incubated at 30° for 48–72 hr. The inhibition zone was measured around each disk (Table IV).

CONCLUSIONS

The present results indicate that the microorganisms tested were sensitive to the action of the anils (IIIi and IVc) and the esters (Va and VIa) except for *A. nigar* and *F. moniliforme*. The results also illustrated that the anils potentiate the activity more than the esters. However, it was observed that the presence of the methoxy group in the *para* position to the benzofuran oxygen (IVc and VIa) increased the activity. The cyclization of Va blocked the activity against most of the microorganisms tested. Such preliminary results would encourage further studies to elucidate the relationship between structure and activity.

REFERENCES

(1) L. Musajo, G. Rodighiero, and G. Caporale, *Chim. Ind. (Milan)*, **35**, 13 (1953); *Chem. Abstr.*, **48**, 4111 (1954).

(2) L. Musajo, G. Rodighiero, and G. Caporale, *Bull. Soc. Chim. Biol.*, **36**, 1213 (1954); *Chem. Abstr.*, **49**, 4871 (1955).

(3) M. A. Pathak, J. H. Fellman, and K. D. Kaufman, *J. Invest. Dermatol.*, **35**, 165 (1960).

(4) G. Rodighiero, B. Perissinotto, and G. Caporale, *Atti Ist. Veneto Sci. Lett. Arti, Cl. Sci. Mat. Nat.*, **114**, 1(1955–56); *Chem. Abstr.*, **51**, 10736 (1957).

(5) A. Schonberg and N. Latif, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(6) O. H. Hishmat, A.-K. M. N. Gohar, and M. E. Wasef, *Acta Helv.*, **52**, 252 (1977).

(7) O. H. Hishmat and A. H. Abd el Rahman, *Aust. J. Chem.*, **27**, 2499 (1974).

(8) L. J. Bellamy "The Infra-Red Spectra of Complex Molecules," 2nd ed., Methuen, London, England, 1966, p. 269.

(9) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

Aspirin—A National Survey V: Determination of Aspirin and Impurities in Enteric Coated Tablets and Suppository Formulations and *In Vitro* Dissolution of Enteric Coated Tablets

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Received September 18, 1981, from the *National Center for Drug Analysis, Food and Drug Administration, St. Louis MO 63101.* Accepted for publication December 9, 1981.

Abstract □ The results of a national survey on the quality of enteric coated aspirin tablets and aspirin suppositories are presented. The tablets were analyzed for strength, salicylic acid content, *in vitro* dissolution rate, and related aspirin impurities. The suppositories were analyzed for strength and salicylic acid content. The methods of analysis and validation of data are also presented.

Keyphrases □ Aspirin—semiautomated procedure for enteric coated tablets □ Dissolution—automated *in vitro* profiles of enteric coated aspirin tablets □ Analgesics—determination of aspirin and impurities in enteric coated tablets

A national survey of aspirin tablet products was conducted at the National Center for Drug Analysis in 1978 and 1979 to ascertain the quality of these products.

Parts I–III (1–3) of this series deal with the analysis of aspirin, salicylic acid, and aspirin related impurities in plain and buffered tablets. Part IV (4) compares *in vitro* dissolution results for these dosage forms using both the USP XX paddle and basket procedures (5). The present report describes the quality of enteric coated tablets with respect to content uniformity, dissolution characteristics, and impurities. Suppository formulations were also checked for content uniformity and impurities.

The official compendia do not provide a method or criterion for the *in vitro* dissolution of enteric coated tablets. Embil and Torosian (6) described the dissolution behavior of two brands of enteric coated tablets using a basket procedure. Over 60% of the aspirin content in the two brands dissolved within 3 hr, but there were significant differences in the release rates. Johansen (7) investigated the correlation between dissolution and absorption rates for plain and enteric coated aspirin tablets. The dissolution rate determinations were made with both a Sartorius apparatus and a USP XIX basket apparatus. Johansen found that the USP XIX basket apparatus, when applied to enteric coated tablets, gave a poor *in vitro/in vivo* correlation. He attributed this to the fact that the USP apparatus dissolved aspirin rather quickly after changing from simulated gastric fluid to intestinal fluid. To obtain a better correlation he recommended decreasing the rotational speed of the basket.

