NOTES

Some Codeine Benzoates

BY CHARLES F. POE AND JOHN G. STRONG

For a series of pharmacological studies, it became necessary to prepare a number of codeine salts from the alkaloid and various substituted benzoic acids. The preparation of these salts is reported in this communication.

None of these codeine salts have been described in the literature except the salicylate. A reference may be found to this salt in Merck's Index,[1] and the method of preparation is described by Martin.[2]

The method of preparation previously used for a series of strychnine benzoates[3] was tried. This procedure consisted of dissolving molecular quantities of the alkaloid and acid separately in alcohol. The two solutions were mixed and heated for several minutes. A number of the codeine salts, however, were so soluble in alcohol that they did not readily crystallize out by this method. The ortho, meta and para nitrobenzoates, the meta and para bromobenzoates, and the meta and para chloro and meta hydroxybenzoates were prepared successfully by the above-mentioned method. It was later found that these salts could be obtained in beautiful crystalline form by recrystallizing from water the sirup obtained after almost all of the alcohol was evaporated. The *o*-chlorobenzoate and *p*-hydroxybenzoate, after being evaporated to a sirup and kept in the ice box at 0° for two weeks, gave crystals which could be recrystallized from alcohol. The *o*-bromobenzoate was prepared with ethyl acetate, and the *o*-hydroxybenzoate was obtained with amyl alcohol and carbon bisulfide.

The benzoate, however, could not be obtained in a crystalline form by any of the methods mentioned above. After about forty different solvents were tried, it was at length discovered that this salt could be obtained by the use of normal pentane as a solvent. The benzoic acid and codeine are only slightly soluble in this solvent; consequently, a large amount of pentane was necessary. When the pentane solutions of the benzoic acid and codeine were mixed, a white amorphous precipitate of codeine benzoate was formed.

The codeine benzoates were analyzed and the results are presented in Table I.

TABLE I

SALTS OF CODEINE

Compound	Formula	Color	Codeine, % Calcd.	Codeine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	M. p., °C. "Bloc Maquenne"
Codeine benzoate	$C_{18}H_{21}O_3N \cdot C_6H_5COOH$	White	71.04	71.20	3.32	3.28	79[a]
Codeine *o*-bromobenzoate	$C_{18}H_{21}O_3N \cdot BrC_6H_4COOH$	White	59.81	59.60	2.80	2.69	139
Codeine *m*-bromobenzoate	$C_{18}H_{21}O_3N \cdot BrC_6H_4COOH$	White	59.81	59.69	2.80	2.84	99
Codeine *p*-bromobenzoate	$C_{18}H_{21}O_3N \cdot BrC_6H_4COOH$	White	59.81	59.50	2.80	2.70	166
Codeine *o*-chlorobenzoate	$C_{18}H_{21}O_3N \cdot ClC_6H_4COOH$	White	65.67	65.50	3.07	3.17	134
Codeine *m*-chlorobenzoate	$C_{18}H_{21}O_3N \cdot ClC_6H_4COOH$	White	65.67	65.80	3.07	2.91	96
Codeine *p*-chlorobenzoate	$C_{18}H_{21}O_3N \cdot ClC_6H_4COOH$	White	65.67	65.69	3.07	3.01	162
Codeine *o*-nitrobenzoate	$C_{18}H_{21}O_3N \cdot NO_2C_6H_4COOH$	Light yellow	64.17	64.39	6.01	5.95	185
Codeine *m*-nitrobenzoate	$C_{18}H_{21}O_3N \cdot NO_2C_6H_4COOH$	Light yellow	64.17	64.14	6.01	5.87	173
Codeine *p*-nitrobenzoate	$C_{18}H_{21}O_3N \cdot NO_2C_6H_4COOH$	Light yellow	64.17	64.18	6.01	5.88	189
Codeine *o*-hydroxybenzoate	$C_{18}H_{21}O_3N \cdot HOC_6H_4COOH$	White	68.43	68.59	3.20	3.14	121[a]
Codeine *m*-hydroxybenzoate	$C_{18}H_{21}O_3N \cdot HOC_6H_4COOH$	White	68.43	68.28	3.20	3.31	148
Codeine *p*-hydroxybenzoate	$C_{18}H_{21}O_3N \cdot HOC_6H_4COOH$	White	68.43	68.54	3.20	3.07	140

[a] Not sharp.

The codeine was determined by the extraction method described by Glycart.[4] The silicotungstate method as proposed by North and Beal[5] was also used, but the results were usually too low, and checks could not be obtained in the majority of cases. The nitrogen content was determined by the official Kjeldahl method to include nitrogen of nitrates.[6] The melting points were determined by the "bloc Maquenne" method.

Most of the salts are somewhat soluble in water. The *p*-chlorobenzoate, the *o*-nitrobenzo-

---

(1) "Merck's Index," Merck and Co., Rahway, N. J., 1930.

(2) F. Martin, *J. Pharm. Chem.*, **26**, 176 (1922).

(3) C. F. Poe and J. F. Suchy, THIS JOURNAL, **56**, 1640 (1934).

