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ABNORMAL OSMIUM TETROXIDE OXIDATION OF N-METHYLMORPHINAN DERIVATIVES

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Abstract—3-Methoxy-N-methylmorphinan and 3-methoxy-N-methylisomorphinan reacted with osmium tetroxide to give the N-formyl compound and 15,16-dioxo-N-methyl derivative. The structure of these compounds was confirmed by chemical and physical methods.

It is well known that the oxidation of the double bond with osmium tetroxide gives a *cis*-diol. Therefore this reagent is widely used for this purpose. However, in general, it is necessary to protect vulnerable groups such as alcohol, phenol, and amine.

It is reported[1] that β-Δ^6-dihydrodesoxycodeine methyl ether (**1**) reacts with osmium textroxide to give *cis* - 6,7 - dihydroxy - β - tetrahydro - desoxycodeine methyl ether (**2**) in high yield. In this case presence of any other by-products was not described.

We found an abnormal oxidation with this reagent on treatment of N-methylmorphinan derivatives. 3 - Methoxy - N - methylmorphinan (**3**), 3 - methoxy - N - methylisomorphinan (**4**) and 14 - hydroxy - 3 - methoxy - N - methyl - morphinan (**5**) were used as starting materials. Though only the formation of an addition product was anticipated, thin layer chromatography of each crude product obtained from **3** and from **4** showed the presence of by-products in addition to starting material. In the case of the compound **5**, however, only the presence of the starting material was observed, probably because of the H-bonding between the 14-OH group and the N atom.

Since it was clear that a new reaction had occurred, the structure of the reaction products was examined. The reaction of (+) - 3 - methoxy - N - methyl - morphinan **3-a*** with osmium tetroxide gave four compounds besides the starting material.

The oily material obtained in a yield of 2·8% has the molecular formula $C_{18}H_{23}O_2N$ and shows a very strong absorption band based on lactam at 1655 cm^{-1} in the IR spectrum. Furthermore no signal due to N-Me grouping was observed in the NMR spectrum. LAH reduction of this lactam afforded the starting material **3-a** and formylation of (+) - 3 - methoxy - morphinan (**6a**) gave the above-mentioned oily product. These facts mean that the structure of this compound is 3 - methoxy - N - formyl - morphinan (**7**).

The crystalline material (**8a**), m.p. 195–196, obtained in 10% yield shows a levo rotation and the formula $C_{18}H_{21}O_3N$ was given by elementary analysis. This compound shows strong absorption bands at 1732 cm^{-1} and 1670 cm^{-1} in the IR spectrum. NMR study reveals the presence of N-Me group at 3·09 ppm.

These facts suggested that the methylene at C_{16} was oxidized. Huang-Minlon reduction of this compound gave the deoxo compound (**9a**), $C_{18}H_{23}O_2N$, m.p. 117–118°, which shows a strong band characteristic of the 6-membered lactam at 1625 cm^{-1}. Furthermore it was observed that the N-Me signal shifted to 2·94 from 3·09 ppm in the NMR spectrum.

This lactam **9a** was easily converted to the starting 3 - methoxy - N - methylmorphinan **3a** by the action of LAH. Catalytic hydrogenation of the keto-lactam **8a** gave ketol (**10a**), $C_{18}H_{23}O_3N$, m.p. 135·5–136·5°, whose IR spectrum showed a strong band due to the lactam at 1640 cm^{-1}.

Acetylation of **10a** gave monoacetate (**11a**) m.p. 194–195°, which shows strong absorption bands at 1740 cm^{-1} and 1651 cm^{-1} in the IR spectrum and a sharp singlet signal due to a proton attached to the C atom bearing acetoxyl group at ppm 5·31 in the NMR spectrum. LAH reduction of **8a** afforded a hydroxyl compound (**12a**), m.p. 129–130°, whose acetylation gave an acetoxyl compound (**13a**), m.p. 163–164°.

