

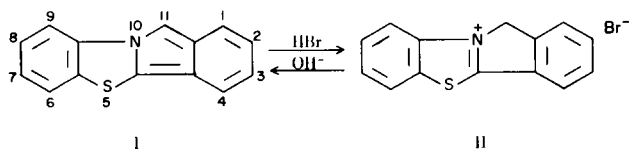
Some Reactions of 5-Methyl-11*H*-isoindolo[2,1-*a*]benzimidazolium Salts

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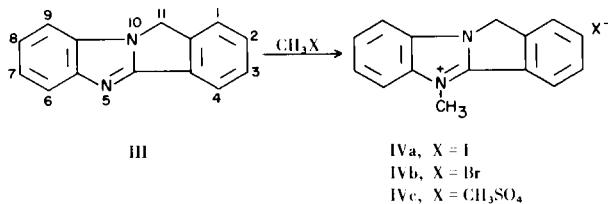
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5-Methyl-11*H*-isoindolo[2,1-*a*]benzimidazolium halide (IV), obtained by direct quaternization of the precursor III, underwent facile condensation reactions at its 11-methylene group similar to those of 11*H*-isoindolo[1,2-*b*]benzothiazolium cation II. Although the treatment of II with alkali regenerated its precursor I, treatment of IV with alkali caused ring opening to a phthalimidine. Attempted thermal cyclization of 2-(alkylaminophenyl)phthalimidines, e.g., VII, resulted in dealkylation to produce III.

Isoindolo[1,2-*b*]benzothiazole (I) and its salt II were prepared in 1963 by Babichev and Kibirev (1). These workers demonstrated the ease with which condensations with aldehydes occurred at the 11-methylene group of II.



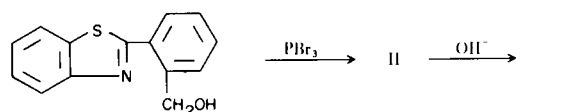
The analogous nitrogen heterocycle, 11*H*-isoindolo[2,1-*a*]benzimidazole (III), was prepared in 1917 by Bistrzycki and Schmutz (2) but has been little studied since their early investigations. Although quaternary salts of III are unknown, they should be easily obtained by direct alkylation of III.



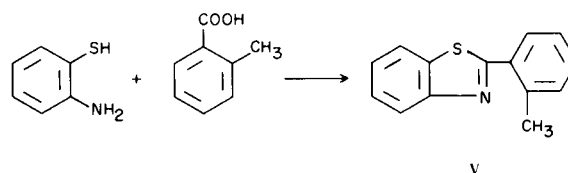
The methylene groups of III and its quaternary salt IV would be expected to undergo condensation reactions with aldehydes, and IV would be expected to resemble II in its reaction with bases.

The purpose of this work was to prepare IV and to compare some reactions of the two heterocyclic systems represented by II and IV.

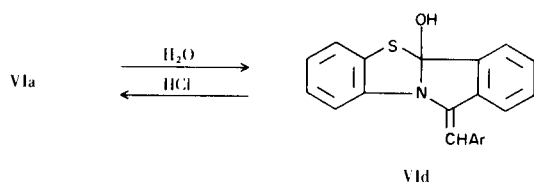
11*H*-Isoindolo[1,2-*b*]benzothiazolium bromide (II) was converted in nearly quantitative yield to the free base I by treatment with alkali.



The lengthy synthetic approach to the benzyl alcohol precursor of II promoted a single attempt by an alternative synthesis. 2-*o*-Tolylbenzothiazole (V) was obtained by the reaction of *o*-aminobenzenethiol with *o*-toluic acid. Attempted α -bromination (by *N*-bromosuccinimide) to the bromomethyl derivative (which would spontaneously cyclize to II) was unsuccessful.



Cation II condensed with aldehydes at its 11-methylene group to produce the violet-blue dyes VIa-c described in Table I. Both the elemental analyses and the vigorous evolution of gas upon melting reflect the tendency of these salts toward hydration. Aqueous solutions of VIa were decolorized by prolonged heating in either water or aqueous sodium bicarbonate, and were decolorized instantaneously by the addition of sodium hydroxide. Although nmr data and melting behavior showed that the decolorization resulted in a mixture of products, the pseudo base VI'd probably was a major product. This probability is supported by the reversibility of the decolorization by mineral acid and the formation of pseudo bases from other quaternary nitrogen heterocycles previously reported



linkage to give the substituted benzyl alcohol XIII. The structure of XIII was confirmed by its elemental analysis and the 2H methylene singlet at 5 ppm in its nmr spectrum.

