SYNTHESIS OF 1-ARYL-3-(3-PYRROLYL)-5-OXOPYRAZOLES

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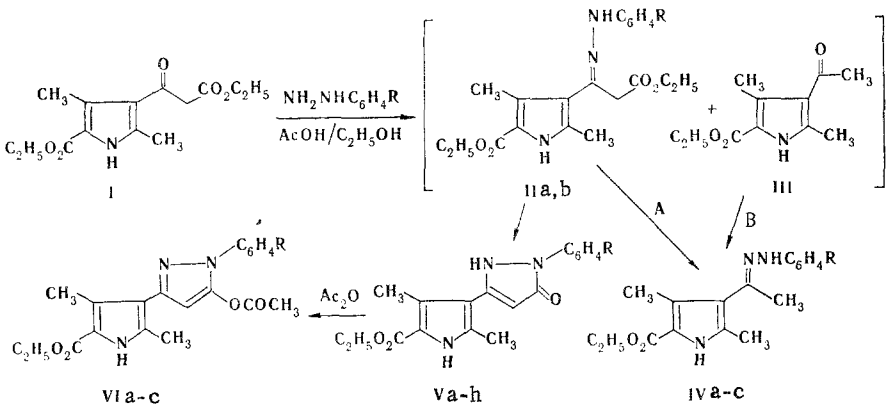
1-Aryl-3-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-5-oxopyrazoles were obtained by condensation of ethyl β-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-β-ketopropionate with arylhydrazines. Electron-donor substituents in the aromatic ring of the arylhydrazines accelerate the cyclization of the intermediate hydrazones, whereas electron-acceptor substituents hinder cyclization.

Both the presence of a substituent in the aromatic ring of hydrazones and steric and electronic factors that are due to the nature of the substituent in the β position of the keto acid derivative affect the reaction of β-keto acid derivatives with arylhydrazines, which is the principal method for the synthesis of 1-aryl-5-oxopyrazoles. In particular, aroylacetic esters react with arylhydrazines under milder conditions than acetoacetic ester and its analogs [1]. In the present research we studied the reaction of a β-keto ester that contains a substituted pyrrole residue in the β position with arylhydrazines. In order to study the effect of the character and position of the substituent in the aromatic ring of the arylhydrazine the reactions were carried out with o- and p-substituted derivatives that contain both electron-donor and acceptor substituents.

The reaction of ethyl β-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-β-ketopropionate (I) with phenylhydrazine in the absence of an acidic catalyst takes place only upon prolonged heating to 150°C without access to air oxygen and is accompanied by considerable decomposition. The reaction proceeds to give the products in good yields in the presence of a mild acidic catalyst, viz., acetic acid in alcohol, at 80°C (Table 1). We also carried out the subsequent condensation under these conditions.

Inasmuch as the hydrochlorides of strongly basic arylhydrazines do not react with pyrrole I (probably because of the reduced nucleophilicity of the NH_2 group), an equimolar amount of sodium or potassium acetate was added to the reaction mixtures in these cases.



I, IIa,b, III, VIa-c, Va-h, IVa-c

II a R=2-NO_2, b R=2,4-NO_2; IV a R=2-NO_2, b R=4-NO_2, c R=2,4-NO_2; V a R=H, b R=4-Me, c R=2-Me, d R=2-OMe, e R=4-OMe, f R=2-NO_2, g R=4-NO_2, h R=2,4-NO_2; VI a R=H, b R=2-Me, c R=4-Me

The presence of an electron-donor methyl group in the aromatic ring of the hydrazine in the para position accelerates the reaction somewhat and increases the yield of corresponding 5-oxopyrazole Vb. A p-methoxy group has an even more significant effect, and the reaction gives the product in a yield that is close to quantitative (Ve, 97% yield). Thus electron-

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TABLE 1. Characteristics of 1-Aryl-3-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-5-oxopyrazoles (Va-h) and Arylhydrazones (IIb and IVa-c)

