5. The release rates of SETD from SETD-synthetic wax-like ester formulations were higher in the alkaline pancreatin medium than in the acid pepsin medium. The initial dissolution rates and the rate constants were also similarly affected. The addition of 10% low molecular weight polyethylene decreased the dissolution rate in alkaline pancreatin medium considerably. The initial dissolution rates in both the acid and alkaline medium were also considerably reduced. The addition of 2.5% ethylcellulose resulted in higher initial dissolution rates with the values of the rate constants also higher and closer to each other. The addition of 10% glyceryl ester of hydrogenated rosin increased the initial dissolution rates and the values of the rate constants.

6. The analysis of the data suggests that for a good sustained-release effect from formulations such as spray-congealed particles, the rate constants should be small and independent of pH and composition of the medium with low initial dissolution rates and high equilibrium values in alkaline pancreatin medium. This investigation attempted to gain some insight in that direction.

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Keyphrases

Spray-congealed formulations

Sulfaethidole–wax—prolonged release formulations

Modifiers, sulfaethidole-wax formulation—*in vitro* dissolution

Particle size—modifiers effect

Colorimetric analysis—spectrophotometer

Preparation and Properties of Some Relatives of Noscapine

By J. SAM, A. V. LOPEZ*, and R. M. SHAFIK

Fusion of phenylacetic acids with phthalic anhydrides resulted in the formation of benzylidenephthalides. Ammonolysis of the phthalides yielded 3-hydroxy-3-benzylphthalimidines which were easily dehydrated to 3-benzylidenephthalimidines. Bromination of 3-hydroxy-3-benzylphthalimidine with *N*-bromosuccinimide yielded 3-(α-bromobenzylidene)phthalimidine. Reaction of the latter with pyrrolidine gave the α-pyrrolidino derivative which on treatment with dilute hydrochloric acid resulted in 3-(α-hydroxybenzylidene)phthalimidine. Treatment of tetrahalobenzylidenephthalides with sodium methoxide produced 1,3-indandione derivatives. Mild sedative properties were noticed in compounds tested.

NOSCAPINE (I), formerly known as narcotine (1), is the most abundant of the opium alkaloids after morphine. Despite the fact that it comes from a plant rich in narcotic alkaloids it possesses none of the undesirable effects of narcotics; however, it possesses mild central nervous system activity similar to that of papaverine (2). Winter and Flataker (3) during their search for antitussive agents, discovered that noscapine was very effective in this respect. Further studies (4, 5) showed that in addition to its central effect noscapine also has bronchodilation activity. These factors prompted the in-

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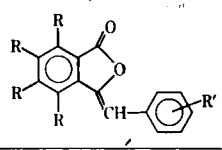
* Present address: Mercer University, Southern School of Pharmacy, Atlanta, Georgia.

TABLE I—3-BENZYLIDENEPHTHALIDES (II)

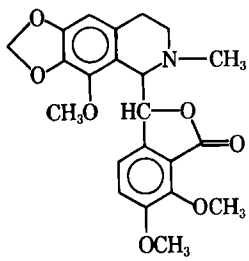


No.	R	R′	M.p., °C.	Yield, %	Molecular Formula	Anal., % Calcd.	Found
II*a*	H	H	98–100[a]	79	$C_{15}H_{10}O_2$[b]		
II*b*	Cl	H	290–291[c]	63	$C_{15}H_6Cl_4O_2$[d]	C, 50.0 H, 1.68 Cl, 39.4	C, 50.2 H, 1.77 Cl, 39.3
II*c*	Br	H	288–289[c]	70	$C_{15}H_6Br_4O_2$	C, 33.5 H, 1.14 Br, 59.4	C, 33.6 H, 1.26 Br, 59.3
II*d*	Cl	3,4-diCH_3O	221–223[c]	75	$C_{17}H_{10}Cl_4O_4$	C, 48.6 H, 2.39 Cl, 33.8	C, 49.0 H, 2.60 Cl, 33.5
II*e*	Br	3,4-diCH_3O	238–240[c]	65	$C_{17}H_{10}Br_4O_4$	C, 34.1 H, 1.68 Br, 53.5	C, 33.9 H, 1.91 Br, 52.5
II*f*	Cl	2-CH_3O	269–270[c]	60	$C_{16}H_8Cl_4O_3$	C, 49.3 H, 2.04 Cl, 36.4	C, 49.2 H, 2.29 Cl, 36.3
II*g*	Br	2-CH_3O	301–302[c]	60	$C_{16}H_8Br_4O_3$	C, 33.8 H, 1.42	C, 33.7 H, 1.70
II*h*	Cl	4-CH_3O	270–271[c]	75	$C_{16}H_8Cl_4O_3$	C, 49.3 H, 2.04 Cl, 36.4	C, 49.8 H, 2.26 Cl, 36.9
II*i*	Br	4-CH_3O	284–286[c]	75	$C_{16}H_8Br_4O_3$	C, 33.8 H, 1.42 Br, 56.3	C, 33.8 H, 1.59 Br, 56.3

