CHEMICAL TRANSFORMATIONS OF 2,4-DIARYL-2,3-DIHYDRO-1H,1,5-BENZODIAZEPINES

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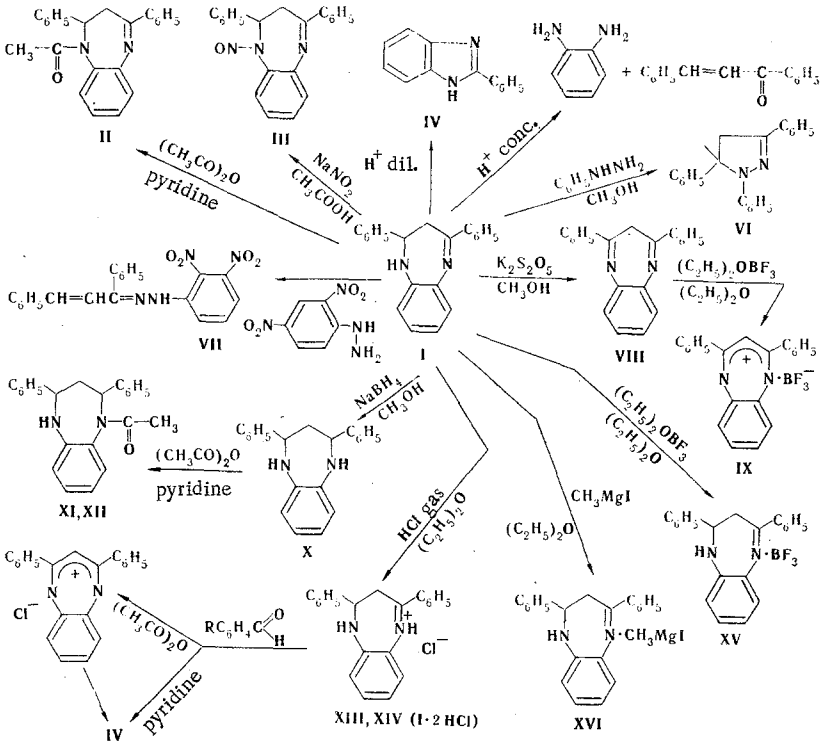
UDC 547.892'785.5'772.2:
542.9:541.634:543.42

The behavior of 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine in acylation, alkylation, nitrosation, oxidation, reduction, salt formation, and opening of the diazepine ring under the influence of various dinucleophiles and acids was studied. It is shown that the dihydrodiazepine ring is extremely sensitive to acidic reagents and undergoes rearrangement to an imidazole ring under their influence. The structure of the cis- and trans-tetrahydroazepines were analyzed thoroughly.

The high pharmacological activity of 1,5-benzodiazepines has stimulated increased interest in them [1]. Compounds with such properties (tranquilizers, anticonvulsants [2], and antineoplastics [3]) are also known among derivatives of 2,3-dihydro-1H-1,5-benzodiazepine. The accessibility of the latter has increased markedly in connection with the establishment of the optimum conditions for their synthesis [4], but very little study has been devoted to their chemical properties. The aim of this research was to fill this gap.

The principal subject of the investigation was 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (I); its transformations are presented in the following scheme:



They can be arbitrarily divided into three groups: reactions of I as a secondary amine, reactions accompanied by opening of the seven-membered ring, and chemical transformations of the dihydrodiazepine ring without ring opening.

Of the reactions that are characteristic for secondary amines, we studied acylation, alkylation, and nitrosation. Thus I is readily acylated in pyridine by means of acetic anhydride to give N-acetyl derivative II. Re-

A. M. Gor'kii Kharkov State University, Kharkov 310077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 830-836, June, 1982. Original article submitted February 2, 1981; revision submitted November 5, 1981.

0009-3122/82/1806-0631 $07.50

placement of pyridine by methanol leads to a substantial decrease in the yield of II; the principal process becomes hydrolytic ring opening, and chalcone and o-phenylenediamine are isolated in addition to II.

Attempts to alkylate dihydrodiazepine I in solvents with different polarities (ether, methanol, dimethylformamide, and acetonitrile) by means of $(CH_3)_2SO_4$ or CH_3I lead only to its resinification even at low temperatures.