Compound	mp, °C	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calc., %			Reaction time, h	Yield, %
			C	H	N		C	H	N		
Va	256—257	3200 (NH), 1670 (CO, COOEt), 1595, 1580 (C=N, C=C)	66,7	6,4	13,4	$C_{18}H_{19}N_3O_3$	66,4	5,9	12,9	5	70
Vb	258—259	3340 (NH), 1715 (C=O), 1690, 1650 (COOEt), 1618, 1590 (C=N, C=C)	67,3	6,4	11,9	$C_{19}H_{21}N_3O_3$	67,2	6,2	12,4	5	78
Vc	219—221	3310, 3230 (NH), 1680 (C=O, COOEt), 1580 (C=N, C=C)	67,0	6,3	12,2	$C_{19}H_{21}N_3O_3$	67,2	6,2	12,4	5	73
Vd	208—210	3200 (NH), 1710 (C=O, COOEt), 1600—1580 (C=N, C=C)	64,9	6,0	11,6	$C_{19}H_{21}N_3O_4$	64,2	6,0	11,8	5	58
Ve	262—264	3300 (NH), 1710 (C=O), 1660 (COOEt), 1580 (C=N, C=C)	65,2	6,5	11,7	$C_{19}H_{21}N_3O_4$	64,2	6,0	11,8	4	97
Vf	215—217	3290 (NH), 1730 (C=O), 1670 (COOEt), 1640, 1580 (C=N, C=C, N—O)	58,6	5,5	15,1	$C_{18}H_{18}N_4O_5$	58,4	4,9	15,1	5	41
Vg	292—294	3290 (NH), 1715 (C=O), 1680 (COOEt), 1600 (C=N, C=C), 1550 (N—O)	58,2	5,1	15,1	$C_{18}H_{18}N_4O_5$	58,4	4,9	15,1	5,5	62
Vh	257—260	3280 (NH), 1740 (C=O), 1675 (COOEt), 1600, 1580 (C=N, C=C, N—O)	53,1	4,5	17,3	$C_{18}H_{17}N_5O_7$	52,0	4,1	16,9	5	67
IIb	105—108	3270, 3110 (NH), 1730 (COOEt), 1665 (COOEt), 1615 (C=N), 1590 (N—O)	51,4	5,1	14,1	$C_{20}H_{23}N_5O_8$	52,1	5,0	15,2	—	89
IVa	207—208	3300 (NH), 1670 (COOEt), 1610 (C=N), 1570 (N—O)	59,1	6,1	16,3	$C_{17}H_{20}N_4O_4$	59,3	5,8	16,3	—	94
IVb	202—204	3300 (NH), 1670 (COOEt), 1600 (C=N), 1570 (N—O)	59,3	6,0	15,4	$C_{17}H_{20}N_4O_4$	59,3	5,8	16,3	—	71
IVc	>300	3300, 3100—3080 (NH), 1670 (COOEt), 1620 (C=N), 1590 (N—O)	53,8	5,3	18,8	$C_{17}H_{19}N_5O_6$	52,4	4,9	18,0	—	77

donor substituents in the para position accelerate the reaction, probably because of the increased nucleophilicity of the nitrogen atom of the arylhydrazine.

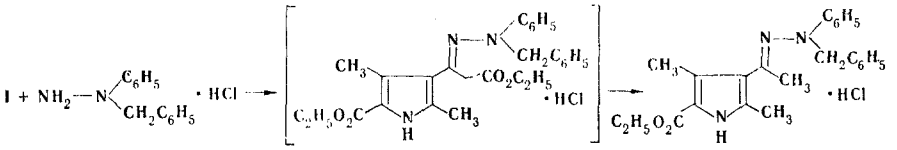
In addition to the positive inductive effect, the introduction of an electron-donor substituent in the ortho position has an effect on the step involving the formation of the heteroring as a consequence of steric hindrance. And, if this effect is not substantial in the case of the CH_3 group (Vc, 73% yield), the yield of oxopyrazole Vd decreases to 58% because of the presence of the considerably bulkier 2-methoxy group.

It should be noted that the formation of 1-aryl-5-oxopyrazoles in a slightly acidic medium is accompanied by decomposition of both starting keto ester I to give primarily pyrrole III and by decomposition of the arylhydrazine, particularly when the reaction time is increased.

