

The Willgerodt Reaction

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The Willgerodt reaction is discussed from a synthetic standpoint including types of compounds for starting material and conditions of operation. The Kindler modification and its usefulness is also indicated. The behavior of heterocyclic compounds in the reaction is mentioned followed by a number of interesting special compounds prepared. The results obtained by applying the reaction conditions to cyclic ketones are covered and, finally, work on the reaction mechanism to date is discussed.

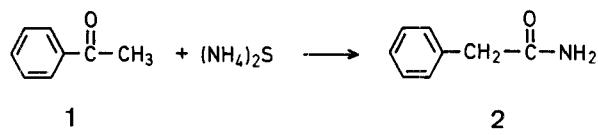
1. Introduction
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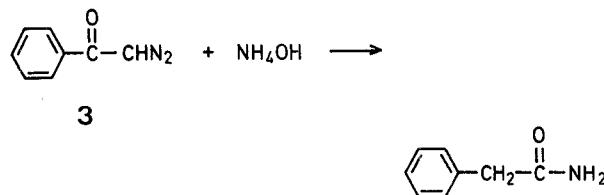
Es werden die synthetische Anwendung, die als Ausgangssubstanzen geeigneten Verbindungsklassen sowie die Reaktionsbedingungen der Willgerodt-Reaktion abgehandelt. Die Kindler-Modifizierung und ihr Anwendungsbereich werden ebenfalls erwähnt. Das Verhalten heterocyclischer Verbindungen, cyclischer Ketone sowie einiger interessanter spezieller Verbindungen wird beschrieben. Abschließend werden die bisherigen Kenntnisse über den Reaktionsmechanismus zusammenfassend diskutiert.

1. Introduction

The Willgerodt reaction which bears his name was first carried out by Conrad Willgerodt in 1887. As originally practiced it involved heating an aryl methyl ketone (**1**) with yellow ammonium sulfide $[(\text{NH}_4)_2\text{S}_x]$, followed by the isolation of an amide (**2**) with the same number of carbon atoms which was the major product (Scheme A). It seemed, therefore, comparable to the Arndt-Eistert reaction of **3** to give **4**, (Scheme B).



Scheme A



Scheme B

It was soon shown, however, that it was possible to convert longer chain ketones such as propiophenone, butyrophenone, and valerophenone to amides in which the terminal methyl group of the ketone became the carboxamide group. In general the yields dropped off with the number of carbon atoms over which the oxidation-reduction process took place.

Willgerodt Reaction of Acetophenone¹:

Acetophenone (2 g), colorless ammonium sulfide solution (10 g), and sulfur (1 g) were heated in a sealed tube at 200–220° for 4 h. After cooling and treatment with hydrochloric acid to decompose the ammonium sulfide, the solution was refluxed with charcoal to remove color and sulfur. The mixture was basified with sodium carbonate and extracted repeatedly with ether to remove the phenylacetamide. The solution was then strongly acidified and extracted again to remove the phenylacetic acid. There were obtained phenylacetamide; yield: 50%, and phenylacetic acid; yield: 14%.

Although the original work was done with ammonium polysulfide in water, other modifications have been tried. The combination sulfur and ammonium hydroxide has been used and a solvent such as dioxan or pyridine may or may not be added.

Originally the starting compounds were alkyl aryl ketones (Tables 1 a–1 e) but soon other starting materials were being investigated such as aliphatic ketones (Table 2), aldehydes (Table 3), unsaturated hydrocarbons (Table 4), saturated hydrocarbons (Table 5), alcohols, amines, and mercaptans (Table 6).

- ¹ C. Willgerodt, F. H. Merk, *J. prakt. Chem.* (2) **80**, 192 (1909).
- ² C. Willgerodt, *Ber. dtsh. chem. Ges.* **20**, 2467 (1887).
- ³ C. Willgerodt, *Ber. dtsh. chem. Ges.* **21**, 534 (1888).
- ⁴ C. Willgerodt, W. Hambrecht, *J. prakt. Chem.* (2) **81**, 74 (1910).
- ⁵ C. Willgerodt, *J. prakt. Chem.* (2) **80**, 183 (1909).
- ⁶ C. Willgerodt, T. Scholtz, *J. prakt. Chem.* (2) **81**, 382 (1910).
- ⁷ Y. Baskakov, N. N. Mel'nikov, *J. Gen. Chem. USSR* **23**, 905 (1953); *C. A.* **48**, 4477 (1954).
- ⁸ D. F. DeTar, M. Carmack, *J. Amer. Chem. Soc.* **68**, 2025 (1946).
- ⁹ M. Carmack, D. F. DeTar, *J. Amer. Chem. Soc.* **68**, 2029 (1946).
- ¹⁰ A. Claus, R. Wehr, *J. prakt. Chem.* (2) **44**, 85 (1891).
- ¹¹ J. A. King, F. H. McMillan, *J. Amer. Chem. Soc.* **68**, 2335 (1946).

Table 1a. Willgerodt Reaction of Aryl Methyl Ketones

	S / NH4OH	
Ar	Yield ^a (%)	References
	31 ^b , 50, 8.8	1, 2, 3, 6, 7, 8, 10
	28, 35 ^b	7
	12	7
	0	7
	0	7
	25	7
	31 ^b , 55 ^b , 63	3, 4, 5, 6, 7, 9
	—	7
	35	7
	39, 45 ^b	7
	68	7
	75	7
	72	7
	88, 93 ^b	7
	75	7
	59	7
	62	7
	0	7
	—	2, 3, 5
	28, 33 ^b	6
	0	7

Table 1a. Continued

Ar	Yield ^a (%)	References
	15, 22 ^b , 42	5, 6, 7, 11
	—, 22 ^b	5, 6
	—	5
	—	5
	88	2, 3, 4, 7, 12, 13
	—, 25 ^b	5, 14
	0	7
	0	7
	86	7
	20	7
	41	7
	0	7
	40	7
	34	7
	20, 84	6, 8, 14
	33, 57 ^b	14
	70	15
	82	8, 16
	—	16, 17
	—	16, 18, 19

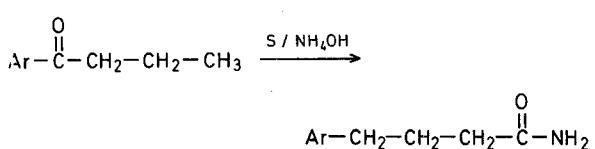
Table 1a. Continued

Ar	Yield ^a (%)	References
	66	20
	56	20
	81	17
	92	21

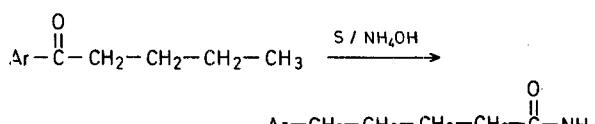
^a The yield is of the expected amide unless otherwise stated.^b This is combined yield of expected amide and its acid.

Table 1b. Willgerodt Reaction of Aryl Ethyl Ketones

Ar	Yield ^a (%)	References
	50 ^b , 82	1, 6, 8
	38 ^b	3, 4
	—	5, 22, 23
	6	6
	68 ^b	19
	—	3, 5
	—	5
	72 ^b	24, 25
	6	6
	66 ^b	8, 27
	0	8
	67 ^b	21

^a The yield is of the expected amide unless otherwise stated.^b This is the combined yield of expected amide and its acid.¹¹ L. I. Smith, C. W. MacMullen, *J. Amer. Chem. Soc.* **58**, 633 (1936).¹² R. Weitzenböck, H. Lieb, *Monatsh. Chem.* **33**, 556 (1912).Table 1c. Willgerodt Reaction of Aryl *n*-Propyl Ketones

Ar	Yield (%)	References
	32	1, 8
	18–20	4
	—	5, 22, 23
	—	5, 22, 23
	—	6
	—	3, 5
	—	6, 28
	55	21

Table 1d. Willgerodt Reaction of Aryl *n*-Butyl Ketones

Ar	Yield (%)	Reference
	29	8
	2	4

Table 1e. Willgerodt Reaction of Other Alkyl Aryl Ketones

Ar	R	Yield ^a (%)	References
	<i>i</i> -C ₃ H ₇	21 ^b	1
	<i>i</i> -C ₄ H ₉	17 ^b	1
	<i>n</i> -C ₆ H ₁₃	25	1
	<i>n</i> -C ₁₅ H ₃₁	—	1, 5
	<i>i</i> -C ₃ H ₇	—	4

Table 1e. Continued

Ar	R	Yield ^a (%)	References
	i-C ₄ H ₉	4	4
	n-C ₁₅ H ₃₁	—	5
	i-C ₃ H ₇	2	5, 22, 23
	n-C ₁₆ H ₃₃	..	5
	i-C ₃ H ₇	0.5	6
	i-C ₄ H ₉	0.1	6
	i-C ₃ H ₇	—	6
	i-C ₄ H ₉	—	6
	i-C ₃ H ₇	0	21
	i-C ₄ H ₉	0	29

^a The yield is of the expected amide unless otherwise stated.^b This is the combined yield of expected amide and its acid.