Brief nitrosation of I with sodium nitrite in glacial acetic gives nitroso derivative III. An increase in the reaction time (to more than 15-20 min) or carrying out the reaction in dilute acid is accompanied by rearrangement to benzimidazole IV.

It was noted that various acids (HBr, HCl, CF_3COOH, and CH_3COOH) in protic and aprotic solvents (alcohols, benzene, acetone, and pyridine) cause rearrangement of dihydrodiazepine I to 2-phenylbenzimidazole (IV). For example, a band with λ 435 nm corresponding to monoprotonated form XIII appears in the UV spectrum when I is dissolved in ethanol containing 10% added 0.1 N HCl. All of the characteristic bands of I vanish at room temperature after 20 h (after 50 h in benzene saturated with HCl), and the spectrum of the salt form of IV (λ_{max} 243, 296 nm [5]) is observed. The rate of rearrangement is directly dependent on the hardness of the acid anion: The yields of benzimidazole IV after 20 h average 80% (Cl^-), 65% (Br^-), 50% (CF_3COO^-), and 20% (CH_3COO^-) at a dihydrodiazepine concentration on the order of 10^{-4} mole/liter in the ethanol–acid system. The rearrangement is, of course, accelerated as the temperature is raised: Refluxing of a methanol solution of the diazepine with catalytic amounts of CH_3COOH for 2 h is sufficient for complete conversion.

The formation of IV is also observed when methanol solutions of dihydrodiazepine I are refluxed with added o-aminophenol, which in this case probably acts as a weak acid.

Simultaneously with the rearrangement one observes hydrolysis of I to give o-phenylenediamine and chalcone; the role of hydrolysis becomes appreciably greater as the acid concentration in solution is increased. This process becomes the principal process when the starting substance is allowed to stand in a solution of acetic anhydride in methanol or when it is nitrated with a nitrating mixture (KNO_3–H_2SO_4) in glacial acetic acid. It is interesting to note that 2,4-dinitrochalcone was isolated from the reaction products in good yields.

The dihydrodiazepine ring is also readily cleaved under the influence of dinucleophilic reagents such as phenylhydrazine and 2,4-dinitrophenylhydrazine. Brief heating of I with phenylhydrazine (or maintenance at room temperature for 6-8 h in the case of dinitrophenylhydrazine) leads to 1,3,5-triphenyl-2-pyrazoline (VI) [or chalcone 2,4-dinitrophenylhydrazone (VII)]. Monitoring by TLC showed that these processes take place through the intermediate formation of chalcone.

At the same time, no appreciable changes occur with dihydrodiazepine I under the influence of alcohol solutions of NaOH or CH_3ONa. These results can be explained if one takes into account the fact that the reaction of o-phenylenediamine with chalcone is a reversible process that is shifted in the presence of base to favor the dihydrodiazepine. The addition of alkalis therefore is not accompanied by conversion of I. Hydrazines are rather strong bases and for this reason should not have promoted retroprocesses. In addition to this, however, hydrazines are capable of irreversible reactions with ketones; these competitive reactions decrease the equilibrium fraction of chalcone in the mixture, thereby promoting cleavage of dihydrodiazepine I.

Oxidation, reduction, and salt formation comprise the third group of processes. It should be noted that attempts to oxidize I with hydrogen peroxide, SeO_2, and peracids lead to resinous unidentifiable reaction products. At the same time, the use of the mild oxidizing agent $K_2S_2O_5$ gives 2,4-diphenyl-3H-1,5-benzodiazepine (VIII) in good yield. No melting-point depression is observed for a mixture of VIII with the product of directed synthesis (the reaction of o-phenylenediamine with dibenzoylmethane [6]); alcohol solutions of VIII become intensely violet upon acidification (because of the formation of a diazatropylium cation). Compound VIII was also identified by means of boron trifluoride complex IX.

The reduction of dihydrobenzodiazepine I with sodium borohydride in methanol leads to tetrahydro derivative X in 97% yield. It should be noted that partial reduction occurs in ethanol but does not take place at all in propyl, isopropyl, and butyl alcohols. By using 80% ethanol (during which the acidity of the medium increases) we were able to isolate X in 87% yield. This process is accompanied by disappearance of the $\nu C=N$ band in the IR spectrum of I and disappearance of the band with λ_{max} 370 nm in the UV spectrum.