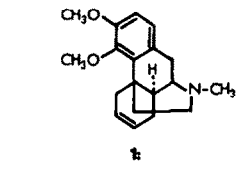
The N-Me signal of the keto-lactam **8** shifted in lower field compared with that of the lactam **9** in the NMR spectrum. This suggests that the lower field shift would be based on anisotropic effect of the oxo group adjacent to the lactam grouping. Accordingly the structure of the ketolactam should be represented as 3 - methoxy - 15, 16 - dioxo - N - methylmorphinan.

Preparative TLC of the product gave an additional two compounds, m.p. 205·5–208° and m.p. 235–235·5°. In the IR spectrum the former showed the absorption bands based on lactam and OH groups and the latter the absorption bands based on CO, lactam and OH groups. The structure of these compounds remains unsolved because of small quantities.

For the purpose of comparison of the reaction behavior, the isomeric (−) - 3 - methoxy - N - methylisomorphinan (**4**) was treated with the same reagent. In this case an oily compound and a crystalline compound, m.p. 168·5–169·5° were separated as non-basic compounds in yields of 2·9% and 17·2%, respectively.

The former showed the strong absorption at 1659 cm^{-1} due to $\rangle N-\overset{\overset{O}{\|}}{C}-$ in the IR spectrum. Formylation of (−) - 3 - methoxyisomorphinan (**14**) afforded the above-mentioned oily material (**15**). The latter has the formula $C_{18}H_{21}O_3N$ and shows the presence of CO and lactam groupings at 1730 cm^{-1} and 1665 cm^{-1} in the IR spectrum and the N-Me signal at 3·10 ppm in the NMR spectrum. Modified Huang-Minlon reduction of the keto-lactam (**16**) did not afford the expected lactam[2] (**17**), but, in a yield of 65%, hydroxylactam (**18**), m.p. 157–158°, which was pre-

*The mark *a* means the compounds of sinomenine series and mark *b* the compounds of thebaine series. All the formulae are shown as the compounds of thebaine series.



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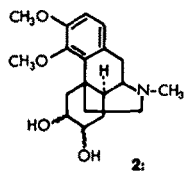

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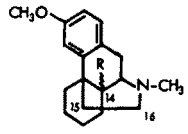

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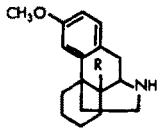
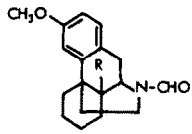
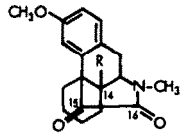
4: R = α-H
5: R = β-OH



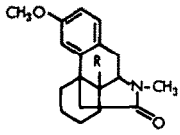
6: R = β-H
14: R = α-H



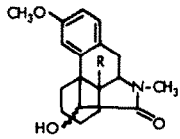
7: R = β-H
15: R = α-H



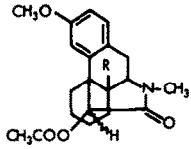
8: R = β-H
16: R = α-H



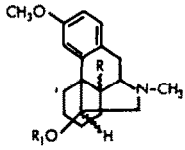
9: R = β-H
17: R = α-H



10: R = β-H
18: R = α-H

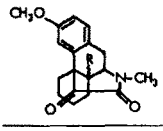
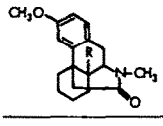
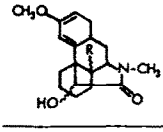
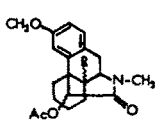
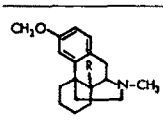


11: R = β-H
19: R = α-H



12: R = β-H R_1 = H
13: R = β-H R_1 = $COCH_3$

Table 1.