Table 2. Aliphatic Ketones in the Willgerodt Reaction

		Yield ^a (%)	References
R ¹	R ²		
CH ₃	CH ₃	—	32
CH ₃	C ₂ H ₅	10	30
CH ₃	n-C ₃ H ₇	25, 31	24, 30, 31
C ₂ H ₅	C ₂ H ₅	43	32
CH ₃	t-C ₄ H ₉	58	31, 33
CH ₃	n-C ₅ H ₁₁	30, 38	30, 31
C ₂ H ₅	n-C ₄ H ₉	23	31
C ₂ H ₅	t-C ₄ H ₉	36	31
CH ₃		20	10
CH ₃	neo-C ₅ H ₁₁	—	34
n-C ₃ H ₇	n-C ₃ H ₇	9, 21	31, 32
n-C ₄ H ₉	n-C ₄ H ₉	24	32
CH ₃		40	31
C ₂ H ₅		27	31
CH ₃		72	8

^a Yield of expected amide.

Table 3. Aldehydes and Acetals in the Willgerodt Reaction

Substrate	Amide Product	Yield (%)	Reference
n-C ₆ H ₁₃ -CHO	n-C ₆ H ₁₃ -CO-NH ₂	—	3
		75	33
		48	8
	n-C ₃ H ₇ -CO-NH ₂	80	33
	n-C ₃ H ₇ -CO-NH ₂	80	33
		48	8

¹³ Y. A. Baskakov, N. N. Mel'nikov, *Zhur. Priklad. Khim.* **28**, 1016 (1955); *C. A.* **50**, 4880 (1956).¹⁴ L. F. Fieser, G. W. Kilmner, *J. Amer. Chem. Soc.* **62**, 1354 (1940).¹⁵ W. E. Bachmann, J. C. Sheehan, *J. Amer. Chem. Soc.* **62**, 2688 (1940).¹⁶ E. Mosettig, J. van de Kamp, *J. Amer. Chem. Soc.* **55**, 3444 (1933).¹⁷ W. E. Bachmann, C. D. Cortes, *J. Amer. Chem. Soc.* **65**, 1329 (1943).¹⁸ C. Willgerodt, and B. Albert, *J. prakt. Chem.* (2) **84**, 387 (1911).¹⁹ M. Carmack, M. A. Spielman, *Org. React.* III Chap. 2, 83 (1946), John Wiley and Sons, New York.²⁰ W. E. Bachmann, M. W. Cronyn, *J. Org. Chem.* **8**, 461 (1943).²¹ W. E. Bachmann, M. Carmack, *J. Amer. Chem. Soc.* **63**, 2494 (1911).²² Bornhauser, *Dissertation*, Freiburg, 1891.²³ A. Claus, *J. prakt. Chem.* (2) **46**, 475 (1892).²⁴ R. T. Arnold, R. Barnes, *J. Amer. Chem. Soc.* **65**, 2393 (1943).²⁵ R. T. Arnold, E. Schultz, H. Klug, *J. Amer. Chem. Soc.* **66**, 1606 (1949).²⁶ H. Rapoport, A. R. Williams, *J. Amer. Chem. Soc.* **71**, 1774 (1949).²⁷ B. Riegel, M. H. Gold, M. A. Kubico, *J. Amer. Chem. Soc.* **65**, 1775 (1943).²⁸ V. Vorländer, *Ber. dtsch. Chem. Ges.* **40**, 4535 (1907).²⁹ M. Carmack, *Dissertation*, University of Michigan, 1940.³⁰ E. Cerwonka, R. C. Anderson, E. V. Brown, *J. Amer. Chem. Soc.* **75**, 28 (1953).³¹ L. Cavalieri, D. B. Pattison, M. Carmack, *J. Amer. Chem. Soc.* **67**, 1783 (1945).³² J. A. King, F. H. McMillan, *J. Amer. Chem. Soc.* **68**, 1369 (1946).

Table 4. Unsaturated Hydrocarbons in the Willgerodt Reaction

Alkene	Amide Product	Yield (%)	Reference
$\text{H}_2\text{C}=\text{CH}-\text{CH}_3$	$\text{H}_3\text{C}-\text{CH}_2-\text{CO}-\text{NH}_2$	75	35
$\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_2\text{C}=\text{C} \\ \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{H}_3\text{C} \\ \\ \text{H}_3\text{C}-\text{CH}-\text{CO}-\text{NH}_2 \end{array}$	70	35
$\text{H}_3\text{C}-\text{CH}=\text{CH}-\text{C}_2\text{H}_5$	$n\text{-C}_4\text{H}_9-\text{CO}-\text{NH}_2$	small	32
$\text{H}_3\text{C}-\text{CH}_2-\text{CH}=\text{CH}-\text{C}_3\text{H}_7-n$	$n\text{-C}_6\text{H}_{13}-\text{CO}-\text{NH}_2$	small	32
$n\text{-C}_3\text{H}_7-\text{CH}=\text{CH}-\text{C}_4\text{H}_9-n$	$n\text{-C}_8\text{H}_{17}-\text{CO}-\text{NH}_2$	small	32
$\text{H}_2\text{C}=\text{CH}-\text{C}_6\text{H}_{13}-n$	$n\text{-C}_7\text{H}_{15}-\text{CO}-\text{NH}_2$	4	32
$\text{H}_2\text{C}=\text{CH}-\text{C}_8\text{H}_{17}-n$	$n\text{-C}_9\text{H}_{19}-\text{CO}-\text{NH}_2$	6	10, 32
$\text{H}_2\text{C}=\text{CH}-\text{C}_{12}\text{H}_{25}-n$	$n\text{-C}_{13}\text{H}_{27}-\text{CO}-\text{NH}_2$	1	32, 43
		67	8, 36
		72	8
		74	8
$\text{H}_2\text{C}=\text{CH}-\text{CH}=\text{CH}_2$	$n\text{-C}_3\text{H}_7-\text{CO}-\text{NH}_2$	20	35
		64	8, 10, 36
	—	—	36
$\text{H}_2\text{C}=\text{CH}-\text{C}_5\text{H}_{11}-n$	$n\text{-C}_6\text{H}_{13}-\text{CO}-\text{NH}_2$	15	37
$\text{HC}\equiv\text{C}-\text{C}_5\text{H}_{11}-n$	$n\text{-C}_6\text{H}_{13}-\text{CO}-\text{NH}_2$	35	36, 37
$\text{H}_2\text{C}=\text{CH}-(\text{CH}_2)_8-\text{COOH}$	$\text{HOOC}-(\text{CH}_2)_9-\text{COOH}$	35	37
		24	36, 37
		31	36, 37
$(\text{C}_6\text{H}_5)_2\text{C}=\text{CH}_2$	$(\text{C}_6\text{H}_5)_2\text{CH}-\text{CO}-\text{NH}_2$	37	37
$\text{H}_2\text{C}=\text{C}-\text{CH}_3$ $\quad\quad\quad\text{C}_6\text{H}_5$	$\begin{array}{c} \text{H}_3\text{C}-\text{CH}-\text{CO}-\text{NH}_2 \\ \\ \text{C}_6\text{H}_5 \end{array}$	—	36, 37
	+		
	$\text{C}_6\text{H}_5-\text{CH}_2-\text{CO}-\text{NH}_2$	—	
$(\text{neo}-\text{C}_5\text{H}_11)_2\text{C}=\text{CH}_2$	$(\text{neo}-\text{C}_5\text{H}_11)_2\text{CH}-\text{CO}-\text{NH}_2$	—	37

Table 5. Aromatic Hydrocarbons in the Willgerodt Reaction

Arene	Product	Yield ^a (%)	References
		20	38, 39
	$\begin{array}{c} \text{C}_6\text{H}_5-\text{CO}-\text{NH}_2 \\ + \\ \text{C}_6\text{H}_5-\text{CH}_2-\text{CO}-\text{NH}_2 \end{array}$	20	38
$\text{H}_3\text{C}-\text{C}_6\text{H}_4-\text{CH}_3$	$\text{H}_2\text{N}-\text{CO}-\text{C}_6\text{H}_4-\text{CO}-\text{NH}_2 + \text{C}_6\text{H}_5-\text{CO}-\text{NH}_2$	20	38, 39
	$\begin{array}{c} \text{C}_6\text{H}_5-\text{CO}-\text{NH}_2 \\ + \\ \text{C}_6\text{H}_5-\text{CH}(\text{CH}_3)-\text{CO}-\text{NH}_2 \end{array}$	20	39

