

Synthesis of Phenyl-3- and Phenyl-5-acetamidosalicylates as Potential Analgesics

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Abstract □ Phenylsalicylate was nitrated to obtain two nitro isomers, which were separated and reduced to the corresponding amines followed by acetylation to give phenyl-5- or phenyl-3-acetamidosalicylate. Phenyl-5-acetamidosalicylate displayed analgesic activity comparable to that of aspirin and phenacetin at doses of 25–50 mg/kg sc and was much less toxic than the latter compounds. Phenyl-3-acetamidosalicylate, however, was ineffective at a similar dose range and caused restlessness at larger doses.

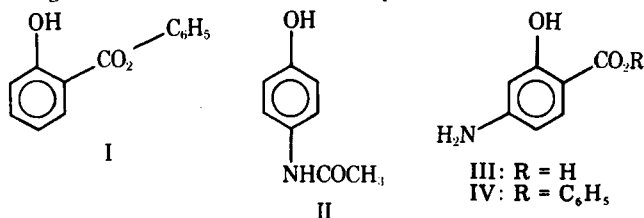
Keyphrases □ Phenylsalicylates—synthesis of phenyl-3- and phenyl-5-acetamidosalicylates, analgesic activity □ Analgesics—phenylsalicylates, derivatives, synthesis, tested for analgesic activity □ Antitubercular agents, potential—phenylsalicylates, synthesis, analgesic activity

Phenylsalicylate (I) has been used as an analgesic and as an enteric coating material for oral dosage forms (1). It also has several other industrial uses (2). However, it has been replaced by more potent and safer analgesic-antipyretic drugs such as aspirin and acetaminophen (II). Aminosalicic acid (III), phenyl-*p*-aminosalicylate (IV), and their corresponding acetyl derivatives have been used for the treatment of tuberculosis (3–6) in conjunction with other antitubercular agents.

This report describes the synthesis of some new phenylsalicylate derivatives (V–X) as potential analgesic-antipyretic agents with possible antitubercular activity. Compound VIII is a combination of phenylsalicylate and acetaminophen in one molecule. Furthermore, VII–X are isomers of phenyl-4-amino- or phenyl-4-acetamidosalicylates, which are used as antitubercular agents.

EXPERIMENTAL¹

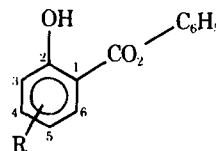
Phenyl-3- and Phenyl-5-nitrosalicylates (V and VI)—A solution of 40 g (0.184 mole) of phenylsalicylate² in acetic acid was treated with 50 ml of nitric acid (68%) in acetic acid (1:1) dropwise with stirring and cooling in an ice bath for 20 min. The temperature was raised to 30–35°



¹ Melting points were determined using a Büchi apparatus and are uncorrected. The structures of all compounds were confirmed by IR, NMR, and mass spectra. IR spectra were recorded on IR-257 and IR-221 spectrophotometers (Perkin-Elmer). NMR spectra were determined as solutions in deuteriochloroform, with tetramethylsilane as the internal standard, on a WH-90 instrument (Bruker). The WH-90 instrument was connected to a computer (model B-NC 12) with a FINMR V 51218 program.

Mass spectra were recorded by Morgan-Schaffer Corp., Montreal, Canada. The spectra of V, VI, and VIII were recorded on a Hitachi Perkin-Elmer mass spectrometer (model RMU-6D) by introducing the samples by direct probe at 40° with an ionization voltage of 70 eV. The mass spectra of VII and X were recorded on a CH-5 mass spectrometer (Varian MAT) by direct probe at 110° and 70 eV. TLC was performed on 0.25-mm pre-coated silica gel plates (Merck silica gel 60 F-254 or silica gel F-254). Materials on plates were detected with a UV lamp. NMR data are expressed in δ . Microanalyses were performed by Dr. Daessle, Organic Micro-Analysis Laboratories, Montreal, Canada.

² Fluka, Buchs, Switzerland.



V: R = 5-nitro
VI: R = 3-nitro
VII: R = 5-amino

VIII: R = 5-acetamido
IX: R = 3-amino
X: R = 3-acetamido

and maintained for 5–6 min, during which time the reaction mixture turned deep orange. The mixture was poured over 200 g of crushed ice. Upon stirring, an orange solid material separated. This material was filtered, washed with alcohol, and dried to give 45 g of nitrated salol.