The purpose of this study was to investigate a semiau-

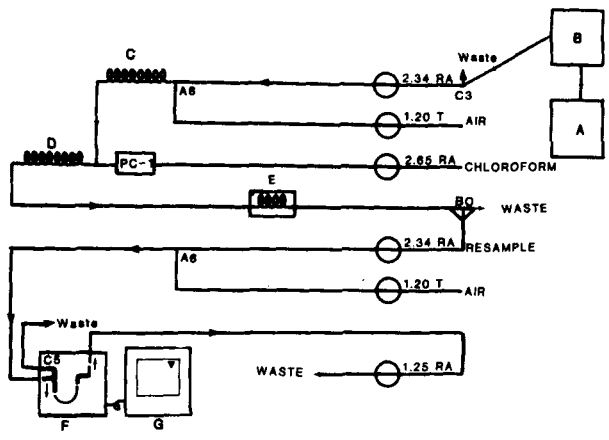

Figure 1—*Flow diagram of automated system for enteric coated aspirin dissolution. Key: (T) Tygon pump tube; (RA) red acidiflex pump tube; (C) 28-turn × 2.4-mm i.d. mixing coil; (D) 28-turn × 2.4-mm i.d. mixing coil with one double end; (E) 5.5-turn setting coil; (F) UV spectrophotometer; (G) recorder; (A) six-spindle dissolution apparatus; (B) automatic sampler. Pump tube sizes are in milliliters per minute. C-3, C-5, A6, and PC-1 are commercially available glass fittings.*

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Table I—Aspirin in Enteric Coated Tablets by Semiautomated Procedure and Salicylic Acid as Percent of Aspirin Declaration

Manufacturer[a]	Tablet Dosage, mg	Aspirin[b], %	Salicylic Acid, %
A	324	101.1 (1.85)	0.3
A	648	96.8 (1.34)	0.2
A	648	95.8 (2.42)	0.1
A	324	99.8 (3.58)	0.1
B	324	100.5 (2.32)	[c]
B	324	100.3 (2.57)	[c]
B	324	99.8 (2.11)	[c]
B	324	100.8[d] (2.23)	[c]
B	324	100.8 (2.61)	[c]
C	320	97.9[d] (2.81)	0.1
C	320	100.0[d] (2.21)	0.2
D	648	100.2 (1.91)	0.2
D	648	99.9 (1.66)	0.1
D	648	100.5 (1.63)	[c]
D	325	99.8 (2.52)	1.2
D	325	96.1 (1.57)	0.6
D	486	99.5 (1.95)	0.4
D	324	100.8 (2.14)	0.1
D	324	100.4 (1.84)	0.5
D	650	97.3 (2.15)	0.6
D	325	99.3 (2.30)	1.6

[a] (A) Eli Lilly & Co., Indianapolis, Ind.; (B) Smith Kline Corp., Philadelphia, Pa.; (C) Vale Chemical Co., Allentown, Pa.; (D) Standard Pharmacal Co., Chicago, Ill. [b] Each value represents 60 determinations unless otherwise noted. Number in parentheses is standard deviation. [c] Met compendial requirements. [d] Represents 30 determinations.

tomated UV (1) method for the determination of aspirin in enteric coated tablets, an automated method for the determination of the *in vitro* dissolution rate of aspirin from enteric coated tablets, and a manual UV method for the determination of aspirin in suppositories. In addition, five batches of enteric coated tablets were tested for aspirin-related impurities by the procedures described previously (3).

EXPERIMENTAL

Content Uniformity of Enteric Coated Tablets—*Apparatus, Reagents, and Determination*—These have been described previously (1).

Standard Preparation—About 325 mg of USP reference standard aspirin was accurately weighed and dissolved in 50.0 ml of buffer–ethanol solution (1:1). The standard solution was prepared fresh daily.

