Color Reactions of Morphine Derivatives

ROBERT G. SPLIES and JAMES M. SHELLOW
University of Wisconsin, Milwaukee, Wis.

Esters of morphine and dihydromorphine were prepared and subjected to a series of typical alkaloid reactions. Crystal structures and colors were compared with results reported in the literature for diacetylmorphine (heroin).

TO CHECK the specificity of various tests for heroin, several esters of morphine and dihydromorphine were synthesized. These esters were treated with color-producing reagents and the results noted in Table I. Crystalline solids were obtained in other tests and the results are listed in Table II. In both tables, heroin is included for comparison although it was not tested in our laboratory. All data for heroin have been obtained from the literature.

EXPERIMENTAL

Reduction of Morphine. A solution of 5.0 grams of morphine in 300 ml. of absolute ethanol was reduced for 1 hour with 0.1 gram of platinum oxide catalyst and hydrogen at a cold pressure of 54.5 p.s.i. After reduction, the solution was filtered to remove the catalyst and 100 ml. of water added. Concentration and cooling of this solution yielded 3.90 grams of dihydromorphine, m.p. 155–157° C. Further concentration of the filtrate yielded an additional 0.75 gram of product.

Preparation of Esters of Morphine and Dihydromorphine. The free base, 0.75 gram, and 5 ml. of acetic or propionic anhydride were allowed to stand for a week at room temperature in 5 ml. of pyridine. The solution was diluted with water and neutralized with solid sodium bicarbonate. The suspension was extracted twice with 25-ml. portions of chloroform and the extract dried over magnesium sulfate. After removing the magnesium sulfate by filtration, the chloroform was evaporated. The oils that resulted were crystallized by cooling and treatment with petroleum ether, b.p. 60–68° C.

Diacetyldihydromorphine, 0.54 gram, was obtained in the form of white needles from diethyl ether. When heated slowly, the solid melted over the range 132–156° C. When placed in a melting point bath at 130° C., melting was complete at 132° C. The hydrochloride salt melted at 218–221° C. The free base was very soluble in chloroform, benzene, pyridine, and toluene, and slightly soluble in petroleum ether, b.p. 60–68° C.

Dipropionyldihydromorphine, on crystallization from petroleum ether, b.p. 60–68° C., yielded a granular solid, m.p. 73–74° C. A high degree of solubility in chloroform, pyridine, and diethyl ether was noted, along with moderate solubility in petroleum ether, b.p. 60–68° C.

Dipropionylmorphine, 0.52 gram, was obtained as an amorphous solid, m.p. 106–108° C., from petroleum ether, b.p. 30–60° C. The solid was very soluble in chloroform and pyridine with moderate solubility in petroleum ether, b.p. 30–60° C.

Reagents. The color-producing and crystal-forming reagents were prepared according to directions given elsewhere (*1*). The color tests were carried out on a porcelain spot-test plate with two drops of the reagent added to a 0.1- to 0.2-mg. sample of the alkaloid. The crystals were examined under 80× magnification after being precipitated on a slide by adding a drop of the reagent to a solution of the alkaloid in dilute hydrochloric acid.

Table I. Colors Produced by Morphine Derivatives

Compound	Test Reagent										
	HNO_3	$FeCl_3$	HIO_3	$HgCl_2$	$PtCl_4$	Marquis	Marme	Wagner	Frodhe	Mecke	Lerner
	(*4*)	(*2*)	(*5*)	(*1*)	(*1*)	(*4*)	(*1*)	(*5*)	(*2*)	(*2*)	(*4*)
Diacetyldihydromorphine	yellow to green	no color change	no color change	white ppt.	yellow ppt.	purple	white ppt.	brown ppt.	purple	blue green	dark yellow
Dipropionyldihydromorphine	yellow to green	no color change	no color change	white ppt.	yellow ppt.	purple	white ppt.	brown ppt.	violet	green	yellow brown
Dipropionylmorphine	yellow to green	no color change	no color change	white ppt.	yellow ppt.	purple	white ppt.	brown ppt.	purple	green	light brown
Diacetylmorphine (heroin)	yellow to green	no color	no color	ppt.	ppt.	purple	ppt.	brown ppt.	violet	blue green	yellow or yellow brown

Table II. Crystalline Descriptions of Morphine Derivatives

Compound	Test Reagent	
	$PtCl_4$	$AuBr_3(HCl)$
Diacetyldihydromorphine	rosettes, yellow needles	sheaves, orange-brown
Dipropionyldihydromorphine	rosettes, yellow blades	sheaves, orange-brown
Dipropionylmorphine	rosettes, yellow blades	sheaves, orange-brown
Diacetylmorphine	rosettes, yellow needles or blades (*3*)	fine sheaves or rosettes (*3*)

LITERATURE CITED

(1) Butler, W.P., Ryan, R.L., *"Methods of Analysis,"* Pub. No. **341** (Rev. 2-60), U.S. Treasury Dept. Internal Revenue Service, Washington, February 1960.
(2) Davis, T.W.C., Farmilo, C.G., Genest, K., *Bull. Narcotics U. N. Dept. Social Affairs* **14**, 47, (1962).
(3) Fulton, C.C., *Ibid.*, **5**, 27 (9153).
(4) Lerner, M., *Anal. Chem.* **32**, 198 (1960).
(5) Small, L.F., Lutz, R.E., "Chemistry of the Opium Alkaloids," p. 154, U. S. Treasury Dept., Public Health Service, Washington, 1932.