^a Total yield of all amides mentioned.³³ C. Jeianek, U.S. Patent 2,527,809, 2,572,810, Gen. Aniline & Film (1951); *C. A.* **46**, 3557 (1952).³⁴ R. Hielmann, G. de Gaudemaris, R. Heindl, *Compt. Rend. Acad. Sci.* **235**, 542 (1952).³⁵ M. A. Naylor, and A. W. Anderson, *J. Amer. Chem. Soc.* **75**, 5392 (1953).³⁶ M. Carmack, D. F. Detar, U.S. Patent, 2,495,567, Rohm and Haas (1950); *C. A.* **44**, 7868 (1950).³⁷ D. B. Pattison, M. Carmack, *J. Amer. Chem. Soc.* **68**, 2033 (1946).³⁸ M. A. Naylor, A. W. Anderson, *J. Amer. Chem. Soc.* **75**, 5395 (1953).³⁹ M. A. Naylor, U.S. Patent 2,610,980, DuPont (1952); *C. A.* **48**, 2775 (1954).

Table 6. Miscellaneous Compounds in the Willgerodt Reaction

Substrate	Products	Yield (%)	References
<i>t</i> -C ₄ H ₉ OH	<i>i</i> -C ₃ H ₇ -CO-NH ₂	1.5	10, 32
	<i>n</i> -C ₄ H ₉ -CO-NH ₂	small	32
	<i>n</i> -C ₃ H ₇ -CO-NH ₂	small	32
	<i>n</i> -C ₃ H ₇ -CO-NH ₂	small	32
	<i>C₆H₅-CH-CO-NH₂</i>	38	37
	<i>C₆H₅-CH-CO-NH₂</i>	14	37
<i>n</i> -C ₄ H ₉ -NH ₂	<i>n</i> -C ₃ H ₇ -CO-NH ₂	20	35
		—	38
C ₂ H ₅ SH	H ₃ C-CO-NH ₂	19	32
<i>n</i> -C ₃ H ₇ SH	C ₂ H ₅ -CO-NH ₂	9	32
<i>n</i> -C ₄ H ₉ SH	<i>n</i> -C ₃ H ₇ -CO-NH ₂	24	32
<i>i</i> -C ₄ H ₉ SH	<i>i</i> -C ₃ H ₇ -CO-NH ₂	15	32
<i>s</i> -C ₄ H ₉ SH	<i>n</i> -C ₃ H ₇ -CO-NH ₂	0.5	32
<i>t</i> -C ₄ H ₉ SH	<i>i</i> -C ₃ H ₇ -CO-NH ₂	0.5	32
<i>n</i> -C ₈ H ₁₇ SH	<i>n</i> -C ₇ H ₁₅ -CO-NH ₂	6	32
<i>n</i> -C ₁₀ H ₂₁ SH	<i>n</i> -C ₉ H ₁₉ -CO-NH ₂	100, 8	10, 32
<i>n</i> -C ₁₂ H ₂₅ SH	<i>n</i> -C ₁₁ H ₂₃ -CO-NH ₂	62	32
		53	32
		44	32
	C ₂ H ₅ -CO-NH ₂	6	32
	<i>n</i> -C ₃ H ₇ -CO-NH ₂	5	32
	<i>n</i> -C ₆ H ₁₃ -CO-NH ₂	1	32
	<i>n</i> -C ₈ H ₁₇ -CO-NH ₂	1	32
		77	41
		63	41
H ₃ C-(CH ₂) ₅ -CH=CH-COOH	<i>n</i> -C ₇ H ₁₅ -CO-NH ₂	69	41
	+	small	42
	+	small	42
	+	—	42
	+	—	42
		97	42
		64	42

Table 6. Continued

Substrate	Products	Yield (%)	References	
		54	42	
		65	42	
		+		42
		61	43	
		31	43	
		63	43	
		66	43	
		32	43	
		40	43	
		66	43	
		87	43	
		53	43	
		72	43	
		80	43	

2. Kindler Modification.

Kindler suggested a modification of the Willgerodt procedure using sulfur and dry amines, ammonia, primary or secondary amines, which leads to formation of the thioamide.⁶⁹ The so-called Willgerodt-Kindler reaction has greatly increased the synthetic scope of the reaction. Since it is possible to use high boiling amines, the operational difficulties of pressure apparatus can be eliminated and the reaction run in open reflux equipment. Morpholine has turned out to be most popular although many other primary and secondary amines have been used, such as aniline, piperazines, di-n-butylamine, etc. The Willgerodt-Kindler reaction has been extended from the original alkyl aryl ketones (Table 7) to aldehydes (Table 8), hydrocarbons, amines, imines and numerous other compounds (Table 9).

Willgerodt-Kindler Reaction of *o*-Benzoyloxyacetophenone⁴⁴:

A mixture of *o*-benzoyloxyacetophenone (11.3 g), morpholine (4.5 g), and sulfur (1.6 g) was heated under reflux for 8 h, poured on to ice, and extracted with ether. The oily residue obtained on evaporation of the ether extract crystallized after standing for 1 day and was recrystallized several times from dilute methanol; yield: 12 g; m.p. 118–119°.

o-Benzoyloxyphenylthioacetomorpholide (9 g) in 10% potassium hydroxide solution (100 ml) was heated under reflux for 12 h. The alkaline solution was acidified, extracted with ether, and the ether extracts dried and evaporated. The residue was recrystallized from benzene/petroleum ether; yield: 4.1 g; m.p. 97–99°.

The thioamides obtained can usually be hydrolyzed to the acids in nearly quantitative yields. Additional reactions of the thioamides, such as hydrolysis to the oxygen amide and reduction to the amine, have enlarged the synthetic utility of the Willgerodt-Kindler reaction.

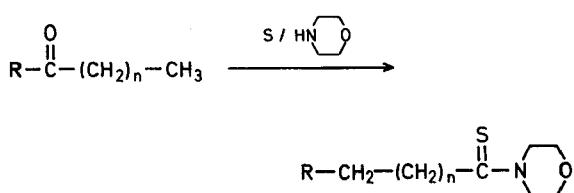
⁴⁰ E. Campagne, P. V. Rutan, *J. Amer. Chem. Soc.* **69**, 1211 (1947).

⁴¹ C. H. Davis, M. Carmack, *J. Org. Chem.* **12**, 76 (1947).

⁴² Y. Yukawa, F. Tokuda, S. Amano, *J. Chem. Soc. Japan* **73**, 498 (1952); *C.A.* **48**, 2,000 (1954).

⁴³ R. T. Gerry, E. V. Brown, *J. Amer. Chem. Soc.* **75**, 740 (1953).

⁴⁴ E. Schwenk, E. Bloch, *J. Amer. Chem. Soc.* **64**, 3051 (1942).

Table 7a. Thiomorpholides from Ketones via the Willgerodt-Kindler Reaction

Ketone	Yield ^a (%)	References
<chem>C(=O)c1ccccc1C</chem>	72 ^a , 92 ^a , 75 ^b , 94 ^a	16, 40, 44, 45, 46, 52
<chem>Oc1ccccc1C(=O)C</chem>	59 ^b	10, 54
<chem>Oc1ccccc1C(=O)C</chem>	66 ^b	10
<chem>Oc1ccccc1C(=O)C</chem>	50 ^b	10, 52, 54
<chem>Nc1ccccc1C(=O)C</chem>	61 ^b	10
<chem>Nc1ccccc1C(=O)C</chem>	51 ^b , 44 ^b	10, 49
<chem>[N+](=O)[O-]c1ccccc1C(=O)C</chem>	7	10, 54
<chem>Clc1ccccc1C(=O)C</chem>	28 ^b , 47 ^b	10, 49, 53
<chem>Brc1ccccc1C(=O)C</chem>	10 ^b , 51 ^b	44, 49
<chem>CCc1ccccc1C(=O)C</chem>	—	53
<chem>OC(=O)c1ccccc1C</chem>	70 ^b , 55 ^b	10, 44
<chem>OC(=O)c1ccccc1C</chem>	82 ^b , 85 ^a	10, 44
<chem>OC(=O)c1ccccc1C</chem>	36 ^b , 62 ^b	49, 51, 52, 53
<chem>CC(=O)c1ccccc1C</chem>	16 ^a	49
<chem>CC(=O)c1ccccc1C</chem>	—	49
<chem>CC(=O)c1ccccc1C</chem>	68 ^a	55
<chem>CC(=O)c1ccccc1N(Ac)H</chem>	75 ^a	10
<chem>CC(=O)c1ccccc1N(Ac)H</chem>	68 ^b	10
<chem>CC(=O)c1ccccc1N(Ac)H</chem>	70 ^b	10