Sample Preparation—Each 325-mg enteric coated tablet was cracked and partially crushed in a piece of weighing paper[1] with a hammer and then transferred to separate 50-ml volumetric flasks. Alcoholic pH 2.2 buffer solution was added, and the flasks were placed in an ultrasonic bath[2] for ~1.5 hr with frequent shaking. The flasks were kept cool with circulating tap water. The flasks then were removed and the contents diluted to volume with alcoholic pH 2.2 buffer solution. After settling for 30 min, the solution in the flasks was analyzed as described previously (1).

Dissolution—*Apparatus*—A dissolution apparatus[3], equipped with a paddle [apparatus 2, (5)], and an automated sampler described previously (8) were used. The USP paddle method was used because it has been preferred historically in the laboratory.

For the determinative step, an automatic analyzer with a pump[4], manifold, spectrophotometer[5], flowcell[6], and recorder[7] was connected to the automatic sampler (8).

Reagents—American Chemical Society (ACS) grade chloroform was washed with water and filtered through paper on the day of use. The 0.4 *N* HCl was prepared by diluting 34.0 ml of concentrated hydrochloric acid to 1.0 liter with water. The simulated gastric fluid and simulated intestinal fluid was prepared according to the procedure in the USP XX (5) but without enzyme.

Standard Preparation—About 324 mg of USP reference standard aspirin was accurately weighed and dissolved in 500.0 ml of simulated intestinal fluid. The standard was prepared fresh daily and used without delay. Similar standards were prepared for the 486- and 648-mg tablets.

Sample Preparation—One tablet was placed in each dissolution vessel, which contained 500 ml of simulated gastric fluid. The paddles were rotated at 50 rpm for 1 hr, then the fluid was replaced with 500 ml of simulated intestinal fluid.

Automated Sampling—The aliquots were removed automatically every 15 min. The six dissolution sample probes were first placed into the standard solution, and the standard was sampled through the first cycle. The probes were then removed from the standard solution and placed in the dissolution medium. The aliquots were diluted with simulated intestinal fluid and stored in the holding–mixing coil. As the aliquots were pumped sequentially out of the holding–mixing coil, the stream was acidified with 0.4 *N* HCl and mixed.

Automated Determination—The automated system was assembled as shown in Fig. 1. Air was first removed from the acidified stream, which was drawn continuously into the manifold. The acidified stream was extracted with chloroform and resampled. The absorbance of the chloroform solution was monitored at 280 nm. The standard reading obtained through each probe was used to calculate the result from the sample reading obtained through that probe.

Suppositories—A recording spectrophotometer[8] and ACS reagent grade chloroform and glacial acetic acid were used.

Standard Preparation—About 100 mg of USP reference standard aspirin was accurately weighed and dissolved in 100.0 ml of chloroform. A 5.0-ml aliquot was diluted to 100.0 ml with a 1% acetic acid in chloroform solution.

Sample Preparation—Each suppository was dissolved in chloroform and diluted to volume with chloroform in an appropriate volumetric flask. An aliquot was taken and diluted with 1% acetic acid in chloroform to give a concentration similar to the standard.

Quantitation—The absorbance of both the standard and sample was measured from 350 to 220 nm in a 1-cm cell with 1% acetic acid in chloroform as the reference solution. The corrected net absorbance at 280 nm was used for the calculation of aspirin in each suppository.

Aspirin Identification and Salicylic Acid Limit Test—An ascending chromatography tank[9] (use unlined), silica gel plates[10], and a fluorescence detector[11] were used. Petroleum ether (bp range 30–60°), ethyl acetate, chloroform, glacial acetic acid, methanol, and ferric chloride hexahydrate were ACS reagent grade and/or suitable for chromatography. The mobile phase consisted of petroleum ether–ethyl acetate–glacial acetic acid (85:18:3).

Standard Aspirin Preparation—A concentration of 20.0 mg/ml of aspirin in chloroform was prepared and used as quickly as possible.

Standard Salicylic Acid Preparation—Solutions containing 0.02, 0.05, 0.10, 0.20, 0.40, and 0.80 mg/ml of salicylic acid in chloroform were prepared by quantitative dilution of a stock solution.