(5-7). Attempted separation of the hydrolysis products invariably resulted in mixtures containing the parent cation VIc.

11H-Isoindolo[2,1-a]benzimidazole (III) and its hydrochloride were obtained by published methods (2). One alternative synthesis was attempted. 11H-Isoindolo[2,1-a]benzimidazol-11-one (XII) was obtained by the reaction of phthalic anhydride with *o*-phenylenediamine (3,4). Although the intermediate *o*-(2-benzimidazolyl)benzoic acid (XI) was easily isolated, it was not necessary to do so to obtain XII. Reduction of an ethereal solution of XII with lithium aluminum hydride did not give III, but resulted instead in the hydrogenolysis of the 10-11 amide

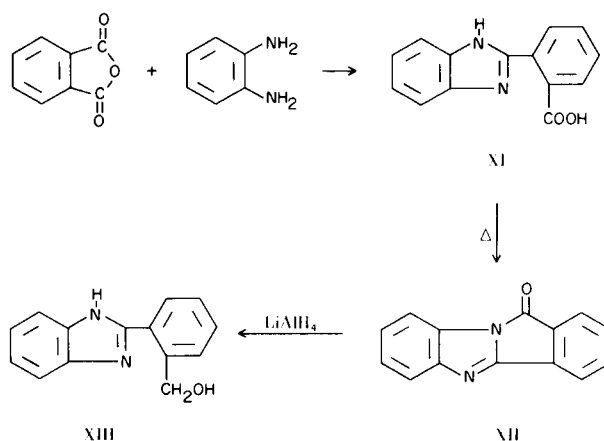
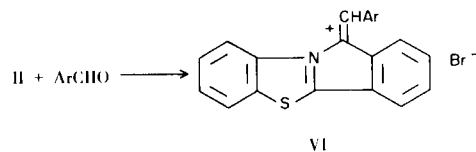
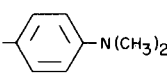

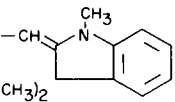


TABLE I

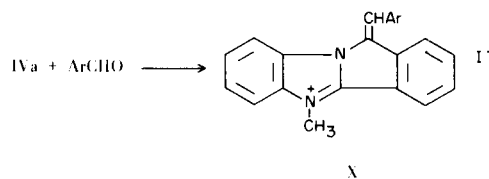
Methine Dyes VI From II



Dye	Ar	Yield (%)	M.p. (°C)	N Analysis		Spectral Properties (a)	
				Calcd.	Found	nm λ max	log ε
VIa		69	215-223 (b)	--	--	588 (c)	4.50
VIb		61	241-243	6.07	5.59	637	4.74
VIc		56	281-282	5.75	5.24	585	4.95

(a) Determined in 95% ethyl alcohol. (b) Lit. (1) 235°. (c) Lit. (1) 587 nm.

TABLE II
Methine Dyes X From IVa

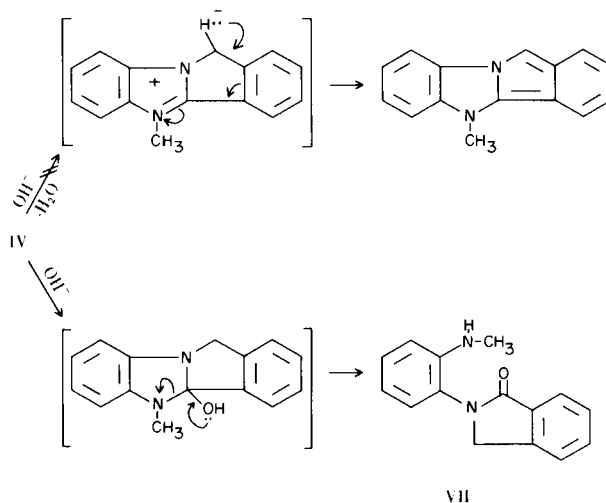


Dye	Yield (%)	M.p. (°C)	N Analysis		Spectral Properties (a)	
			Calcd.	Found	nm λ max	log ε
Xa 	23	> 200 (b)	8.76	8.37	491	4.20
Xb 	38	> 300	8.32	7.46	530	4.44
Xc 	40	> 300	7.91	8.00	538	4.80

(a) Determined in 95% ethyl alcohol. (b) Gas evolved.