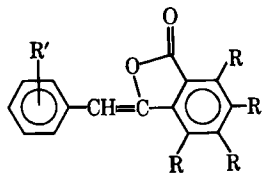
[a] Recryst. from ethanol. [b] *References 15, 16.* [c] Recrysd. from 2-ethoxyethanol (Cellosolve). [d] *Reference 17.*

vestigation of a series of substituted 3-benzylidenephthalides (II, Table I) and some of their nitrogen isosters (3-benzylidenephthalimidines). The 3-hydroxy-3-benzylphthalimidines (III) also possess a structural resemblance to chlorthalidone (IV) (6) which is a potent diuretic agent of long duration (7) and effective in the treatment of patients with cardiac edema (8). The latter, however, contains the sulfonamide group characteristic of diuretics. The 1,3-indandiones (X) were prepared for possible anticoagulant and anti-inflammatory activity (9–15).

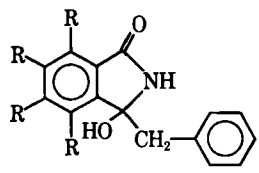
3-Benzylidenephthalides (II, Table I) were prepared using a slight modification of the method described by Gabriel (16) by fusing at high temperature a mixture of the appropriate phenylacetic acid and phthalic anhydride with a catalytic amount of anhydrous sodium acetate. The ammonolysis of 3-benzylidenephthalides with ammonium hydroxide solution resulted in the formation of 3-hydroxy-3-benzylphthalimidines (III) and not 2-phenylacetylbenzamide (V) as was reported by Gabriel (16). The structures (III) were substantiated by nuclear magnetic resonance spectra (NMR) and by the ease with which dehydration occurred on heating at 250–300° to give 3-benzylidenephthalimidines



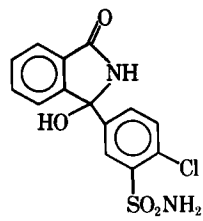
I



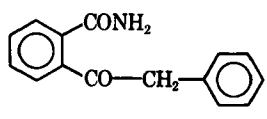
II



III

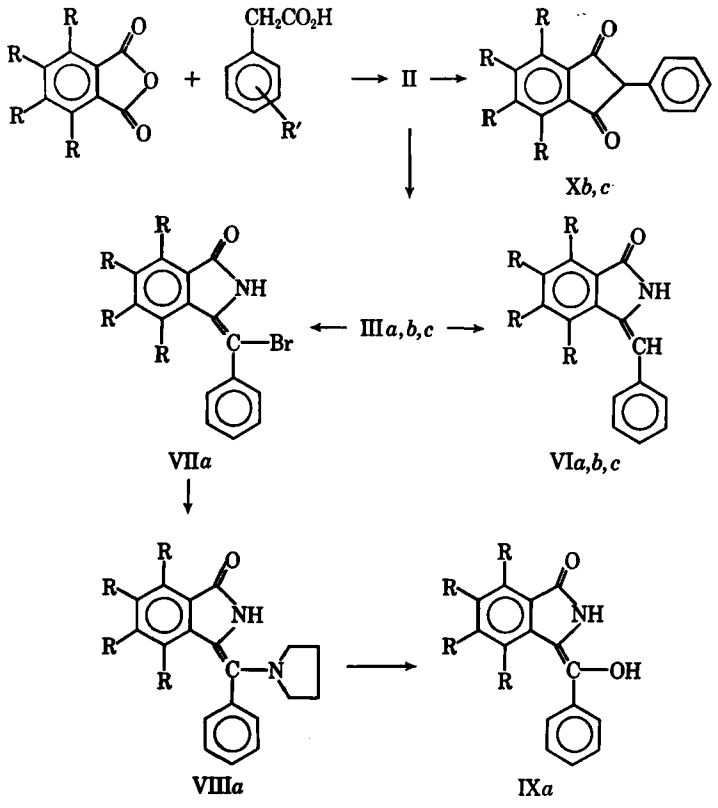


IV



V

(VI). Treatment of III*a* with *N*-bromosuccinimide gave 3-(α-bromobenzylidene)phthalimidine (VII*a*). Refluxing VII*a* with excess pyrrolidine



