Transesterification of glycidic esters using Flow Chemistry and their applications as ingredients in flavors and fragrances

Prasad Rao K.R.K.[1,2] and Sharma G. Veera Raghava[1*]
1. Department of Chemistry, School of Science, GITAM (Deemed to be) University, Visakhapatnam 530045, AP, INDIA
2. Prasad Organics Pvt. Ltd., Ongole, Andhra Pradesh, INDIA
*sganapav@gitam.edu

Abstract
Esters find a significant place in the aroma industry, particularly ethyl phenyl glycidate is proven to be an important ingredient/intermediate in flavor and fragrances. In the present communication, several new esters were prepared from ethyl phenyl glycidate using tubular flow chemistry and a simple yet high-yielding transesterification methodology. A few other non-glycidate esters were also prepared using the same methodology.

All synthesized products were characterized by NMR, IR, Mass etc. The olfactory property of each new compound was checked and was found to be noteworthy.

Keywords: Transesterification, Flavors and Fragrances, Continuous flow Chemistry, New esters, Characterization.

Introduction

Besides their many applications, esters have been very useful ingredients for flavors and fragrances. Specifically, glycidic esters have been in use for their floral, sweet and fruity fragrance for over a century, ever since they were invented by Darzen around 1905, condensing aldehydes or ketones with chloro esters in the presence of a base.

In this study, several novel ester molecules were made using trans-esterification methods. Taking known glycidic esters like ethyl methyl phenyl glycidate along with different alcohols in the presence of a catalytic amount of sodium ethoxide, novel ester molecules were made in the continuous flow reaction system of the laboratory.[1-3,5-7]

We have focused on designing experimental protocols for making novel ester molecules and have established their structures using spectral data. Some novel molecules have exhibited interesting fragrance and flavor characteristics of fruity and sweet odors. In recent years, the tubular flow process has become one of the most popular technologies that can significantly improve the existing manufacturing processes.

This tubular flow technology involves a safe process, precise control of reaction variables, occurrence of process conditions under high pressure and high temperature (process intensification), high reproducibility, automation, compliance of production scale, line of purification and smaller size of manufacturing area. Continuous flow technology has been successfully applied in active pharmaceutical manufacturing. In the present study, we have used this technology to obtain the desired products in high yields.[6]

Material and Methods

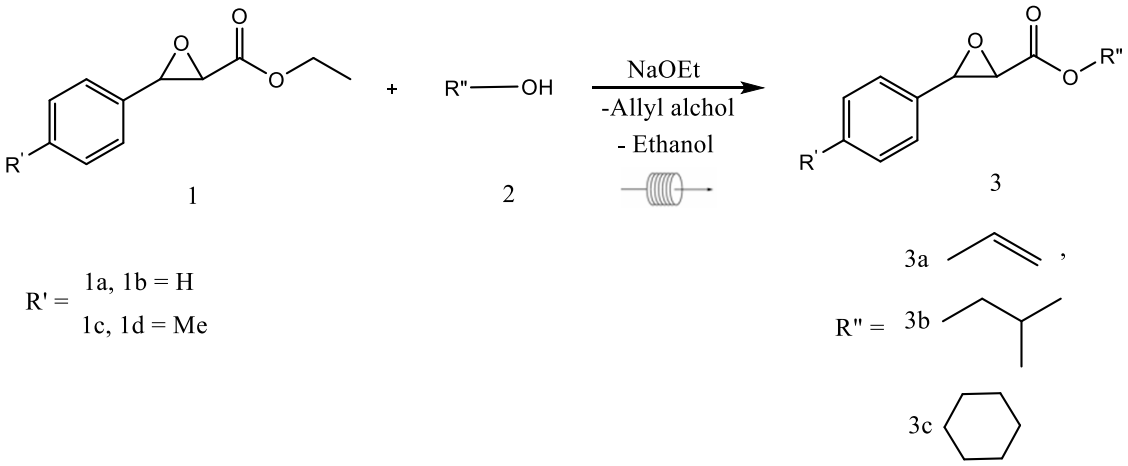
Experimental: Chemicals and reagents were purchased from Aldrich or ACROS and used as such without purification. Solvents are dried by usual methods. The yields and recoveries were based on a single experiment and were not optimized. NMR was recorded on a 500 MHz Jeol instrument using $CDCl_3$ or DMSO-D6 as solvents. IR was recorded on FT-IR, while mass was recorded using LC-MS. Typical experimental procedures and analyses are given as representative examples.

