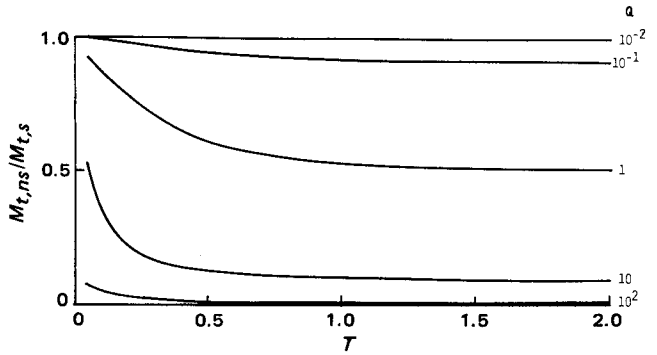

Figure 6—*Comparison of sink* versus *nonsink conditions at long times.*

DISCUSSION

Figure 2 shows the release profile generated using the full solution given by Eq. 14. The figure also shows Eqs. 16 and 18, the two approximations. It is apparent that Eq. 16 is correct up to values of $T \sim 0.5$; from this time onwards, Eq. 18 is applicable.

No unique mathematical expression is obtainable to describe the nonsink conditions. Therefore, concentration is focused on long and short time approximations because it is not possible to predict accurately the release profile for T values approximating to unity. Figure 3 shows the short time approximation given by Eq. 26 for $Q = 1$. The curve generated shows a smooth release pattern not unlike that given by the more simple $t^{1/2}$ approximation applicable to sink conditions. However, there are slight differences as T increases, as shown in Fig. 3. This result would be expected at short periods of time since there is no appreciable concentration buildup in the receptor phase.

The long time approximation, given by Eq. 28, is plotted in Fig. 4. The variation with Q is indicated, and a series of simple first-order curves is obtained. The curves approach the limit, as $T \rightarrow \infty$, of $(1 + Q)^{-1}$, as predicted by Eq. 28. When $Q < 1$, the nonsink limit approaches the long time limit for sink conditions, as expected. This situation corresponds to the experimental conditions of a large receptor volume or large partition coefficient.

Figure 5 compares sink and nonsink conditions at short times for $Q = 1$. At extremely short times, the ratio is unity, as expected. However, as T increases, the deviation from unity becomes more marked and the effect of nonsink conditions becomes apparent. As expected, this general deviation is more pronounced at long times (Fig. 6) and is most noticeable for large values of Q corresponding to small values of the volume of the receptor phase and low partition coefficient.

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Physicochemical and Analytical Characteristics of Itanoxone

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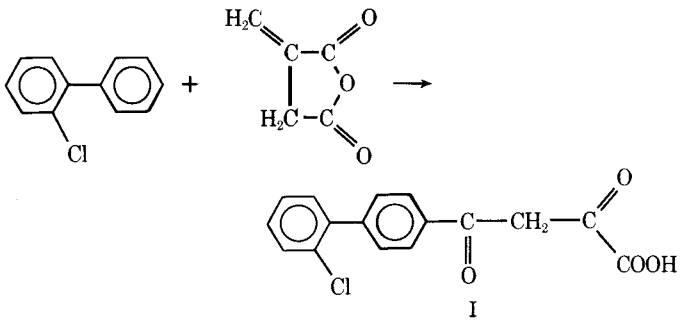
Received March 5, 1980, from the *P. Fabre S.A. Research Center, 17 Avenue Jean Moulin, 81106 Castres, France.* Accepted for publication March 27, 1981.

Abstract □ The analytical and spectroscopic characteristics of itanoxone were determined. These data can be used to identify or assay this new drug.

Keyphrases □ Itanoxone—physicochemical and analytical characteristics of itanoxone □ Spectroscopy—itanoxone, physicochemical and analytical characteristics □ Hyperlipidemic agents—itanoxone, physicochemical and analytical characteristics □ Hyperuricemic agents—itanoxone, physicochemical and analytical characteristics

Itanoxone is the internationally designated name (1) for 4-[4′-(2-chlorophenyl)phenyl]-4-oxo-2-methylenebutanoic acid (I). This compound has pharmacological and clinical properties (2) suitable for the treatment of hyperlipidemia (3–5) and hyperuricemia (6). Theoretical impurities of I (7) and an industrial purification process (8) were studied previously. This paper considers some physical and physicochemical properties of I.