Sample Preparation—For the tablets a portion of a powdered composite was mixed with a 1.5% acetic acid in methanol solution to give an aspirin concentration of 20 mg/ml. The solution was centrifuged to obtain a clear supernate.

The suppositories were dissolved in chloroform to give a concentration of 20 mg/ml, except the 60-mg dose, which was diluted to a final concentration of 10 mg/ml.

Determination—About 100 ml of mobile phase was poured into the developing tank. The TLC plate was prewashed. The plate was removed and protected from evaporation by covering with two clear glass plates. The protective glass plates were separated to expose the origin or spotting line. One-microliter aliquots of each sample and standard were spotted 2 cm apart on the origin line. The mobile phase used for prewash was replaced with fresh mobile phase. The plate was developed until the solvent front had migrated at least 10 cm from the origin line. The plate was removed and dried on a hot plate until only a faint odor of acetic acid remained.

[1] Glassine paper (8.5 × 8.5 cm), Scientific Products, McGaw Park, IL 60085.
[2] Sonicor Model SC 400T, ultrasonic cleaner with timer, Randall Manufacturing Co., Hillside, NJ 08406.
[3] Model 72RL, Easi-Lift multiple spindle dissolution drive, Hanson Research Corp., Northridge, CA 91324.
[4] AutoAnalyzer proportioning pump III, 133-A014-04, Technicon Instruments Corp., Tarrytown, NY 10591.
[5] Model PM2DL, Carl Zeiss, Oberkochen, West Germany.
[6] Ten millimeters, 18 μl (886881), or 80 μl (886878), Beckman Instruments, Fullerton, CA 92634.
[7] Servo/Riter II, PS01WGA, Texas Instruments, Houston, TX 77001.
[8] Cary 118C, Varian Corp., Sunnyvale, CA 94086.
[9] Brinkmann Instruments, Inc., Westbury, CT 11590.
[10] Silica gel 60 F-254, 250 μm on a 20 × 20-cm plate, Curtis Matheson Scientific, Inc., Maryland Heights, MO 63043.
[11] Schoeffel Model SD 3000 spectrodensitometer. Excitation 310 nm, emission 440 nm. Schoeffel Instrument Corp., Westward, NJ 07675.

Table II—Dissolution Results [a] of Enteric Aspirin (Percent of Label Declaration) with Paddle at 50 rpm

Time, min	Manufacturer/Batch [b] A_1 Dosage, mg 324	A_2 648	B_1 324	C_1 324	D_1 324	D_2 486	D_3 486
15	49.5 (3.30)	40.0 (3.37)	44.8 (9.40)	0	0	0.1 (0.01)	0
30	63.3 (6.02)	52.8 (2.82)	55.9 (7.03)	0	0.1 (0.19)	0.1 (0.01)	0
45	70.3 (5.09)	61.9 (4.41)	61.1 (6.05)	0	1.0 (0.58)	0.6 (0.01)	0
60	74.3 (3.73)	67.1 (4.50)	65.7 (4.91)	0	1.7 (0.99)	1.1 (0.01)	0.9 (0.43)
75	77.6 (3.07)	71.3 (4.92)	68.4 (4.87)	0	2.6 (0.99)	1.5 (0.31)	1.5 (0.46)
90	79.0 (2.42)	74.4 (5.83)	69.8 (3.23)	0.2 (0.39)	3.2 (1.11)	2.1 (0.39)	2.0 (1.02)
105	81.3 (3.26)	75.1 (7.64)	69.8 (1.53)	0.6 (0.70)	3.7 (1.34)	2.1 (0.48)	2.9 (0.82)
120	82.4 (3.88)	76.9 (8.74)	68.6 (3.59)	1.2 (1.12)	4.3 (1.59)	2.1 (0.52)	3.5 (0.90)
135	82.8 (4.57)	76.9 (8.74)	67.9 (4.58)	1.7 (1.49)	5.0 (1.70)	2.4 (0.67)	4.1 (1.18)
150	84.4 (4.57)	76.6 (11.01)	66.2 (6.54)	2.5 (1.86)	5.5 (1.86)	2.7 (0.81)	4.7 (1.21)
165	83.4 (6.91)	75.8 (11.17)	62.3 (11.56)	3.1 (2.50)	6.1 (2.03)	2.9 (0.88)	5.2 (1.34)
180	84.8 (9.47)		57.8 (15.65)	3.7 (3.22)	6.7 (2.17)	3.1 (0.93)	5.6 (1.54)
195	83.0 (12.13)	—	56.0 (14.22)	4.3 (3.48)	7.2 (2.23)	3.3 (1.00)	6.0 (1.68)
210	82.6 (8.57)	—	52.3 (11.33)	5.3 (4.60)	7.8 (4.24)	3.5 (0.97)	6.6 (1.47)
225	83.4 (10.54)	—	—	6.3 (5.46)	8.3 (2.53)	3.6 (1.02)	6.8 (1.83)
240	81.7 (12.01)	—	—	7.2 (6.09)	9.0 (2.74)	—	7.3 (2.02)
255	—	—	—	8.4 (7.04)	9.5 (2.88)	—	7.7 (2.13)
270	—	—	—	9.3 (7.79)	10.2 (2.96)	—	8.4 (2.25)
285	—	—	—	10.4 (8.89)	—	—	—
300	—	—	—	11.7 (10.09)	—	—	—

