), 25 ml of acetic acid, 25 ml of hydriodic acid, 5 ml of hypophosphorous acid, and 0.6 g of paraformaldehyde were heated for 3 h under nitrogen at 100°. The cooled solution was poured into water, the mixture was made alkaline with ammonia, and the product was extracted into ether. Ether was removed from the extract and the residue was distilled at ca. 95° (10 mm).

(d) Using HCl–AcOH–Zn: 14.5 (i.e. $R^3 \neq$ Me) from 15.1

Acetic anhydride (20 ml) was added to 5 ml of concentrated hydrochloric acid with cooling. The pyrrole 15.1 (0.004 mole), paraldehyde (0.008 mole) and 10 g of zinc amalgam (20 mesh) were added to this at 25° and stirred for 25 min. The zinc was then separated and the product was isolated as under (*a*) above.

H_2SO_4

(a) Removal of Carbethoxy Groups cf. (3p): 11.1 from 6.1

2-Methyl-4-ethyl-3-carbethoxypyrrole (9.05 g) in 24 ml of concentrated sulfuric acid and 10 ml of water was

heated for 3 h on the steam bath. The mixture was then made alkaline with 20% NaOH at ≤15°. The product, 2-methyl-4-ethylpyrrole, was extracted into ether then distilled at ca. 86° (20 mm).

(b) Partial Hydrolysis cf. (3g): 12.1 from 7.8

2-Methyl-4-*n*-pentyl-3,5-dicarbethoxypyrrole (7.8) (2 g) was stirred for 1 h at 40° in 4 ml of concentrated sulfuric acid. The product was precipitated by water and dissolved in aqueous NaOH which was then washed with ether. The product, 2-methyl-4-*n*-pentyl-5-carbethoxypyrrole-3-carboxylic acid (12.1) was reprecipitated by acid and recrystallized from ethanol as tiny colorless plates.

NaOH. Removal of Carbethoxy groups cf. (3i): 11.1 from 6.1

2-Methyl-4-ethyl-3-carbethoxypyrrole (9.05 g) was heated for 6 h at 175° with 40 ml of 10% aqueous NaOH in a Teflon lined screw-capped metal tube. The product, 2-methyl-4-ethylpyrrole, was extracted into ether then distilled at ca. 86° (20 mm).

250°. Decarboxylation cf. (3q): 15.2 from 12.1

2-Methyl-4-*n*-pentyl-5-carbethoxypyrrole-3-carboxylic acid (12.1) was decarboxylated at 250°. The product, 2-methyl-4-*n*-pentyl-5-carbethoxypyrrole, 15.2, was sublimed at ca. 60° (0.05 mm) then recrystallized from ether–pentane as prisms.

Knorr. Ring Synthesis of 7.7 cf. (3r)

Ethyl propionylacetate (5.12 g) in 25 ml of acetic acid was nitrosated at ≤5° with 2.46 g of sodium nitrite in a little water. After 15 h at 0°, 5.63 g of ethyl *n*-butyrylacetate in 25 ml of acetic acid were added. The solution was stirred while 10 g of zinc dust were added at 65° Then, after 1 h at 85° the solution was decanted into water. The 2-*n*-propyl-4-ethyl-3,5-dicarbethoxypyrrole which separated was recrystallized from 50% ethanol then twice from *n*-pentane as long colorless needles (25%), m.p. 84–86° and 99–101°.

Anal. Calcd. for $C_{15}H_{23}O_4N$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.20; H, 8.41; N, 5.02.

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