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THE REACTION OF TRIFLUOROMETHANESULFENYL CHLORIDE WITH ENAMINES OF ß-KETO CARBOXYLIC ACID ANILIDES

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SUMMARY

1-Morpholino-cyclopenten-2-carboxylic acid anilides react with CF_3SCl in molar ratio 1 : 2 to give products of the displacement of two hydrogen atoms at C-2 and C-5. The analogous reaction with enamines of cyclohexanono- and cycloheptanono- 2-carboxylic acid anilides and benzoylacetanilides proceeds in 1 : 1 molar ratios affording enamines and keto compounds.

INTRODUCTION

Enamines of 2-substituted cyclic ketones exist as a mixture of two isomeric forms A and B. The quantitative ratio of both isomeric forms depends on the nature of the substituent, the kind of the amine moiety [1], and the size of the cycloalkene ring [2].

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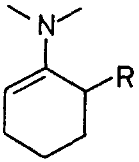
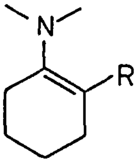


A



B

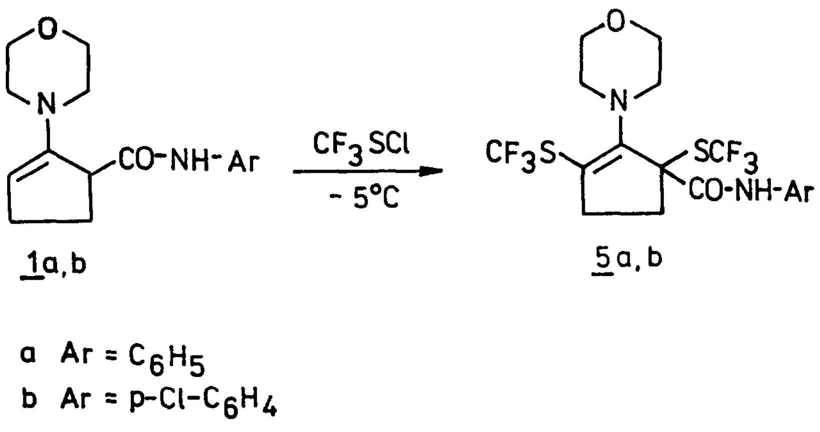
The percentage of the form A, as determined by integration of the vinyl proton signal, indicates that the morpholine enamine of cyclohexanone contains the form A in amounts varying from 59 % for 2-phenylcarbomoyl to 78 % for the 2-carboethoxy derivative. The percentage of this form found in the piperidine enamines ranged from 33 to 79 % for the same substituents, respectively [3]. The presence of a vinyl hydrogen atom in the form A allows the introduction of the second substituent into these compounds that react readily with various electrophilic reagents, such as ethyl azodicarboxylate or phenylisocyanate, to give 2,6-disubstituted products [1, 3]. However, House and Schellenbaum [4] reported that pyrrolidine enamine of 2-methylcyclohexanone and methylacrylate gave a 1 : 1 mixture of 2,2- and 2,6-substituted enamines.

In this work we investigated the sulfenation of 2-substituted enamines by means of CF_3SCl. Kühne reported that sulfenation of enamines by 2-nitrobenzenesulfenyl chloride afforded 2,6-disubstituted derivatives [5]. Vilsmaier *et al.* have obtained a 2-methylthio enamine using succinimidosulfonium chloride, morpholinocyclohexene and sodium cyanide as reagents [6].

RESULTS AND DISCUSSION

In this report we describe results of the reaction of enamines of β-keto carboxylic acid anilides with CF_3SCl. Starting materials were the easily available morpholine enamines of cyclic ß-ketoacid anilides containing five- 1, six- 2 and seven 3 membered rings, and morpholine enamines of benzoylacetanilides 4. All reactions of enamines with CF_3SCl were carried out in dry toluene solution in the presence of pyridine. We used a small - up to 10 % - excess of CF_3SCl. The completion of the reaction was indicated by the precipitation of pyridine hydrochloride.

