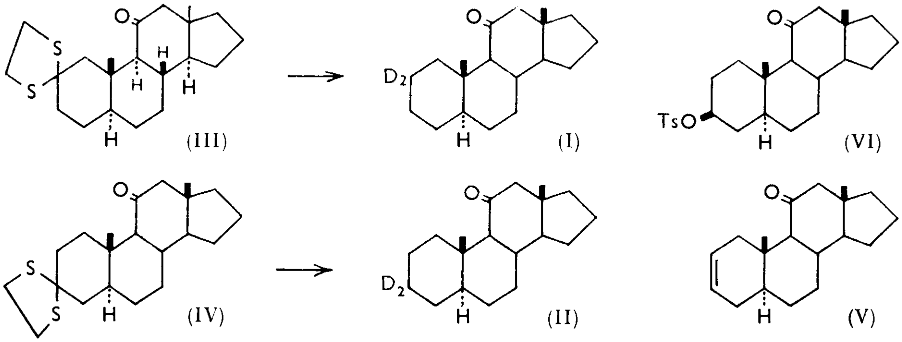
768. *Studies in Organic Sulphur Compounds. Part XIV.*[1] *Formation of Olefins on Desulphurisation of Ethylene Thioketals by Raney Nickel.*

By Carl Djerassi and D. H. Williams.

Olefins have been isolated as products of the desulphurisation of steroidal ethylene dithioketals by Raney nickel. Olefin formation is favoured by the use of deactivated W7 Raney nickel catalysts.

In connection with work under way in this laboratory on the hydrogen transfers involved in the mass-spectrometric fragmentation of 5α-androstan-11-one, the preparation of $[2,2\text{-}^2H_2]$- (I) and $[3,3\text{-}^2H_2]$-5α-androstan-11-one (II) was undertaken by desulphurisation of the respective ethylene dithioketals (III) and (IV) on a Raney nickel catalyst containing active deuterium. This catalyst was prepared by dissolving Raney nickel alloy in deuterium oxide containing sodium deuterium oxide at 50° ± 2°. The catalyst was washed three times with deuterium oxide and twice with methan$[^2H]$ol and therefore approximates to W7 Raney nickel[2] in activity, although it probably contains slightly more alkali (further washing was not undertaken).



(III) (I) (VI)

(IV) (II) (V)

(Ts = $p\text{-}C_6H_4Me\cdot SO_2$)

Desulphurisation of the thioketal (IV) (14 pt.) with a normal, fresh W7 Raney nickel (1 pt.) gave 5α-androstan-11-one as sole product. When the catalyst : substrate ratio was reduced to 1 : 8, 5α-androstan-11-one was acccompanied by one-third of its weight of 5α-androst-2-en-11-one (V) [an authentic sample of the keto-olefin (V) was prepared by elimination, on basic alumina,[3] of the toluene-*p*-sulphonyloxy-group from 3β-toluene-*p*-sulphonyloxy-5α-androstan-11-one (VI)]. Desulphurisation of the thioketal (III) with a Raney nickel catalyst containing active deuterium similarly gave $[2,2\text{-}^2H_2]$-5α-androstan-11-one (I), along with deuterated analogues of the unsaturated ketone (V).

The production of olefins on desulphurisation of ethylene dithioketals by Raney nickel has not previously been reported. However, there are two examples of olefins obtained in a similar manner in the steroid series, *viz.*, desulphurisation of 1ξ,3,3-trisbenzylthiocholestane (VII) on Raney nickel deactivated by 15 minutes' refluxing with acetone gave a mixture of cholest-1-ene and cholest-2-ene.[4] The dihydroxy-disulphide (VIII) was

[*Added in Proof.*] After submission of this paper, a publication dealing with similar findings has appeared (cf. Fishman, Torigoe, and Guzik, *J. Org. Chem.*, **1963**, **28**, 1443). In addition, an isolated example of an olefin being obtained in an analogous manner has been reported (cf. Steele, Cohen, and Mosettig, *J. Amer. Chem. Soc.*, 1963, **85**, 1134).