It is known that the formation of 1-aryl-5-oxopyrazoles in the reactions of β-keto esters with arylhydrazines in the presence of acids proceeds through the intermediately formed arylhydrazones, which were isolated in a number of cases. Their subsequent cyclization makes it possible to establish unambiguously the position of the aromatic substituent in the heteroring [2].

The formation of intermediate hydrazones was not noted in the reaction of keto ester I with arylhydrazines, even at reduced temperatures. The introduction of a protective benzyl group at the α-nitrogen atom of the arylhydrazine should have led to a stable arylhydrazone, which, after debenzylation, could then be converted to the known 1-phenyl-5-oxopyrazole Va.

However, the corresponding hydrazone VII was not formed even upon prolonged refluxing of a mixture of keto ester I and the N-benzyl-N-phenylhydrazine base in the presence of acetic acid. Only hydrazone hydrochloride VIII, which was also synthesized from the corresponding acetylpyrrole III, was isolated from the reaction with N-benzyl-N-phenylhydrazine hydrochloride. Cleavage of the ester group of both β-keto ester I (which was demonstrated by us) and the intermediately formed hydrazone VII probably occurs under the reaction conditions.



VII VIII

The position of the N-aryl substituent in the heteroring and, consequently, the occurrence of the reaction through the corresponding hydrazone were proved by a different pathway. It is known that the mutual spatial orientation of both rings changes when a substituent is introduced in the pyrazole ring adjacent to the aromatic residue; this is reflected in the PMR spectra [3]. For this purpose we obtained 5-acetoxypyrazoles VIa-c by the reaction of Va-c with excess acetic anhydride. The multiplets of the protons of the aromatic ring in the PMR spectra of oxopyrazoles Va-c are located over a wider range (0.8-1.5 ppm) than in the case of their acetoxy derivatives VIa-c (0.2-0.4 ppm); this constitutes evidence for a decrease in the degree of planarity of the aromatic ring and the heteroring because of steric interactions of the aryl ring and the adjacent acetoxy group. Consequently, the reaction of pyrrolyl-β-keto ester I with arylhydrazines proceeds through the corresponding hydrazones, which undergo rapid cyclization to 1-aryl-5-oxopyrazoles Va-e.

The absence of appreciable amounts of arylhydrazones in the reaction mixtures is probably explained by both their low stabilities, due to the electron-surplus character of the pyrrole ring, which is similar to that of phenol derivatives [4], and, evidently, by their favorable spatial configurations, in which the α-nitrogen atom of the hydrazone draws close to the carbon atom of the carbonyl group of the side chain.

The reaction of keto ester I with arylhydrazines that contain an electron-acceptor nitro group proceeds in a somewhat more complex manner. And, if the yield of oxopyrazole Vg only decreases because of the deactivating effect of the p-nitro group, the overall pattern of the reaction of keto ester I with o-nitrophenylhydrazine hydrochloride then seems to be different. At room temperature the principal reaction product is extremely unstable hydrazone IIa, which we were unable to isolate in sufficiently pure form; it was therefore characterized only by the IR and PMR spectra. When the reaction is carried out in refluxing ethanol, hydrazone IIa undergoes partial cyclization to the corresponding 2-nitrophenyl-5-oxopyrazole Vf in ∿40% yield. Yet another substance, which was found to be identical, with respect to its physicochemical properties, to the product of the reaction of acetylpyrrole III with o-nitrophenylhydrazine, viz., hydrazone IVa, was isolated from the reaction mixture, in addition to Vf. It was obtained in 30% yield.

In contrast to mononitro-substituted arylhydrazines, 2,4-dinitrophenylhydrazine does not react at all with keto ester I in alcohol solutions of acetic acid. The corresponding hydrazone IIb, which does not undergo subsequent cyclization under these conditions, is formed in the presence of 48% HBr; upon prolonged refluxing only the ester group of the side chain is split out to give the 2,4-dinitrophenylhydrazine (IVc) of acetylpyrrole III in ∿50% yield. Its structure was confirmed by comparison with a genuine sample. The formation of hydrazone IVc probably proceeds via two independent pathways A and B, which is in agreement with the data in [5], and it was also demonstrated by appropriate experiments. Similar results were also obtained when the reaction was carried out in acetic acid in the presence of 48% HBr.