Synthesis of ethyl 2- (2-phenylpropoxy) acetate

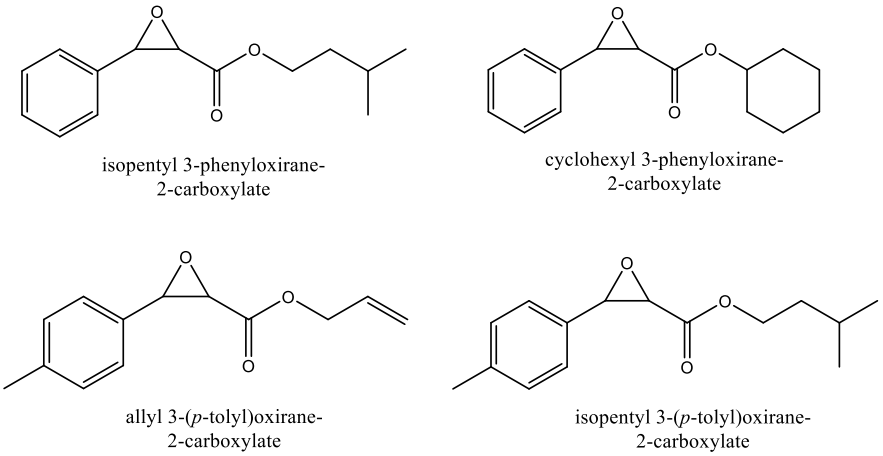
Procedure: Experiments are conducted initially on a gram scale and then scaled up to 500 gms. For example, 500 grams of Ethyl Methylphenylglycidate and 2500 grams of Allyl alcohol in a 1:5 ratio. Passing the glycidic ester and alcoholic solution of a catalytic amount of 10 grams of sodium ethoxide from different pumps into a tubular reactor at about 100 degrees and recirculating for one hour. Then, the excess allyl alcohol and ethanol were distilled off. Once the temperature reached 130 degrees, indicating the end of alcoholic distillation, the reaction mixture was drawn out and cooled to room temperature.

1500 Grams of water were added and the pH was adjusted to 7 using acetic acid. The reaction mixture was transferred to a separating funnel and the aqueous layer was drained after shaking well and settling for 30 minutes. A second wash was given with 1000 grams of water to eliminate all the inorganics. The resultant crude was distilled under a high vacuum with a 2-foot fractional column. Other compounds are prepared using similar procedures.

Synthesis of isopentyl 3-phenyloxirane-2-carboxylate:
^{1}H NMR δ (DMSO-d_6): 7.35 (m, 5H.), 4.18 (m, 1H.), 4.05 (t, 1H, J_1 = 3.8 Hz), 3.97 (m, 1H), 1.94 (m, 2H), 1.65 (m, 1H), 1.50 (s, 1H), 1.50 (m, 1H), 0.88 (d, 6H, J_1 = 6.9 Hz), 0.92 (d, 3H, J_1 = 6.9 Hz).**^{13}C NMR δ ($CDCl_3$):** 167.70, 135.00, 128.62, 128.44, 128.15, 126.28, 63.58, 62.75, 58.96, 36.64, 23.90, 22.16, 21.97. **Mass (m/z):** 234.13 ($M+H^+$). **IR (neat) cm^{-1}:** 2932.23, 2872.45, 1754.9, 1199.51.

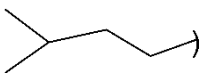
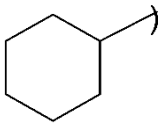
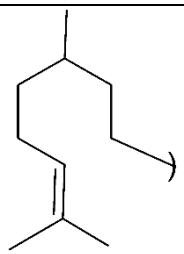
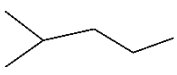
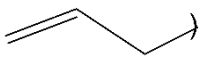