Enamines 1a,b reacted with CF_3SCl rapidly at ambient temperature yielding a deep-red coloured mixture, which was difficult to purify. The best results were obtained when the reaction was performed at -5°C. On the basis of analytical and MS spectral data of products 5a,b we found, that the enamines 1a,b reacted with CF_3SCl in the molar ratio 1 : 2. Taking into account these findings we considered for compounds 5a,b the structure with two geminal CF_3S groups at C-5 or with the CF_3S groups attached to carbon atoms C-2 and C-5 (Scheme 1). The final structure assignment of 5a,b was made on the basis of ^{19}F-, ^{13}C- and ^{1}H-NMR data.



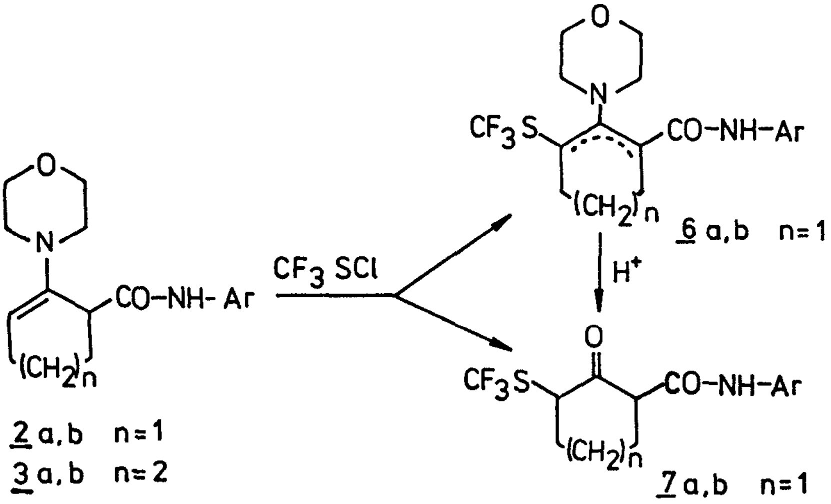
Scheme 1

The ^{19}F-NMR spectrum of 5a displays two signals at δ = -38.27 ppm and δ = -42.80 ppm. This suggests that the CF_3S groups are connected to two different carbon atoms C-2 and C-5. These signals of 5a and b in the ^{13}C-NMR spectrum appear at δ = 70.55 ppm (C-2) and δ = 114.60 ppm (C-5). The ^{1}H-NMR spectra of 5a,b are in agreement with the proposed structure. The most characteristic feature of these spectra are four multiplets, each consisting of eight signals (J = 3.3 Hz), corresponding to hydrogens of four methylene groups of the morpholine moiety. This seems to be caused by the presence of bulky substituents at C-2 and C-5, which hinder the interconversion of the morpholine ring.

Compounds 5a,b were found to be strongly temperature sensitive: when heated in methanol or toluene, a colour change to deep-red and signs of decomposition could be observed.

Enamines 2a,b, containing six-membered rings, reacted with CF_3SCl at 0°C to give the products 6a,b (Scheme 2) in yields of 21 % for 6a and 26 % for 6b. The structure assignment of compounds 6a,b was made on the basis of analytical and spectral data. In the ^{1}H-NMR spectra of 6a,b the signal of the proton at C-2 or C-6 appears as an unresolved broad singlet at δ = 4.35 ppm (6a) and δ = 4.40 ppm (6b), therefore the assignment of the C=C double bond position was not possible.

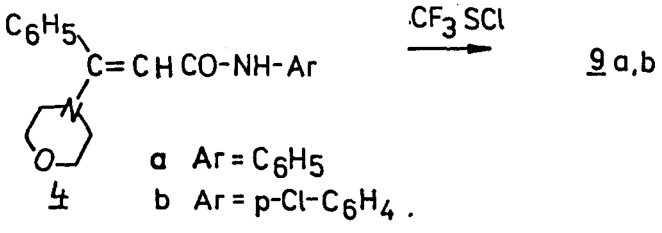
The reaction of enamines 3a,b with CF_3SCl required 48 h for completion at ambient temperature. Working up the reaction mixture gave instead of the expected enamines only keto compounds 8a,b as the sole products (Scheme 2).