2,4-Dinitrophenylhydrazone IIb undergoes cyclization to give the corresponding 5-oxopyrazole Vh in good yield in an anhydrous medium in the presence of p-toluenesulfonic acid. Pyrrolyl-β-keto ester I can also be converted to 5-oxopyrazole Vh when one carried out the condensation with 2,4-dinitrophenylhydrazine by removing the resulting water in the form of an azeotropic mixture with toluene and without isolation of the intermediately formed hydrazone IIb.

Pyrrolyl-substituted oxopyrazoles Va-h are high-melting slightly soluble substances that are colorless (Va-e) or orange (Vf-h). Intense absorption bands of NH groups at ∿3200-3300 cm^{-1} and absorption maxima of carbonyl and ester groups at 1670-1720 cm^{-1} are present in their IR spectra. In addition to signals of substituents attached to the pyrrole ring and multiplets of the aromatic residue, a singlet at ∿5.4-5.5 ppm [1H, the proton attached to the $C_{(4)}$ atom of the heteroring] is present in the PMR spectra; this constitutes evidence that these compounds exist in solutions in the NH and OH forms. Assignment of the signals

of the protons of the methyl groups of the pyrrole and aromatic rings, as well as the acetoxy groups, is not possible in view of the closeness of their chemical shifts.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were obtained with a Perkin-Elmer 577 spectrometer. The PMR spectra of solutions in $(CD_3)_2SO$ were recorded with a Tesla BS-467 spectrometer. Silufol UV-254 and silica gel L 100/150 μm plates were used for chromatography.

1-Aryl-3-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-5-oxopyrazoles (Va-e, Table 1). A solution of 10 mmole of ethyl ester I [6], 11 mmole of the arylhydrazine, and 2 ml of acetic acid in 25-30 ml of alcohol was refluxed for 4-5 h; the completion of the reaction was monitored by means of thin-layer chromatography (TLC) in a benzene–ethyl acetate system (2:1).

The reaction mixture was cooled, and the resulting precipitate was removed by filtration, washed successively with a small amount of alcohol and benzene, dried *in vacuo*, and crystallized from dimethylformamide (DMF)–water. When the hydrochlorides of the arylhydrazines (Vb-e) were used, an equimolar amount of sodium or potassium acetate was added to the reaction mixtures. At the end of the reaction, the resulting precipitate was washed with alcohol and several times with water and then dried *in vacuo*.

2,4-Dimethyl-3-acetyl-5-ethoxycarbonylpyrrole N-Benzyl-N-phenylhydrazone Hydrochloride (VIII). A) A mixture of 2.1 g (10 mmole) of pyrrole III [7], 2.4 g (10 mmole) of N-benzyl-N-phenylhydrazine hydrochloride, and 20 ml of ethanol was refluxed for 5 h until starting pyrrole III disappeared, according to TLC [benzene–ethyl acetate (2:1)], after which it was cooled, and the precipitate was removed by filtration, washed with a small amount of cold alcohol, and dried *in vacuo* to give 3.2 g (75%) of a product with mp 182-186°C (from methanol). IR spectrum: 2400-2700 ($\overset{+}{N}H$); 1700 (COOEt); 1615 (C=N); 1600, 1560 cm^{-1} (C=N, C=C). PMR spectrum: 1.30 (3H, t, CH_2CH_3); 2.23, 2.35 (three 3H, CH_3); 4.27 (2H, q, CH_2CH_3); 4.74 (2H, s, $CH_2C_6H_5$); 6.8-7.7 (10H, m, aromatic); 12.0 ppm (NH, broad). Found: 68.2; H 6.8; Cl 8.4; N 9.5%. $C_{24}H_{27}N_3O_2 \cdot HCl$. Calculated: C 67.7; H 6.6; Cl 8.3; N 9.9%.