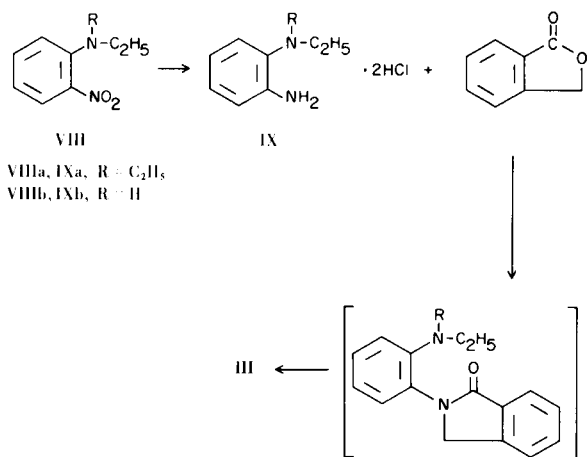
The alkylation of III required somewhat rigorous conditions. Although low yields of alkylated products were obtained by reaction at reflux with methyl iodide in ethyl alcohol, dimethyl sulfate was required for efficient alkylation to generate IV.

It was noted earlier that the treatment of the cation II with base gave the neutral parent heterocycle. Although a similar reaction might be predicted for IV, the benzimidazolium cation underwent an unexpected ring opening to the phthalimidine VII. The assignment of structure VII was based on elemental analyses, the position of the intense carbonyl band at 1670 cm^{-1} , and the consistency of the nmr spectrum with the proposed structure. The difference in behavior of II and IV toward bases indicates the greater acidity of the 11-methylene hydrogen atoms of II relative to those of IV. This difference would be predicted from the relative acidities (or electron-acceptor character) of the two heterocyclic systems involved. Because of the low acidity of the methylene hydrogens in



IV, addition of hydroxide ion predominates over abstraction of hydrogen.

N-Ethyl-*o*-phenylenediamine dihydrochloride (IXb) and *N,N*-diethyl-*o*-phenylenediamine dihydrochloride (IXa), obtained by reduction of the corresponding nitro compounds, were heated with phthalide in an attempt to obtain the quaternary salt IV directly. Dealkylation occurred in both reactions to give III.



The hydrochloride of III would not react with aldehydes under the conditions used to prepare the dyes VIa-c. However, the quaternary salt IV reacted readily (but at much slower rate than II) to yield dyes Xa-c (Table II). These dyes had absorption maxima in the visible region at shorter wavelengths than the corresponding dyes VIa-c. The rates of reaction and the spectral properties of the dyes produced are consistent with the fact that the benzothiazolium moiety has a greater electronegativity than the benzimidazolium moiety.

EXPERIMENTAL

Analyses.

Infrared spectra were obtained on a Baird Model AB-2 spectrophotometer, ultraviolet-visible spectra were run on either a Cary Model 14 or a Coleman-Hitachi Model 124 spectrophotometer, and nmr analyses were made on a Varian A-60 spectrometer. Elemental analyses were performed in the Tennessee Eastman Company Research Laboratories. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

1*H*-Isoindolo[1,2-*b*]benzothiazolium bromide (II).

The salt II was obtained in a 91% yield from the cyclization of *o*-(2-benzothiazolyl)benzyl alcohol by the method of Babichev and Kibirev, crystals, m.p. 243-258° (lit. (1) 256° dec.).

Isoindolo[1,2-*b*]benzothiazole (I).

A solution of II (5 g.) in water (100 ml.) was basified to pH 12 by addition of 5% aqueous sodium hydroxide solution. The yellow solid that separated was collected on a filter, washed with water, and dried. The yield of I was 3.4 g. (92%). Recrystallization from *N,N*-dimethylformamide gave yellow plates, m.p. 181-198° dec. (lit. 197°).

