The Antidiabetic Activity of 3,5-Dimethylpyrazoles

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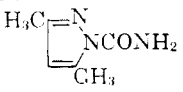
Forty-one pyrazoles were investigated for antidiabetic activity. A number of those containing methyl groups in both the 3- and 5-positions were found to possess hypoglycemic activities as great as 100 times that of tolbutamide in glucose-primed, intact, fasted rats.

During the course of an investigation in our laboratories of a series of compounds for antidiabetic activity it was found that 3,5-dimethylpyrazole-1-carboxamide (I) possessed hypoglycemic activity 25 times that of

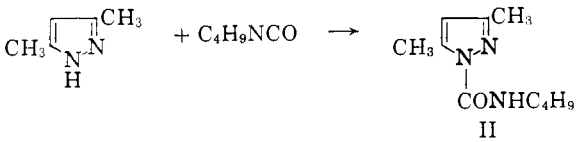


I

tolbutamide in glucose-primed, intact, fasted rats. Accordingly, a detailed study was made of the structure–activity relationship in compounds of this general class.

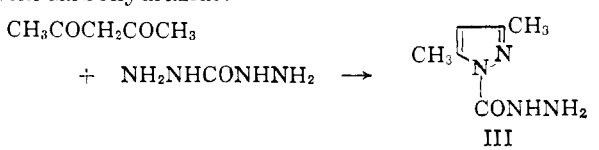
Chemistry.—The new pyrazoles that were prepared are listed in Table I. Table II gives the activity of these compounds along with that of a number previously reported in the chemical literature. The majority of the compounds were prepared by the reaction between β-diketones and hydrazines or semicarbazides.

1-*n*-Butylcarbamyl-3,5-dimethylpyrazole (II) was prepared by treatment of 3,5-dimethylpyrazole with *n*-butyl isocyanate.



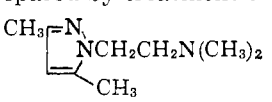
II

3,5-Dimethylpyrazole-1-carboxylic acid hydrazide (III) was prepared by treatment of 2,4-pentanedione with carbohydrazide.



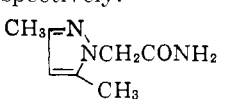
III

A number of the 1-substituted pyrazoles were prepared by alkylation or acylation of 3,5-dimethylpyrazole. 1-(β-Dimethylaminoethyl)-3,5-dimethylpyrazole (IV) was prepared by treatment of the sodium salt

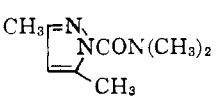


IV

of 3,5-dimethylpyrazole with β-dimethylaminoethyl chloride. Similar alkylations were carried out with chloroacetamide and dimethylcarbamyl chloride to give the corresponding 1-substituted derivatives V and VI, respectively.

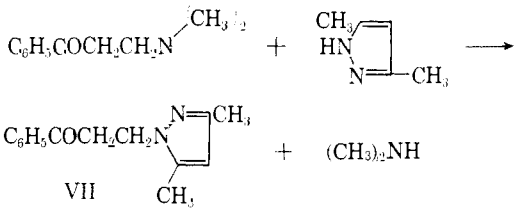


V



VI

β-(3,5-Dimethyl-1-pyrazolyl)-propiophenone (VII) was prepared by heating the Mannich base β-dimethylaminopropiophenone with 3,5-dimethylpyrazole on the steam bath.



VII

Biological Testing and Results.—The compounds listed in Table II were tested in male Sprague Dowley rats following overnight fast. At the time of treatment with the test compound the rats were injected subcutaneously with 100 mg. of glucose. The blood sugar lowering ability was compared with that for tolbutamide. Potency estimates were made by determining from the dose response curves, doses of compounds which produce comparable blood sugar lowering.