Table 7a. Continued

Ketone	Yield ^a (%)	References
<chem>CC(=O)c1ccc(C(N)(C)C)c(C)c1</chem>	—	63
<chem>c1ccc(cc1)C(=O)C</chem>	94 ^a , 82 ^a	49, 170
<chem>c1ccc(cc1)Sc2ccccc2C(=O)C</chem>	48 ^b	48
<chem>c1ccc(cc1)Oc2ccccc2C(=O)C</chem>	72 ^a	44
<chem>COc1ccc(cc1)C(=O)C</chem>	—	54
<chem>COc1ccc(cc1)Oc2ccccc2C(=O)C</chem>	28 ^b	44
<chem>COc1ccc(cc1)Oc2ccccc2C(=O)C</chem>	21 ^a	60
<chem>CCc1ccc(cc1)C(=O)C</chem>	60–85 ^a	60
<chem>COc1ccc(cc1)Oc2ccccc2C(=O)C</chem>	—	54
<chem>CCc1ccc(cc1)C(=O)C</chem>	21 ^c	65, 66
<chem>CCc1ccc(cc1)C(=O)C</chem>	—	53
<chem>CC(=O)c1ccc(cc1)Oc2ccccc2C(=O)C</chem>	45 ^b	58
<chem>CC(=O)c1ccc(cc1)Oc2ccccc2C(=O)C</chem>	44 ^b	60
<chem>CC(=O)c1ccc(cc1)Oc2ccccc2C(=O)C</chem>	89 ^a	60
<chem>CC(=O)c1ccc(cc1)Oc2ccccc2C(=O)C</chem>	63 ^a	60
<chem>CC(=O)c1ccc(cc1)Oc2ccccc2C(=O)C</chem>	44 ^b	60
<chem>CC(=O)c1ccccc1C</chem>	65 ^b	49, 63
<chem>CC(=O)c1ccc(cc1)Oc2ccccc2C(=O)C</chem>	51 ^b , 78 ^b	49, 52
<chem>CC(=O)c1ccc(cc1)Oc2ccccc2C(=O)C</chem>	80 ^b	55
<chem>CC(=O)c1ccc(cc1)N(C)C</chem>	—	63

Table 7a. Continued

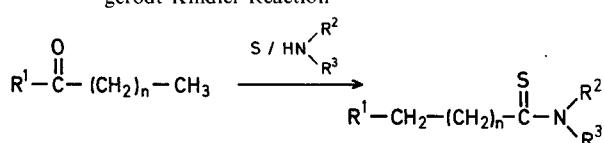
Ketone	Yield ^a (%)	References
	30 ^c	66
	36 ^b , 49 ^a	49, 56
	—	63
	8.8 ^c	66
	14 ^b	49
	61 ^a	56
	73 ^a	56
	—	62
	—	62
	89 ^a	49
	—	64
	—	64
	68	

^a Expected thiomorpholide.^b Expected acid after hydrolysis of the thiomorpholide.^c Ketothiomorpholides are produced.⁴⁵ G. Purrello, *Gazz. Chim. Ital.* **97**, 539 (1967).⁴⁶ R. Mayer, J. Wehl, *Angew. Chem.* **76**, 861 (1964); *Angew. Chem. Internat. Edit.* **3**, 705 (1964).⁴⁷ G. Dupont, R. Dulou, G. Clement, N. G. Martinez, *Compt. Rend. Acad. Sci.* **239**, 178 (1954).⁴⁸ H. H. Szmant, F. P. Palopoli, *J. Amer. Chem. Soc.* **72**, 1757 (1950).⁴⁹ E. Schwenk, D. Papa, *J. Org. Chem.* **11**, 798 (1946).⁵⁰ J. L. Siemons, M. Vignau, *Bull. Soc. Chim. France*, **1951**, 90.⁵¹ E. C. Kornfeld, *J. Org. Chem.* **16**, 131 (1951).⁵² C. G. Joshi, J. L. Bose, *J. Sci. Ind. Res. (India)* **21B**, 284 (1962).⁵³ H. L. J. Halter, W. F. Barthel, U.S. Patent, 2,358,925, U.S. Secretary of Agriculture (1944); *C. A.* **39**, 1948 (1945).⁵⁴ British Patent 633,427, Sterling Drug (1949); *C. A.* **44**, 4925 (1950).

Table 7b. Dimethylthioamides from Ketones via the Willgerodt-Kindler Reaction

Ketone	Yield (%)	References
	70	69, 70
	80	70
	75	69, 70, 71
	40	70
	68, 65	70, 72
	58	70
	78	73
	79	73
	74	73
	—	73
	58	55, 73
	—	25, 27, 28, 30, 55, 56, 73, 74
	—	55, 73
	—	27, 30, 55, 73
	—	27, 30, 38, 55, 73, 84
	42	25, 27, 28, 30, 55, 56, 73, 74
	—	27, 30, 55, 73

⁵⁵ S. Lecolier, *French Patent* 1,409,441 (1965), Etat Francais (1965); *C. A.* **64**, 2019 (1966).⁵⁶ F. Asinger, A. Saas, S. Mayer, *Monatsh. Chem.* **98**, 825 (1967).⁵⁷ M. S. Newman, *J. Org. Chem.* **9**, 521 (1944).⁵⁸ C. D. Gutsche, F. A. Hoyer, *J. Amer. Chem. Soc.* **72**, 4285 (1950).⁵⁹ E. Dyneser, *Acta Chem. Scand.* **13**, 360 (1959).⁶⁰ O. Dann, J. Lang, H. Vohl, *Liebigs Ann. Chem.* **631**, 116 (1960).⁶¹ M. Hartmann, W. Bosshard, *Helv. Chim. Acta* **24**, 28E (1941).

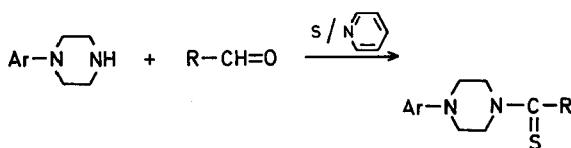
Table 7c. Miscellaneous Thioamides from Ketones via the Willgerodt-Kindler Reaction

Ketone	Amine	Yield (%)	Reference
	$\text{HN}(\text{C}_6\text{H}_5)_2$	48	70
	$\text{HN}(\text{C}_6\text{H}_5)_2$	50	75
	$\text{HN}(\text{C}_6\text{H}_5)_2$	38	51
	$\text{H}_2\text{N}-\text{CH}_3$	—	71
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$	23	75
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$	32	75
	$\text{HN}(\text{C}_6\text{H}_5)_2$	16	75
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$	40	76
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$	42	76
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{OCH}_3$	36	76
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{OC}_2\text{H}_5$	75	76
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{OC}_3\text{H}_7-i$	58	76
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{OC}_3\text{H}_7-n$	46	76
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{OC}_4\text{H}_9-n$	42	76
	$\text{HN}(\text{C}_6\text{H}_5)_2$	—	70
	$\text{HN}(\text{C}_6\text{H}_5)_2$	—	70
	$\text{HN}(\text{C}_6\text{H}_5)_2$	—	70
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$	26	77

⁶² D. Nightingale, R. A. Carpenter, *J. Amer. Chem. Soc.* **71**, 3560 (1949).

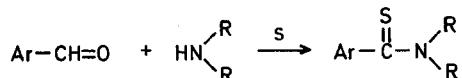
see also G. Purrello, *Gazz. Chim. Ital.* **95**, 699 (1965).

⁶³ P. A. Barrett, *J. Chem. Soc.* **1957**, 2058.

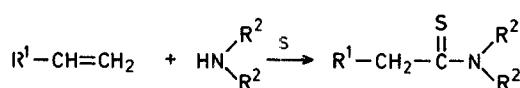
Table 7d^a. Thioamides from Piperazines⁷⁸

Ar	R	Yield (%)
	$\text{H}_3\text{C}-\text{CH}(\text{CH}_3)_2-$	50
	C_3H_7-	38
	C_6H_5-	77
	$\text{C}_6\text{H}_5-\text{CH}_2-$	32
	CH_2-	4
	$\text{S}_2\text{C}_6\text{H}_5-$	51
	$\text{O}_2\text{N}-\text{C}_6\text{H}_4-$	62

^a The examples given in this table are representative only. The original article⁷⁸ contains a total of 47 reactions with yields ranging from 3 to 86%.