Compounds V and VI were separated by fractional crystallization from ethanol; V crystallized immediately from the hot alcoholic solution. Further recrystallization of this fraction from alcohol gave 20 g (0.078 mole, 42%) of white needle-like crystals, mp 148–150°. Compound VI was obtained upon standing and cooling of the alcoholic mother liquor to give colorless crystals, mp 87–89°. Further recrystallization of this fraction from alcohol gave 22 g (0.097 mole, 52%) of VI, mp 99–100°.

The mass spectra of V and VI showed identical molecular ions at m/e 259 ($C_{13}H_9NO_5$); IR of V ($CHCl_3$): ν_{max} 3250–3090, 3010, 1690, 1630, 1530, 1350, and 840 cm^{-1} ; NMR of V ($CDCl_3$): δ 11.18 (1H, s), 9.04 (1H at C-6, d, J = 2.6 Hz), 8.42 (1H at C-4, dd, J = 9.4 and 2.6 Hz), 7.16 (1H at C-3, d, J = 9.6 Hz), and 7.6–7.18 (5H, complex m) (one replaceable proton); IR of VI ($CHCl_3$): ν_{max} 3250–3090, 3010, 1690, 1630, 1530, 1350, 900, 860, and 840 cm^{-1} ; NMR of VI ($CDCl_3$): δ 11.71 (1H, s), 8.32 (1H at C-4, dd, J = 8 and 1.7 Hz), 8.22 (1H at C-6, dd, J = 8.2 and 1.7 Hz), and 7.6–7.01 (6H, complex m) (one replaceable proton).

Nitro Derivative Reduction—A sample of 13 g of V or VI (0.05 mole) was dissolved in a minimum amount of chloroform and mixed with 200 ml of methanol or ethanol, 0.3 g of platinum oxide or palladium, and 1–2 g of activated charcoal. The mixture was placed in a hydrogenator³, and hydrogenation of the nitro derivatives was allowed to proceed until no more hydrogen was absorbed. The reduction yield was based on the amount of hydrogen absorbed by the nitro derivatives.

In both cases, complete reduction was obtained, as indicated by the absorption of 3.4 liters (3 equivalents) of hydrogen in each reduction process. The reduction mixture was filtered, and the residue was washed with ~50 ml of alcohol. The combined filtrate and washings were taken to dryness under vacuum, and the residue was dissolved in 5% HCl. The amine hydrochloride was used for the next step without further purification.

Amine Acetylation—The aqueous solution of the hydrochloride of VII or IX was heated to 50° and mixed with 60 ml of acetic anhydride. A freshly prepared solution of 100 g of sodium acetate in 100 ml of water was heated to 50° and added to the mixture with stirring and cooling in an ice bath for 30 min. The acetamido derivatives were filtered and purified by recrystallization from ethanol or ethanol-water. Compound VIII was obtained in an 84% yield, and X was obtained in an 80% yield. The physical constants of VIII and X are shown in Table I.

Compound VIII was white to slightly pink needle-like crystals, mp 174–177°. Its mass spectrum showed a molecular ion at m/e 271; IR ($CHCl_3$): ν_{max} 3430, 3250, 3010, 1680, 1670, 1610, 1360, 1270, and 1050 cm^{-1} ; NMR ($CDCl_3$): δ 2.17 (3H, s), 6.98 (1H at C-3, d, J = 8.8 Hz), 7.12–7.54 (5H, complex m), 7.62 (1H at C-4, dd, J = 8.5 and 2.4 Hz), and 8.22 (1H at C-6, d, J = 2.6 Hz).

Compound X was white to slightly greenish flakes, mp 165–166°. Its mass spectrum showed a molecular ion at m/e 271; IR ($CHCl_3$): ν_{max} 3420, 3180, 3010, 1680, 1670, 1610, 1360, 1280, 1060, and 980 cm^{-1} ; NMR ($CDCl_3$): δ 2.23 (3H, s), 6.98 (1H at C-5, t, J = 8 Hz), 7.15–7.58 (5H, complex m), 7.78 (1H at C-4, dd, J = 8 and 1.5 Hz), and 8.65 (1H at C-6, dd, J = 8 and 1.5 Hz).