From the data presented in Table II it appears that the most active of the compounds tested are those containing methyl groups in both the 3- and 5-positions. Substitution of one or more of the methyl groups with a hydrogen, ethyl, trifluoromethyl, carboxyl, benzyl, phenoxymethyl, or phenyl group in the compounds tested lowers activity appreciably. The most active compounds also appear to be those that are unsubstituted in the 4-position and in the 1-position possess either a H, $-CONH_2$, $-CONHC_6H_5$, $-CON(CH_3)_2$, $-CONHNH_2$ or $-COC_6H_5$ grouping. The possibility exists that some or all of the active compounds listed above that contain groupings other than hydrogen in the 1-position owe their activity to hydrolysis to 3,5-dimethylpyrazole in the gut or to a metabolic transformation in tissue to this compound. Compounds of this general type are known to be hydrolyzed somewhat readily.[1,2]

Experimental[3]

3,5-Diethylpyrazole Hydrochloride. A.—To a solution of 13.0 g. (0.1 mole) of hydrazine sulfate in 75 ml. of a 10% aqueous sodium hydroxide solution cooled to 10–15° was added 12.8 g. (0.1 mole) of 3,5-heptanedione. The reaction mixture was stirred at this temperature for 1 hr. To the mixture was then added 50 ml. of water and the resulting mixture extracted with ether. The ethereal extracts were washed with a saturated salt solution and dried over anhydrous sodium sulfate. The **hydrochloride** was prepared by addition of gaseous dry hydrogen chloride to the ethereal solution.

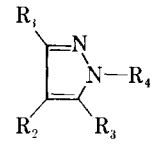
(1) T. Posner, *Ber.*, **34**, 3980 (1901).

(2) A detailed report from these laboratories on the hypoglycemic activity of 3,5-dimethylpyrazole was presented by G. C. Gerritsen and W. E. Dulin at the Annual Meeting of the American Diabetes Association, Atlantic City, N. J., June 14, 1963 (*J. Am. Diabetes Assoc.*, in press).

(3) All melting points were corrected and were taken in a capillary tube. All boiling points are uncorrected.

TABLE I

PYRAZOLES

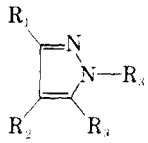


R_1	R_2	R_3	R_4	Procedure	Yield, (%)	M.p., °C.	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
C_2H_5	H	C_2H_5	H	A	88	78–83[a]	$C_7H_{12}N_2 \cdot HCl$	52.33	8.16	17.44[b]	52.15	7.99	17.00[b]
CH_3	H	CF_3	H	A	48	88.5–89.5[c]	$C_5H_5N_2F_3$	40.01	3.36	18.66	39.73	2.98	18.43
CH_3	H	$C_6H_5CH_2$	H	A	96	72–73.5[d]	$C_{11}H_{12}N_2$	76.71	7.02	16.27	76.77	6.83	16.16
CH_3	H	$C_6H_5OCH_2$	H	A[e]	81	88.5–90[d]	$C_{11}H_{12}N_2O$	70.18	6.43	14.88	70.14	6.37	14.57
CH_3	$(C_2H_5)_2NCH_2CH_2$—	CH_3	H	B		223.5–31.5[f]	$C_{11}H_{21}N_3 \cdot 2HCl \cdot H_2O$	[g]	[g]	14.68	[g]	[g]	14.98
CH_3	H	CH_3	—CH_2CH_2OH	B	78	77.5–78.5[d]	$C_7H_{12}N_2O$	59.97	8.63	19.99	59.53	8.50	19.98
CH_3	H	CH_3	$CH_2CH_2N(CH_3)$		75	175–8[f,h]	$C_9H_{17}N_3 \cdot 2HCl$	[i]	[i]	17.50	[i]	[i]	17.22
CH_3	H	CH_3	H_2NCOCH_2	C	20	192.5–93[j]	$C_7H_{11}N_3O$	54.88	7.24	27.43	54.80	6.79	27.11
CH_3	H	CH_3	$C_6H_5COCH_2CH_2$		18	70.5–71[c]	$C_{14}H_{16}N_2O$	73.65	7.06	12.27	73.55	6.74	11.99
C_2H_5	H	C_2H_5	NH_2CO		63	66–7[k]	$C_8H_{13}N_3O$	57.46	7.84	25.13	57.53	7.52	25.09
CH_3	H	CH_3	C_4H_9NHCO		100	34.5–36	$C_{10}H_{17}N_3O$	61.51	8.78	21.52	61.54	8.45	21.63
CH_3	H	CH_3	$(CH_3)_2NCO$	C	48	[l]	$C_8H_{13}N_3O$	57.46	7.84	25.13	57.32	7.68	24.71
CH_3	H	CH_3	NH_2NHCO		62	107.5–8.0[m]	$C_6H_{10}N_4O$	46.74	6.54	36.34	47.05	6.50	36.01
CH_3	H	CH_3	p-$HOCOC_6H_5$		80	158.5–60.0[n]	$C_{12}H_{12}N_2O_2$	66.55	5.60	12.96	66.54	5.56	12.92
CH_3	H	CH_3	p-$H_2NCOC_6H_5$	D	63	158.5–59.5[n]	$C_{12}H_{13}N_3O$	66.96	6.09	19.52	66.93	6.17	19.69
CH_3	H	CH_3	p-$CH_3NHCOC_6H_5$	D[o]	20	117–18.5[d]	$C_{13}H_{15}N_3O$	68.10	6.59	18.33	68.05	6.66	18.31
CH_3	H	CH_3	p-$(CH_3)_2NCOC_6H_5$	D[p]	61	103–4[q]	$C_{14}H_{17}N_3O$	69.11	7.04	17.27	69.05	6.97	17.10
CH_3	H	CH_3	p-$H_2NSO_2C_6H_5$		95	239.5–41.5[r]	$C_{11}H_{13}N_3O_2S$	52.57	5.21	12.76	52.25	5.09	12.72
CH_3	H	CH_3	p-$NH_2CONHSO_2C_6H_5$		73	192.5–4.0[j]	$C_{12}H_{14}N_4O_3S$	48.97	4.79	19.04[s]	48.96	4.68	18.27[s]
CH_3	H	CH_3	p-ClC_6H_4CO		56	108 (0.1 mm.)	$C_{12}H_{11}ClN_2O$	61.41	4.72	11.94	61.53	4.87	11.91