	R	IR >C=O	IR >N-C=O	NMR C_{15}-H	NMR >N-CH_3
	β-H	1732 cm^{-1}	1670 cm^{-1}		3.09 ppm
	α-H	1730 cm^{-1}	1665 cm^{-1}		3.10 ppm
	β-H		1625 cm^{-1}		2.94 ppm
	α-H	not isolated.			
	β-H		1640 cm^{-1}	3.86 ppm t like	2.91 ppm
	α-H		1640 cm^{-1}	4.58 ppm d like	2.90 ppm
	β-H	1740 cm^{-1}	1651 cm^{-1}	5.31 ppm	2.91 ppm
	α-H	1742 cm^{-1}	1652 cm^{-1}	5.96 ppm	2.90 ppm
	β-H				2.38 ppm
	α-H				2.31 ppm

pared from **16** by its sodium borohydride reduction. Its monoacetate (**19**), m.p. 206–207°, shows a sharp signal based on the proton attached to a carbon bearing acetoxyl group at 5·96 ppm in the NMR spectrum.

These facts confirm that the structure of the keto-lactam is represented as 3 - methoxy - 15,16 - dioxo - N - methylisomorphinan (**16**).

The reaction of the compounds **3** and **4** with ruthenium tetroxide also gave the above-mentioned products judging from each gas chromatogram.

It is of interest to note that 3 - methoxy - 15,16 - dioxo - N - methylisomorphinan **16** is less reactive compared with isomeric N-methylmorphinan derivative **8**.

EXPERIMENTAL

All m.ps. and b.ps. are uncorrected. IR spectra were obtained in $CHCl_3$ on JASC DS403-G.

NMR spectra were obtained in $CDCl_3$ unless otherwise stated and peaks were measured using TMS as an internal reference.

The reaction of (+) - 3 - *methoxy* - N - *methylmorphinan* (**3a**) *with osmium tetroxide.* A soln of **3a** (7·75 g) and OsO_4 (7·23 g) in 500 ml dry benzene was allowed to stand at room temp for 16 hr. The soln became black and a ppt separated. The mixture was refluxed for 8 hr. The ppt was collected and washed with 100 ml hot benzene. The insoluble material was again refluxed with 240 ml benzene-alcohol (4:1) for 1 hr and the filtrate was combined with the above soln. The residue obtained from the organic layer was extracted with 15% HCl. The crude basic product (3·72 g), m.p. 109·5–110·5°, was not depressed on admixture with starting material **3a**.

The non-basic product (1·441 g) was chromatographed over alumina and developed successively with benzene, benzene-chloroform (1:1) and chloroform. Each product was purified through preparative TLC. The black ppt were dissolved in a mixture of 60 ml pyridine and 200 ml MeOH. The soln was treated with excess H_2S and the ppt was removed. The residue from this soln was taken into 70% MeOH. The insoluble material was removed by filtration and washed with dichloromethane. The residue from the MeOH soln was separated into basic and non-basic compounds as above.

The non-basic product (0·465 g) was purified through preparative TLC and each component was combined with the above-mentioned respective compound.

The oily material **7a**. This compound was purified by distillation to give 0·248 g the oily material, which on standing crystallized, b.p.$_{0.01}$ 185–195° (bath temp). Recrystallization from n-hexane-benzene raised its m.p. to 106·5–107·5°. $[\alpha]_D^{27}$ + 194·7 ± 4·3° (*c*, 0·545, alc); IR, 1655 cm^{-1} (vs). (Found: C, 75·95; H, 8·02; N, 4·76. $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; 4·91%). LAH reduction of this compound in dry THF gave the crystalline material, m.p. 103–107·5°. This compound proved to be (+) **3a** by mixed m.p.

The crystalline material **8a**. This compound was recrystallized from isopropanol to give 0·891 g the pure compound, m.p. 195–196°, $[\alpha]_D^{23}$ – 104·2 ± 2·0° (*c*, 1·017, alc.); IR: 1729 cm^{-1} (s), 1670 cm^{-1} (vs); UV: mμ (ε): 225 (12,400), 255 (4700), 362 (660). NMR: ppm 3·09, 3H (>N-CH_3), 3·78, 3H (OCH_3). (Found: C, 72·44; H, 7·11; O, 16·48; N, 4·69. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; O, 16·03; N, 4·68%).