[a] Average of six tablets; number in parenthesis is standard deviation. [b] See Table I, footnote *a*.

Salicylic acid was determined by scanning the plate with the densitometer. The spot intensities of the standard and sample were compared. An amount of salicylic acid in the spotted sample corresponding to the 0.20-mg/ml standard would be equivalent to the 1% limit. After the limit test, the remaining spots were visualized by spraying with ferric chloride TS (5) and heating at 110° for 10 min. Aspirin was identified by comparison of the R_f of the sample and standard spots.

Table III—National Survey Results (Percent of Label Declaration) for Aspirin in Suppositories and Salicylic Acid Results

Manufacturer [a]	Dosage, mg	Aspirin [b], %	Salicylic Acid, %
A	648	100.2 [c] (2.12)	0.3
A	648	100.8 [c] (1.15)	0.6
A	648	99.9 [c] (2.99)	0.3
A	648	102.0 [c] (2.07)	[d]
A	324	102.4 [c] (2.50)	0.7
A	324	102.7 [c] (2.84)	0.8
A	324	104.7 [c] (2.99)	0.6
E	600	102.8 (1.60)	0.2
E	300	103.1 (2.69)	0.4
E	300	105.0 (3.00)	0.2
E	200	104.8 (1.31)	0.5
E	200	104.2 (1.70)	0.4
E	150	102.5 (0.98)	0.8
E	120	106.1 (2.12)	0.7
E	120	105.1 [c] (3.88)	0.8
E	60	107.4 (1.79)	0.9
E	120	101.0 (1.88)	0.3
E	600	103.2 (4.32)	0.2
E	600	102.8 (1.61)	0.2
E	120	104.7 (0.99)	0.7
E	120	103.5 (1.56)	0.6
E	120	103.8 (1.63)	0.4
E	60	105.8 (2.53)	1.7 [e]
E	60	107.0 (1.09)	1.9 [f]
E	60	106.3 (2.88)	2.0 [g]
F	600	103.8 (2.23)	[d]
G	600	102.8 (4.03)	0.3
G	600	100.9 (3.63)	0.3
G	600	101.9 (3.56)	0.3
G	300	97.3 (1.14)	0.5
G	300	94.4 (2.27)	0.7
G	300	95.3 (2.64)	0.4
G	125	102.1 (1.71)	0.4
G	125	96.5 (1.29)	0.4
H	650	102.9 [c] (4.44)	0.1
H	325	106.4 [c] (12.29)	0.1

[a] (A) Eli Lilly & Co., Indianapolis, Ind.; (E) Suppositoria Labs, Inc., Farmingdale, N.Y.; (F) Wyeth Labs, Inc., Malvern, Pa.; (G) G&W Labs, Inc., So. Plainfield, N.J.; (H) Dr. Rose, Inc., Madison, Conn. [b] Each value represents 10 determinations unless otherwise noted; number in parentheses is standard deviation. [c] Thirty determinations. [d] Met compendial requirements. [e] The result for salicylic acid using the USP procedure was 2.3%. [f] The result for salicylic acid using the USP procedure was 1.5%. [g] The result for salicylic acid using the USP procedure was 2.1%.