[a] M.p. of hydrochloride. [b] Calcd: Cl, 22.07. Found: Cl, 22.23. [c] Recrystallized from petroleum ether (Skellysolve B). [d] Recrystallized from cyclohexane. [e] The product precipitated from the reaction mixture and was separated by filtration rather than by ether extraction. [f] Dihydrochloride. [g] Calcd.: Cl, 24.77. Found: Cl, 24.58. [h] Recrystallized from 2-propanol. [i] Calcd.: Cl, 29.52. Found: Cl, 29.54. [j] Recrystallized from ethanol. [k] Recrystallized from a benzene–petroleum ether (Skellysolve B) mixture. [l] B.p. 92–95° (3.5 mm.). [m] Recrystallized from ether. [n] Recrystallized from ethyl acetate. [o] An equivalent amount of a 40% methylamine solution was used in place of ammonium hydroxide. [p] An equivalent amount of a 25% dimethylamine solution was used in place of ammonium hydroxide. [q] Recrystallized from cyclohexane–ethyl acetate (3:1). [r] Recrystallized from acetic acid. [s] Calcd.: S, 10.89. Found: S, 10.93.

TABLE II

ANTIDIABETIC ACTIVITY OF PYRAZOLES



R_1	R_2	R_3	R	Hypoglycemic activity (tolbutamide = 1)
H[a]	H	H	H	<4
H[a]	H	CH_3	H	<4
CH_3[a]	H	CH_3	H	50–60
CH_3[b]	CH_3	H	H	<2
C_2H_5[c]	H	C_2H_5	H	<2
COOH[a]	H	COOH	H	1–2
CH_3	H	CH_3	H	<2
CH_3	H	$-CH_2C_6H_5$	H	<2
CH_3	H	$-CH_2OC_6H_5$	H	4
CH_3[d]	CH_3	CH_3	H	4
CH_3[e]	Br	CH_3	CH_3	<2
C_6H_5[f]	H	C_6H_5	H	2
CH_3	$2HCl\cdot(C_2H_5)_2NCH_2CH_2$	CH_3	H	<2
CH_3[g]	H	CH_3	CH_3	4–8
CH_3	H	CH_3	$-CH_2CH_2OH$	<2
CH_3	H	CH_3	$-CH_2CH_2N(CH_3)_2\cdot 2HCl$	<2
CH_3	H	CH_3	$-CH_2CONH_2$	<1
CH_3	H	CH_3	$-CH_2CH_2COC_6H_5$	<2
CH_3[h]	H	CH_3	$-C(=NH)NH_2\cdot HNO_3$	2
H[g]	H	H	$-CONH_2$	<2
CH_3[i]	CH_3	H	$-CONH_2$	<2
CH_3[j]	H	CH_3	$-CONH_2$	25
CH_3[k]	H	C_2H_5	$-CONH_2$	<2
C_2H_5	H	C_2H_5	$-CONH_2$	<1
CH_3	H	CH_3	$-CONHC_4H_9$	4–8
CH_3	H	CH_3	$-CON(CH_3)_2$	30
CH_3[l]	H	CH_3	$-CONHC_6H_5$	20–30
CH_3[k]	H	CH_3	$-CON(C_6H_5)_2$	<1
CH_3	H	CH_3	$-CONHNH_2$	16
CH_3[l]	CH_3	CH_3	$-CONH_2$	<1
CH_3[m]	H	CH_3	p-$SO_2C_6H_4CH_3$	<1
CH_3[n]	H	CH_3	p-$C_6H_5NH_2$	<2
CH_3	H	CH_3	p-C_6H_5COOH	<1
CH_3	H	CH_3	p-$C_6H_5CONH_2$	<1