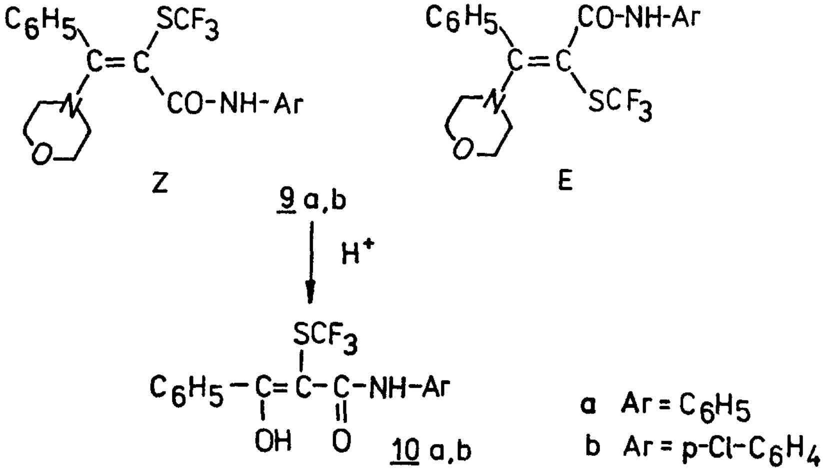
Scheme 2

The morpholine enamines of benzoylacetanilides 4a,b react with CF_3SCl readily at ambient temperature furnishing 9a,b in yields of 50 % and 54 %, respectively. Two signals in the ^{19}F-NMR spectrum of 9a at δ = -47.72 ppm and δ = -48.24 ppm and that of 9b at δ = -47.78 ppm and δ = -48.34 ppm indicate that these compounds are mixtures of Z and E isomers (Scheme 3). The attempted separation of these isomers by column chromatography on silica gel was unsuccessful.

Acid hydrolysis of the enamines 6a,b proceeds readily at room temperature yielding keto compounds 7a,b. Enamines 9a,b were less sensitive towards acids. They were hydrolyzed to β-ketoacid anilides 10a,b [7] in boiling ethanol-hydrochloric acid solution.



Scheme 4



Scheme 3

Since enamines of ß-ketoacid anilides are known to react with malononitrile giving pyridine derivatives [8], we hoped that substituted enamines obtained in this work could be used in the synthesis of pyridine derivatives having CF_3S groups. However, the attempted condensations of enamines 6a and 9a or ketone 7a with malononitrile in various solvents were unsuccessful. Under these conditions only unchanged starting materials were isolated from the reaction mixture. The resistance of these enamines to reaction with malononitrile may be attributed to steric as well as electronic effects of the CF_3S group.

EXPERIMENTAL

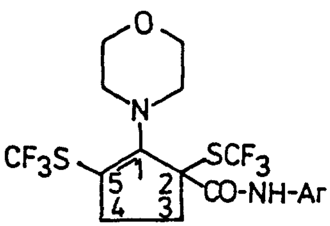
Melting points are uncorrected. IR spectra were recorded in Nujol mulls on a IR-Specord 75 apparatus. ^{1}H-NMR spectra were obtained on a Bruker WP 80 SY spectrometer. ^{19}F- and ^{13}C-NMR spectra were obtained on a Bruker WM 250 PFT spectrometer. All spectra were

measured in $CDCl_3$ solutions using TMS (^1H-, ^{13}C-) or C_6F_6 (^{19}F-) as internal standard. Fluorine chemical shifts were calibrated against $CFCl_3$. Mass spectra were obtained on a Varian MATCH-7 spectrometer at an ionization potential of 70 eV.
Starting enamines 1 - 4 were prepared according to the method described in [9, 10].

The reaction of trifluoromethanesulfenyl chloride with enamines of ß-keto carboxylic acid anilides

10 mmol of CF_3SCl were condensed at -80°C into a glass tube reactor containing the appropriate enamine (10 mmol) dissolved in 100 ml of dry toluene and 1.5 ml of dry pyridine. The reaction mixture was stirred at -5°C for 30 min. (1a,b) and at 0°C for 1 h in the case of enamines 2a,b and for 48 h and 24 h for enamines 3a,b and 4a,b, respectively. The precipitated pyridine hydrochloride was filtered off and toluene was removed on a rotary evaporator. The resinous product was chromatographed (5a,b, 9a,b) on silica gel using chloroform as eluent, or recrystallized from appropriate solvents.