Table 8. Aldehydes in the Willgerodt-Kindler Reaction

Aldehyde	Amine	Yield (%)	References
	NH_3	—	69, 71
	$\text{HN}(\text{CH}_3)_2$	80	69, 70
	$\text{HN}(\text{C}_2\text{H}_5)_2$	—	69
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$	—	69
	$\text{HN}(\text{O})$	23–94 ^a	79
	$\text{HN}(\text{C}_6\text{H}_5)_2$	10–73 ^a	79
	$\text{H}_2\text{N}-\text{CH}_3$	—	69
	$\text{HN}(\text{CH}_3)_2$	—	69, 71
	$\text{HN}(\text{O})$	9–64 ^a	79

Table 9a. Hydrocarbons in the Willgerodt-Kindler Reaction

Hydrocarbon	Amine	Yield (%) of Thioamide	References
		58	8
		51	8, 36
	$\text{H}_2\text{N}-\text{C}_7\text{H}_{15-n}$	59	10
	$\text{H}_2\text{N}-\text{CH}_2-\overset{\text{C}_2\text{H}_5}{\underset{\parallel}{\text{C}}}-\text{C}_4\text{H}_9-n$	49	10
	$\text{H}_2\text{N}-\text{CH}_2-\text{C}_6\text{H}_5$	34	10
	$\text{H}_2\text{N}-\text{C}_6\text{H}_5$	23	10
	$\text{H}_2\text{N}-\overset{\text{CH}_2\text{CH}_2\text{OH}}{\underset{\text{CH}_2\text{CH}_2\text{OH}}{\text{CH}_2\text{C}-\text{OH}}}$	10	10
	$\text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{OH}$	3.5	10
		63	10
		59	10
		61	10
		—	36
		—	36

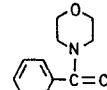
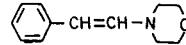
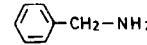
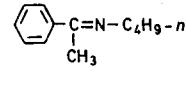
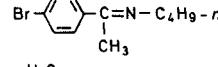
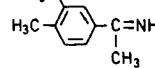
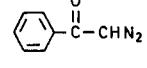
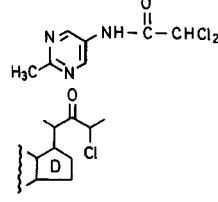
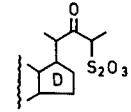
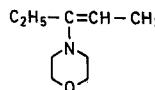
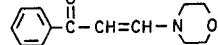
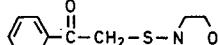
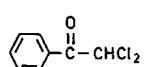
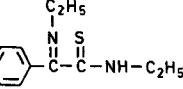
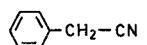
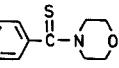
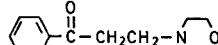
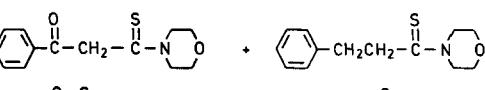
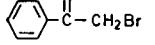
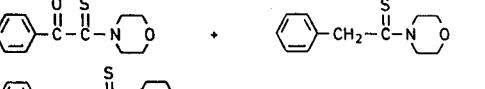
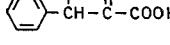
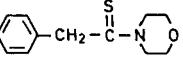
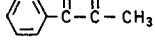
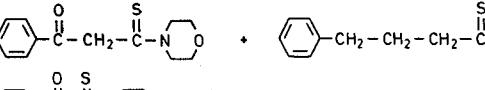
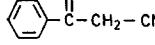
Table 8. Continued

Aldehyde	Amine	Yield (%)	References
		10-92 ^a	79
	$\text{HN}-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{CH}}}$	—	69
		69	81
		62	81
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_2$	56	81

^a Solvent and temperature changes

- ⁶⁴ R. Fischer, O. Jeger, *Helv. Chim. Acta* **34**, 1084 (1951).
⁶⁵ W. Ried, W. Ochs, H. Liebig, K. Wagner, *Liebigs Ann. Chem.* **757**, 147 (1972).
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⁶⁸ R. H. Bible, Jr., *J. Amer. Chem. Soc.* **79**, 3924 (1957).
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⁷⁰ K. Kindler, *Arch. Pharm.* **265**, 389 (1927).
⁷¹ K. Kindler, *German Patent* 405,675 (1924); *Chem. Zentr.* **96**, I, 1529 (1925).
⁷² K. Kindler, W. Peschke, *Arch. Pharm.* **272**, 236 (1934).
⁷³ K. Kindler, S. Li, *Ber. dtsch. chem. Ges.* **74**, 321 (1941).
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⁷⁵ J. Stanek, *Chem. Listy* **41**, 159 (1947).
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⁷⁸ C. B. Pollard, J. C. Brown, *J. Amer. Chem. Soc.* **77**, 6685 (1955).
⁷⁹ A. Carayon-Gentil, M. Minot, P. Chabrier, *Bull. Soc. Chim. France* **1964**, 1420.
⁸⁰ P. Chabrier, S. H. Renard, *Compt. Rend. Acad. Sci.* **228**, 850 (1949).
⁸¹ E. Golovinshii, A. Spasov, *Compt. Rend. Acad. Bulg. Sci.* **15**, 507 (1962); *C. A.* **60**, 5391 (1964).
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⁸³ G. Purrello, *Gazz. Chim. Ital.* **97**, 557 (1967).
⁸⁴ F. Asinger, A. Saus, H. Offermanns, F. A. Dagga, *Liebigs Ann. Chem.* **723**, 119 (1969).

Table 9b. Amines, Imines, etc. in the Willgerodt Reaction

Substrate	Amine	Products ^a	Yield (%)	Reference
		— ^b	75	46
		— ^b	18	83
		— ^b	41	82
	—	— ^{b, c}	26-82	84
	—	— ^c	—	84
	—	— ^c	—	95
		— ^b	—	84
		— ^b	—	85
		— ^b	—	95
	—	— ^c	35	96
	—	— ^c	60	96
	—	— ^c	—	97
	$\text{H}_2\text{N}-\text{C}_2\text{H}_5$		—	86
			44 ^d	87, 88
			—	89
			—	90
			—	91
			—	92
			—	88

^a Expected thioamide as product unless otherwise stated.^b Dimethylformamide as solvent.^c Only sulfur added.^d Loss of cyano group.

3. Reaction of Heterocyclic Compounds

A large number of heterocyclic ketones have been converted to amides by the Willgerodt reaction (Table 10). The reaction has also been applied to aldehydes, unsaturated hydrocarbons, saturated hydrocarbons and alcohols in various series (Table 11).

Willgerodt Reaction of 5-Ethylthiophen-2-yl Methyl Ketone¹⁰²:

5-Ethylthiophen-2-yl methyl ketone (10 g), sulfur (25 g), concentrated ammonium hydroxide solution (25 ml), and dioxan (30 ml) were sealed in a Carius tube and heated at 150–160° for 11–12 h. The contents of the tube were evaporated to dryness and the residue was extracted several times with boiling water. The aqueous extracts were cooled and the crude amide separated by filtration. 5-Ethylthiopheneacetamide was obtained; yield: 42%; m.p. 148°.

In the same manner, 2-thiophencarboxaldehyde was converted to 2-thiophencarboxamide; yield: 63%; m.p. 180°.

Table 10a. Willgerodt Reaction of Heterocyclic Methyl Ketones^c

Ar in Ketone	Yield (%)	References
	70	61
	83	98
	1–53 ^b	99, 100, 101
	5–13 ^b	102
	20–28 ^b	102
	27–29 ^b	102
	41–54 ^b	102
	42–55	102
	40–55	102
	1–34 ^b	101, 102
	19–95 ^b	99, 101, 102
	10	104
	18–27 ^b	104
	70	105
	53	105
	58	105

Table 10a. Continued

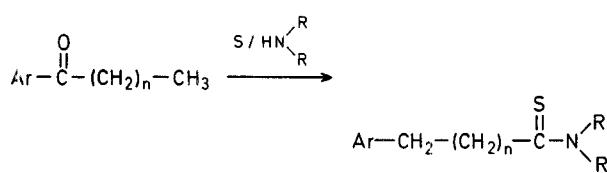
Ar in Ketone	Yield ^a (%)	References
	85	105
	68	105

^a Yield of expected amide.

^b Changes of temperature and solvent.

^c For 10 examples in the thianaphthyl methyl ketone (yields: 27 to 86%) series see Lit.^{106,107}.