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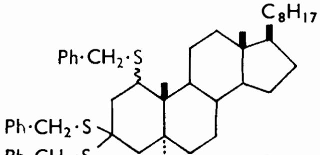
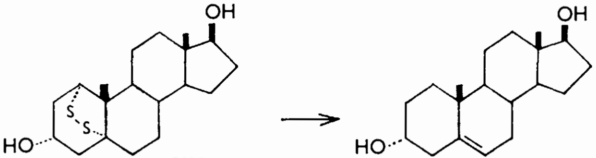
[1] Part XIII, Lightner and Djerassi, *Chem. and Ind.*, **1962**, 1236.
[2] *Org. Synth.*, Coll. Vol. III, 176.
[3] Douglas, Ellington, Meakins, and Swindells, *J.*, 1959, 1720.
[4] Plattner, Fürst, and Els, *Helv. Chim. Acta*, 1954, **37**, 1399.

desulphurised with Raney nickel (activity unspecified) to androst-5-ene-3α,17β-diol (IX) in 20% yield.[5] The only other reported isolation of olefins on Raney nickel desulphurisation is due to Hauptmann and Walter,[6] who reported that treatment of dioctyl disulphide with degassed Raney nickel at 180° yielded a mixture of octane and octene, disproportionation of octyl radicals being presented as an explanation of this result. Analogous behaviour was shown by dicyclohexyl disulphide. However, it is of interest that desulphurisation of a number of α-hydroxyethylene dithioketals [7-9] results, not only in removal of the thioketal, but also in oxidation of the adjacent hydroxyl to a ketone group. Since, in two cases,[7,8] isolated hydroxyl functions in the same molecule are unaffected, it appears possible that the oxidation of the hydroxyl group adjacent to the reaction site proceeds through an enol and that these cases may be further examples of "olefins from thioketals."



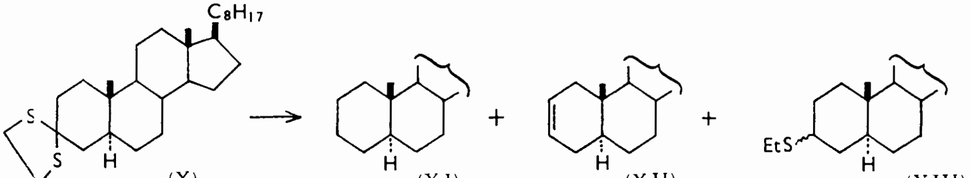
(VII)



(VIII) (IX)

In view of the above results, it was decided to study the desulphurisation of cholestan-3-one ethylene dithioketal by W2 and W7 Raney nickel of various ages with various ratios of substrate to Raney nickel. It was expected that quantitative analyses of the resulting mixtures of cholestane and cholest-2-ene would be possible by vapour-phase chromatography on a polydiethylene glycol succinate column.[10]

Batches of W2 [11] and W7 [2] Raney nickel were prepared and 50 mg. samples of cholestan-3-one ethylene dithioketal [12] (X) were desulphurised with ratios of substrate to Raney nickel equal to 1 : 1·5, 1 : 6, and 1 : 12; both types of nickel were used when fresh, 10 days old, and 32 days old. All isolated products were investigated qualitatively by thin-layer chromatography; all contained cholestane (XI) and in many cases cholest-2-ene (XII), 3ξ-ethylthiocholestane (XIII), and unchanged thioketal (X) were obtained. In all cases where sulphur-containing products remained, the hydrocarbon fraction was isolated by column chromatography on alumina. Good resolution of an authentic mixture of cholestane and cholest-2-ene was obtained by vapour-phase chromatography on a polydiethylene glycol succinate column,[10] operating at 215°, the retention times being 18·5 and 21·7 min., respectively; the measured peak areas agreed with the percentage composition of the injected mixture within 1%. The composition of all the hydrocarbon fractions was therefore determined by this method and the results are summarised in



(X) (XI) (XII) (XIII)

[5] Tweit and Dodson, *J. Amer. Chem. Soc.*, 1959, **81**, 4409.
[6] Hauptmann and Walter, *Chem. Rev.*, 1962, **62**, 347.
[7] Narasimha Rao and Gollberg, *Tetrahedron*, 1962, **18**, 1251.
[8] Fishman, *Chem. and Ind.*, 1962, 1467.
[9] Wilds, Zeitschel, Sutton, and Johnson, *J. Org. Chem.*, 1954, **19**, 255.
[10] Clayton, *Biochem. J.*, 1962, **1**, 257.
[11] *Org. Synth.*, 1941, **21**, 15.
[12] Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945.