CH_3	H	CH_3	p-$C_6H_5CONHCH_3$	<2
CH_3	H	CH_3	p-$C_6H_5CON(CH_3)_2$	<2
CH_3	H	CH_3	p-$C_6H_5SO_2NH_2$	<1
CH_3	H	CH_3	p-$C_6H_5SO_2NHCONH_2$	<2
CH_3[o]	H	CH_3	$-COC_6H_5$	100
CH_3	H	CH_3	p-COC_6H_5Cl	25–50
CH_3[p]	H	CH_3	p-$COC_6H_5NO_2$	25

[a] Purchased from the Aldrich Chemical Co., Milwaukee, Wis. [b] O. Wallach, *Ann.*, **329**, 132 (1903). [c] Tested as the hydrochloride [d] T. Posner, *Chem. Ber.*, **34**, 3981 (1901). [e] T. Posner, *ibid.*, **34**, 3984 (1901). [f] L. Knorr, *Ann.*, **279**, 232 (1894). [g] F. L. Scott and J. Reilly, *J. Am. Chem. Soc.*, **74**, 4562 (1952). [h] O. Wallach, *Ann.*, **329**, 132 (1903). [i] G. M. Mkryan and N. A. Papazyan, *Dokl. Akad. Nauk Arm. SSR*, **16**, 103 (1953). [j] R. A. Henry and W. M. Dehn, *J. Am. Chem. Soc.*, **71**, 2297 (1949); A. S. Wheeler and R. D. Norton, *ibid.*, **50**, 2488 (1928). [k] F. L. Scott, A. Ahearne, and J. Reilly, *J. Org. Chem.*, **22**, 1688 (1957). [l] T. Posner, *Chem. Ber.*, **34**, 3982 (1901). [m] K. A. Jensen and O. R. Hansen, *Acta Chem. Scand.*, **6**, 195 (1952). [n] D. Dal Monte Casoni, A. Mangini, and R. Passerini, *Boll. Sci. Fac. Chim. Ind. Bologna*, **12**, 147 (1954); *Chem. Abstr.*, **49**, 8701*h* (1955). [o] W. Ried and B. Schleimer, *Angew. Chem.*, **70**, 164 (1958).

1-(β-Dimethylaminoethyl)-3,5-dimethylpyrazole Dihydrochloride.—A mixture of 19.2 g. of 3,5-dimethylpyrazole, 200 ml. of dry toluene, and 15.6 g. (0.4 mole) of sodamide was refluxed with stirring for 2.5 hr. The mixture was cooled, 26.0 g. (0.2 mole) of β-dimethylaminoethyl chloride hydrochloride was added, and the mixture heated under reflux for 4 hr. Water (200 ml.) was added, the toluene layer separated, and the aqueous layer extracted with benzene (100 ml.). The combined toluene–benzene extracts were distilled through a Vigreux column. There was obtained 25.28 g. (76%) of a colorless oil boiling at 79–82° (0.45 mm.), n_D^{24} 1.4800. The **dihydrochloride** was prepared by adding gaseous hydrogen chloride to an ethereal solution of the free base.