B) A mixture of 2.8 g (0.01 mole) of pyrrole I and 2.4 g (10 mmole) of N-benzyl-N-phenylhydrazine hydrochloride in 20 ml of alcohol was refluxed for 11 h, after which it was allowed to stand for 2 days. The resulting precipitate was removed by filtration, washed successively with a small amount of cooled ethanol and hexane, and dried *in vacuo* to give 2.5 g (59%) of hydrazone VIII. The IR spectra of VIII obtained by methods A and B coincided completely.

1-Phenyl-5-acetoxy-3-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)pyrazole (VIa). A mixture of 0.98 g (3 mmole) of the corresponding 5-oxopyrazole Va and 10 ml of acetic anhydride was refluxed for 30 min, after which the reaction mixture was evaporated in vacuo, and the residue was triturated in hexane. The solid material was removed by filtration and recrystallized from benzene–hexane to give 1 g (94%) of a product with mp 149-151°C. IR spectrum: 3300 (NH), 1790 ($OCOCH_3$), and 1665 cm^{-1} (COOEt). PMR spectrum: 1.20 (3H, t, $CH_2\mathbf{CH_3}$); 2.24, 2.30, 2.37 (three 3H, three s, CH_3); 4.13 (2H, q, CH_2CH_3); 6.30 (1H, s, 4-H); 7.2-7.6 (5H, m, aromatic); 11.4 ppm (NH, broad). Found: 65.2; H 5.8; N 10.8%. $C_{20}H_{21}N_3O_4$. Calculated: C 65.4; H 5.8; N 11.4%.

A similar procedure was used to obtain the following compounds. 1-(p-Tolyl)-5-acetoxy-3-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)pyrazole (VIb), with mp 153-155°C, was obtained in 95% yield. IR spectrum: 3280 (NH), 1790 ($OCOCH_3$), and 1665 cm^{-1} (COOEt). PMR spectrum: 1.20 (3H, t, CH_2CH_3); 2.20, 2.24, 2.27 (four 3H, three s, CH_3); 4.14 (2H, q, CH_2CH_3); 6.28 (1H, s, 4-H); 7.21, 7.44 ppm (two 2H, two d, J = 8.5 Hz, aromatic). Found: C 66.2; H 6.1; N 10.6%. $C_{21}H_{23}N_3O_4$. Calculated: C 66.1; H 6.1; N 11.0%. 1-(o-Tolyl)-5-acetoxy-3-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)pyrazole (VIc), with mp 167-170°C, was obtained in 94% yield. IR spectrum: 3290 (NH), 1795 ($OCOCH_3$) and 1660 cm^{-1} (COOEt). PMR spectrum: 1.19 (3H, t, $CH_2\mathbf{CH_3}$); 2.04-2.06, 2.27, 2.34 (four 3H, three s, CH_3); 4.14 (2H, q $\mathbf{CH_2}CH_3$); 6.24 (1H, s, 4-H); 7.14-7.31 (4H, m, aromatic); 11.3 ppm (NH, broad). Found: C 66.0; H 6.1; N 11.0%. $C_{21}H_{23}N_3O_4$. Calculated: C 66.1; H 6.1; N 11.0%.

2,4-Dimethyl-3-acetyl-5-ethoxycarbonylpyrrole Nitrophenylhydrazones (IVa-c, Table 1). A 5.5-mmole sample of the corresponding nitrophenylhydrazine and 0.5 ml of 48% HBr were added to a solution of 5 mmole of 2,4-dimethyl-3-acetyl-5-ethoxycarbonylpyrrole III in 50 ml of alcohol, after which the mixture was refluxed for 30 min and then cooled. The resulting bright-red precipitate of the hydrazone was removed by filtration, washed with alcohol, and recrystallized from DMF–water.