Tables 1 and 2. The thioether (XIII) was isolated in only one instance, by column chromatography on alumina; it had m. p. 81—82° and was identified by its mass spectrum, which showed a molecular ion at *m/e* 432 and a base peak corresponding to the loss of the elements of ethanethiol (*M*, −62).

The results show that, when a ratio of substrate to Raney nickel of 1 : 1·5 is used (much less than used in " normal " desulphurisations), the thioketal can be recovered in yields varying from 50% to 76%. In the case of W2 Raney nickel, cholestane was obtained in yields of 12—15%, along with a roughly equal amount of cholest-2-ene (13—15%), independently of age. W7 Raney nickel gave smaller amounts of combined hydrocarbons in every case, the percentage yield decreasing slightly with the age of the nickel. The outstanding feature of the 1 : 6 experiments is that, whilst in every case W2 Raney nickel gave an almost quantitative yield of cholestane, independently of age, the activity of the W7 catalyst deteriorated rapidly and only in the case of fresh W7 Raney nickel was cholestane obtained as sole product. As the age of the W7 Raney nickel increased, so did the amount of recovered thioketal and the ratio of cholest-2-ene to cholestane. Whilst almost quantitative recovery of material was possible in the case of the W2 catalyst, recovery from the W7 experiments lay in the range 72—81%, indicating strong adsorption of some material on the nickel. The 1 : 12 experiments give further support to the above generalisations. Indeed, W7 Raney nickel, aged for 32 days, gave more cholest-2-ene (22%) than cholestane (17%), despite the large ratio of catalyst to substrate.

TABLE 1.

Yields (%) in desulphurisations with W7 Raney nickel of various ages.

	Fresh	10 days	32 days	Fresh	10 days	32 days	Fresh	10 days	32 days
Products (%)	Substrate: Ni = 1 : 1·5			Substrate: Ni = 1 : 6			Substrate: Ni = 1 : 12		
Cholestane (XI) ...	14	11	11·5	72	36	13	63	46	17
Cholest-2-ene (XII)	7	5	3·5	—	12	12	—	17	22
Thioether (XIII)	4·5	—	—	—	Trace	—	—	Trace	—
Thioketal (X)	68	72	76	—	26	56	—	—	38

TABLE 2.

Yields (%) in desulphurisation with W2 Raney nickel of various ages.

Products (%)	Fresh	10 days	32 days	Fresh	10 days	32 days	Fresh	10 days	32 days
	Substrate: Ni = 1 : 1·5			Substrate: Ni = 1·6			Substrate: Ni = 1 : 12		
Cholestane (XI) ...	13	12	15	98	100	100	100	95	88
Cholest-2-ene (XII)	15	13	15	—	—	—	—	—	—
Thioether (XIII)	Trace	Trace	Trace	—	—	—	—	—	—
Thioketal (X)	64	70	50	—	—	—	—	—	—

Thus olefin formation is favoured when a large excess of aged W7 Raney nickel is used. A final experiment was therefore conducted with W7 Raney nickel, which had been deactivated by refluxing it in acetone for 24 hr., and a ratio of substrate to catalyst of 1 : 16. This experiment gave no thioketal, only traces of the thioether (XIII), cholest-2-ene (48%), and cholestane (22%).

The accepted mechanism for the normal path of desulphurisations by Raney nickel[13] is that the intermediate (XIV) would gain two hydrogen radicals from the catalyst to give the thioether (XIII), which could then undergo further desulphurisation to cholestane. The isolation of the thioether (XIII) in the present work supports this mechanism. It is possible that, when the concentration of hydrogen radicals is low (*i.e.*, with small amounts of catalyst or deactivated catalyst), the diradical yields a thioenol ether (XV) by intramolecular hydrogen-radical abstraction from C-2. Desulphurisation of the enol ether would then yield cholest-2-ene. A similar explanation can be put forward to rationalise