Table IV—Comparison of Salicylic Acid (Percent of Aspirin) Data from the TLC and USP XX Procedures

Material	TLC	USP
648-mg Enteric coated tablet composite	1.3	1.3
Aspirin powder	0.1	0.1
324-mg Enteric coated tablet composite	0.6	0.5
648-mg Suppository composite	0.7	0.6
120-mg Suppository composite	0.2	0.3

RESULTS AND DISCUSSION

Tablet Content Uniformity Validation Test—The original validation for the content uniformity determination was described previously (1). Portions of a ground tablet composite equivalent to single tablets were analyzed by the proposed method and the USP XX (5). The ground tablet composite was prepared from a commercial 648-mg enteric coated tablet. The average of 22 results was 102.0% with a coefficient of variation of 1.91%. The USP XX result was 103.2%. The results obtained for the content uniformity determination of aspirin and the salicylic acid concentrations in enteric coated tablets are given in Table I. No batches were found outside USP XX specifications for strength or salicylic acid.

Dissolution Validation Tests—A series of validation tests were performed on the automated dissolution system. A linear response was obtained when four solutions of standard containing from 0.324 to 1.296 mg of aspirin/ml (corresponding to 50–200% of a 324-mg label declaration) were tested. Carry-over for 100–200–100–50% series of aspirin solutions was also determined with satisfactory results. A portion of the ground composite equivalent to one tablet was accurately weighed and subjected to the dissolution test for 5 hr. The analysis obtained for aspirin was 101.3% of that declared. The hydrolysis rate of aspirin determined on this sample over 5 hr was calculated to be 2.1%/hr.

Table V—Impurities [a] as Percent of Label Declaration of Aspirin Found in Enteric Coated Aspirin Tablets

Manufacturer [b] Batch	Tablet Dosage, mg	I,%	II,%	III,%
A_1	324	— [c]	0.243	— [d]
A_2	648	— [c]	0.224	— [d]
B_1	324	— [c]	0.094	Trace [e]
C_1	324	— [c]	0.050	— [d]
D_2	486	0.006	0.087	— [d]

[a] Impurities: I, acetylsalicylic anhydride; II, acetylsalicylsalicylic acid; III, *O*-salicylsalicylic acid. [b] See Table I, footnote *a*. [c] Assay could not be performed on this formulation. Colloidal suspension in benzene layer. [d] Not detected. [e] Trace = 0.01%.

Table II shows the dissolution rates for the batches representing various manufacturers. The batch results are not corrected for aspirin hydrolysis. Only three of the seven batches showed significant amounts of dissolution in the 3–4 hr period. A physical inspection of the residues from batches C_1, D_1, D_2, and D_3 revealed that the tablets were still firm and 90% intact. Batch D_3, which gave one of the lowest percentage rates, was analyzed again at a paddle speed of 100 rpm. There was no increase in dissolution. The percentages were almost identical to the results obtained at 50 rpm. No sample showed signs of dissolution in the 1-hr pretreatment with gastric fluid.

Both batch A_1 and D_1 gave similar salicylate blood level concentrations[12]. Therefore, this dissolution test, in its present form, is not satisfactory for predicting bioavailability.

Suppository Validation Test—Portions of a composite prepared from a commercial 324-mg suppository were analyzed by the USP XX and the dilute-and-read procedures. The result for the USP procedure was 102.5% of declared and 104.9% for the proposed procedure. The UV curves obtained from the standard and sample solutions were nearly identical and showed very little background interference from the suppository excipients. The results obtained for the content uniformity determination of aspirin and the salicylic acid concentrations in suppositories are given in Table III. Three batches from Manufacturer E exceeded the USP XX limit for salicylic acid.