I

Scheme I

EXPERIMENTAL

Synthesis—Itanoxone (I) was synthetized by the Friedel–Crafts reaction between itaconic anhydride and 2-chlorobiphenyl (9, 10) (Scheme I).

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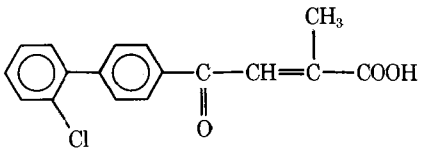


II

Apparatus—A GLC chromatograph[1] was equipped with a glass 3 m × 4-mm i.d. column, packed with 10% (w/w) Carbowax 20 *M* on Chromosorb W.A.W. (60–80 mesh). The carrier gas was nitrogen at 50 ml/min, the column temperature was 130°, and the injection detector temperature was 200°. Potentiometric measurements were made with a titration device[2] fitted with a combined electrode[3]. Melting points were determined on a hot stage[4] and were not corrected.

PMR spectra were recorded at 40° on a spectrometer[5] using solutions in dimethyl sulfoxide-d_6 containing tetramethylsilane as the internal standard. IR spectra were measured on a spectrophotometer[6] using potassium bromide pellets at ~1% (w/w) concentration. A mass spectrometer[7] with the probe at 160° and an ionizing voltage of 70 ev, was used.

Identification and Assay of Impurities—Secondary products of I were described previously (7), but that report did not include tests and detection limits for impurities. The solvents used in the reaction and during recrystallization were determined by GLC. Traces of aluminum from the aluminum chloride catalyst were identified by emission spectrography[8] (low voltage alternating arc, carbon electrodes) (11).

Determination of pKa—The pKa values were determined by potentiometric titration using a glass electrode. A water-jacketed beaker connected to a circulating water bath maintained the temperature of the titrating vessel at 25°. Stirring was accomplished by introducing a slow nitrogen stream under the surface of the solution to be titrated.

The titrant of carbonate-free potassium hydroxide (0.100 *N* KOH) was delivered from a micrometer syringe; for each addition of titrant, the pH was measured and the pKa was determined from the half-neutralization point.

Solubility Conditions—The solubilities, expressed in percentage (weight/volume), were determined as follows. The solvent and solute were placed in 50-ml test tubes with a suitable amount of undissolved I. The tubes were stoppered and shaken for 1 hr at 25 ± 1° to avoid isomerization of I into II (7). The tubes were then centrifugated, and the liquid was filtered through a sintered-glass funnel. The clear liquid was diluted and spectrophotometrically[9] assayed for I.

Partition Coefficients—Itanoxone was partitioned between buffer solutions saturated with organic solvents and organic solvent saturated with buffer solutions. Usually 50 ml of buffer solution containing a known amount of solute was shaken with an equal volume of organic solvent. The sample was maintained at 25 ± 1° and mechanically[10] shaken for 1.5 hr until equilibrium was obtained (12, 13). After stirring, the two phases were separated by centrifugation at 3000 rpm for 30 min. The amount of I in the water layer was determined spectrophotometrically.

RESULTS AND DISCUSSION

Assay of Impurities—Methylene chloride reaction solvent and dimethylformamide recrystallization solvent had retention times of 1.5 and 3.5 min, respectively. Under these conditions, solvent amounts of <0.05% (w/w) were detected in itanoxone (I). The most sensitive rays characteristic of aluminum (11) were not observed in the spectrum of I. The lower limit of detection sensitivity of metal in I is 0.02 μg.

Melting Points—Itanoxone occurs as a white crystalline powder in the monoclinic system (14) with an instantaneous melting point of 212 ± 1°. It is overlapped by the standard melting points of saccharin and dicyanodiamide.