Scheme I

resulted in the formation of 3-(α-pyrrolidinobenzylidene)phthalimidine (VIII*a*) which upon treatment with dilute hydrochloric acid provided 3-(α-hydroxybenzylidene) phthalimidine (IX*a*). 3 - Hydroxy - 3 - benzyl - 4,5,6,7 - tetrahalophthalimidines could not be brominated in the same way using *N*-bromosuccinimide; dehydration to the corresponding benzylidenephthalimidines (VI*b*,*c*) occurred. Reaction of 3-benzylidene-4,5,6,7-tetrahalophthalides (II*b* and II*c*) with sodium methoxide yielded the tetrahaloindandiones (X*b* and X*c*). The IR spectral data of the compounds reported in this study are summarized in Table II.

PHARMACOLOGICAL RESULTS[1]

Compounds II*b*, II*c*, VI*b*, and VII*a* were administered by intraperitoneal injection to 25–30-g. albino mice as suspensions in 10% acacia solution. The mice were observed during the 3 hr. following injection and rechecked at 12 and 24 hr. No deaths were observed with any of the compounds among groups of 3–5 mice at maximum dosages of 1.5–2.0

TABLE II—INFRARED SPECTRAL DATA (cm.$^{-1}$)[a]

No.	OH	NH	C=O	C=C
II*a*			1,780	1,660
II*b*			1,800	1,645
II*c*			1,790	1,640
II*d*			1,770	1,640
II*e*			1,765	1,640
II*f*			1,790	1,640
II*g*			1,790	1,645
II*h*			1,785	1,640
II*i*			1,780	1,640
III*a*	3,350	3,200	1,690	
III*b*	3,550	3,300	1,700	
III*c*	3,450	3,320	1,700	
VI*a*		3,200	1,700	1,650
VI*b*		3,200	1,710	1,640
VI*c*		3,350	1,710	1,640
VII*a*		3,200	1,710	1,655
VIII*a*[b]		3,150	1,670	1,610
IX*a*	3,070	3,180	1,700	1,605
X*b*			1,740, 1,700	
X*c*			1,730, 1,705	

[a] The compounds in this table all exhibited characteristic aromatic absorptions, single band from 1,625–1,560 and multiple bands in region of 900–680. [b] Pyrrolidine methylene groups exhibit a doublet at 2,950–2,850.

[1] The authors are grateful to Dr. Marvin Davis, Department of Pharmacology, School of Pharmacy, The University of Mississippi, for the pharmacological data.

g./kg. With each of the compounds the mice showed inactivity, apparently being sedated slightly for more than 12 hr. None showed loss of righting, grasping, or pain reflexes and they remained reactive to loud sound stimuli. Ptosis was evident at 1.5 g./kg. with either IIc or VIIa.

Compounds IIa, IId, and IXa were administered by intramuscular injection to male albino mice, weighing from 25–50 g. with an average of 35 g., as a 10% suspension in 5% acacia soluion at maximum dosages of 1 g./kg. During the observation period of 24 hr. the animals were housed in small single-animal isolation cages. No food or water was available. The animals were observed for 2 hr. after injection and rechecked at 4, 6, 18, and 24 hr. Only slight sedation was observed with IIa and IId; no noticeable effects were seen with IXa and no deaths were observed with either of the three compounds.

EXPERIMENTAL[2]

3-Benzylidenephthalides (II, Table I)—Utilizing a method similar to that described by Gabriel (16), an intimate mixture of 0.67 mole of the proper phthalic anhydride, 0.80 mole of the desired phenylacetic acid, and 2.3 g. of anhydrous sodium acetate was heated at a temperature of 250–300° for 2–4 hr. The crude materials were purified by recrystallization from appropriate solvents to yield 60–79% of products.

The NMR spectrum of IIa showed a one-proton methine singlet (6.4) and a nine-proton aromatic multiplet (7.2–8.0).

3-Hydroxy-3-benzylphthalimidine (IIIa)—A solution of 75 g. (0.337 mole) of 3-benzylidinephthalide (IIa) in 100 ml. of ethanol and 100 ml. of concentrated ammonium hydroxide solution was refluxed for 4 hr. The resulting solution was poured over 200 g. of crushed ice and the solid was collected and recrystallized from water to yield 70 g. (87%) of product, m.p. 165–166°.