2-*o*-Tolylbenzothiazole (V).

A mixture of *o*-toluic acid (299 g., 2.1 moles), *o*-aminothiophenol (218 g., 2.0 moles), and 1,2,4-trichlorobenzene (150 ml.) was heated slowly to 215° while water and trichlorobenzene were removed by distillation. The mixture was stirred for 15 hours at 215°, then cooled to 100°, and diluted with 1600 ml. of 5% aqueous sodium hydroxide solution. The organic layer was washed at 80° with water and distilled. The fraction b.p. 134-139°/1 mm. (194 g., 46% yield) crystallized in the receiver (m.p. 59-67°). Two recrystallizations from hexane gave the analytical sample, m.p. 65-67°.

Anal. Calcd. for C₁₄H₁₁NS: C, 74.63; H, 4.92; N, 6.22. Found: C, 74.68; H, 4.92; N, 6.57.

Reaction of II with Aldehydes to Produce Dyes VIa-c.

A mixture of II (2 mmoles), aldehyde (2.2 mmoles), and acetic anhydride was stirred at 90° for 45 minutes. The mixture was then cooled to 5° and filtered. Recrystallization from acetic anhydride gave the analytical samples of VIa-c, whose properties are shown in Table I.

1*H*-Isoindolo[2,1-*a*]benzimidazole (III).

An intimate mixture of *o*-phenylenediamine dihydrochloride (0.11 mole) and phthalide (0.11 mole) was heated to 200° in 1 hour and held at 200° for 15 minutes. The resulting solid was cooled to 25° and recrystallized once from 175 ml. of 90/10 ethyl alcohol/concentrated hydrochloric acid and once from 175 ml. of 98/2 ethyl alcohol/concentrated hydrochloric acid. The yield of III hydrochloride, m.p. 243-257°, was 13.5 g. (52%). A solution of 12 g. of this material in 200 ml. of 10/90 water/ethyl alcohol was treated with concentrated ammonium hydroxide until the pH was above 7. Filtration gave 8.2 g. of crude III. Recrystallization from 6/1 toluene/hexane gave colorless crystals of III, m.p. 205-210° (lit. (2) 210-213°); infrared (potassium bromide), 1610, 1540, 1470, 1320, 738, 727 cm⁻¹.

5-Methyl-1*H*-isoindolo[2,1-*a*]benzimidazolium Iodide (IVa).

A mixture of III (6.2 g., 0.03 mole) and dimethyl sulfate (30 ml.) was stirred for 5 minutes at 155°, for 30 minutes at 98°, and then poured slowly into ethyl ether (400 ml.). Filtration gave 9.8 g. of light gray solid IVc. The solid was dissolved in 200 ml. of water and reprecipitated by adding 20 ml. of 30% aqueous potassium iodide. The yield of light gray solid was 8.4 g. (81%). Recrystallization from water gave the analytical sample, dec. > 250°; infrared (potassium bromide), 1620, 1600, 1575, 1480, 1460, 1030, 760 cm⁻¹.

Anal. Calcd. for C₁₅H₁₃IN₂: N, 8.05. Calcd. for the dihydrate C₁₅H₁₇IN₂O₂: N, 7.28. Found: N, 7.25.

5-Methyl-1*H*-isoindolo[2,1-*a*]benzimidazolium Bromide (IVb).

Aqueous potassium bromide (15 g./50 ml. solution) was added to a 90° solution of IVc (13 g.) in water (400 ml.). The precipitate was collected by filtration, recrystallized three times from water, and dried at 25°/1 x 10⁻⁵ mm. to give IVb as the colorless hydrate, m.p. 290-300°.

Anal. Calcd. for the monohydrate C₁₅H₁₅BrN₂O: C, 56.44; H, 4.74; N, 8.78. Found: C, 55.88; H, 4.55; N, 8.75.

Drying at 200°/1 x 10⁻⁵ mm. pressure gave colorless IVb, m.p. > 300°.