4-Diethylaminoethyl-3,5-dimethylpyrazole Dihydrochloride. B.—To a stirred solution of 6.0 g. (0.03 mole) of 3-diethylaminoethyl-2,4-pentanedione[4] in 5 ml. of water was added at 5–10° a solution of 1.5 g. (0.03 mole) of hydrazine hydrate in 5 ml. of water. The mixture was heated under reflux for 1 hr. The solution was saturated with potassium carbonate and extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate and the **dihydrochloride** prepared by addition of an ethereal solution of hydrogen chloride. The solid was sep-

(4) V. Reřicha and M. Protiva, *Chem. Listy*, **44**, 232 (1950).

arated by filtration and purified by recrystallization from 2-propanol to give 0.65 g. of colorless prisms.

3,5-Dimethylpyrazole-1-acetamide. C.—To 4.3 g. (0.11 mole) of sodamide was added a solution of 9.6 g. (0.1 mole) of 3,5-dimethylpyrazole in 100 ml. of dry benzene. The reaction mixture was heated under reflux for 30 min. To the mixture was then added 9.4 g. (0.1 mole) of chloracetamide and refluxing was continued for 1 hr. The mixture was allowed to cool to room temperature and was filtered. The solid was slurried with hot chloroform, filtered, and the filtrate evaporated to dryness. The residue was recrystallized from ethanol.

β-(3,5-Dimethylpyrazole-1)propiophenone.—A mixture of 17.7 g. (0.1 mole) of β-dimethylaminopropiophenone and 9.67 g. of 3,5-dimethylpyrazole was heated on a steam bath for 3 hr. The mixture, which partially solidified upon cooling, was triturated with a small amount of petroleum ether. The solid was removed by filtration and recrystallized from petroleum ether (Skellysolve B).

3,5-Diethylpyrazole-1-carboxamide.—To a solution of 11.2 g. (0.1 mole) of semicarbazide hydrochloride in 30 ml. of water was added a solution of 12.8 g. (0.1 mole) of 3,5-heptanedione in 10 ml. of ethanol over a period of 10 min. Stirring was continued for 4 hr., the solid removed by filtration, and purified by recrystallization.

N-Butyl-3,5-dimethylpyrazole-1-carboxamide.—A mixture of 9.6 g. (0.1 mole) of 3,5-dimethylpyrazole and 19.8 g. (0.2 mole) of *n*-butyl isocyanate was heated on the steam bath for 1 hr. To the reaction mixture was then added 25 ml. of ether and the ethereal solution washed with 25 ml. of 5% sodium carbonate solution and then with 25 ml. of water. Removal of the ether gave a colorless oil which solidified upon standing.

3,5-Dimethylpyrazole-1-carboxylic Acid Hydrazide.—To a solution of 9.0 g. (0.1 mole) of carbohydrazide in 35 ml. of water at 15° was added a solution of 10.0 g. (0.1 mole) of 2,4-pentanedione in 5 ml. of ethanol and the mixture stirred at 10–15° for 30 min. The mixture was extracted 3 times with 10-ml. portions of ether. The aqueous layer on standing overnight precipitated a colorless solid. This was removed by filtration, washed with cold water and ether, and purified by recrystallization from ether.

***p*-(3,5-Dimethylpyrazole-1)benzoic Acid.**—A mixture of 9.55 g. (0.096 mole) of 2,4-pentanedione, 14.55 g. (0.096 mole) of *p*-hydrazinobenzoic acid, 7.84 g. (0.096 mole) of anhydrous sodium acetate, 10 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. The mixture was cooled in an ice bath and neutralized with concentrated hydrochloric acid. The solid was filtered, washed with water, and recrystallized from ethyl acetate.

***p*-(3,5-Dimethylpyrazole-1)benzamide. D.**—A stirred mixture of 4.0 g. (0.0185 mole) of *p*-(3,5-dimethylpyrazolyl-1)benzoic acid, 3.3 g. (0.028 mole) of thionyl chloride and 100 ml. of dry benzene was heated under reflux for 1.25 hr. The hot mixture was filtered and the solid washed with ether. The filtrate and ether were concentrated *in vacuo* on a steam bath. Two 50-ml. portions of benzene were added and then were removed *in vacuo* on a steam bath. To the crude acid chloride was added 6 ml. of concentrated ammonium hydroxide and the mixture stirred for 1 hr. The mixture was diluted with water and filtered. The cake was washed with water and purified by recrystallization.