³ Hyna.

Table I—Nitro- and Acetamidophenylsalicylates

Compound	R	Melting Point	Recrystallization Solvent	Yield, %	Formula	Analysis, %		<i>R_f</i> Values ^a		
						Calc.	Found	Chloroform	Benzene	Ethyl Acetate
V	5-NO ₂	148–150° ^b	Ethanol	42	C ₁₃ H ₉ NO ₅	C 60.10 H 3.47 N 5.78	59.89 3.68 5.52	0.496 0.690	0.256 0.536	— —
VI	3-NO ₂	92–93° ^c	Ethanol	52	C ₁₃ H ₉ NO ₅ ·H ₂ O	C 56.32 H 3.97 N 5.05	56.62 3.58 4.87	0.423 0.560	0.146 0.330	— —
VIII	5-NHCOCH ₃	174–176°	Ethanol or ethanol-water	84	C ₁₅ H ₁₃ NO ₄	C 66.42 H 4.79 N 5.16	66.36 5.04 5.29	0.023 0.073	0.013 — ^d	0.631 0.877
X	3-NHCOCH ₃	165–166°	Ethanol or ethanol-water	80	C ₁₅ H ₁₃ NO ₄	C 66.42 H 4.79 N 5.16	66.27 5.08 5.32	0.122 0.303	0.013 0.043	0.821 0.922

^a Two *R_f* values are reported for each compound in different solvents. The first value represents the *R_f* on silica gel 60 F-254 (slow moving); the second value represents the *R_f* on silica gel F-254 (fast moving). ^b Lit. (7, 8) mp 150–151°. ^c Lit. (8) mp 101–102° for anhydrous. The compound was dried after analysis to give mp 99–100°. ^d The compound did not move.

Biological Testing of VIII and X—Solutions of VIII or X in dimethyl sulfoxide or propylene glycol or suspensions in 1% methylcellulose were administered to groups of six, eight, or 10 albino MRI female or male mice weighing 18–20 g. The doses were 25, 50, 100, 200, 300, 400, and 500 mg/kg. Twenty minutes later, the mice were given, intraperitoneally, 0.2 ml of a 0.02% solution of phenyl-*p*-quinone in water containing 5% alcohol.

The mice for each dose were placed in separate cages and observed for 20 min. Those that showed signs of writhing were removed from the cage. The ED₅₀ data of VIII are shown in Table II. Compound X was ineffective at doses of 50 and 200 mg/kg.

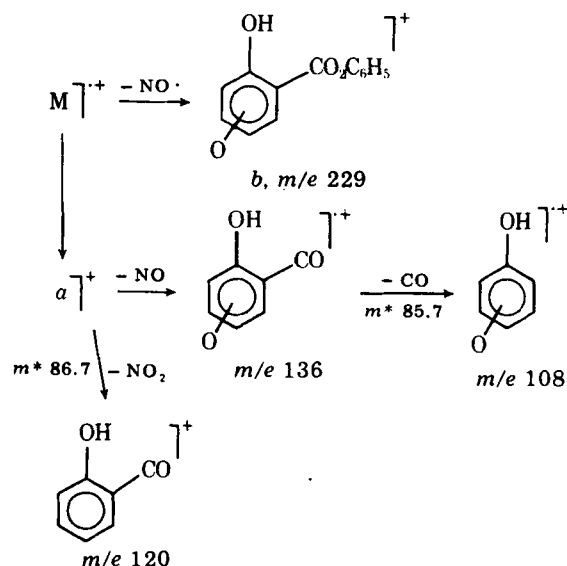
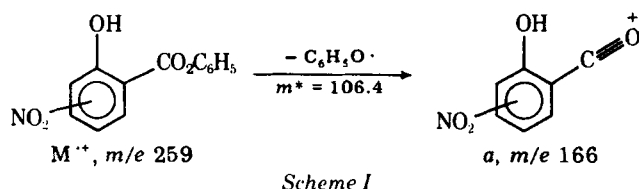
RESULTS AND DISCUSSION

Chemistry—Several nitro derivatives of phenylsalicylate have been made by treatment of nitrosalicylic acid and phenol with phosphorus oxychloride or by treatment of salicylic acid and nitrophenol with phosphorus oxychloride (7–9). Other investigators (10) nitrated salicylic acid and salicylamide by treatment of these compounds with nitric acid to obtain the corresponding 3- and 5-nitro derivatives. Our approach to the synthesis of V and VI also involved direct nitration of I with nitric acid. This procedure achieved almost complete conversion of I into V and VI.