The region of the PMR spectrum (294 MHz) of the reduction product that characterizes the protons of the tetrahydrodiazepine ring is presented in Fig. 1. It follows unambiguously from the spectrum that two isomeric compounds are present in solution; judging from the constants, the quartet with δ 3.81 ppm, the quartet

TABLE 1. Characteristics of the 1,5-Benzodiazepine Derivatives Obtained

Compound	mp, °C	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$), in ethanol	ν, *cm^{-1} NH	ν, *cm^{-1} C=N	PMR spectrum (in $CDCl_3$), ppm	N found, %	Empirical formula	N calc., %	Yield, %
II	169—171	310 (6,8)	—	1605	1,76 (CH_3, s); 3,02—3,24 (CH_2, m); 6,33 (CH, q)	8,1	$C_{23}H_{20}N_2O$	8,2	60
III	141—142	358 (6,1)	—	1609	—	12,5	$C_{21}H_{17}N_3O$	12,8	91
VIII	138	260 (44,0)	—	1594	—	9,1	$C_{21}H_{16}N_2$	9,5	75
X	139—140	293 (4,0)	3353	—	2,03—2,34 (CH_2, m); 3,02 (NH, s), 3,81 (CH, q) 2,25—2,30 (CH_2, m); 3,02 (NH, s); 5,02 (CH, q)	9,0	$C_{21}H_{20}N_2$	9,3	97
XI	232—233	296 (2,8)	3308	—	1,89 (CH_3, s); 2,09—2,44 (CH_2, q); 4,67 (NH, s); 5,58 (CH, q)	8,0	$C_{23}H_{22}N_2O$	8,2	70
XII	217—218	294 (0,6)	3308	—	1,79 (CH_3, s); 2,36—2,49 (CH_2, m); 4,66 (NH, s); 5,32 (CH, q)	8,0	$C_{23}H_{22}N_2O$	8,2	18
XIII	166—167 (dec.)	435 (6,1)	3380	1623	—	8,3	$C_{21}H_{18}N_2 \cdot HCl$	8,4	89
XIV	175—180 (dec.)	452 (7,2)	3416	1621	—	7,3	$C_{21}H_{18}N_2 \cdot 2HCl$	7,6	65
XV	139—141 (dec.)	450 (5,6)	3390	1626	2,02—2,62 (CH_2, m); 3,46 (NH, s); 5,30 (CH, t)	7,6	$C_{21}H_{18}N_2 \cdot BF_3$	7,5	67

*The $\nu C=O$ band is found at 1672, 1660, and 1644 cm^{-1} in the spectra of II, XI, and XII, respectively; $\nu N=O$ 1440 cm^{-1} for the N—N=O fragment of III, and $\nu \overset{+}{N}H_2$ (XIV) 2575 cm^{-1}.

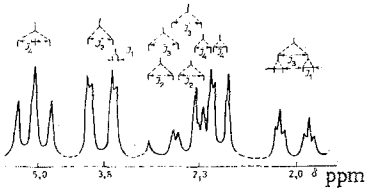
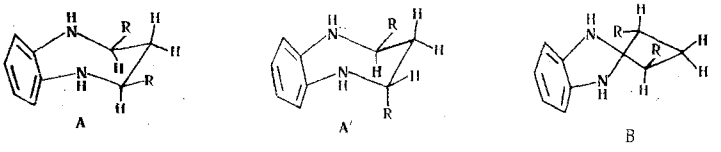


Fig. 1. PMR spectra of the protons of the tetrahydrodiazepine ring on the cis and trans isomers of X ($CDCl_3$, 294 MHz): $J_1 = 1.6$, $J_2 = 10.8$, $J_3 = 13.0$, and $J_4 = 7.2$ Hz.