Table 10b. Willgerodt Reaction of Alkyl Heterocyclic Ketones



Ketone	Yield (%)	Reference
	25–42 ^a	101
	18–37 ^a	101
	48–80 ^a	103
	22–27 ^a	103
	6.5–7.8 ^a	103

^a Changes of solvent and temperature

⁸⁵ G. Purrello, *Ann. Chim. (Rome)* **51**, 143 (1961).

⁸⁶ F. Asinger, H. Schermann, A. Saus, *Monatsh. Chem.* **100**, 724 (1969).

⁸⁷ G. Purrello, *Gazz. Chim. Ital.* **95**, 1089 (1965).

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⁹⁸ A. Dornow, W. Schacht, *Chem. Ber.* **82**, 117 (1949).

⁹⁹ O. Dann, H. Distler, *Chem. Ber.* **84**, 423 (1957).

Table 11. Miscellaneous Heterocyclic Compounds in the Willgerodt Reaction

Heterocyclic compound	Yield (%) of Product	Reference
	63-70 ^a	102
	23-30 ^a	102
	22-35 ^a	102
	10-20 ^a	104
	45	113
	27	36

^a Changes in solvent and temperature.

The Kindler modification has also been successful with a number of heterocyclic ketones (Table 12) as well as with certain hydrocarbons (Table 13). This is particularly true of methyl groups in α or γ positions to the nitrogen of the ring since they are activated.

Table 12. Willgerodt-Kindler Reaction of Heterocyclic Ketones

Ketone	Amine	Yield (%)	References
		66	103, 109
		40	103, 109
		—	109
		—	110
		—	111
		—	106, 112
		74	49, 112
		86	112
		46	114

Table 12. Continued

Ketone	Amine	Yield (%)	References
		27 ^b	114
		—	114
		27	114
		24-30 ^c	115
		4 ^c	115
		16-34 ^c	115
		35 ^c	115
		16 ^c	115
		35	116
		2	116
		—	117
		—	70
		—	118
		65	49
		9	63

Table 12. Continued

Ketone	Amine	Yield (%)	Reference
		25	119
		22	119
		9.7	119
	Alk-NH ₂	—	70
		—	118

^a Yield of expected thioamide unless otherwise indicated.^b Yield based on acid obtained on hydrolysis.^c Yield based on ester obtained on hydrolysis and esterification.

- ¹⁰⁰ O. Dann, German Patent 832,755 (1952); C. A. **52**, 11943 (1958).
- ¹⁰¹ J. A. Blanchette, E. V. Brown, *J. Amer. Chem. Soc.* **74**, 1066 (1952).
- ¹⁰² J. A. Blanchette, E. V. Brown, *J. Amer. Chem. Soc.* **73**, 2779 (1951).
- ¹⁰³ E. V. Brown, J. A. Blanchette, *J. Amer. Chem. Soc.* **72**, 3414 (1950).
- ¹⁰⁴ J. A. Blanchette, E. V. Brown, *J. Amer. Chem. Soc.* **74**, 2098 (1952).
- ¹⁰⁵ H. Gilman, S. Avakian, *J. Amer. Chem. Soc.* **68**, 2104 (1946). N. P. Buu-Hoi, R. Royer, *Rec. Trav. Chim. Pays-Bas* **67**, 175 (1948).
- ¹⁰⁶ Y. Matsuki, T. Kanda, *Nippon Kagaku Zasshi* **86**, 643 (1965); C. A. **65**, 674 (1966).
- ¹⁰⁷ Y. Matsuki, T. Kanda, *Nippon Kagaku Zasshi* **86**, 99 (1965); C. A. **62**, 16172 (1965).
- ¹⁰⁸ A. Dornow, G. Petsch, *Chem. Ber.* **86**, 1404 (1953).
- ¹⁰⁹ N. P. Buu-Hoi, Nguyen-Hoan, *Rec. Trav. Chem. Pays-Bas* **68**, 5 (1949).
- ¹¹⁰ J. H. Ford, G. C. Prescott, D. R. Colingsworth, *J. Amer. Chem. Soc.* **72**, 2109 (1950).
- ¹¹¹ D. L. Turner, *J. Amer. Chem. Soc.* **70**, 3961 (1948).
- ¹¹² R. L. Malan, P. M. Dean, *J. Amer. Chem. Soc.* **69**, 1797 (1947).
- ¹¹³ C. R. Noller, E. A. Wunderlich, *J. Amer. Chem. Soc.* **74**, 3835 (1952).
- ¹¹⁴ J. Cejka, M. Ferles, S. Chladek, J. Labsky, M. Zelinka, *Collect. Czech. Chem. Commun.* **26**, 1429 (1961).
- ¹¹⁵ E. Bisagni, R. Royer, *Bull. Soc. Chim. France* **1962**, 86.
- ¹¹⁶ K. L. Rinehart, Jr., R. J. Curby, Jr., P. E. Sohol, *J. Amer. Chem. Soc.* **79**, 3420 (1957).
- ¹¹⁷ G. Vasiliu, O. Maior, I. Baciu, *Rev. Chim. (Bucharest)* **15**, 47 (1964); C. A. **61**, 1854 (1964).
- ¹¹⁸ British Patent 558,774, Soc. Chem. Ind. (Basle) (1942); Brit. C. A. **BII**, 102 (1944).
- ¹¹⁹ V. G. Avramenko, T. Y. Shivnyuk, V. P. Alekseva, N. N. Suvorov, *Tr. Mosk. Khim. Tekhnol. Inst.* **1972**, (70), 116; C. A. **79**, 5303 (1973).
- ¹²⁰ Y. M. Yutilov, I. A. Sverilova, *Metody Poluch. Khim. Reakt. Prep.* **20**, 189 (1969); C. A. **76**, 19267 (1972).

Table 13. Willgerodt-Kindler Reaction of Miscellaneous Heterocyclic Compounds

Substrate	Amine	Yield (%)	References
	H ₂ N-	63	120-125, 129, 130
	H ₂ N-	22	124, 126
	H ₂ N-	—	129
	H ₂ N-	—	129
	H ₂ N-	—	129
	H ₂ N-	—	129
	H ₂ N-	—	129
	H ₂ N-	—	129
	H ₂ N-	—	129
	H ₂ N-	0	126
	H ₂ N-	40	124, 126
	H ₂ N-	—	131
	H ₂ N-	19, 31 ^a	125, 132
	H ₂ N-	17, 29 ^a	132
	H ₂ N-	—	127
	H ₂ N-	—	134
	H ₂ N-	57	132
	H ₂ N-	50	132
	H ₂ N-	21	132
	H ₂ N-	28	132
	H ₂ N-	29	132
	H ₂ N-	—	135
	H ₂ N-	—	126
	H ₂ N-	—	127
	H ₂ N-	23 ^b	126
	H ₂ N-	—	127

Table 13. Continued

Substrate	Amine	Yield (%)	References
	$\text{H}_2\text{N}-[\text{CH}_2]_4-\text{C}_6\text{H}_9-t$	—	128, 135
		127	
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-$	—	127
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_3$	—	122
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-$	—	134
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-$	—	122
		—	127
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-$	—	134
	$\text{H}_2\text{N}-[\text{CH}_2]_4-\text{C}_6\text{H}_9-t$	—	135
	$\text{H}_2\text{N}-\text{C}_6\text{H}_9-t$	—	135
		—	127
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-$	65	136
$\text{H}_2\text{C}=\text{CH}-$	$t\text{-Alk-NH}_2$	—	128, 135
		50	137
		—	127
		—	124
		—	124
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-$	—	124
	$\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{NH}_2$	—	124
	various amines	—	138
		—	124
$\text{C}_2\text{H}_5\text{O}-$		—	124
		—	127
		—	127

^a Product was mostly 2-(4-pyridyl)benzothiazole.^b Product was mostly 2-(β -4-pyridyl)benzothiazole.

4. Special Syntheses

A number of special syntheses using the Willgerodt reaction or the Kindler modification of it have been carried out and many of these have industrial significance. It has been shown that by proper operation¹³⁹ of the Kindler modification on hydrocarbons using sulfur and ammonia, it is possible to prepare nitriles instead of thioamides. This is done by pressure release at high temperature when the thioamides will lose hydrogen sulfide to give nitriles directly. 2,3-Dihydro-4*H*-pyran-2-carboxaldehyde can be converted to the diamide of adipic acid under Willgerodt conditions¹⁴⁰. Monsanto Chemical Company has announced a process for the preparation of urea from carbon monoxide, sulfur, and ammonia. Another interesting synthesis is that of saccharin by the Willgerodt reaction of *o*-chloromethylbenzenesulfonyl chloride in which a 30% yield is claimed¹⁴¹.

