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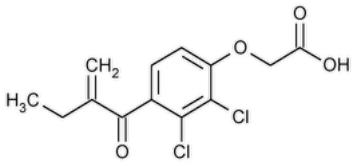
Ethacrynic Acid



$C_{13}H_{12}Cl_2O_4$ 303.14

Acetic acid, [2,3-dichloro-4-(2-methylene-1-oxobutyl)phenoxy]-;

[2,3-Dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid CAS RN®: 58-54-8; UNII: M5DP350VZV.

DEFINITION

Ethacrynic Acid contains NLT 97.0% and NMT 102.0% of ethacrynic acid ($C_{13}H_{12}Cl_2O_4$), calculated on the dried basis.

[**Caution—**Use care in handling Ethacrynic Acid, because it irritates the skin, eyes, and mucous membranes.]

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197M ▲or 197A▲ (USP 1-Dec-2021)

Delete the following:

▲• **B. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U

Analytical wavelength: 271 nm

Sample solution: 50 µg/mL in methanol

Acceptance criteria: Absorptivities, calculated on the dried basis, do not differ by more than 3.0%.▲ (USP 1-Dec-2021)

Add the following:

▲• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Dec-2021)

Delete the following:

▲• **C. Procedure**

Sample solution: 12.5 mg/mL in 1 N sodium hydroxide

Analysis: Heat 2 mL of *Sample solution* for several min in a boiling water bath. Cool the solution, acidify with 0.25 mL of 18 N sulfuric acid, add 0.5 mL of chromotropic acid sodium salt solution (1 in 10), then add, cautiously, 2 mL of sulfuric acid TS.

Acceptance criteria: A deep violet color is produced.▲ (USP 1-Dec-2021)

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** Triethylamine and water (1:100). Adjust with phosphoric acid to a pH of 6.8.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
15	75	25
18	45	55

Time (min)	Solution A (%)	Solution B (%)
20	75	25

Diluent: Acetonitrile and water (25:75)

Standard solution: 0.1 mg/mL of USP Ethacrynic Acid RS in *Diluent*. Sonicate to dissolve.

Sample solution: 0.1 mg/mL of Ethacrynic Acid in *Diluent*. Sonicate to dissolve.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 25-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1.8 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ethacrynic acid ($C_{13}H_{12}Cl_2O_4$) in the portion of Ethacrynic Acid taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of ethacrynic acid from the *Sample solution*

r_S = peak response of ethacrynic acid from the *Standard solution*

C_S = concentration of USP Ethacrynic Acid RS in the *Standard solution* (mg/mL)

C_U = concentration of Ethacrynic Acid in the *Sample solution* (mg/mL)▲ (USP 1-Dec-2021)

Acceptance criteria: 97.0%–102.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Add the following:

▲• **Organic Impurities**

Solution A, Solution B, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	75	25
20	75	25
45	45	55
50	45	55
51	75	25
60	75	25

System suitability solution: 1 mg/mL of USP Ethacrynic Acid RS and 1.5 µg/mL of USP Ethacrynic Acid Related Compound A RS in *Diluent*. Sonicate to dissolve.

Sensitivity solution: 0.3 µg/mL of USP Ethacrynic Acid RS in *Diluent*

Standard solution: 3 µg/mL of USP Ethacrynic Acid RS in *Diluent*

Sample solution: 1 mg/mL of Ethacrynic Acid in *Diluent*. Sonicate to dissolve.

System suitability

Samples: *System suitability solution*, *Sensitivity solution*, and *Standard solution*

[NOTE—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between the ethacrynic acid related compound A and ethacrynic acid peaks, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Ethacrynic Acid taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of ethacrynic acid from the *Standard solution*

C_S = concentration of USP Ethacrynic Acid RS in the *Standard solution* (mg/mL)

C_U = concentration of Ethacrynic Acid in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.03%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ethacrynic acid dimethylamino analog[a]	0.26	1.49	0.15
Ethacrynic acid related compound A	0.74	1.61	0.15
Ethacrynic acid	1.0	—	—
Ethacrynic acid trichloro analog[b]	1.56	1.18	0.15
Ethacrynic acid pyrane dimer[c]	3.47	0.73	0.3
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] {2,3-Dichloro-4-[2-{(dimethylamino)methyl}butanoyl]phenoxy}acetic acid hydrochloride.

[b] {2,3-Dichloro-4-[2-(chloromethyl)butanoyl]phenoxy}acetic acid.

[c] {4-[2-(4-(Carboxymethoxy)-2,3-dichlorobenzoyl]-2,5-diethyl-3,4-dihydro-2*H*-pyran-6-yl}-2,3-dichlorophenoxy)acetic acid. ▲(USP 1-Dec-2021)

SPECIFIC TESTS

• **LOSS ON DRYING ⟨731⟩**

Analysis: Dry at a pressure not exceeding 5 mm of mercury at 60° for 2 h.

Acceptance criteria: NMT 0.25%

Delete the following:

▲• **EQUIVALENT WEIGHT**

Sample solution: 400 mg in 100 mL of methanol. Add 5 mL of water.

Analysis: Titrate with 0.1 N sodium hydroxide VS, using a calomel–glass electrode system or other appropriate electrode (see *Titrimetry ⟨541⟩*). Perform a blank determination, and make any necessary correction. Calculate the equivalent weight on the dried basis.

Acceptance criteria: Between 294 and 309▲ (USP 1-Dec-2021)

Delete the following:

▲• **Toluene Extractives**

Sample solution: 1 g into a glass-stoppered, 100-mL cylinder. Add 50 mL of sodium sulfite solution (2 in 25), and agitate until the solid dissolves. Allow to stand for 20 min, and add 5 mL of hydrochloric acid.

Analysis: Divide the solution between two centrifuge tubes, each of which contains 15 mL of toluene. Close each tube tightly, using a polyethylene stopper, and shake vigorously for 2 min, occasionally relieving the pressure from the sulfur dioxide by loosening the stoppers. Centrifuge the tubes, withdraw most of the upper layer by means of a syringe, avoiding withdrawal of any of the lower, aqueous phase, and transfer the toluene extracts to a tared evaporating dish. Repeat the extraction twice with additional 15-mL portions of toluene, and evaporate the combined extracts on a steam bath to dryness. Dry the residue at a pressure not exceeding 5 mm of mercury at 60° for 2 h. Cool, and weigh.

Acceptance criteria: NMT 2.0%▲ (USP 1-Dec-2021)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Ethacrynic Acid RS

▲ USP Ethacrynic Acid Related Compound A RS

(4-Butyryl-2,3-dichlorophenoxy)acetic acid.

$C_{12}H_{12}Cl_2O_4$ 291.13▲ (USP 1-Dec-2021)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
ETHACRYNIC ACID	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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