5a Colourless needles from ethanol, m.p. 108°C, yield 26 %.
Anal. calcd. for $C_{18}H_{18}F_6N_2O_2S_2$ (472,47): C, 45,76; H, 3,84; N, 5,93; S, 13,57. Found: C, 45,2; H, 3,9; N, 5,9; S, 13,3.
IR (nujol, cm^{-1}) 3270 (NH), 1650 (CO), 1080-1150, 750 (CF_3). ^{19}F-NMR δ = -42,80 ppm (s), δ = -38,27 ppm (s). ^1H-NMR δ = 2,77-2,96 (m, 4H, CH_2-CH_2); 3,10-3,19 (m, 2H, CH_2-N, J = 3,3 Hz); 3,36-3,45 (m, 2H, CH_2-N, J = 3,3 Hz); 3,62-3.70 (m, 2H, CH_2-O, J=3,3 Hz); 3,72-3,81 (m, 2H, CH_2-=, J=3,3 Hz); 7,15-7,49 (m, 5H arom.); 7,94 (s, 1H, NH). ^{13}C-NMR C-1, 153,47 ppm; C-2,



70,55 ppm; C-3, 34,98 ppm; C-4, 35,83 ppm; C-5, 114,60 ppm; morpholine ring 50,01 ppm (2C, $\underline{C}H_2$-N); 66,49 ppm (2C, $\underline{C}H_2$-O); 129,25 ppm (CF_3); 128,49 ppm (CF_3); 119,81 ppm, 125,32 ppm, 136,54 ppm (C arom.); 167,72 ppm (CO). MS (m/z, %) 472 (91) M^+, 403 (22), 371 (91), 352 (35), 284 (83), 278 (100), 250 (26), 214 (29), 209 (49), 208 (52), 182 (30), 120 (48), 92 (34), 77 (63).

5b Colourless needles from petroleum ether, m.p. 120-122°C, yield 28%. Anal. calcd. for $C_{18}H_{17}ClF_6N_2O_2S_2$ (506,92): C, 42,65; H, 3,38; N, 5,53; S, 12,65. Found: C, 42,5; H, 3,3; N, 5,5; S, 12,8. IR (nujol, cm^{-1}) 3280 (NH), 1650 (CO), 1090-1150, 750 (CF_3). ^{19}F-NMR δ=-42,57 ppm (s), -38,18 ppm (s). ^{1}H-NMR δ= 2,75-2,95 (m, 4H, CH_2-CH_2); 3,08-3,17 (m, 2H, CH_2-N, J=3,4 Hz); 3,32-3,40 (m, 2H, CH_2-N, J=3,4 Hz); 3,62-3,80 (m, 4H, CH_2-O-CH_2, J=3,4 Hz); 7,25-7,45 (m, 4H arom.); 8,01 (s, 1H, NH). MS (m/z, %): 506 (83) M^+, 437 (20), 407 (30), 405 (76), 352 (36), 284 (86), 278 (100), 250 (28), 210 (25), 209 (48), 208 (54), 182 (29), 126 (34), 97 (25).

6a Pale yellow prisms from methanol, m.p. 135-137°C, yield 21%. Anal. calcd. for $C_{18}H_{21}F_3N_2O_2S$ (386,44): C, 55,95; H, 5,48; N, 7,25; S, 8,30. Found: C, 55,4; H, 5,4; N, 7,2; S, 8,9. IR (nujol, cm^{-1}) 3180 (br. NH), 1650 (CO), 1080-1150, 750 (CF_3). ^{19}F-NMR δ= -41,52 ppm (s). ^{1}H-NMR δ=1,85-1,88 (m, 2H, CH_2); 2,17-2,20 (m, 2H, CH_2); 2,84 (d, 2H, CH_2); 3,14-3,18 (m, 4H, CH_2-N-CH_2); 3,75-3,81 (m, 4H, CH_2-O-CH_2); 4,35 (br. s, 1H,CH); 7,08-7,65 (m, 5H arom.); 10,51 (s, 1H, NH). MS (m/z, %) : 386 (9) M^+, 294 (80), 293 (36), 285 (30), 193 (32), 192 (100), 77 (26).

6b Pale yellow prisms from methanol, m.p. 126°C, yield 26%. Anal. calcd. for $C_{18}H_{20}Cl\ F_3N_2O_2S$ (420,88): C, 51,37; H, 4,79; N, 6,66; S, 7,62. Found: C, 51,0; H, 4,6; N, 6,5; S, 7,7.