Preparation of Saccharin¹⁴¹:

o-Chloromethylbenzenesulfonyl chloride (4.49 g) was heated in a sealed tube with concentrated ammonium hydroxide solution (30 ml) and sulfur (6.4 g) for 6 h at 165°. The reaction mixture was evaporated to dryness, taken up in hot water, treated with charcoal, filtered, and the saccharin precipitated by addition of concentrated hydrochloric acid; yield: 1.1 g (30%); m.p. 216–218°.

There have been several reports and patents in the area of dibasic acid production by the Willgerodt reaction. Reactions of *o*-xylene to phthalic acid, *p*-

- ¹²¹ T. Hisano, H. Koga, *Yakugaku Zasshi* **90**, 552 (1970).
- ¹²² T. P. Sycheva, M. N. Shchukina, *Biol. Aktion. Soedin. Akad. Nauk SSSR* **1965**, 42; *C. A.* **64**, 6607 (1966).
- ¹²³ M. Carmack, M. A. Spielman, *Org. React.* III Chap. 2, 83 (1946), John Wiley and Sons, New York.
- ¹²⁴ J. Schmitt, M. Suquet, *Bull. Soc. Chim. France* **1956**, 755.
- ¹²⁵ P. E. Maller, G. L. Oliver, J. R. Dann, J. W. Gates, Jr., *J. Org. Chem.* **22**, 664 (1957).
- ¹²⁶ H. D. Porter, *J. Amer. Chem. Soc.* **76**, 127 (1954).
- ¹²⁷ German Patent 1,149,356 Bayer AG (1963); *C. A.* **59**, 11441 (1965).
- ¹²⁸ R. C. Mansfield, *J. Org. Chem.* **24**, 1111 (1959).
- ¹²⁹ A. Spassov, E. Golovinski and K. Markov, *Nauchni. Tr. Viss. Med. Inst. Sofia* **7**, 275 (1960); *C. A.* **56**, 14225 (1962).
- ¹³⁰ H. Saikachi, T. Hisano, S. Yoshina, *J. Pharm. Soc. Japan* **74**, 1318 (1954); *C. A.* **49**, 15892 (1955).
- ¹³¹ British Patent 749,417 Bayer AG (1956); *C. A.* **51**, 2880 (1957).
- ¹³² N. Saikachi, T. Hisano, *Chem. Pharm. Bull. (Tokyo)* **7**, 716 (1959); *C. A.* **55**, 23494 (1961).
- ¹³³ M. Carmack, M. A. Spielman, *Org. React.* III Chap. 2, 83 (1946), John Wiley and Sons, New York.
- ¹³⁴ B. Emmert, *Chem. Ber.* **91**, 1388 (1958).
- ¹³⁵ J. L. Rainey, R. C. Mansfield, U.S. Patent 2,938,907, Rohm & Haas (1960); *C. A.* **54**, 19720 (1960).
- ¹³⁶ A. N. Kost, P. B. Terent'ev, L. A. Golovleva, *Vestn. Mosk. Univ. Ser II Khim.* **19**, 56 (1964); *C. A.* **62**, 9099 (1965).
- ¹³⁷ S. I. Suminov, *Khim. Geterotsikl. Soedin.* **2**, 375 (1968); *C. A.* **69**, 86920 (1968).
- ¹³⁸ O. N. Chupakhin, Z. V. Pushkareva, Z. Y. Kokoshko, M. I. Podgornaya, *Zh. Organ. Khimi*, **1**, 772 (1965).
- ¹³⁹ W. G. Toland, *J. Org. Chem.* **27**, 870 (1962).
- ¹⁴⁰ H. Feichtinger, W. Konkol, *Angew. Chem. Internat. Edit.* **6**, 944 (1967); *Angew. Chem. Internat. Edit.* **6**, 944 (1967).
- ¹⁴¹ H. Feichtinger, *Chem. Ber.* **104**, 1697 (1971).

xylene to terephthalic and of dimethylnaphthalenes to the corresponding dibasic acids have been carried out to make materials useful in the various plastic industries¹⁴². Certain keto-acids available from natural products have been converted to useful dibasic acids by the Willgerodt reaction, as for example, levulinic acid to glutaramide^{145, 153} and pinonic to homopinonic acid¹⁴⁴. In one case a tribasic acid has been prepared by the Kindler modification. Starting with the 1,3,5-triacetobenzene, it was converted to 1,3,5-benzenetriacetic acid¹⁴⁶.

5. Results with Cyclic Ketones

Because of the impossibility of terminal oxidation, cyclic ketones make interesting starting materials for the Willgerodt and particularly for the Kindler modification. 7-Methyl-1-tetralone when heated with morpholine and sulfur gave 7-methyl-2-morpholinonaphthalene¹⁴⁷. Similarly, 6-methoxy-1-tetralone gave 6-methoxy-2-morpholinonaphthalene¹⁴⁸. Earlier this reaction had been done with 1-tetralone¹⁴⁹ and the product was shown to have the morpholine in the 2-position. However, it was not clear which way the movement took place.

Preparation of 4-(2-Naphthyl)-morpholine¹⁴⁹:

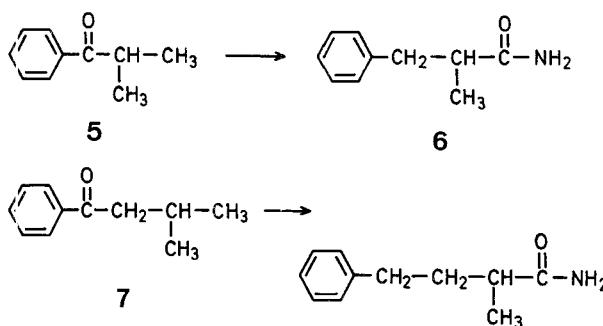
A mixture of α -tetralone (4.0 g, 0.027 mol), morpholine (2.48 g, 0.028 mol), and powdered sulfur (0.86 g, 0.027 g-atom) was heated under reflux in an oil bath at 128–135° for 8 h. The reaction mixture was allowed to cool to room temperature and stand over-night, whereupon it solidified. The solid was treated with a warm solution of concentrated hydrochloric acid (5 ml) in water (10 ml) and then decanted to a filter. This treatment was repeated twice. The oil remaining undissolved was washed with water and the washings added to the acidic filtrate. The cooled filtrate was made basic with ammonia, the suspension of the dark precipitate was cooled, filtered, and the solid washed with water to give the crude amine, which was then dried; yield: 2.87 g. Steam distillation and three recrystallizations from aqueous ethanol gave thin rods of 4-(2-naphthyl)-morpholine; m. p. 87–90°.

4-Methylcyclohexanone on heating with sulfur and morpholine rapidly equilibrates to a mixture of the 4-, 3-, and 2-ketones¹⁵⁰. This same equilibration was applied to heptan-4-one with the result that 70% 4-, 21% 3-, and 9% of the heptan-2-one were produced. If *n*-heptaldehyde were used then 83% of 2- and 17% of the 3-heptanone could be obtained with none of the aldehyde remaining¹⁵⁰. Camphor also equilibrated to give a mixture of camphor and epicalphor¹⁵⁰. Fluorenone was converted to 9,9'-difluorene by morpholine and sulfur¹⁵¹. Thiacyclobutanone opened up to the thiomorpholide of glyoxalic acid¹⁵²

instead of simply forming an enamine as did the larger thiacyclopentones.

6. The Overall Mechanism

Willgerodt thought that there was no skeletal rearrangement on the basis of the following results¹, (Scheme C)



Scheme C

However, these experiments were difficult to verify and Kindler suggested a skeletal rearrangement⁶⁹. Schantz and Rittenberg¹⁵⁴ subjected a ¹³C-labelled acetophenone to the Willgerodt-Kindler conditions and showed that there was no skeletal rearrangement. Dauben and co-workers^{155, 156} used a ¹⁴C-labelled acetophenone under Willgerodt conditions and concluded that the phenylacetamide had not rearranged but that the small amount of phenylacetic acid was produced by a rearrangement. Brown and coworkers reinvestigated this situation and showed that there was no rearrangement in either the amide or acid¹⁵⁷.

¹⁴⁶ M. S. Newman, H. S. Lawrie, *J. Amer. Chem. Soc.* **76**, 6196 (1954).

¹⁴⁷ R. Barone, *Thesis*, University of Pennsylvania 1953.

¹⁴⁸ W. G. Dauben, R. P. Ciula, J. B. Rogan, *J. Org. Chem.* **22**, 362 (1957).

¹⁴⁹ W. J. Horton, J. Van Der Bergle, *J. Amer. Chem. Soc.* **70**, 2425 (1948).

¹⁵⁰ M. Behforouz, *Thesis*, University of Indiana, 1965.