Anal. Calcd. for C₁₅H₁₃BrN₂: C, 59.81; H, 4.35; N, 9.30. Found: C, 59.71; H, 4.30; N, 9.06.

2-[*o*-(Methylamino)phenyl]phthalimidine (VII).

Aqueous potassium hydroxide solution (20%) was added to an

80° aqueous solution of IVa (3.3 g./400 ml. solution) to a pH of > 12. The resulting yellow solid was collected at 30° and recrystallized from benzene to obtain 1.0 g. of colorless crystals, m.p. 158-163°. Recrystallization from ethyl alcohol gave the analytical sample of VII, m.p. 161-163°; infrared (potassium bromide), 3160, 1670, 1165, 752, 730 cm^{-1} ; nmr (deuteriochloroform), δ 8.0-6.5 (multiplet, 8 aromatic protons), 4.62 (singlet, 2 methylene protons), 4.0 (broad NH, 1 proton), 2.70 (singlet, 3 methyl protons).

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.83; H, 6.48; N, 11.85.

N,N-Diethyl-*o*-nitroaniline (VIIIa).

A mixture of 1-chloro-2-nitrobenzene (158 g.), diethylamine (150 g.), and water (150 ml.) was heated for 6 hours at 150° in a sealed autoclave. The resulting mixture was washed successively at 25° with water, 10% aqueous sodium hydroxide solution, and water. The resulting red oil VIIIa (168 g., 87% yield) was refluxed with a suspension of Raney nickel (5 g.) in ethyl alcohol (150 ml.) and filtered. The solution of VIIIa in ethyl alcohol was used for subsequent reactions without further purification.

N,N-Diethyl-*o*-phenylenediamine Dihydrochloride (IXa).

A solution of VIIIa (168 g.) in ethyl alcohol (150 ml.) was hydrogenated over Raney nickel (20 g.) at 100° and 1000 psi. Hydrogen uptake was complete in 1.5 hours. The mixture was filtered, and the filtrate was diluted with 200 ml. of ethyl alcohol and 400 ml. of ethyl ether. Anhydrous hydrogen chloride was added to precipitate IXa. The yield of reddish, granular solid, m.p. 134-144°, was 116.5 g. (57%).

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{Cl}_2\text{N}_2$: N.E., 118.5. Found: N.E., 119.7.

Reaction of IXa With Phthalide to Produce III.

A mixture of phthalide (2.86 g., 0.02 mole) and IXa (4.74 g., 0.02 mole) was held at 210° for 1.5 hours. The mixture was then cooled to 25° and slurried in water. The solid was recrystallized from isopropyl alcohol to obtain 0.6 g. of colorless crystals, m.p. 195-208°. Recrystallization from isopropyl alcohol/hexane gave analytically pure III, m.p. 204-209°; infrared (potassium bromide), 1610, 1540, 1470, 1325, 742, 731 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2$: C, 81.53; H, 4.88. Found: C, 81.21; H, 4.93.

Reaction of IXb With Phthalide to Produce III.

A mixture of phthalide (28.6 g., 0.21 mole), IXb (44 g., 0.21 mole), and 1,2,4-trichlorobenzene (150 ml.) was heated to 200° in 1 hour and was then held at 200° for 2 hours longer. The mixture was then cooled to 25°, and phosphorus trichloride (34.3 g., 0.25 mole) was added. The resulting mixture was stirred at 90° for 0.5 hour and then poured onto 1000 ml. of ice. Solids were collected by filtration, washed with 30% aqueous potassium chloride solution, and then recrystallized from isopropyl alcohol/hexane to obtain 21.7 g. (43.1% yield) of III hydrochloride (infrared spectrum identical with that of an authentic sample). Addition of aqueous potassium hydroxide solution to a 3% aqueous solution of III hydrochloride liberated the free base III. Successive recrystallizations from isopropyl alcohol and then from benzene gave the analytical sample of III, m.p. 200-205°; infrared (potassium bromide), 1610, 1535, 1470, 1320, 739, 728 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2$: C, 81.6; H, 4.89; N, 13.58. Found: C, 81.1; H, 5.00; N, 13.48.

Reaction of IV With Aldehydes to Produce Dyes Xa-c.