with δ 2.34 ppm, and the sextet with δ 2.04 ppm corresponds to one of them, while the triplet with δ 5.02 ppm and the quartet* with δ 2.19 ppm corresponds to the other. A substantial difference in the δ values of the CH groups of the compounds is observed ($\Delta\delta = 1.21$ ppm); the chemical shifts of the protons of the CH_2 groups in the spectrum of one of the isomers differ by 0.3 ppm, as compared with no more than 0.03 ppm in the spectrum of the second isomer. Judging from the intensities of the signals of the corresponding protons, the isomer ratio is 1 : 1; this ratio is independent of the temperature. It follows from these data above all that a mixture of diastereomeric cis and trans forms of X is present in solution. This can be explained by the fact that reduction by means of sodium borohydride is a reaction of the hydride type [7], and the resulting intermediate carbanion therefore forms the cis and trans isomers with equal probabilities upon reaction with a proton.

It follows from Stuart—Briegleb and Dreiding models that "chair" (A and A') and twist (B) forms are quite probable for the seven-membered tetrahydrodiazepine ring. Since the phenyl ring is characterized by considerable conformational energy (13 kJ/mole [8]), the probability of the existence of the A' form is low. In other words, the e,e-orientation of the phenyl rings determines the preferableness of the A and B forms for the cis and trans isomers, respectively.



In the A form the protons of the methylene group are essentially nonequivalent to the adjacent methylidyne protons, and the first of the above-mentioned groups of signals (two quartets and a sextet) therefore belong to

*This quartet is complicated by additional splitting.

the PMR spectrum of the cis isomer; J_3 is a geminal spin–spin coupling constant (SSCC), J_1 and J_2 are vicinal SSCC, and the J_2 value is characteristic for constants of the J_{aa} type [9]. On the other hand, in the twist form the methylene protons are magnetically equivalent, and the geminal constant therefore does not appear in the spectrum; the second group of signals (the triplet and the quartet), which we assign to the trans isomer, corresponds to this condition.

It is interesting to note that Hunter and Webb [10] in an analysis of the PMR spectrum of 2,4-dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine arrived at the conclusion that the pseudochair form is preferable. The problems of geometrical isomerism are not discussed in [10], but the molecular model presented is characterized by a cis orientation of the methyl groups, and our conclusions regarding the conformation of the seven-membered ring consequently are in agreement.

We were unable to separate the mixture of isomers of tetrahydro derivative X, but cis form XI crystallized out initially from the reaction mixture when it was acylated by means of acetic anhydride in pyridine, after which trans isomer XII precipitated from the filtrate. The assignment of the isomers follows unambiguously from the PMR spectrum, specifically from the character and chemical shift of the multiplets of the methylene protons (Table 1).

Salts with a 1 :1 or 1 :2 composition are formed when a stream of dry HCl is passed into an ether solution of I. The ratio of these salts depends on the time during which HCl is passed into the solution. Thus hydrochloride XIII separates out when the reaction is carried out for 10-15 min. Salt formation in this case takes place at the more basic azomethine nitrogen atom, and this is confirmed unambiguously by means of the IR and UV spectra. Thus the νN–H values were close (3362 and 3370 cm^{-1}, respectively) in the IR spectra of free base I and its salt XIII, whereas the νC = N value underwent a 15 cm^{-1} increase as a result of salt formation. An increase in the time during which HCl was passed into the solution to 30 min leads to dihydrochloride XIV. Salts XIII and XIV are unstable; in aqueous solutions they are gradually converted to 2-phenylbenzimidazole derivatives (this behavior is also characteristic for 3H-1,5-benzodiazepine salts [11]).

It is known that 1,5-benzodiazepine salts [12] can give styryl derivatives involving the methylene group. However, attempts to carry out the similar condensation of dihydro derivative I and its hydrochloride XIII with 4-R-benzaldehydes [R = H, NO_2, $N(CH_3)_2$] were unsuccessful. Thus heating in pyridine or carrying out the reaction in anhydrous acetic anhydride at room temperature ultimately leads to 2-phenylbenzimidazole; in the case of acetic anhydride the reaction proceeds through the intermediate formation of a diazotropylium cation.

An interesting phenomenon is observed in the action of a Grignard reagent on an ether solution of I. This reaction gives a red precipitate, in the IR spectrum of which (in mineral oil) the band of an NH group is retained, and the band of the C = N group is shifted 22 cm^{-1}. The substance is readily hydrolyzed in air to give starting I. The structure of complex XIV was assigned to the reaction product (see the scheme presented above).