Determination of pKa—In view of the low solubility of I in water, the pKa value was determined at 25° by extrapolation from a series of dissociation constants in water–dioxane mixtures evaluated by potentiometry. The results are expressed by introducing an experimental parameter, $g(S)$, which is characteristic of each solvent (15). This quantity takes care of all types of solvent–solute interactions, such as hydrogen bonding and structural effects, and its measurement gives the magnitude of solvent effects on acid–base reactions. Measurement of the dissociation constant of itanoxone, ${}^{S}K_I$, and of salicylic acid, ${}^{S}K_{\text{ref}}$, used as the standard compound in each S medium indicates that the difference between both pKa values is a linear function of $g(S)$ according to the formula:

$$\text{p}{}^{S}K_{a\text{I}} - \text{p}{}^{S}K_{a\text{ref}} = \alpha + \beta g(S) \qquad \text{(Eq. 1)}$$

in which α and β are constants dependent only on I. Itanoxone transfer between water and dioxane may be expressed by:

$$\log {}^{\text{water}}T^{\text{dioxane}}(\text{I}) = \log C_{\text{sat}}^{\text{water}}(\text{I}) - \log C_{\text{sat}}^{\text{dioxane}}(\text{I}) \qquad \text{(Eq. 2)}$$

where $C_{\text{sat}}^{\text{water}}(\text{I})$ and $C_{\text{sat}}^{\text{dioxane}}(\text{I})$ are the solubilities (weight/volume) of I in water–dioxane. Thus, $\log {}^{\text{water}}T^{\text{dioxane}}$ (I) is proportional to the solvent variable $g(S)$:

$$\log {}^{\text{water}}T^{\text{dioxane}}(\text{I}) = f(\text{I}) \times g(S) \qquad \text{(Eq. 3)}$$

where $f(\text{I})$ is a constant characteristic of I. The measurement of solubility of I in water–dioxane enables the calculation of values proportional to the solvent variable $g(S)$. The agreed convention is then expressed as:

$$g(S) = -\log {}^{\text{water}}T^{\text{dioxane}}(\text{I}) \qquad \text{(Eq. 4)}$$

For each $g(S)$ calculation, the relative water and dioxane contents of the medium must be considered.

Extrapolation to pure water gives $g(S) = 0$. Any $g(S)$ is given by:

$$g(S) = -\log {}^{\text{water}}T^{\text{dioxane}}(\text{I}) = -\log a(0.019)/b(3.9) \qquad \text{(Eq. 5)}$$

where a and b represent the water and dioxane contents, respectively.

The values of $g(S)$ for different percentage volumes of dioxane and the pKa values of salicylic acid (the reference compound) are shown in Table

Table I—Dissociation Constants in Water–Dioxane Mixtures

Dioxane, % (v/v)	$g(S)$	pKa_{ref}[a]	pKa_{I}[b]	$\text{pKa}_{\text{I}} - \text{pKa}_{\text{ref}}$
0.6	2.49	4.60	6.68	2.08
0.8	2.92	5.50	7.55	2.05
0.9	3.26	6.40	8.38	1.98

[a] The pKa of salicylic acid. [b] The pKa of itanoxone.