Salicylic Acid Limit Test Validation by TLC—A linear calibration curve was obtained for salicylic acid when concentrations from 0 to 800 ng/μl were spotted. The fluorescent readings were made by scanning the chromatogram with the spectrodensitometer in the reflectance mode at a fluorescence excitation wavelength of 310 nm and an emission wavelength of 410 nm. Table IV shows the data obtained by the TLC and USP XX (5) procedures on commercial samples. Salicylic acid has a relative R_f value of 1.7 compared to aspirin. In addition, five batches of enteric coated tablets (A_1, A_2, B_1, C_1, and D_2) were analyzed for aspirin-related impurities by the HPLC method described previously (3). Table V shows the amounts of impurities found in these batches. Suppository samples were not tested for impurities.

[12] R. D. Kirchhoefer, unpublished data.

REFERENCES

(1) W. E. Juhl and R. D. Kirchhoefer, *J. Pharm. Sci.*, **69**, 544 (1980).

(2) R. D. Kirchhoefer and W. E. Juhl, *ibid.*, **69**, 548 (1980).

(3) R. D. Kirchhoefer, J. C. Reepmeyer, and W. E. Juhl, *ibid.*, **69**, 550 (1980).

(4) W. E. Juhl and R. D. Kirchhoefer, *ibid.*, **69**, 967 (1980).

(5) "The United States Pharmacopeia," 20th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1980, pp. 57, 1104.

(6) K. Embil and G. Torosian, *J. Pharm. Sci.*, **68**, 1290 (1979).

(7) H. Johansen, *Arch. Pharm. Chem. Sci. Ed.*, **7**, 33 (1978).

(8) J. W. Myrick and C. E. Wells, *J. Assoc. Off. Anal. Chem.*, **62**, 56 (1979).

NOTES

Potential Anticonvulsants IV: Condensation of Isatin with Benzoylacetone and Isopropyl Methyl Ketone

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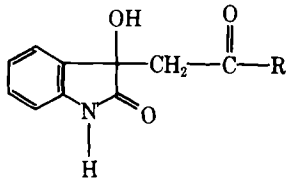
Abstract □ A series of new 3-hydroxy-3-substituted oxindoles were prepared and screened for anticonvulsant activity. A number of these 3-hydroxyoxindoles had activity in the maximal electroshock seizure test.

Keyphrases □ Anticonvulsants—condensation of isatin, benzoylacetone, isopropyl methyl ketone □ Isatin—anticonvulsants, condensation, benzoylacetone, isopropyl methyl ketone □ Benzoylacetone—anticonvulsants, condensation of isatin, isopropyl methyl ketone □ Isopropyl methyl ketone—anticonvulsants, condensation of isatin, benzoylacetone

The anticonvulsant activity[1] of 3-hydroxy-3-phenacyloxindole (I) (1) and 3-hydroxy-3-acetonyloxindole (II) has been reported previously. In a study of analogs of I and II (2) it was found in initial screening that III, derived from isatin and benzoylacetone and having features of both I and II, was inactive at 600 mg/kg in the maximal electroshock seizure test (MES)[1] but was active at 100 mg/kg in the pentylenetetrazol seizure threshold test (Met)[1]. Compound IV related to II and derived from isatin and isopropyl methyl ketone, was active at 100 mg/kg in the MES test and inactive in the Met test. This report de-



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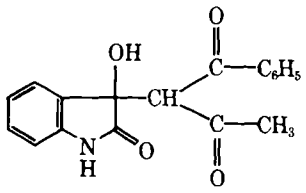
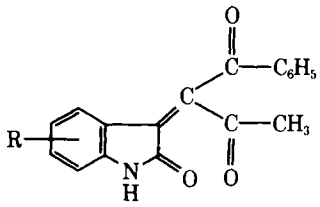
II R = CH_3
IV R = $CH(CH_3)_2$



III



V

[1] Anticonvulsant screening was carried out through the Antiepileptic Drug Development Program, National Institutes of Health. The standard screening protocol of that group was followed.

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