The substance, m.p. 205·5–208°. Recrystallization of the crude product from isopropanol gave 0·106 g this compound: IR: 3390 cm^{-1} (w), 3180 cm^{-1} (w), 1655 cm^{-1} (vs). (Found: C, 74·37; H, 7·77; O, 13·25; N, 5·03%).

The substance, m.p. 235–235·5°. Recrystallization of the crude product from isopropanol gave 0·102 g this compound; IR: 3380 cm^{-1} (w), 3190 cm^{-1} (w), 1730 cm^{-1} (s), 1682 cm^{-1} (vs). (Found: C, 71·31; H, 5·59; O, 17·64; N, 4·99%).

The same reaction of (−) **3b** afforded (−)-**7b** m.p. 106–107°, $[\alpha]_D^{22.5}$ – 188·1 ± 2·3° (*c*, 1·019, alc.) and (+)-**8b**, m.p. 192·5–193·5°, $[\alpha]_D^{23}$ + 106·6 ± 1° (*c*, 2·032, alc.).

Formylation of (+)-3-*methoxymorphinan* (**6a**). A soln of **6a** (0·529 g) and 5 ml anhydrous formic acid was heated at 130–135° for 3·5 hr. The residue obtained by distillation of the excess reagent was heated at 153–159° for 40 min and extracted with benzene. Removal of the solvent followed by distillation under reduced pressure gave 0·548 g an oily material, which on standing crystallized. Recrystallization from n-hexane-benzene afforded **7a**, m.p. 106–109°, $[\alpha]_D^{27}$ + 194·2 ± 4·0° (*c*, 0·591, alc.). (Found: C, 76·02; H, 8·14; N, 4·84. $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; N, 4·91%).

Huang-Minlon reduction of the compound **8a**. A soln of **8a** (60 mg) and 80% hydrazine hydrate (1·5 g) in 6 g triethylene glycol was heated under N_2 at 120° for 2 hr and 102 mg KOH pellets added to this soln. The mixture was heated under N_2 at 180° for 2 hr, diluted with 20 ml water on cooling and extracted with benzene. Removal of the solvent followed by alumina chromatography developing with benzene gave 43 mg crystalline material **9a**, which was recrystallized from n-hexane-benzene, m.p. 117–118°, $[\alpha]_D^{22}$ – 111·5 ± 2° (*c*, 1·042, alc); IR: 1625 cm^{-1} (vs). (Found: C, 75·41; H, 8·21; O, 11·49; N, 5·22. $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; O, 11·21; N, 4·91%).

LAH reduction of this compound gave (+)-**3a**, m.p. 106–108°.

The reaction of the compound (**8a**) *with 80% hydrazine hydrate.* A soln of **8a** (30 mg) and 80% hydrazine hydrate (0·75 g) in 3 ml triethylene glycol was heated at 125–130° for 4 hr, diluted with water and extracted with benzene. Preparative TLC of the crude product (35 mg) followed by alumina chromatography developing with dichloromethane gave two compounds.

The hydrazone (18 mg) was obtained as an oily material; IR: 3470 cm^{-1}, 3250 cm^{-1}, 1634 cm^{-1} (vs). (Found: C, 69·94; H, 7·47; N, 12·32. $C_{18}H_{23}O_2N_3$ requires: C, 68·98; H, 7·40; N, 13·41%).

The crystalline material (10 mg) was recrystallized from n-hexane-benzene, m.p. 133·5–134·5° (sinterring at 130°); IR: 3500 cm^{-1}, 1640 cm^{-1} (vs). This compound was proved to be identical with the compound prepared by the catalytic reduction of **8a**.