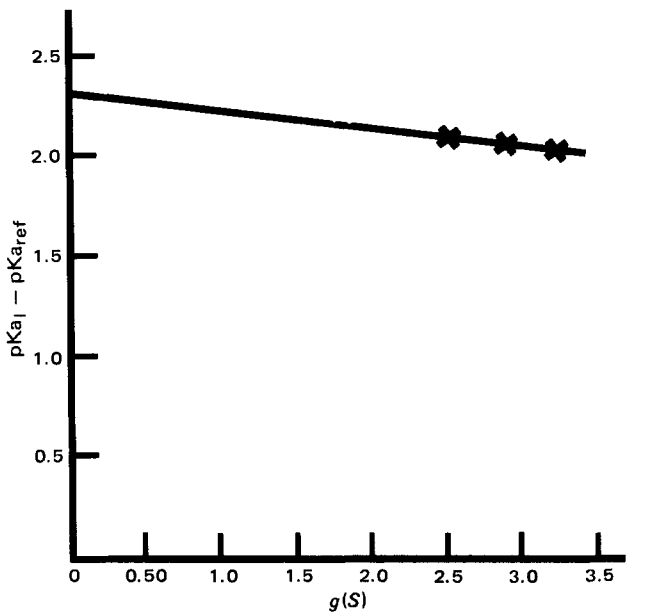
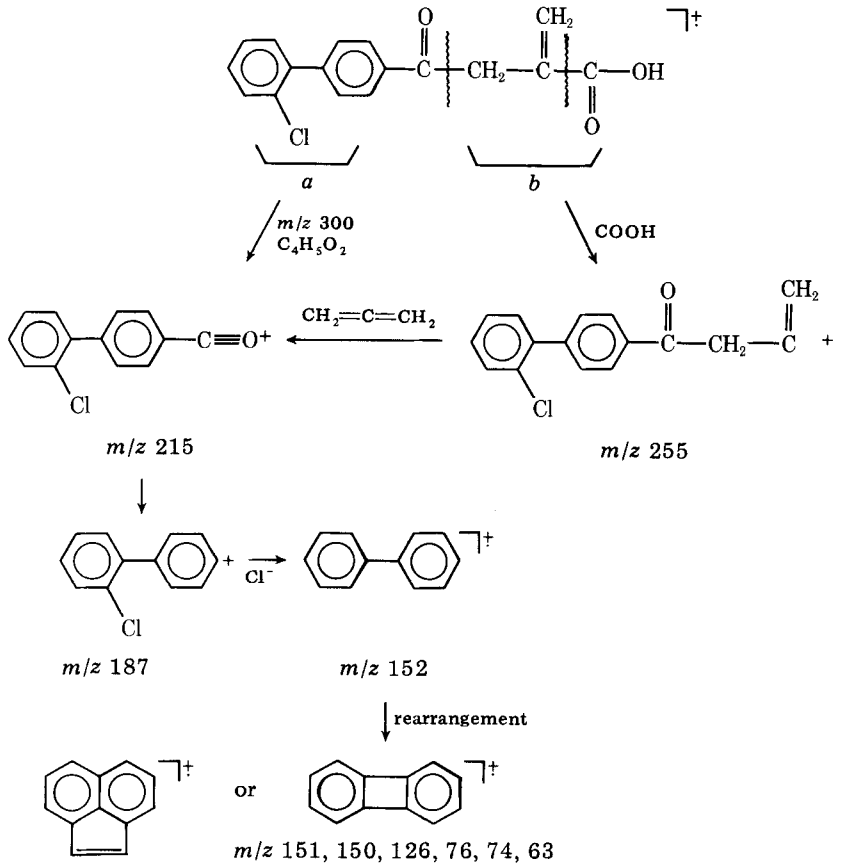


Figure 1—*Determination of pKa of itanoxone by extrapolation. The solid line gives the difference between pKa_I and pKa_{ref} determined on the same water–dioxane media* versus g(S) *($pKa_I = pKa_{ref} + 2.3 = 3.0 + 2.3 = 5.30$).*

[1] Girdel 3000, Giravions Dorand, Suresnes, France.
[2] Mettler Instruments, Greifensee, Zürich, Switzerland.
[3] Tacussel TCBG II/HS, Solea, Villeurbanne, France.
[4] Kofler, C. Reichert AG, Wein XVII, Austria.
[5] Model R-24B, Hitachi Perkin-Elmer, Hitachi Ltd., Tokyo, Japan.
[6] Model 177, Perkin-Elmer Ltd., Beaconsfield, Buckinghamshire, England.
[7] Ribermag R-10-10B, Nermag S. A., Rueil-Malmaison, France.
[8] Model E-478, Hilger spectrograph.
[9] Model DK-2A, Beckman Instruments, GMBH, München 45, West Germany.
[10] New Brunswick Scientific Co., Edison, N.J.



Scheme II—Fragmentation mechanism.