1-(*p*-Sulfamylphenyl)-3,5-dimethylpyrazole.—A stirred mixture of 19.88 g. (0.106 mole) of *p*-sulfamylphenylhydrazine,[5] 8.70 g. (0.106 mole) of 2,4-pentanedione, 60 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. The mixture was then neutralized by the addition of 8.7 ml. of concentrated hydrochloric acid, the solid removed by filtration, and washed with ethanol.

***p*-(3,5-Dimethyl-1-pyrazolyl)benzenesulfonylurea.**—A mixture of 4.0 g. (0.016 mole) of 1-(*p*-sulfamylphenyl)-3,5-dimethylpyrazole, 1.3 g. (0.016 mole) of potassium cyanate, 20 ml. of ethanol, and 5 ml. of water was heated under reflux for 7 hr. The unchanged starting material (0.68 g.) was removed by filtration and the filtrate concentrated to dryness. The residue was diluted with 15 ml. of water and acidified with acetic acid. The resulting solid was collected by filtration and purified by recrystallization.

1-(*p*-Chlorobenzoyl)-3,5-dimethylpyrazole.—To a slurry of 9.6 g. (0.1 mole) of 3,5-dimethylpyrazole in 100 ml. of anhydrous ether at 10–15° was added dropwise with stirring 8.7 g. (0.05 mole) of *p*-chlorobenzoylchloride. The mixture was stirred at room temperature for 1 hr. and then filtered. The filtrate was washed with water, dried, concentrated, and the residue distilled under vacuum. There was obtained 6.6 g. of material boiling at 108° (0.1 mm.) $n^{24}D$ 1.5850.

Acknowledgments.—We are indebted to Dr. Robert Rinehart and co-workers for microanalyses. We are especially indebted to Mr. Albert Lallinger, Mr. A. Lazuk, Mrs. F. L. Schmidt, and Mrs. M. C. Blanks for much technical assistance.

(5) K. Itano, *J. Pharm. Soc. Japan*, **75**, 441 (1955).

Notes

Derivatives of Morphine. III.[1] Sulfur Analogs of 14-Hydroxydihydrocodeinone

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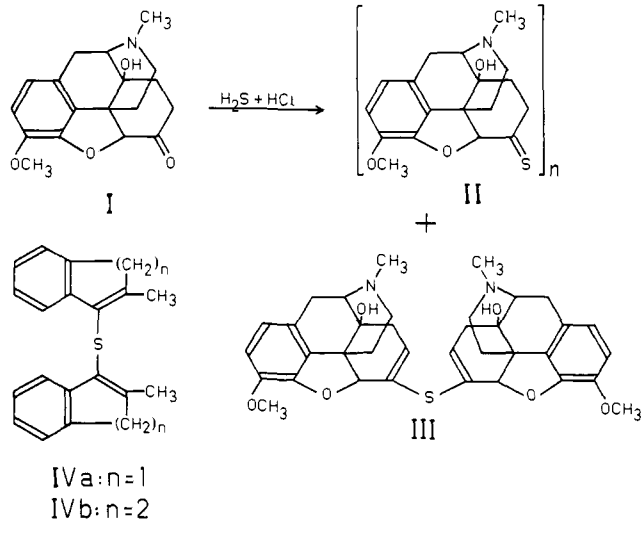
During the search for analgesic drugs with improved therapeutic properties, it appeared desirable to prepare some sulfur analogs of ketones of the morphine series. It has long been know that ketonic compounds of this series have a particularly strong analgesic action, and indeed the majority of those transformation products of morphine and codeine which have found use in therapeutic practice are ketones. It seemed, therefore, that corresponding sulfur compounds might be of interest. Because of its strong analgesic action, 14-hydroxydihydrocodeinone (I)[2] was chosen as the starting material.



(1) Paper II: U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957).

(2) M. Freund and E. Speyer, *J. Prakt. Chem.*, **94**, 135 (1916).