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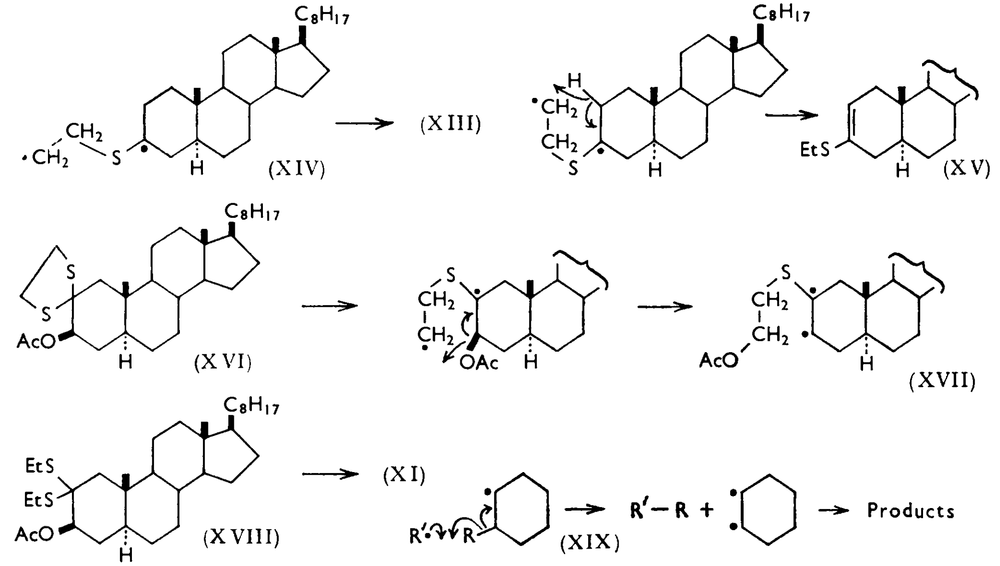
[13] Pettit and van Tamelen, *Org. Reactions*, 1962, **12**, 356.

the production of cholestane (XI) from the thioketal acetate (XVI);[14] the intermediate (XVII) would be expected to yield cholestane on an active catalyst. The production of cholestane from the diethyl dithioketal (XVIII)[14] can be explained on this basis if it is assumed that ethyl radicals are held at the site of the reaction on the surface of the catalyst (see XIX). It can be seen that, if the desulphurisation of 5α-androstane-2,11-dione 2-(ethylene dithioketal) (III) with Raney nickel containing active deuterium did take place through a thioenol ether, then [2-^{2}H]-5α-androst-2-en-11-one would be the product. In fact, the most important species were mono- (28%) and di-deuterated (33%); that this deuterium could only be incorporated at positions 1—4 was established because the peak at *m*/*e* 218 in the mass spectrum[15] of 5α-androst-2-en-11-one, corresponding to the retro-Diels–Alder reaction (the charge remaining with the ketonic fragment), was unmoved in the spectrum of the deuterated analogue. However, interpretation of these results is hazardous in view of the likelihood of exchange of vinyl and allylic hydrogen for deuterium at the surface of the catalyst.



On the evidence available, the only possible generalisation appears to be that a radical intermediate (XIX; R = OAc or H) in a desulphurisation can undergo further reaction by homolysis of the adjacent C–R bond, probably in the presence of a second radical, R'• (=H•, Et•, etc.).

EXPERIMENTAL

M. p.s were determined in capillaries and are corrected. All aged samples of Raney nickel had been kept at 0° under absolute ethanol. Unless otherwise stated, chromatographies were carried out on neutral alumina (E. Merck A.-G., Darmstadt, Germany).