RECEIVED for review July 19, 1965. Accepted October 6, 1965.

Slush Baths

R. E. RONDEAU

Air Force Materials Laboratory, Wright-Patterson AFB, Ohio

The preparation of constant temperature slush baths is described and 86 common slush baths are tabulated in order of decreasing temperature from 13° to −160° C. Some experimental applications of these cooling agents are also described.

THE ACCOMPANYING TABLE lists 86 common solvents and their slush bath temperatures in order of decreasing temperature from 13° to −160° C. A slush bath can be defined as a coolant consisting of a low melting liquid which has been partially frozen by mixing with liquid nitrogen. It is prepared by slowly pouring liquid nitrogen into a Dewar flask containing the solvent while continuously stirring the mixture until the desired consistency is obtained. When properly mixed, the consistency of the crystallized solvent is that of a fluid slush which will maintain a constant temperature as long as the bath is kept slushy by occasionally blending in more liquid nitrogen.

Rondeau and Harrah (*2*) made use of an ethyl bromide slush bath in measuring the melting point of 3-hexyne. The temperature rise of this particular slush was approximately 0.2° C. per minute when left standing at room temperature in an uncovered 47 × 125 mm. Dewar flask.

With certain solvents, such as diethylene glycol and some of the alcohols, a heavy sirup is formed. Although not as convenient to handle, a viscous bath is still useful for cooling purposes. The solvents in Table I that form a highly viscous coolant have been marked with an asterisk.

The temperatures listed in the table are given to the nearest degree centigrade. Measurements were made with a calibrated toluene thermometer for temperatures above −95° C. and with a calibrated pentane thermometer for readings below −95° C. All of the solvents used were reagent grade chemicals. In general, the purer the compound, the narrower its slush bath temperature range; however, the variation in temperature with purity has not been studied.

Slush baths are especially useful in degassing liquids and fractionating mixtures. Newton (*1*) has designed a low temperature reflux condenser in which the liquid can be refluxed under vacuum at a temperature where its vapor pressure is negligible. The method requires the use of a constant temperature cooling bath to maintain the desired temperature. The convenience of a table of slush bath temperatures in using such a technique is readily apparent.

Volatile mixtures can be separated in a vacuum system by fractional condensation through a series of three traps cooled to successively lower temperature. Here again, the judicious selection of the proper slush bath temperature determines the efficiency of the separation.

Table I. Materials for Low Temperature Slush Baths (with Liquid Nitrogen)

Solvent	Temp., ° C.	Solvent	Temp., ° C.
p-Xylene	13 ±1°	Ethyl acetate	−84
p-Dioxane	12	*n*-Hexyl bromide	−85
Cyclohexane	6	Methyl ethyl ketone	−86
Benzene	5	Acrolein	−88
Formamide	2	Amyl bromide	−88
Aniline	−6	*n*-Butanol [a]	−89
Diethylene glycol [a]	−10	*s*-Butanol [a]	−89
Cycloheptane	−12	Isopropyl alcohol [a]	−89
Methyl benzoate	−12	Nitroethane	−90
Benzonitrile	−13	Heptane	−91
Benzyl alcohol	−15	*n*-Propyl acetate	−92
Propargyl alcohol	−17	2-Nitropropane	−93
1,2-Dichlorobenzene	−18	Cyclopentane	−93
Tetrachloroethylene	−22	Ethyl benzene	−94
Carbon tetrachloride	−23	Hexane	−94
1,3-Dichlorobenzene	−25	Toluene	−95
Nitromethane	−29	Cumene	−97
o-Xylene	−29	Methanol	−98
Bromobenzene	−30	Methyl acetate	−98
Iodobenzene	−31	Isobutyl acetate	−99
m-Toluidine	−32	Amyl chloride	−99
Thiophene	−38	Butyraldehyde	−99
Acetonitrile	−41	Propyl iodide	−101
Pyridine	−42	Butyl iodide	−103
Benzyl bromide	−43	Cyclohexene	−104
Cyclohexyl chloride	−44	*s*-Butyl amine	−105
Chlorobenzene	−45	Isooctane	−107
m-Xylene	−47	1-Nitropropane	−108
n-Butyl amine	−50	Ethyl iodide	−109
Benzyl acetate	−52	Propyl bromide	−110
n-Octane	−56	Carbon disulfide	−110
Chloroform	−63	Butyl bromide	−112
Methyl iodide	−66	Ethyl alcohol [a]	−116
tert-Butyl amine	−68	Isoamyl alcohol [a]	−117
Trichloroethylene	−73	Ethyl bromide	−119
Isopropyl acetate	−73	Propyl chloride	−123
o-Cymene	−74	Butyl chloride	−123
p-Cymene	−74	Acetaldehyde	−124
Butyl acetate	−77	Methyl cyclohexane	−126
Isoamyl acetate	−79	*n*-Propanol [a]	−127
Acrylonitrile	−82	*n*-Pentane	−131
n-Hexyl chloride	−83	1,5-Hexadiene	−141
Propyl amine	−83	*iso*-Pentane	−160

[a] High viscosity slush.

LITERATURE CITED

(1) Newton, A.S., *Anal. Chem.* **28**, 1214 (1956).
(2) Rondeau, R.E., Harrah, L.A., J. CHEM. ENG. DATA **10**, 84 (1965).

RECEIVED for review April 20, 1965. Accepted September 16, 1965.