Anal.—Calcd. for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.48; N, 5.86. Found: C, 75.4; H, 5.40; N, 6.00.

The NMR spectrum showed a one-proton hydroxyl singlet (2.9), a two-proton methylene singlet (3.4), a one-proton imino singlet (5.5), a five-proton aromatic singlet (7.2), and a four-proton aromatic multiplet (7.4–7.7).

3-Hydroxy-3-benzyl-4,5,6,7-tetrachlorophthalimidine (IIIb)—A mixture of 66 g. (0.183 mole) of 3-benzylidene-4,5,6,7-tetrachlorophthalide (IIb), 300 ml. of 2-ethoxyethanol, and 300 ml. of concentrated ammonium hydroxide solution was heated at 60–70° for 4 hr. The resulting pinkish reaction mixture was filtered; the filtrate was poured onto 200 g. of crushed ice and the solid was collected and recrystallized from ethanol to yield 20 g. (30%) of product, m.p. 215–217°.

Anal.—Calcd. for $C_{15}H_9Cl_4NO_2$: C, 47.8; H, 2.41; Cl, 37.6; N, 3.72. Found: C, 48.2; H, 3.00; Cl, 38.0; N, 3.61.

The NMR spectrum showed a one-proton hydroxyl singlet (2.9), a two-proton methylene multiplet (3.3–4.0), a five-proton aromatic singlet (7.2), and a one-proton imino singlet (8.6).

3-Hydroxy-3-benzyl-4,5,6,7-tetrabromophthalimidine (IIIc)—The above procedure was followed using 10 g. (0.018 mole) of 3-benzylidene-4,5,6,7-tetrabromophthalide (IIc), 300 ml. of 2-ethoxyethanol, and 300 ml of concentrated ammonium hydroxide solution. The yield of product was 7 g. (70%), m.p. 243–244°.

Anal.—Calcd. for $C_{15}H_9Br_4NO_2$: C, 32.5; H, 1.64; Br, 57.6. Found: C, 32.2; H, 1.79; Br, 57.3.

3-Benzylidenephthalimidine (VIa)—One gram (0.0042 mole) of 3-hydroxy-3-benzylphthalimidine (IIIa) was heated in an open vessel at 200–230° for 1 hr. The crude material which solidified on cooling was recrystallized from ethanol to yield 0.83 g. (91%) of product, m.p. 182–184°.

Anal.—Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.00; N, 6.33. Found: C, 80.9; H, 4.96; N, 6.85.

The NMR spectrum showed a one-proton methine singlet (6.5), a nine-proton aromatic multiplet (7.2–8.0), and a one-proton imino singlet (8.6).

3-Benzylidene-4,5,6,7-tetrachlorophthalimidine (VIb)—Two grams (0.0053 mole) of 3-hydroxy-3-benzyl-4,5,6,7-tetrachlorophthalimidine (IIIb) was heated in an open vessel at 300° for 30 min. The crude material which solidified on cooling was recrystallized from 2-ethoxyethanol to yield 1.8 g. (95%) of product, m.p. 331–332°.

Anal.—Calcd. for $C_{15}H_7Cl_4NO$: C, 50.2; H, 1.97; Cl, 39.5; N, 3.90. Found: C, 50.4; H, 1.88; Cl, 39.5; N, 4.06.

3-Benzylidene-4,5,6,7-tetrabromophthalimidine (VIc)—The above procedure was followed using 2 g. (0.0036 mole) of 3-hydroxy-3-benzyl-4,5,6,7-tetrabromophthalimidine (IIIc). The yield of product was 1.5 g. (70%), m.p. 304–305°.

Anal.—Calcd. for $C_{15}H_7Br_4NO$: C, 33.6; H, 1.31; Br, 59.5; N, 2.60. Found: C, 33.4; H, 1.32; Br, 59.3; N, 2.66.

3-(α-Bromobenzylidene)phthalimidine (VIIa)—The procedure described by Ziegler (18) for allylic brominations was followed using 40 g. (0.168 mole) of 3-hydroxy-3-benzylphthalimidine (IIIa), 28 g. (0.17 mole) of *N*-bromosuccinimide, and 1 l. of anhydrous chloroform. The mixture was refluxed for 12 hr., concentrated to 200 ml., and then allowed to cool to room temperature. Both succinimide and the product precipitated from solution. The succinimide was removed by washing the mixture with three successive portions of 100 ml. of boiling water. The residual material was recrystallized from ethanol to yield 29 g. (60%) of product, m.p. 211–213°.