IR (nujol, cm^{-1}) 3170 (br. NH), 1650 (CO), 1080-1150, 750 (CF_3). ^{19}F-NMR δ= -41,54 ppm (s). ^{1}H-NMR δ=1,55-2,30 (m, 4H, CH_2-CH_2); 2,70-3,00 (m, 2H, CH_2); 3,10-3,25 (m, 4H, CH_2-N-CH_2); 3,70-3,90 (m, 4H, CH_2-O-CH_2); 4,40 (br. s, 1H, CH); 7,30-7,70 (m, 4H arom.); 10,60 (s, 1H, NH). MS (m/z, %): 420 (5) M$^+$, 319 (22), 294 (100), 293 (22), 193 (30), 192 (83).

9a Pale yellow prisms from methanol, m.p. 153°C, yield 50%. Anal. calcd. for $C_{20}H_{19}F_3N_2O_2S$ (408,44): C, 58,81; H, 4,69; N, 6,86; S, 7,85. Found: C, 58,9; H, 4,7; N, 7,2; S, 8,4. IR (nujol, cm^{-1}) 3290 (NH), 1630 (CO), 1090-1150, 750 (CF_3). ^{19}F-NMR δ= -47,72 ppm (s), -48,24 ppm (s). ^{1}H-NMR δ= 3,34-3,37 (m, 4H, CH_2--N-CH_2 , J=5,2 Hz); 3,75-3,79 (m, 4H, CH_2-O-CH_2, J=5,2 Hz); 7,05-7,60 (m, 10H arom.); 8,43 (s, 1H, NH). MS (m/z, %) 408 (14) M$^+$, 339 (20), 316 (100), 134 (29).

9b Pale yellow prisms from methanol, m.p. 161°C, yield 54%. Anal. calcd. for $C_{20}H_{18}ClF_3N_2O_2S$ (442,89): C, 54,24; H, 4,09; N, 6,33; S, 7,24. Found: C, 54,3; H, 4,1; N, 6,6; S, 7,6. IR (nujol, cm^{-1}) 3340 (NH), 1630 (CO), 1080-1140, 740 (CF_3). ^{19}F-NMR δ= -47,78 ppm (s), -48,34 ppm (s). ^{1}H-NMR δ= 3,34-3,38 (m, 4H, CH_2-N-CH_2, J=5,2 Hz); 3,76-3,80 (m, 4H, CH_2-O-CH_2, J=5,2 Hz), 7,26-7,56 (m, 9H arom.), 8,43 (s, 1H, NH). MS (m/z, %): 442 (0,8) M$^+$, 317 (17), 316 (100), 134 (21).

8a Colourless prisms from petroleum ether, m.p. 83-84°C, yield 45 %. Anal. calcd. for $C_{15}H_{16}F_3NO_2S$ (331,36): C, 54,37; H, 4,87; N, 4,23. Found: C, 54,4; H, 5,1; N, 4,2. IR (nujol, cm^{-1}) 3340 (NH), 1670 (br. CO), 1080-1150, 740 (CF_3). ^{19}F-NMR δ= -39,03 ppm (s). ^{1}H-NMR δ= 1,40-2,35 (m, 8H, CH_2); 2,60-2,75 (m, 1H, CH); 2,80--3,00 (m, 1H, CH); 7,10-7,60 (m, 5H arom.); 8,80 (s, 1H, NH). MS (m/z, %): 331 (48) M$^+$, 212 (100), 202 (39), 143 (50), 120 (22), 93 (63), 81 (69), 77 (45), 65 (24), 55 (39).

8b Colourless needles from n-pentane, m.p. 93-95°C, yield 27%. Anal. calcd. for $C_{15}H_{15}ClF_3NO_2S$ (365,80): C,49,25; H, 4,13; N, 3,83. Found: C, 49,3; H, 4,4; N, 3,9. IR (nujol, cm^{-1}): 3280 (NH), 1670 (br. CO), 1100-1150, 750 (CF_3). ^{19}F-NMR δ= -38,67 ppm (s). ^{1}H-NMR δ=1,65-1,90 (m, 6H, CH_2); 2,25-3,10 (m, 4H, CH_2);

7,25-7,55 (m, 4H, arom.); 9,00 (s, 1H, NH). MS (m/z, %): 365 (52) M^+, 236 (38), 212 (96), 153 (42), 143 (52) , 129 (28), 127 (100), 125 (23), 111 (30), 99 (26), 81 (92), 55 (70).