I. The difference between the two pKa values is a linear function of $g(S)$. The determination of the pKa of I in water by extrapolation of measurements made on water–dioxane mixtures is plotted *versus* $g(S)$ determined for each water–dioxane system (Fig. 1). The pKa of salicylic acid determined in water is 3.0. The pKa of I determined in water–dioxane with extrapolation of the results to zero dioxane concentration is 3.0 + 2.3 = 5.30.

Solubility—The maximum values are expressed in Table II as percentage (weight/volume). This technique cannot be used for ketonic solvents having absorptions in the same range.

Partition Coefficients—The I concentration was determined in the aqueous phase by UV spectroscopy at 265 nm. The apparent partition coefficient is calculated by the formula:

$$\text{Apparent partition coefficient} = \frac{C_{\text{octanol}}}{C_{\text{buffer}}} = \frac{(C_1 - C_2) \times a}{C_2 \times b} \quad \text{(Eq. 6)}$$

where C_1 and C_2 are the I concentrations (weight/volume) in the aqueous phase before and after equilibration, respectively, and a and b are the volumes of the aqueous and octanol phases, respectively. By working at a fixed pH and knowing the pKa for I, the partition coefficient can be determined using:

$$\text{Partition coefficient} = \frac{C_{\text{octanol}}}{C_{\text{buffer}}\,(1 - \alpha)} \quad \text{(Eq. 7)}$$

where α is the degree of ionization. Details are given in Table III.

For a good extraction yield of I from biological media such as blood and urine, it is imperative to use an acidic pH. Under these conditions, 98% of the drug is extracted from the aqueous phase during the first extraction. Ethyl acetate is recommended to reduce emulsion effects.

The TLC procedure reported previously (7) was used to demonstrate that I did not isomerize during the 1–1.5 hr needed to determine solubility or partition coefficients. In the media used to determine solubilities and partition coefficients, traces of II were detected after the 2nd hr of TLC. The amount of II ranged from 0.1 to 0.3%, depending on the solvent. Isomerization continued, but the lack of II in the first 2 hr confirmed the validity of solubility and partition data.

IR Spectroscopy—The IR spectrum revealed characteristic bands (16) that agreed with the suggested structure: 3000–3080 (aromatic and ethylenic CH), 2910 (aliphatic CH), 1690 (C=O acid), 1675 (C=O conjugated ketone), and 1630 (ethylenic C=C) cm^{-1} (Fig. 2).

UV Spectroscopy—The spectrum was obtained in ethanolic solution using 1-cm quartz cells, λ_{max} 265 (ϵ 18,350 ± 30) nm.

PMR Spectroscopy—Assignments (17) were: δ 4.1 (s, 2H, $COCH_2$), 5.75 (d, 1H, J = 1.2 Hz, *trans*-*H*C=CCOOH), 6.3 (d, 1H, J = 1.2 Hz, *cis*-*H*C=CCOOH), 7.3–7.7 (m, 6H, aromatic protons), 8.05 (d, 2H, J = 8 Hz, aromatic protons *ortho* to C=O), and 11–13.5 (s, 1H, COOH) ppm.

Table II—Solubilities at 20°, Percent (weight/volume)

Solvent	Solubility, g/100 ml
n-Hexane	0.00025
Water	0.019
Chloroform	0.15
Ether	0.17
Acetonitrile	0.20
Ethyl acetate	0.24
Methanol	0.39
Ethanol	0.50
n-Octanol	0.75
Dioxane	3.9
Tetrahydrofuran	4.34
Dimethylformamide	28.5
Dimethyl sulfoxide	38.4

Table III—Itanoxone Partition Coefficients between *n*-Octanol and Buffered Solutions

Buffer Solution	Apparent Partition Coefficient[a]	Partition Coefficient	Log P
pH 10[b]	2.12	2120	7.66 (0.021)
pH 7.4[c]	16.6	2075	7.64 (0.020)
pH 2.2[d]	2098	2100	7.65 (0.043)

[a] All determinations were done in triplicate, and the average value for log P was determined. Values in parentheses indicate standard deviations. [b] Ammonium chloride buffer (0.05 M). [c] Phosphate buffer (0.05 M). [d] Potassium chloride buffer (0.05M).