Evidence for structural identification of V and VI was obtained from mass spectral (Table III) and NMR studies. Both compounds had a molecular ion at *m/e* 259 with relative intensities of 95% for V and 76.5% for VI. These data indicate that one nitro group is introduced in both compounds and that the molecular ion of V is more stable than that of VI⁴ (11). Isotopic analysis gave good agreement with the theoretical value for C₁₃H₉NO₅ (Table IV). The mass spectra of both compounds were similar except for the quantitative differences in the relative peak intensities.

Both V and VI showed peaks at *m/e* 166 (100%) upon electron impact. This peak may be represented by ion *a* (Scheme I), which indicated the introduction of the nitro group onto the salicylate ring of I.

The peak at *m/e* 229 may be represented by ion *b* (M – NO). This ion may result from the rearrangement of the nitro group prior to loss of the NO group (12–16). The intensity difference of this peak in the mass spectra of V and VI can be attributed to the differences in the nitro group position in the two molecules (12–16). Such rearrangement has been reported for several *para*- and *meta*-substituted nitrobenzene derivatives. The *ortho*-derivatives lack such rearrangement or show peaks of very low intensity corresponding to ions resulting from this rearrangement. This type of rearrangement was also observed for ion *a* (Scheme II and Table III).



The IR spectra of various V and VI concentrations also were studied to reveal the effect of the nitro group on hydrogen bonding in phenylsalicylate. Both compounds showed broad absorption bands at 3300–3090 cm⁻¹ in concentrations ranging between 2.5 and 12.5% in chloroform. No shift was observed in the absorption band of the hydroxyl group in this region. This result may indicate that the nitro group position in the salicylate ring had no effect on the intramolecular hydrogen bond that exists in I (17–19) between the hydroxyl group and the carboxyl group.

The mass spectral data for V and VI suggest that the former compound may have a 1,2,5-substitution and that the latter may have a 1,2,3-substitution. NMR and decoupling studies confirmed this evidence. At the low field end of the aromatic region of the NMR spectrum of V, there was a doublet at δ 9.04 with splitting of 2.6 Hz. The chemical shift indicated the resonance of the proton at C-6 with the two *ortho*-positions occupied by electron-withdrawing groups. The *J* value indicated the presence of a *meta*-proton (20–23), indicating the presence of a proton at C-4 whose signal appeared as two doublets at 8.42 with splitting of 9.4 and 2.6 Hz. This finding indicated the presence of *meta*- (at C-6) and *ortho*- (at C-3) protons. The signal of the latter appeared as a doublet at 7.16 with

Table II—Biological Testing Data of VIII

Dose, mg/kg	Number of Mice	Percent Protection
25	8	37.50
50	6, 6, 8 ^a	50.00
100	8, 8, 10 ^a	66.60
200	6	83.30
300	6	83.30
500	6, 8 ^a	100.00

^a The experiment was repeated using the number of animals shown, and percent protection represents the average.

⁴ R. Schaffer, Morgan-Schaffer Corp., Montreal, Canada, 1977, personal communication.

Table III—Mass Spectral Data of V and VI

<i>m/e</i>	Percent	
	V	VI
92	64.4	22.4
108	11.2	3.0
120	81.4	69.2
121	15.0	10.0
166	100.0	100.0
229	11.9	3.3
259	95.1	76.5
260	43.9	17.0
261	6.3	2.9

splitting of 9.6 Hz, which indicated the presence of an *ortho*-proton (at C-4). The decoupling study confirmed this assignment since irradiation of H-3 removed the *ortho*-coupling to H-4, which appeared as a doublet with *meta*-splitting. Irradiation of H-4 removed the *ortho*-coupling to H-3, which appeared as a singlet, and the *meta*-coupling to H-6, which also appeared as a singlet. Irradiation of H-6 removed the *meta*-coupling to H-4, which appeared as a doublet with *ortho*-splitting only. These data indicate that the salicylate ring protons in V have a 1,2,4-relationship.