Hydrolysis of enamines 6a,b and 9a,b

To a methanolic solution (25 ml) of the appropriate enamine (1 g) 1 ml of conc. hydrochloric acid was added. The completion of the reaction was indicated by the disappearance of the yellowish colour of the solution. In the case of enamines 9a,b it required boiling for 15 min. The cooled solution was poured into ice-water. The precipitate was filtered off and recrystallized from methanol (10a,b) or petroleum ether (7a,b). Average yield 80 %.

7a Colourless needles from petroleum ether, m.p. 89-91°C, yield 74%. Anal. calcd. for $C_{14}H_{14}F_3NO_2S$ (317,33): C, 52,99; H, 4,45; N, 4,41; S, 10,10. Found: C, 53,0; H, 4,4; N, 4,4; S, 10,5. IR (nujol, cm^{-1}) 3270 (NH), 1700, 1670 (CO), 1080-1150, 730 (CF_3) ^{19}F-NMR δ= -38,44 ppm (s). ^1H-NMR δ=1,90-2,65 (m, 6H, CH_2); 2,80--2,90 (m, 1H,CH); 2,90-3,00 (m, 1H,CH); 7,20-7,50 (m, 5H, arom.); 8,50 (s, 1H,NH). MS (m/z, %): 317 (56) M^+, 198 (100), 188 (69), 129 (65), 119 (25), 93 (47), 77 (41), 67 (64).

7b Colourless needles from petroleum ether, m.p. 99-101°C, yield 82%. Anal. calcd. for $C_{14}H_{13}ClF_3NO_2S$ (351,78): C, 47,80; H, 3,73; N, 3,98; S, 9,11. Found: C, 48,0; H, 3,9; N, 4,1; S, 9,2. IR (nujol, cm^{-1}) 3280 (NH), 1700, 1670 (CO), 1080-1150, 760 (CF_3). ^{19}F- NMR δ=-36,90 ppm (s). ^1H-NMR δ= 1,89-2,16 (m, 4H, CH_2); 2,31-2,42 (m, 1H, CH_2); 2,48-2,60 (m, 1H, CH_2); 2,83--2,94 (m, 2H, CH) ; 7,30-7,49 (m, 4H arom,); 8,65 (s, 1H, NH). MS (m/z, %) : 351 (46) M^+, 222 (46), 198 (100), 153 (47), 129 (65), 127 (54), 125 (24), 101 (23), 95 (20), 67 (70), 63 (20), 55 (37).

<u>10a</u> Colourless prisms from methanol, m.p. 115-116°C, yield 86%. <u>Anal</u>. calcd. for $C_{16}H_{12}F_3NO_2S$ (339,34) : C, 56,63; H, 3,56; N, 4,13; S, 9,45. Found: C, 56,7; H, 3,7; N, 4,4; S, 9,8. IR (nujol, cm^{-1}) 3360 (NH), 1610 (CO), 1100-1150, 740 (CF_3). ^{19}F-NMR δ= -46,81 ppm(s). ^{1}H-NMR δ=7,40-7,70 (m, 10H, arom.); 8,70 (s, 1H, NH); 16,6 (s, 1H, =C-OH). MS (m/z, %): 339 (24) M^+, 105 (81), 93 (100), 77 (52).

<u>10b</u> Colourless prisms from methanol, m.p. 141-142°C, yield 81%. <u>Anal</u>. calcd. for $C_{16}H_{11}ClF_3NO_2S$ (373,78) : C, 51,41; H, 2,97; N, 3,75; S, 8,58. Found: C, 51,1; H, 3,0; N, 3,6; S, 9,1. ^{19}F-NMR δ= -46,81 ppm (s). ^{1}H-NMR δ=7,40-7,60 (m, 9H, arom.); 8,7 (s, 1H, NH); 16,50 (s, 1H, =C-OH). MS (m/z, %) : 373 (20), M^+, 129 (32), 127 (100), 105 (80), 77 (46).

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