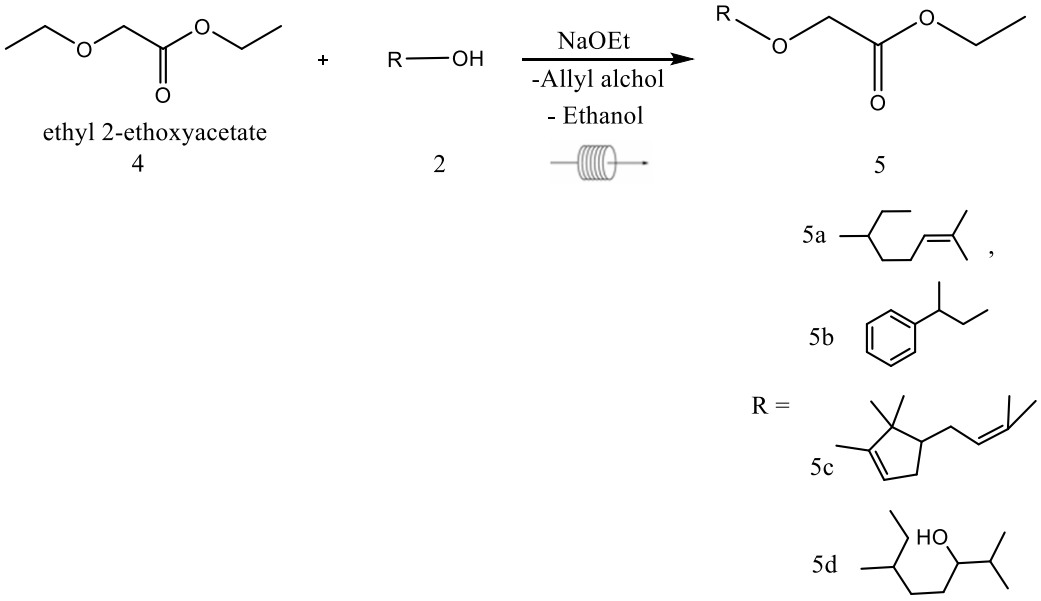
Synthesized compounds:



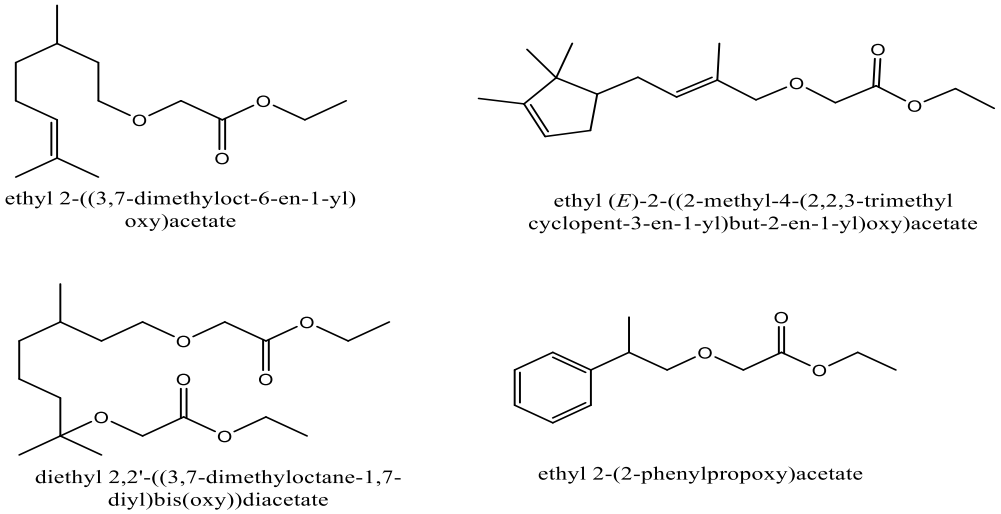
Scheme 1: Compounds synthesised using the methodology

Table 1
Reaction conditions, yields, purity and odour

S.N.	R_1	R_2	Temp. (Deg C)	Time (hrs)	Yield (%)	Purity (%) and Odour
1	H		120	8	92	97 Strawberry Fruity
2	H		130	8	89	95 Fruity
3	H		120	8	91	96 Mild Strawberry Fruity
4	Me		120	8	92	97 Strawberry Fruity
5	Me		120	7	93	97 Fruity

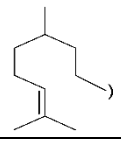
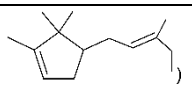
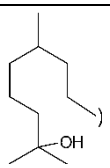
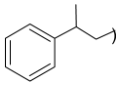