In conclusion, it should be noted that most of the processes described above are also characteristic for 2,3-dihydro-1H-1,5-benzodiazepine derivatives that contain other substituents in the 2 and 4 positions.

EXPERIMENTAL

The IR spectra of KBr pellets of II-XV were recorded with a UR-20 spectrometer. The UV spectra of 10^{-4}-10^{-5} mole/liter solutions of the compounds in ethanol and chloroform were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of 0.3-0.4 mole/liter solutions of the compounds in $CDCl_3$ were obtained with Bruker WH-90 (90 MHz) and Varian XL-100 (100 MHz) spectrometers and with a spectrometer with a superconducting solenoid with an operating frequency of 294 MHz developed and prepared at the Branch of the Institute of Chemical Physics, Academy of Sciences of the USSR (the internal standard was tetramethyl silane). The individuality of the substances was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates by elution with chloroform or, in some cases, with chloroform–methanol (3 :1).

2,4-Diphenyl-2,3-dihydro-1-acetyl-1,5-benzodiazepine (II). An 8-ml (75 mmole) sample of acetic anhydride was added to a solution of 1 g (3.4 mmole) of I in 8 ml of pyridine, and the mixture was allowed to stand for 24 h. The solution was poured over ice, and the precipitated light-yellow crystals (0.69 g) of N-acetyl derivative II were removed by filtration and crystallized from methanol (see Table 1).

2,4-Diphenyl-2,3-dihydro-1-nitroso-1,5-benzodiazepine (III). A 0.14-g (2 mmole) sample of $NaNO_2$ was added carefully to a solution of 0.6 g (2 mmole) of benzodiazepine I in 25 ml of glacial acetic acid. At the end of the reaction (as monitored by means of starch-iodide paper), the mixture was poured into cold water, and the orange crystals of III (0.6 g) were removed rapidly by suction filtration (see Table 1).

2-Phenylbenzimidazole (IV). Three drops of 10% HCl were added to a solution of 0.5 g (1.7 mmole) of I in 25 ml of methanol, and the mixture was heated for 2 h with a reflux condenser. The filtrate was evaporated with a rotary evaporator, and the oily residue was recrystallized from toluene to give 0.2 g (60%) of benzimidazole (IV) with mp 297°C [13].

Hydrolytic Cleavage of 2,4-Diphenyl-2,3-dihydro-1H-1,5-benzodiazepine. A) A solution of 0.5 g (1.7 mmole) of I in 20 ml of methanol and 10 ml of glacial acetic acid was maintained at room temperature for 24 h, after which the solvent was evaporated, and the oily product was crystallized from benzene to give 0.13 g (37%) of chalcone with mp 57°C [13]. Analysis of the reaction mixture by means of TLC (elution with chloroform) made it possible to identify o-phenylenediamine and 2-phenylbenzimidazole (R_f 0.15 and 0.09, respectively).

B) a 16-ml (150 mmole) sample of acetic anhydride was added to a solution of 1 g (3.4 mmole) of I in 40 ml of methanol, and the mixture was allowed to stand for 24 h. The solution was then poured over ice, and the oily reaction product was crystallized from benzene–hexane (1 : 2) to give 0.5 g (71%) of chalcone with mp 57°C [13].

2,4-Dinitrochalcone (V). A nitrating mixture (1 g of KNO_3 in 15 ml of H_2SO_4) was added dropwise with stirring to a solution of 3.0 g (10 mmole) of I in 75 ml of glacial acetic acid, and stirring was continued for another hour. The entire process was carried out at no higher than 10°C. The reaction mixture was poured into ice water, and the dark precipitate was crystallized from chloroform to give 2.2 g (74%) of dinitrochalcone V with mp 206°C.

1,3,5-Triphenyl-2-pyrazoline (VI). Equimolar amounts (1.7 mmole) of I (0.5 g) and phenylhydrazine (0.24 g) were heated in 25 ml of methanol for 2-2.5 h, during which the solution took on a bright-red color and blue fluorescence. Cooling yielded 0.3 g (60%) of pyrazoline VI with mp 137°C (from methanol) (138°C [14]). The filtrate contained a very small amount of chalcone [R_f 0.5 (elution with chloroform)].