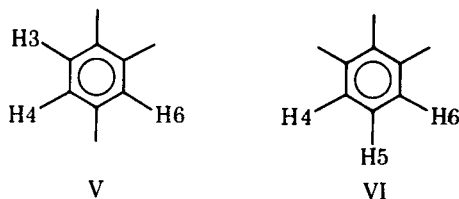
The NMR spectrum of VI showed a two-doublet signal at δ 8.32 with splitting of 8 and 1.7 Hz, characteristic of *ortho*- and *meta*-splitting, respectively (20–23). This signal was assigned to the proton at C-4. The signal representing the C-6 proton of the salicylate ring also appeared as a doublet at δ 8.21 with splitting of 8.2 and 1.7, which indicated the presence of *ortho*- and *meta*-protons at C-5 and C-4, respectively. However, the signal representing C-5 proton was included in the complex multiplet at δ 7.60–7.01. The decoupling study confirmed this assignment since H-5 irradiation removed the *ortho*-splitting with H-4 and H-6 and both appeared as doublets with *meta*-splitting to each other. Irradiation of H-4 or H-6 removed the *meta*-splitting to each other, and their signals appeared as doublets with *ortho*-splitting. These data indicate that the nitro group occupies the 3-position and that the protons in VI have a 1,2,3-relationship.

Reduction of the isomeric nitro salols was achieved by simple catalytic hydrogenation in very high yields. The corresponding amines were acetylated by treatment of the amines with acetic anhydride to produce the corresponding acetamido derivatives (VIII and X) in high yields. In contrast to the IR spectra of V and VI, the IR spectra of VIII and X showed a clear difference in the hydroxyl group absorption band. The hydroxyl absorption band in the IR spectrum of X appeared at 3180 cm^{-1} ; in the IR spectrum of VIII, it appeared at 3250 cm^{-1} . This difference may be based upon the different types of hydrogen bonding the molecules undergo.

The mass spectra of VIII and X also were similar (Table V), and the fragmentation pattern was comparable to that of the nitro derivatives. The appearance of a peak at *m/e* 178 (100%) may have arisen from the loss of a phenoxide radical from the molecular ion (*m/e* 271), as shown in Scheme III together with the other important fragmentations.

The NMR spectra of VIII and X and the decoupling study were consistent with the positional assignment of the acetamido group (Table VI).

Biological Testing and Toxicity—Compounds VIII and X were

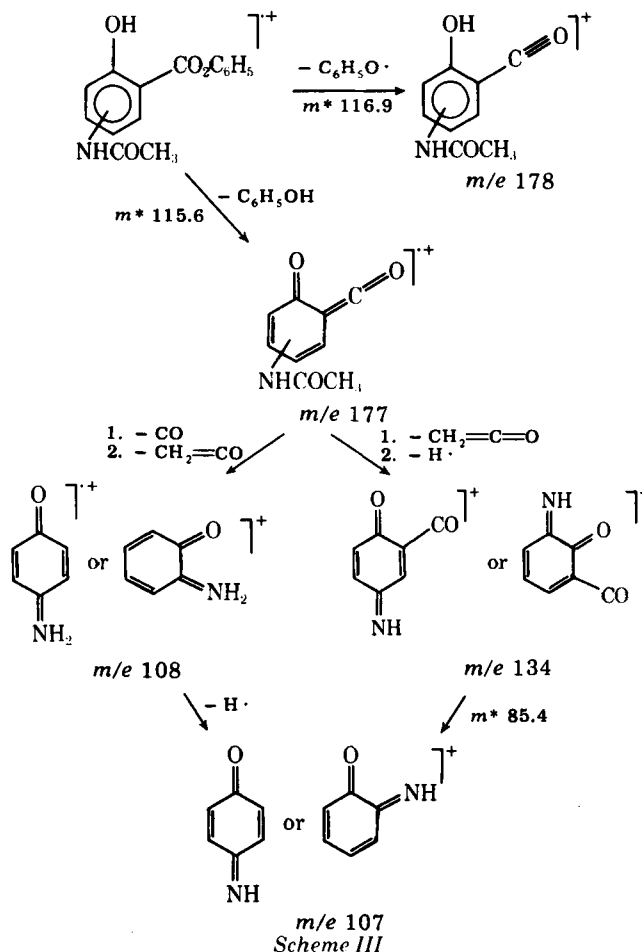
Table IV—Mass Spectral Isotopic Analysis^a of V and VI

Compound	<i>m/e</i>	$\text{C}_{13}\text{H}_9\text{NO}_5$	
		Theoretical	Found
V	259	100.00	100.00
	260	14.77	14.70
	261	2.01	2.09
VI	259	100.00	100.00
	260	14.77	14.79
	261	2.01	2.05

^a Analysis performed by Morgan-Schaffer Corp., Montreal, Canada.