Synthesized compounds:



Scheme 2: Compounds synthesised using the methodology

Table 2
Reaction conditions, yields, purity and odour

S.N.	R	Temp.	Time	Yield(%)	Purity (%) and Odour
1		120-140 deg C	8 hrs	91	97 Mild floral fruity rosy
2		152 deg C	8 hrs	78	96.5 Mild Sandal Fruity, Woody
3		165 deg C	10 hrs	19.7	97 Sweet, Oil Fruity
4.		130 deg C	7 hrs	81	97.5 Fruity Sweet

Synthesis of cyclohexyl 3-phenyloxirane-2-carboxylate:
^{1}H NMR δ (DMSO-d_6): 7.49 (m,2H.), 7.31 (m, 3H.), 4.83 (m, 1H), 4.38 (d, 1H, J_1 = 4.8 Hz), 3.78 (d, 1H, J_1 = 1.4 Hz), 1.75 (m, 4H), 1.29 (m, 1H). **^{13}C NMR δ ($CDCl_3$):** 167.03, 136.56, 130.40, 130.32, 128.40, 127.08, 73.44, 56.97, 56.01, 30.86, 24.72, 23.05, 22.94. **Mass (m/z):** 246.13 ($M+H^+$). **IR (neat) cm^{-1}:** 2932.23, 2871.49, 1728.87, 1196.61.

Synthesis of ethyl 2- (2-phenylpropoxy) acetate:
^{1}H NMR δ (DMSO-d_6): 7.30 (m, 4H), 7.22 (m, 1H), 4.19 (d, 2H J_1 = 3.4 Hz), 4.01 (s, 2H), 3.41 (q, 2H, J_1 = 7.1Hz), 3.08 (m, 1H), 1.23 (d, 3H, J_1 = 6.9 Hz), 1.07 (t, 3H, J_1 = 7.2 Hz). **^{13}C NMR δ ($CDCl_3$):**170.21, 142.59, 128.22, 126.47, 126.98, 69.15, 67.65, 66.77, 38.63, 17.12, 14.71. **Mass(m/z):** 222.13 ($M+H^+$). **IR (neat) cm^{-1}:** 3648.66, 2975.62, 1755.87, 1133.94.

Synthesis of diethyl 2,2'-((3,7-dimethyloctane-1,7-diyl)bis(oxy))diacetate:
^{1}H NMR δ (DMSO-d_6): 4.24 (s, 14H.), 4.07 (s, 4H.), 3.49 (q, 2H, J_1 = 6.9 Hz), 11.73 - 1.66 (m, 2H), 1.56 – 1.53 (m, 1H), 1.46 – 1.41 (m, 4H), 1.25 (s, 6H),51.20 (s, 6H), 1.18 – 1.15 (m, 2H), 0.92 (d, 3H, J_1 = 6.9 Hz). **^{13}C1NMR1δ ($CDCl_3$):** 170.29, 70.32, 67.67, 21.24, 66.75, 62.93, 43.71, 37.00, 35.06, 29.41, 28.90, 28.81, 19.09, 14.64. **Mass (m/z):** 346.24 ($M+H^+$)**. IR (neat) cm^{-1}:** 3443.28, 2935.13, 2872.45, 1754.9.

Synthesis of ethyl 2-((3,7-dimethyloct-6-en-1-yl)oxy)acetate:
^{1}H NMR δ (DMSO-d_6): 5.06 (m, 1H), 4.21 (m, 2H), 3.93 (m, 2H), 3.63 (t, 2H), 1.88 (m, 2H), 1.64 (s, 6H), 1.53 (m, 2H), 1.28 (m, 2H), 1.01 (m, 1H), 0.88 (d, 3H, J_1 = 10.7 Hz). **^{13}C1NMR1δ:** 166.43, 139.72, 128.42, 72.78, 63.25, 61.00, 47.85, 36.35, 28.74, 25.39, 24.78, 19.02, 17.37, 16.47. **Mass (m/z):** 242.20 $(M+H)^+$ **IR(neat) cm^{-1}:** 2965.98, 2915.84, 1756.83.