Ethyl β-(2,4-Dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-β-ketopropionate o-Nitrophenylhydrazone (IIa). A 1.4-g (5 mmole) sample of keto ester I was added to a solution of 1 g (5 mmole) of o-nitrophenylhydrazine hydrochloride in a mixture of 50 ml of ethanol and 20 ml of acetic acid, and the mixture was allowed to stand at 20°C for 4 days, after which it was evaporated *in vacuo* at 40°C. The oily residue was chromatographed with a column packed with silica gel (25 × 250 mm) by elution with benzene–ethyl acetate (20:1). The fraction containing a bright-orange substance was evaporated, and the oily resudue was dried *in vacuo* to give 1 g (48%) of product. IR spectrum: 3300 (NH), 1660-1740 (COOEt), 1610 (C=N), and 1570 cm^{-1} (N–O). PMR spectrum (CCl_4): 1.13, 1.27 (two 3H, two t, CH_2CH_3); 2.17, 2.19 (two 3H, two s, CH_3); 3.39 (2H, s, CH_2COOEt); 3.97, 4.20 (two 2H, two q, CH_2CH_3); 6.3-8.3 (4H, m, aromatic); 10.0 (pyrrole NH, broad); 10.7 ppm (hydrazone NH, broad).

1-(o-Nitrophenyl)-3-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-5-oxopyrazole (Vf). A 1.9-g (0.01 mole) sample of o-nitrophenylhydrazine hydrochloride was added to a solution of 2.8 g (0.01 mole) of keto ester I in a mixture of 10 ml of alcohol and 5 ml of acetic acid, and the mixture was refluxed for 4 h, after which it was cooled. The resulting bright-red precipitate was removed by filtration, washed with hot alcohol, and dried to give 0.9 g (27%) of o-nitrophenylhydrazone IVa, which was identical, with respect to its properties, to the substance synthesized in the preceding experiment from pyrrole III. The combined filtrates, after separation of hydrazone IVa, were evaporated *in vacuo*, and the residue was triturated in 40 ml of chloroform. The resulting light-yellow precipitate was removed by filtration, washed with chloroform, and recrystallized from alcohol (Table 1).

Reaction of Pyrrolyl-β-keto Ester I with 2,4-Dinitrophenylhydrazine. A 2.0-g (0.01 mole) sample of 2,4-dinitrophenylhydrazine and 1 ml of 48% HBr were added to a solution of 2.8 g (10 mmole) of keto ester I in 50 ml of alcohol, after which the mixture was refluxed for 30 min until the starting pyrrole vanished [according to TLC, benzene–ethyl acetate (2:1)], and the mixture was allowed to stand at 20°C for 16 h. The resulting red precipitate was removed by filtration, washed with 30 ml of hot benzene, and dried to give 0.2 g of 2,4-dinitrophenylhydrazone IVc, which was identical, with respect to its properties, to the sample previously obtained. The combined filtrates were diluted with 50 ml of benzene–ethyl acetate (1:1), neutralized with 10% sodium acetate solution, washed with water, dried, and evaporated *in vacuo*. The residue was triturated in petroleum ether–benzene (10:1), and the solid material was removed by filtration and dried. The yield and properties of ethyl β-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-β-ketopropionate 2,4-dinitrophenylhydrazone (IIb) are presented in Table 1.

In the case of 7-8 h refluxing of the reaction mixture the yield of hydrazone IVc was 1.9 g (49%). Its properties were identical to the previously obtained substance.

1-(2,4-Dinitrophenyl)-3-(2,4-dimethyl-5-ethoxycarbonyl-3-pyrrolyl)-5-oxopyrazole (Vh). A) A mixture of 5.6 g (12 mmole) of hydrazone IIb, 0.6 g of p-toluenesulfonic acid, and 250 ml of toluene was refluxed with a Dean–Stark trap for 7 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration, washed successively with benzene and ether, and recrystallized from DMF–water (Table 1).

B) A 2-g (10 mmole) sample of 2,4-dinitrophenylhydrazine and 0.2 g (1 mmole) of p-toluenesulfonic acid monohydrate were added to a solution of 2.8 g (10 mmole) of keto ester I in 30 ml of toluene, after which the mixture was refluxed with a Dean–Stark trap for 5 h. The mixture was cooled, and the resulting precipitate was removed by filtration and washed successively with toluene and ether to give 3 g (72%) of product. With respect to its properties, the product was identical to a previously obtained sample.

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