Table V—Mass Spectral Data of VIII and X

<i>m/e</i>	Percent	
	VIII	X
107	4.8	11.0
108	9.0	16.5
134	3.6	58.3
135	9.6	47.2
177	11.4	20.0
178	100.0	100.0
179	10.8	1.6
271	43.4	72.7
272	8.4	13.8
273	1.2	1.6



tested for analgesic activity in the writhing test (24). Compound VIII had comparable analgesic activity to that of aspirin and phenacetin. The ED_{50} of VIII under the experimental conditions was 56 mg/kg (27–122) when the writhing material was injected 20 min after treatment of the mice. However, X was ineffective at 50 mg/kg and caused restlessness at 200 mg/kg upon injection of the writhing material. Compound VIII was nontoxic at doses of 1 and 2 g/kg sc and caused 10% death of the mice at 3 g/kg ip during 24 hr.

Table VI—NMR Data of VIII and X

Proton	δ	J_{meta} , Hz	J_{ortho} , Hz
Compound VIII			
H3	6.98 d	—	8.8
H4	7.62 dd	2.4	8.5
H6	8.22 d	2.6	—
Compound X			
H4	7.78 dd	1.5	8.0
H5	6.98 dd ^a	—	—
H6	8.65 dd	1.5	8.0

^a Collapsed into triplet at $J = 8.0$ Hz.

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Conductivity and Hardness Changes in Aged Compacts

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Abstract □ Batches of sodium, potassium, and ammonium chloride tablets containing no excipients and spray-dried lactose tablets containing 0.5% magnesium stearate were stored at 20 and 76% relative humidity. Electrical resistance and hardness measurements were made within 1 hr after compression and at intervals during a 45-day period. Hardness values of sodium, potassium, and ammonium chloride tablets stored at 20% relative humidity increased from 70 to 200% at 45 days, while conductances decreased 10-fold. Tablets stored at 76% relative humidity showed no increases or slight decreases in hardness with slight increases in conductance. Lactose tablets decreased slightly in hardness with corresponding increases in conductance.

Keyphrases □ Conductivity, electrical—effect of aging and humidity, various compressed tablets □ Hardness—effect of aging and humidity, various compressed tablets □ Tablets, compressed—effect of aging and humidity on electrical conductivity and hardness

The effect of aging on the physical characteristics of tablets has been discussed by several investigators. Increased hardness was reported in hydrochlorothiazide tablets formulated with acacia (1). Dibasic calcium phosphate dihydrate tablets displayed no significant changes in hardness over a 4-month period but showed significant increases in disintegration and dissolution times when stored at 25° and 50% relative humidity (RH) (2).

The crushing strength of sodium chloride compacts prepared from dried samples doubled 1 hr after compaction (3). No significant changes in crushing strength were observed when compacts were stored for longer periods at

low humidities. This phenomenon was attributed to time-dependent relaxations, resulting in stress release within the compacts which increased interparticulate contact and bonding. Compacts with higher moisture content possessed low tensile strength compared to those with lower moisture content, which was attributed to weakening of interparticulate bonding by trace moisture (3).

Significant increases in hardness were observed in sodium chloride tablets stored for several days (4). These changes correlated with changes in electrical conductances calculated from measured dissipation factors.

The electrical conductance of a compact is determined in part by the number of interparticulate contact points and the effective internal surface area resulting from microscopic cracks and imperfections (5). Hardness changes in compacts should be associated with conductance changes that reflect changes in the contact area and internal surface. Increases in compact strength should be correlated with decreases in electrical conductance, measured under conditions in which there is no substantial increase in compact moisture content.

This study was designed to verify the expected relationship between conductance and hardness changes in compacts and to establish the role of moisture in affecting these changes in compacts of directly compressible salts.