Results and Discussion

The present investigation focuses on developing commercially viable transesterification procedures for making value-added products used in the fragrance and flavor industry. Traditionally, glycidic esters are the preferred choice and the same is used in the present work. The glycidic ester is treated with an alcohol in the presence of sodium ethoxide in a tubular reactor for a specified time and temperature until the starting materials are completely consumed. The reaction was subjected to a work-up procedure. Then, the products were characterized using 1HNMR, 13CNMR, IR and LC-MS.

The reactions were optimized under different variables, such as temperature and time. The most optimized conditions are given. During the characterization, proton and carbon signals in NMR spectra are analyzed, particularly for methylene attached to oxygen and carbonyls, methyl groups and aromatic hydrogens. The products are characterized without any doubt using 1HNMR and 13CNMR. IR data is analyzed for a carbonyl group of esters, while LC-MS data is analyzed for the molecular ion peak to confirm the structure.

The above results clearly indicate the formation of new esters after transesterification in high yields and purity. Further, all the reactions are scalable to large scales to provide products that are highly useful in the flavor and fragrance industry.

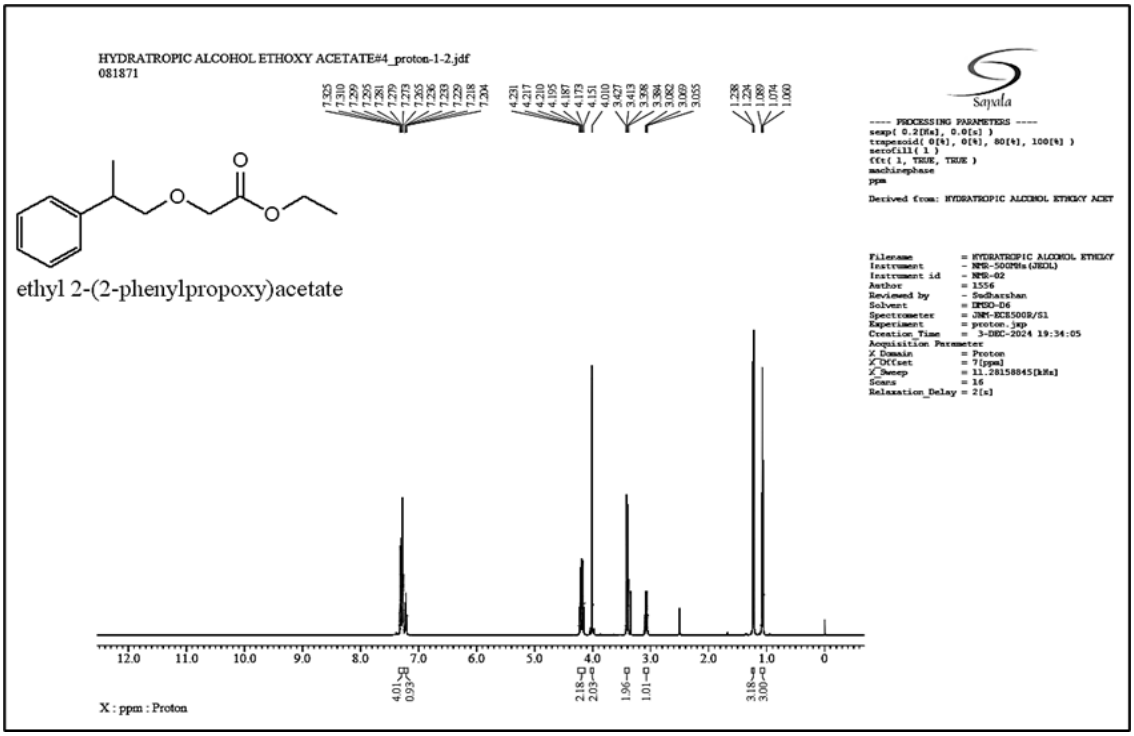


Fig. 1: ^{1}H NMR spectrum

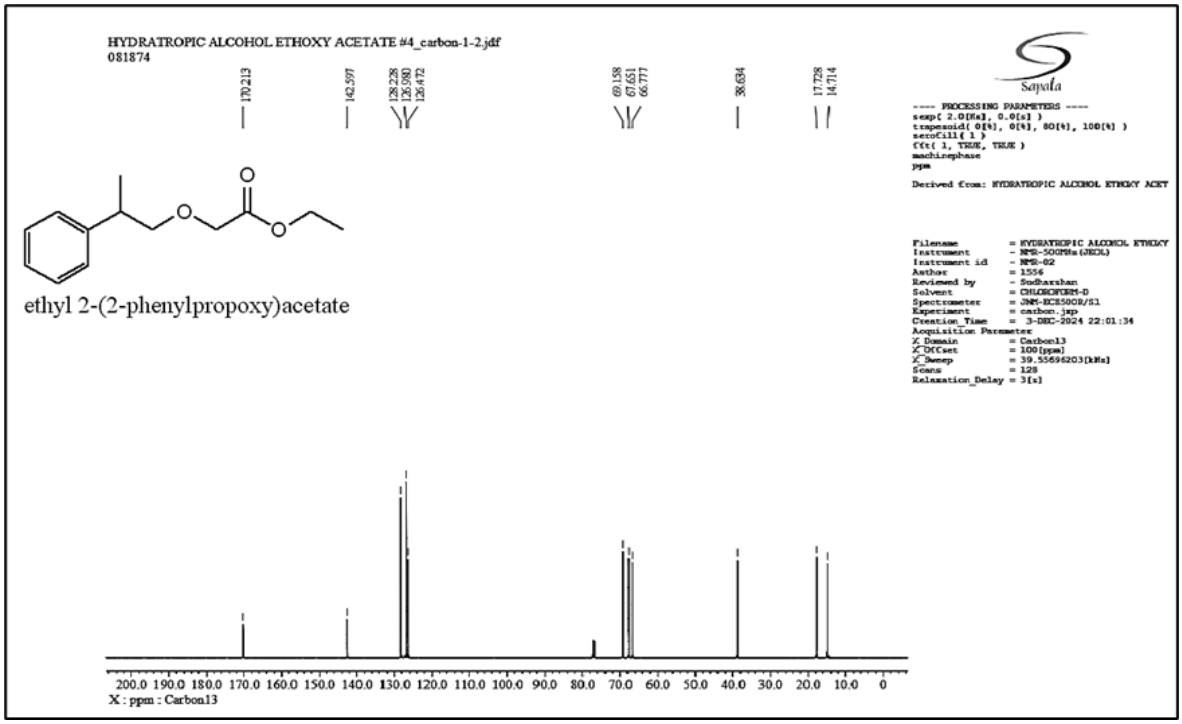


Fig. 2: ^{13}C NMR spectrum

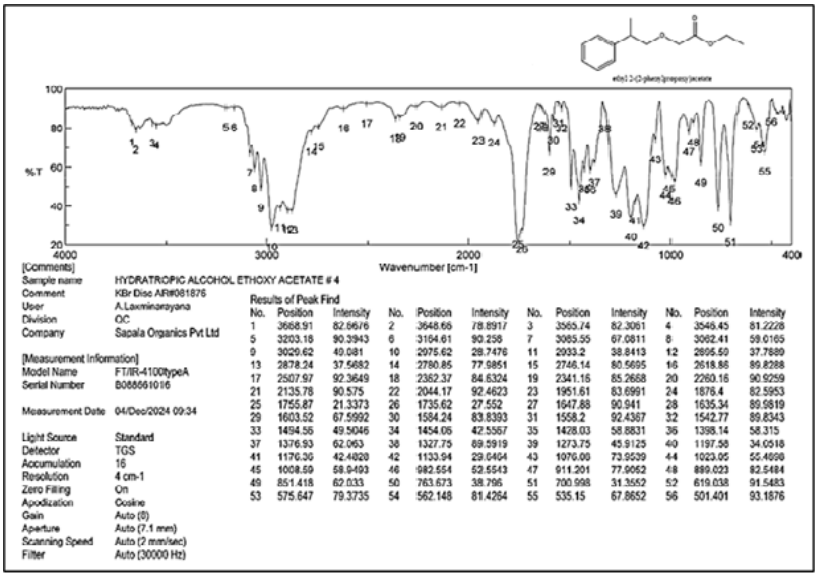


Fig. 3: IR spectrum

Conclusion

In summary, we have presented a simple yet elegant method of transesterification using glycidic esters and ethoxy ethyl acetate using flow chemistry to obtain new esters of importance in the fragrance and flavor industry. The products obtained in high yields were purified and characterized by spectral data. The olfactory properties of the synthesized compounds are impressive. Further, the method can be scaled up to 500 gms and beyond.

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