Anal.—Calcd. for $C_{15}H_{10}BrNO$: C, 60.0; H, 3.36; Br, 26.6; N, 4.67. Found: C, 60.2; H, 3.13; Br, 26.9; N, 4.78.

The NMR spectrum showed a nine-proton aromatic multiplet (7.2–7.9) and a one-proton imino singlet (8.6).

3-(α-Pyrrolidinobenzylidene)phthalimidine (VIIIa)—A mixture of 15 g. (0.05 mole) of 3-(α-bromobenzylidene)phthalimidine (VIIa) and 125 ml. of pyrrolidine was refluxed for 6 hr. after which time water was added to the solution until precipitation occurred. The crude yellow product was collected and recrystallized from ethanol to yield 7 g. (50%) of product, m.p. 176.5–178°.

[2] Melting points were taken in open glass capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer Model 137 Infracord spectrophotometer using potassium bromide pellets. NMR spectra were determined on a Varian A-60A spectrometer, using tetramethylsilane as an internal standard; chemical shifts are recorded as δ values.

Anal.—Calcd. for $C_{19}H_{18}N_2O$: C, 78.6; H, 6.25; N, 9.65. Found: C, 79.1; H, 6.21; N, 9.39.

The NMR spectrum showed a four-proton methylene multiplet (1.7–2.1), a two-proton methylene triplet (2.9–3.2), a two-proton methylene triplet (3.3–3.6), a nine-proton aromatic multiplet (6.8–7.6), and a one-proton imino singlet (11.0).

A picrate was prepared in the usual manner and recrystallized from ethanol; m.p. 198–200°.

Anal.—Calcd. for $C_{25}H_{21}N_5O_8$: C, 57.8; H, 4.07; N, 13.50. Found: C, 57.8; H, 4.12; N, 13.30.

3-(α-Hydroxybenzylidene)phthalimidine (IXa)—A mixture of 4 g. (0.0137 mole) of 3-(α-pyrrolidinobenzylidene)phthalimidine (VIII*a*) and 400 ml. of a 10% hydrochloric acid solution was heated on a steam bath for 2 hr. The white solid was collected and recrystallized from ethanol to yield 2 g. (61%) of product, m.p. 185–187°.

Anal.—Calcd. for $C_{15}H_{11}NO_2$: C, 75.9; H, 4.67; N, 5.90. Found: C, 75.9; H, 4.60; N, 5.74.

The NMR spectrum showed a broad hydroxyl peak (3.5–4.0), a nine-proton aromatic multiplet (7.2–7.9), and a one-proton imino singlet (8.9).

2-Phenyl-4,5,6,7-tetrachloro-1,3-indandione (Xb)—The procedure described by Zalukajevs (15) for the preparation of 2-phenyl-1,3-indandione was followed using 3.6 g. (0.01 mole) of 3-benzylidene-4,5,6,7-tetrachlorophthalide (II*b*) and 50 ml. of 2-ethoxyethanol. The mixture was heated until solution occurred and while still hot was added to 30 ml. of methanol in which 0.5 g. of sodium had been dissolved. The solution was allowed to cool to room temperature and then diluted with 50 ml. of methanol and 150 ml. of water, respectively. The solution was then acidified with concentrated hydrochloric acid whereupon precipitation of a crude yellow material occurred. The material was collected by filtration and recrystallized from glacial acetic acid to yield 3 g. (83%) of product, m.p. 222–223°.

Anal.—Calcd. for $C_{15}H_6Cl_4O_2$: C, 50.0; H, 1.68; Cl, 39.4. Found: C, 50.4; H, 1.19; Cl, 39.6.

2-Phenyl-4,5,6,7-tetrabromo-1,3-indandione (Xc)—The above procedure was followed using 5.37 g. (0.01 mole) of 3-benzylidene-4,5,6,7-tetrabromophthalide (II*c*). The crude material was recrystallized from glacial acetic acid to yield 3.75 g. (70%) of product, m.p. 257–258°.

Anal.—Calcd. for $C_{15}H_6Br_4O_2$: C, 33.5; H, 1.14; Br, 59.4. Found: C, 33.7; H, 1.22; Br, 59.5.

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Keyphrases

Noscapine-related compounds—synthesis
Sedative activity—noscapine-related compounds
NMR spectroscopy—structure
IR spectrophotometry—structure