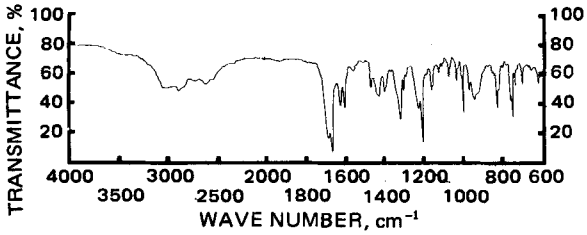


Figure 2—*IR spectrum of itanoxone*

The exchangeable acid proton appeared faintly in dimethyl sulfoxide-d_6, but a very marked singlet was obtained in pyridine-d_5 at 9.9 ppm.

Mass Spectroscopy—The molecular peak was observed at *m/z* 300, corresponding to the molecular mass of the product. The most characteristic fragments of I gave a series of peaks at *m/z* 302, 300, 277, 255, 217, 215, 152, and 76. The peak at *m/z* 302 corresponded to the chlorine 37 isotope. The isotopic peaks at p + 2 were also observed in the various fragments containing chlorine.

Fragmentation is shown in Scheme II. The $C_{12}H_8$ ion (*m/z* 152) (18, 19) was followed by the series of ions at *m/z* 151, 150, 126, 76, 75, 74, and 63. The relative intensities of these ions in the spectrum of I were very close to those in the Cornu–Massot catalog (20) for diphenylene and acenaphthene. This result indicates that the ion obtained after the removal of C=O and the chlorine atom rearranges to give a radical ion with a structure close to diphenylene or acenaphthene.

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Effect of Docusate Sodium on Drug Release from a Controlled-Release Dosage Form

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Abstract □ This study was designed to determine the effect of a clinically used surfactant, docusate sodium, on the release of chlorpheniramine from a controlled-release dosage form (encapsulated coated pellets). *In vivo* treatments consisted of the controlled-release capsule alone or with 200 mg of docusate sodium. Plasma chlorpheniramine levels were determined, and the *AUC* was calculated. No significant difference in *AUC* values was observed between the two treatments. At a concentration below the CMC, docusate sodium enhanced the *in vitro* drug release rate. The surfactant exerted a greater effect on the release of the first one-third of the drug contained in nonwax-coated pellets. At the CMC, 0.02% (w/v), docusate sodium rapidly entrapped chlorpheniramine in micelles. The overall enhanced dissolution rate *in vivo* may have been offset by micellar drug entrapment.

Keyphrases □ Docusate sodium—effect on drug release from a controlled-release dosage form □ Controlled-release formulations—effect of docusate sodium on drug release □ Surfactants—effect on drug release of controlled-release dosage forms

Most long-acting oral dosage forms utilize a physical barrier to decrease the rate of drug release into the GI tract. The wax coating on the pellets of a controlled-release capsule serves as this barrier (1).

Disintegration of the wax coat is thought to be controlled by the penetration of moisture through pores (2). The pH of the medium reportedly does not affect disintegration (3) although surface tension is thought to be important. The surface tension of intestinal fluid is less than gastric fluid due to bile salts in the intestines. This lowered surface tension may lead to the release of more drug into the intestinal fluids (2). The effect of lowered surface tension in the GI tract on the release of drug from wax-coated pellets has not been reported.

BACKGROUND

Numerous studies have been performed to determine the effect of surfactants on drug absorption, mainly with surfactants that promote oral absorption of a poorly absorbed drug. The exact mechanism by which docusate sodium and other surfactants enhance drug absorption is unknown. The most popular theory has been that surfactants directly alter membrane permeability of the GI tract (4–14). Although the mechanism of this "hyperabsorptive state" is unknown, most investigators believe that the surfactant disrupts the integrity of the epithelial membrane in a reversible fashion (4–11). The removal of proteins (12, 13) and phos-

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