¹⁵¹ J. Stanek, *Collect. Czech. Chem. Commun.* **15**, 392 (1950).

¹⁵² K. F. Funk, R. Mayer, *J. prakt. Chem.* **21**, 65 (1963).

¹⁵³ M. Matsui, H. Kubo, M. Kibi, *Nippon Nogei Kagaku Kaishi* **29**, 893 (1955); *C.A.* **52**, 9955 (1958).

¹⁵⁴ E. M. Shantz, D. Rittenberg, *J. Amer. Chem. Soc.* **68**, 2109 (1946).

¹⁵⁵ W. G. Dauben, J. C. Reid, R. E. Yankwich, M. Calvin, *J. Amer. Chem. Soc.* **68**, 2117 (1946).

¹⁵⁶ W. G. Dauben, J. C. Reid, R. E. Yankwich, M. Calvin, *J. Amer. Chem. Soc.* **72**, 121 (1950).

¹⁵⁷ E. V. Brown, E. Cerwonka, R. C. Anderson, *J. Amer. Chem. Soc.* **73**, 3735 (1951).

¹⁵⁸ M. Carmack, G. A. Berchtold, M. Behforouz, Abstracts 147th A.C.S. Meeting page 11N (1964).

¹⁵⁹ J. A. King, F. H. McMillan, *J. Amer. Chem. Soc.* **68**, 525 (1946).

¹⁶⁰ J. A. King, F. H. McMillan, *J. Amer. Chem. Soc.* **68**, 632 (1946).

¹⁶¹ F. H. McMillan, J. A. King, *J. Amer. Chem. Soc.* **69**, 1207 (1947).

¹⁶² F. H. McMillan, J. A. King, *J. Amer. Chem. Soc.* **69**, 1207 (1947).

¹⁴² H. J. Aroyan, J. B. Wilkes, *U.S. Patent* 2734080, 2734079, California Research Corp.; *C. A.* **50**, 13092 (1956).

¹⁴³ D. Klamann, V. Kroemer, *Erdoel Kohle* **15**, 438 (1962).

¹⁴⁴ J. S. Stenson, R. V. Lawrence, *J. Org. Chem.* **19**, 1047 (1954).

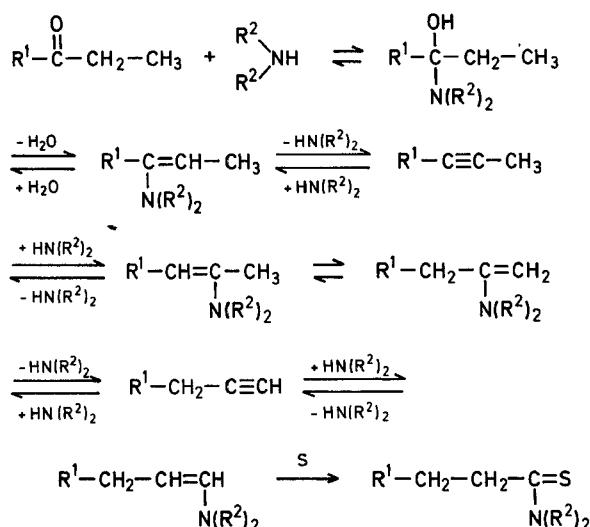
¹⁴⁵ Y. Hara, S. Fujise, *J. Chem. Soc. Japan* **74**, 698 (1953); *C. A.* **48**, 11341 (1954).

M. Matsui, H. Kubo, M. Kibi, *Nippon Nogei Kagaku Kaishi* **29**, 893 (1955); *C. A.* **52**, 9955 (1958).

The confusion in the latter case was apparently caused by an oxidation of the toluene formed on decarboxylation of the phenylacetic acid. The benzoic acid thus formed decarboxylated to cloud the issue.

7. The Detailed Mechanism

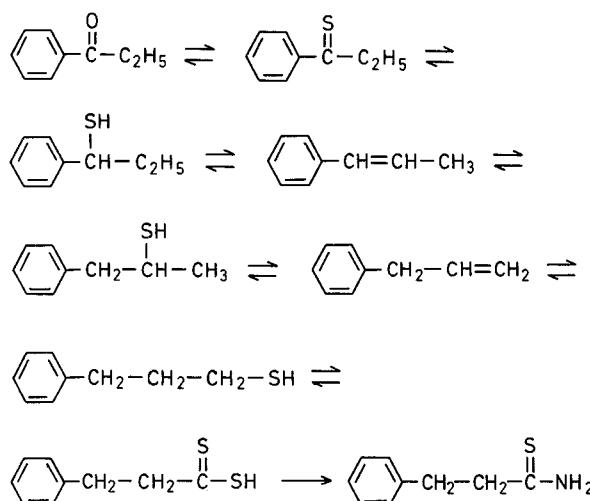
With the Willgerodt and the Kindler modification shown to involve no skeletal rearrangement the next point involves the question of how the oxidation-reduction reactions move in the chain. Carmack and DeTar very early made a suggestion as to this mechanism⁸. Carmack subsequently offered an altered version of this mechanism¹⁵⁸ (Scheme D).



R = H, alkyl

Scheme D

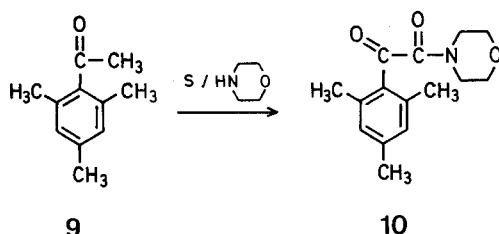
Another mechanism proposed by King and McLellan^{32, 159-163} is the following (Scheme E).



Scheme E

A somewhat modified combination of these two mechanisms was proposed by Yukawa and co-workers⁴². Somewhat unsatisfactory attempts to choose between these early suggestions were made using deuterium labelling¹⁶⁴ and optically active ketones¹⁶⁵.

However, it has been shown by Dauben and others^{63,66} that under some conditions the keto group is left intact and the attack is at the alpha-carbon atom. This had led to several suggestions to explain the migration of the oxidized state to the terminal carbon with reduction of the carbonyl group at some intermediate state, i.e., those of Dauben, Ciula and Rogan¹⁴⁸, Asinger, Schafer, and Halcour¹⁶⁶, Funk and Mayer¹⁵², and Belforouz¹⁵⁰.



It is probably unreasonable to expect the Willgerodt and the Willgerodt-Kindler reactions with so many different kinds of starting materials to proceed by the same mechanism. A final decision on an acceptable mechanism for the Willgerodt reaction on alkyl aryl ketones awaits further experimental work. Interesting by-products and intermediate types (thiazolines and imidazolines), have been investigated using essentially room temperature conditions instead of the originally rather high temperature¹⁶⁶.

Several reviews on the Willgerodt and Willgerodt-Kindler reactions have been published, i.e. by Asinger and Offermanns¹⁶⁷, Asinger and Thiel¹⁶⁸, Wegler, Kühle and Schäfer¹⁶⁹, Carmack and Spielman¹⁷⁰, Walter and Bode¹⁷¹, and Kaltwasser¹⁷². The literature has been reviewed through 1972 in the present article.

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¹⁶⁵ M. B. Bochner, *Thesis*, Princeton University, 1963.

¹⁶⁶ F. Asinger, et al., *Angew. Chem.* **75**, 1050 (1963); *Angew. Chem. Internat. Edit.* **3**, 19 (1964).

¹⁶⁷ F. Asinger, H. Offermanns, *Angew. Chem.* **79**, 953 (1967); *Angew. Chem. Internat. Edit.* **6**, 907 (1967).

¹⁶⁸ E. Asinger, M. Thiel, *Angew. Chem.* **70**, 667 (1958).

¹⁶⁹ R. Wegler, E. Kibble, W. Schäfer, *Angew. Chem.* **70**, 351 (1958).

¹⁷⁰ M. Carmack, M. A. Spielman, *Org. React.* III Chap. 2, 83 (1946). John Wiley and Sons, New York.

¹⁷¹ K. H. Boltze, H. D. Dell, *Angew. Chem.* **78**, 114 (1966); *Angew. Chem. Internat. Edit.* **5**, 125 (1966).

¹⁷² H. Kaltwasser, *Chem. Tech.* **9**, 392 (1957).

H. Kaltwasser, *Chem. Tech.* **9**, 392 (1957).

¹⁶³ F. H. McMillan, J. A. King, *J. Amer. Chem. Soc.* **70**, 4143 (1948).

¹⁶⁴ E. Cerwonka, R. C. Anderson, E. V. Brown, *J. Amer. Chem. Soc.* **75**, 30 (1953).