(4) C. K. Glycart, *J. Assoc. Off. Agri. Chem.*, **5**, 150 (1921); **7**, 6 (1923).

(5) E. O. North and G. D. Beal, *J. Am. Pharm. Assoc.*, **13**, 889, 1001 (1924).

(6) "Official and Tentative Methods of Analysis," Assoc. Official Agri. Chemists, 1930, 3d ed.

ate and the *o*-hydroxybenzoate are quite soluble in water. The benzoate and the *o*-bromo, *o*-chloro and *o*-hydroxy salts are very soluble in water. All of the salts are fairly soluble in chloroform and in ethyl alcohol, and slightly soluble in ether.

CHEMISTRY DEPARTMENT
UNIVERSITY OF COLORADO
BOULDER, COLORADO
RECEIVED NOVEMBER 19, 1934

Some New Amidine Hydrochlorides

BY JOHN B. EKELEY, DIRK V. TIESZEN AND ANTHONY RONZIO

We have prepared a number, as given below, of required amidine hydrochlorides not yet noted in the literature, by the usual method from the corresponding cyanides. They were recrystallized from water and dried in a vacuum over concentrated sulfuric acid. They are colorless crystals and exhibit the reactions of amidines. The melting points were made using a short-stem Anschütz thermometer.

TABLE I

R AMIDINE HYDROCHLORIDES

			Analyses					
			N, %			Cl, %		
R	M. p., °C.	Formula	Calcd.	Found		Calcd.	Found	
Isocapro-	113.5	$C_6H_{14}N_2 \cdot HCl$	23.50	23.77	23.53	18.59	18.70	18.75
Phenoxybutyro-	150	$C_{10}H_{14}ON_2 \cdot HCl$	16.52	16.68	16.52	13.06	13.12	13.05
m-Tolenyl-	185.5	$C_8H_{10}N_2 \cdot HCl$	20.78	20.75	20.95	16.41	16.24	16.47
p-Chlorobenz-	241–242	$C_7H_6ClN_2 \cdot HCl$	18.57	18.73	18.74	14.91	14.91	14.80

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
BOULDER, COLORADO
RECEIVED DECEMBER 28, 1934

The Reaction of Magnesium with α-Halo Ketones

BY C. HAROLD FISHER

In the preparation of organic magnesium compounds by the interaction of magnesium and α-halo ketones it should be possible to avoid complications arising from reactions of the carbonyl group by working with hindered halo ketones. An exploratory examination, which cannot be continued, has shown that this is true in the case of α-bromoacetylmesitylene. After decomposition of the magnesium derivative with dilute acid the products were acetomesitylene (45%), 1,2-di-(2,4,6-trimethylbenzoyl)-ethane (10%), and starting material (18%).

$$(CH_3)_3C_6H_2COCH_2Br \xrightarrow{Mg} (CH_3)_3C_6H_2C(OMgBr){=}CH_2 + [(CH_3)_3C_6H_2COCH_2]_2$$

Approximately 60% of the theoretical amount of magnesium required to give the enolate was consumed in the reaction. It is believed that the organic magnesium compound is the enolate because of its solubility behavior in ether and ether–benzene solutions, which is similar to that of the bromomagnesium enolate[1] formed in the reaction of ethylmagnesium bromide with acetomesitylene.

Refluxing a mixture of 4.82 g. of bromoacetylmesitylene, 0.54 g. of magnesium and 40 cc. of ether for one-half hour caused the appearance of a white, milky precipitate, which dissolved after the addition of 60 cc. of hot benzene. The mixture was heated for one hour longer, and filtered from unreacted magnesium (0.2 g.). Addition of water caused a precipitate to appear which dissolved when hydrochloric acid was added. The ether–benzene solution was dried and distilled. On vacuum distillation of the remaining oil there was obtained 1.45 g. of acetomesitylene and 0.88 g. of α-bromoacetylmesitylene. The residue, after several crystallizations from alcohol, melted at 136–137.5°. When mixed with a sample of di-(2,4,6-trimethylbenzoyl)-ethane prepared by Conant and Lutz[2] the melting point was 137–138.5°. The acetomesitylene was identified by conversion into 3,5-dinitroacetylmesitylene[3] (m. p. 138–139.5°), which was compared with an authentic specimen.

Under similar conditions magnesium reacted also with α-bromo-β-phenylbenzalacetophenone. However, the reaction mixture gave a negative test[4] for the Grignard reagent; and treatment with dilute acid gave a sticky yellow solid which was not identified. After partial purification had been accomplished by washing with hot alcohol the product was halogen-free and failed to melt under 250°. Efforts to effect crystallization from benzene and ligroin were unsuccessful, and its study was abandoned.

HARVARD UNIVERSITY
CAMBRIDGE, MASS.
RECEIVED JANUARY 2, 1935

---

[1] Kohler and Tishler, THIS JOURNAL, **57**, 221 (1935).

[2] Conant and Lutz, *ibid.*, **45**, 1306 (1923).

[3] Walker and Fuson, *ibid.*, **52**, 3273 (1930).

[4] Gilman and Schulze, *ibid.*, **47**, 2002 (1925).