A mixture of IV (0.015 mole), aldehyde (0.018 mole), and acetic anhydride (10 ml.) was refluxed for 1 hour and then stirred at 98° for 6 hours. The solution was cooled to 25°, then poured

into 200 ml. of water and stirred until the acetic anhydride had reacted. Solid potassium iodide (10 g.) was added, and the mixture was filtered after 2 hours to obtain the dye. Recrystallization from acetic anhydride gave the analytical samples of the dyes listed in Table II.

o-(2-Benzimidazolyl)benzoic Acid (XI).

A 40% yield of XI was obtained by the reaction of *o*-phenylenediamine with phthalic anhydride by the previously reported procedure (4), m.p. 265° with gas evolution (lit. 271.5°); infrared (potassium bromide), 1700, 1445, 1255, 1073, 748 cm^{-1} .

1*H*-Isoindolo[2,1-*a*]benzimidazol-11-one (XII).

A 53% yield of XII was obtained by the reaction of *o*-phenylenediamine with phthalic anhydride by the previously reported procedure (3), m.p. 208° (lit. 211-212°); infrared (potassium bromide), 1760, 1720, 1620, 1365, 928, 871, 762, 743, 712 cm^{-1} .

2-[*o*-(Hydroxymethyl)phenyl]benzimidazole (XIII) From Lithium Aluminum Hydride Reduction of XII.

A mixture of lithium aluminum hydride (1.9 g., 0.05 mole) in anhydrous ethyl ether (100 ml.) was stirred at 5 to 10° during the portionwise addition of finely powdered XII (2.2 g., 0.01 mole) in 45 minutes (slight exotherm). The mixture was allowed to warm to 25° in 1 hour and was then stirred at 25° for 3 hours. Moist ether (20 ml.) was then added dropwise, and this addition was followed by the dropwise addition of a solution of 2.5 g. of sodium hydroxide in 10 ml. of water over 30 minutes. Inorganic solids were removed by filtration and washed with chloroform (100 ml.). The combined filtrates were concentrated to a volume of 20 ml. and diluted with 50 ml. of hexane. Filtration at -15° gave 0.3 g. of colorless, crystalline XIII, m.p. 193-197°. Recrystallization from aqueous ethyl alcohol gave the analytical sample, m.p. 197-199°; infrared (potassium bromide), 1480, 1440, 1410, 1010, 958, 738 cm^{-1} ; nmr (deuteriopyridine), δ 8.8 (OH, NH unresolved), 8.4 to 7.3 (multiplet, 8 aromatic protons), 5.0 (singlet, 2 methylene protons).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.67; H, 5.35; N, 12.36.

Basic Hydrolysis of VIa.

A mixture of VIa (5 g.), sodium bicarbonate (5 g.), and water (1500 ml.) was stirred for 15 hours at 80°, then cooled to 25° and filtered. The solids were washed with water and dried to obtain 4.2 g. of greenish yellow solid, m.p. 140-162°; soluble in acetone and toluene. Nmr indicated a mixture of products. Treatment of this material with 1% aqueous hydrochloric acid solution regenerated the parent cation.

Anal. Calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_5\text{S}\cdot\text{H}_2\text{O}$: C, 70.74; H, 5.68; N, 7.17. Found: C, 71.96; H, 5.22; N, 6.28.

REFERENCES

- (1) F. S. Babichev and V. K. Kibirev, *J. Gen. Chem. USSR (Engl. trans.)*, **33**, 1946 (1963).
- (2) A. Bistrzycki and W. Schmutz, *Ann. Chem.*, **415**, 1 (1918).
- (3) A. Bistrzycki and A. Lecco, *Helv. Chim. Acta*, **4**, 425 (1921).
- (4) J. Arient and J. Marhan, *Coll. Czech. Chem. Commun.*, **26**, 98-106 (1961); *Chem. Abstr.*, **55**, 15488 (1961).
- (5) A. Hantsch and M. Kalb, *Ber.*, **32**, 3109 (1899).
- (6) J. J. Dobbie and C. K. Tinkler, *J. Chem. Soc.*, **87**, 269-273 (1905).
- (7) S. Hünig and W. Kniese, *Ann. Chem.*, **708**, 170-197 (1967).

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