5α-Androstan-11-one and 5α-Androst-2-en-11-one (V).—5α-Androstane-3,11-dione 3-(ethylene dithioketal) (IV)[15] (249 mg.) in 95% ethanol (20 c.c.) was heated under reflux with freshly prepared W7 Raney nickel (from 4·0 g. of alloy) for 4 hr. The catalyst was then removed and the filtrate evaporated, giving an oil (143 mg.) which was adsorbed on a column of alumina (50 g.; grade II) in light petroleum (b. p. 30—60°). The column was developed by the same solvent (200 c.c.), and crude 5α-androstan-11-one (64 mg.) was eluted in a further 125 c.c. of

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[14] Sheehan and Erman, *J. Amer. Chem. Soc.*, 1957, **79**, 6050.
[15] Williams, Wilson, Budzikiewicz, and Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, in the press.

eluate containing 2% of benzene; pure material (43·7 mg.), m. p. 50—51° (lit., 49—50°,[16] 50—52° [17]), having a mass spectrum identical with that obtained previously,[18] was obtained by one crystallisation from methanol at −15°. Development was continued with light petroleum containing 4% of benzene, and the next fractions (50 c.c.) eluted a mixture of products. The following fractions (90 c.c.) eluted almost pure 5α-*androst*-2-*en*-11-*one* (V) (20·5 mg.), from which traces of the saturated ketone were removed by two recrystallisations from methanol at −15°. Material obtained in this manner had m. p. 88—89°, $\lambda_{max.}$ (in $CHCl_3$) 5·86 μ; its mass spectrum showed the expected molecular ion at *m*/*e* 272 and a strong peak at *m*/*e* 218 corresponding to loss of butadiene in a retro-Diels–Alder reaction (Found: C, 83·6; H, 10·6. $C_{19}H_{28}O$ requires C, 83·75; H, 10·35%).

5α-*Androst*-2-*en*-11-*one* (V) *from* 3β-*Toluene*-p-*sulphonyloxy*-5α-*androst*-11-*one* (VI).—Basic alumina (Woelm; 630 mg.; grade I) was added to a solution of the ester [15] (VI) (55 mg.) in anhydrous benzene (0·5 c.c.), and the mixture kept at room temperature for 5 days with occasional shaking, then poured on a column of similar alumina (700 mg.) in benzene. Elution with benzene gave crystals (24 mg.), which recrystallised from methanol, giving 5α-androst-2-en-11-one (19 mg.), m. p. 89—91·5° alone or mixed with the preceding specimen.

Preparation of a Raney Nickel Catalyst containing " Active " Deuterium.—Sodium (190 mg.) was dissolved in deuterium oxide (1·2 ml.), and Raney nickel alloy (250 mg.) added during 8 min., the temperature being kept at 50° ± 2°. The supernatant liquid was then removed and the residue washed with deuterium oxide (3 × 2 c.c.) and then with methan[^{2}H]ol (2 × 1 c.c.). The catalyst was used immediately as indicated below and washed into the reaction vessel by the methan[^{2}H]ol in which the desulphurisation was carried out.

2,2-[$^2H_2$]-5α-*Androstan*-11-*one* (I) *and* 2,3-[$^2H_2$]-5α-*Androst*-2-*en*-11-*one*.—5α-Androstan-2,11-dione 2-(ethylene dithioketal) (III) (8 mg.) and Raney nickel (D) (from 250 mg. of alloy) in methan[^{2}H]ol (2 c.c.) were heated under reflux for 2 hr. The isolated product and sodium hydroxide (30 mg.) in 70% aqueous methanol (3 c.c.) were heated under reflux for 3 hr. A colourless oil (5·2 mg.) was recovered and shown by thin-layer chromatography [silica gel G, E. Merck A.-G., Darmstadt, Germany, as adsorbant; plate developed by benzene containing 30% of light petroleum (b. p. 60—80°)] to contain 5α-androst-11-one (R_F 0·73) and a smaller quantity of 5α-androst-2-en-11-one (R_F 0·67). Vapour-phase chromatography on a polydiethylene glycol succinate column at 215° with a nitrogen pressure of 30 lb./sq. in. (Hy-FI instrument, Wilkens Instruments and Research, Walnut Creek, California) supported these structural assignments and indicated that the unsaturated product formed 25% of the mixture. For a preparative separation, a 2 mg. sample was injected on to a 15% polydiethylene glycol succinate column operating at 173° with a helium pressure of 50 lb./sq. in. (Aerograph instrument, Wilkens Instruments and Research). 2,2-[$^2H_2$]-5α-Androstan-11-one (0·7 mg.), identified by its mass spectrum (d_1, 12%; d_2, 33%; d_3, 16%; d_4, 18%; d_5, 12%; d_6, 9%) was collected from the column in the period 57—63 min. [1—3-^{2}H]-5α-Androst-2-en-11-one (0·3 mg.) was collected as a crystalline solid in the period 68—77 min.; its mass spectrum showed d_0, 8%; d_1, 28%; d_2, 33%; d_3, 19%; d_4, 7%; d_5, 1%; d_6, 3%; d_7, 1%) and the characteristic fragmentation pattern [15,18] confirmed the structural assignment.