Chalcone 2,4-Dinitrophenylhydrazone (VII). Under similar conditions the reaction of 2,4-dinitrophenylhydrazine (at room temperature for 6-8 h) gave hydrazone VII, with mp 248°C [15], in quantitative yield.

2,4-Diphenyl-3H-1,5-benzodiazepine (VIII). A 4.5-g (15 mmole) sample of I was dissolved by heating in methanol, and the solution was mixed with a solution of 3.3 g (15 mmole) of $K_2S_2O_5$ in 25 ml of water. The mixture was heated for 4-5 h until benzodiazepine I vanished completely (as monitored by TLC), after which one third (by volume) of the solvent was removed with a rotary evaporator, and the residue was cooled and filtered to give 3.1 g (75%) of colorless crystals of diazepine VIII with mp 139°C (from methanol) (mp 140°C [11]).

2,4-Diphenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (X). A 6.0-g (20 mmole) sample of I was dissolved by heating in 100 ml of methanol, the solution was cooled to 30°C, and 1.25 g (32 mmole) of $NaBH_4$ was added in portions. The resulting suspension was heated with a reflux condenser for 1 h, after which it was cooled and treated with water. The precipitated colorless crystals were crystallized from 70% aqueous methanol to give 5.9 g (92%) of a mixture (1 : 1) of the cis and trans isomers of X with mp 139-140°C (Table 1).

cis- and trans-Monoacetyl Derivatives XI and XII. These isomers were obtained by the method presented for II. The product was crystallized from 70% aqueous methanol to give 1.6 g (70%) of the cis isomer and 0.4 g (18%) of the trans isomer (see Table 1).

2,4-Diphenyl-2,3-dihydro-1H-1,5-benzodiazepine Mono- and Dihydrochloride (XIII and XIV). A stream of dry HCl was passed into a solution of 0.5 g (1.7 mmole) of I in 75 ml of absolute ether for 15 min, and the precipitate was removed by filtration and washed thoroughly on the filter with absolute ether to give 0.5 g (89%) of hydrochloride XIII with mp 166-167°C (dec.).

Double salt XIV was obtained in the same way as XIII, except that HCl was passed into the solution for 30 min. Workup gave 0.42 g (67%) of salt XIV (see Table 1).

Reaction of 2,4-Diphenyl-2,3-dihydro-1H-1,5-benzodiazepine with p-Dimethylaminobenzaldehyde. A 3.26 g (10 mmole) sample of XIII and 1.5 g (10 mmole) of p-dimethylaminobenzaldehyde were dissolved in 25 ml of freshly distilled acetic anhydride, and the mixture was maintained at room temperature for 2 days, during which the solution turned dark red. A bright-violet coloration appeared after the mixture was poured over ice (as a result of the formation of a diazatropylium cation). The mixture was extracted with chloroform to give 1.2 g (61%) of IV.

Complex of 2,4-Diphenyl-2,3-dihydro-1H-1,5-benzodiazepine with BF_3. Eight drops of boron trifluoride etherate were added to a solution of 0.3 g (1 mmole) of I in 50 ml of absolute ether, during which the mixture

warmed up slightly, and a brick-red precipitate formed. The precipitate was removed by filtration and crystallized from chloroform to give 0.25 g (67%) of XV with mp 139-140°C (dec.).

Compound IX was obtained by a similar method. Workup of the reaction mixture gave 0.27 g (73%) of a product with mp 199-200°C (dec.).

Complex of 2,4-Diphenyl-2,3-dihydro-1H-1,5-benzodiazepine with a Grignard Reagent (XVI). A solution of 0.3 g (1 mmole) of I in 50 ml of absolute ether was added dropwise with stirring to a solution of a Grignard reagent prepared from 1.25 mmole of methyl iodide, after which the reaction mixture was heated with stirring on a water bath for 30 min, during which a red precipitate, which hydrolyzed readily in air, formed. Workup gave 0.38 g (82%) of complex XVI. IR spectrum (in mineral oil): νNH 3362 and νC=N 1630 cm^{-1}.

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