Example of a Desulphurisation of Cholestan-3-*one* 3-(*Ethylene Dithioketal*) (XI) *with W*7 *Raney Nickel and a Ratio of Substrate to Raney Nickel*, 1 : 15.—A stirred solution of the thioketal (50 mg.), m. p. 145—146°, $[\alpha]_D$ +30·2° (*c* 1·32 in $CHCl_3$) {lit.,[12] m. p. 146—147·5°, $[\alpha]_D$ +32·0° (*c* 2·09 in $CHCl_3$)} and freshly prepared W7 Raney nickel (75 mg.) were heated under reflux for 6 hr. A thin-layer chromatogram on silica gel G, developed by light petroleum (b. p. 60—80°), indicated the presence of cholestane (XI) (R_F 1·0), cholest-2-ene (XII) (R_F 0·96), starting material (X) (R_F 0·25), and a compound of intermediate polarity (R_F 0·4). Ether (10 c.c.) was added to the cooled solution, which was then filtered and evaporated, giving a crystalline residue (47 mg.). This residue in light petroleum (b. p. 30—60°) (3 c.c.) was adsorbed on alumina (20 g.; grade I), and the column was developed with light petroleum (b. p. 60—80°). The first fractions (50 c.c.) eluted a mixture of cholestane and cholest-2-ene (8·4 mg.) which crystallised. After further development with light petroleum (100 c.c.), a second crystalline fraction (2·1 mg.) was eluted by light petroleum (50 c.c.); recrystallisation of this material from ethanol gave 3ξ-ethylthiocholestane (XIII) (0·7 mg.) as needles, m. p. 81—82°; its mass spectrum showed the expected

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[16] Sondheimer, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 1090.
[17] Steiger and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 817.
[18] Budzikiewicz and Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 1430.

molecular ion at *m*/*e* 432 and the base peak (*M*, − 62) corresponded to loss of ethanethiol. Finally, elution with 9 : 1 light petroleum (b. p. 60—80°)–ether (80 c.c.) gave cholestan-3-one ethylene dithioketal (34·2 mg.), m. p. 141—142°.

Analysis of the Mixture of Cholestane and Cholest-2-ene.—A sample of the hydrocarbon mixture obtained from the above chromatography was injected in carbon disulphide on to a column employing polydiethylene glycol succinate as liquid phase and operating at 215° with a nitrogen pressure of 35 lb./sq. in. (Hy-FI instrument). Cholestane and cholest-2-ene came off the column after 18·5 min. and 21·7 min., respectively, the ratio of the peak areas being 2·1 : 1.

Desulphurisation of Cholestan-3-one Ethylene Dithioketal by Acetone-deactivated W7 Raney Nickel.—Freshly prepared W7 Raney nickel (from 10 g. of alloy) was heated under reflux with acetone (45 c.c.) for 20 hr. and the supernatant liquid was then removed. A solution of the thioketal (X) (366 mg.) in ethanol (30 c.c.) was added and the stirred mixture heated under reflux for 20 hr. Ether (20 c.c.) was added to the cooled solution, which was then filtered, the residue being washed with ether. Evaporation of the filtrate gave a colourless gum (224 mg.). A thin-layer chromatogram, under conditions outlined above, showed the absence of the starting material and the presence of only traces of the thioether (XIII). A fraction of this product (119 mg.) in light petroleum (b. p. 30—60°) (6 c.c.) was adsorbed on a column of alumina (30 g.; grade I), and the hydrocarbons (90 mg.) were eluted by the same solvent (45 c.c.). Analysis of this hydrocarbon mixture by vapour-phase chromatography showed its composition to be cholestane, 31%, and cholest-2-ene, 69%.

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