Catalytic reduction of the compound (**8a**). A soln of **8a** (50 mg) in 6 ml AcOH was hydrogenated with Adams' catalyst. The crude basic product (52·5 mg) was chromatographed over alumina developing successively with benzene, benzene-chloroform (1:1) and chloroform. The benzene-chloroform eluate and the chloroform eluate were combined and the residue recrystallized from n-hexane-benzene to give 41 mg the crystalline material **10a**, m.p. 135–136°; $[\alpha]_D^{22}$ + 119·9 ± 2° (*c*, 1·021, alc); IR: 3490 cm^{-1}, 1640 cm^{-1} (vs); NMR: ppm 2·91, 3H (>N-CH_3), 3·76, 3H (OCH_3), 3·86, 1H (C_{15}-H). (Found: C, 71·43; H, 7·89; O, 16·28; N, 4·75. $C_{18}H_{23}O_3N$ requires: C, 71·73; H, 7·69; O, 15·93; N, 4·65%).

This compound (197 mg) was acetylated by the action of 2 ml Ac_2O and 2 ml dry pyridine. The crude acetate **11a** was recrystallized from alcohol, 182 mg, m.p. 194–195°; $[\alpha]_D^{22}$ + 98·5 ± 2° (*c*, 1·068, alc); IR: 1740 cm^{-1}, 1651 cm^{-1} (vs); NMR: ppm 2·17, 3H (-OAc), 2·91, 3H (N-CH_3), 3·76, 3H (OCH_3), 5·31, 1H (C_{15}-H).

Lithium aluminium hydride reduction of the compound (**8a**). To a soln of **8a** (135 mg) in 15 ml dry THF was added 86 mg LAH and the soln refluxed for 2 hr under stirring. To this mixture was again added LAH (48 mg) because of the presence of the unreacted starting material and the reaction continued for additional 2 hrs. After decomposition of the excess reagent with EtOAc, the mixture was extracted with ether and washed with water. The crude non-basic product (26 mg) was proved to be the recovered material.

The basic product (108 mg) was recrystallized from n-hexane-benzene to give 55 mg of **12a**, m.p. 129–130°, $[\alpha]_D^{23}$ + 26·6 ± 2° (*c*, 0·946, alc); IR: 3570 cm^{-1}. (Found: C, 75·14; H, 8·95; N, 4·90. $C_{18}H_{25}O_2N$ requires: C, 75·22; H, 8·77; N, 4·87%).

This compound was acetylated with Ac_2O and pyridine. The crude acetate was recrystallized from isopropanol, m.p. 163–164°, $[\alpha]_D^{22}$ + 17·1 ± 2° (*c*, 1·009, alc). (Found:, 72·53; H, 8·53; N, 4·42. $C_{20}H_{27}O_3N$ requires: C, 72·92; H, 8·26; N, 4·26%).

The reaction of (−) - 3 - *methoxy* - N - *methylisomorphinan* (**4**) *with osmium tetroxide.* A soln of **4** liberated from the picrate (2·03 g) and osmium tetroxide (1·034 g) in 70 ml dry benzene was reacted as in normal morphinan. Treatment as above gave 0·475 g basic and 0·402 g non-basic products.

The basic product was purified as the picrate (0·677 g), m.p. 214–215° and identified as starting **4**.

From the non-basic material, 0·063 g oily and 0·286 g crystalline compounds were separated. The former was purified by distillation, b.p.$_{0.01}$ 170–188° (bath temp). $[\alpha]_D^{23}$ – 156·5 ± 3° (*c*, 0·774, alc); IR: 1659 cm^{-1} (vs). (Found: C, 75·68; H, 8·30; N, 4·79. $C_{18}H_{23}O_2N$ requires: C, 75·75; H, 8·12; N, 4·91%).

The IR spectrum was identical with that of (−)-**15** described below.

The latter compound (**16**) was purified by recrystallization from isopropanol, m.p. 168·5–169·5°, $[\alpha]_D^{22}$ + 148·8 ± 2° (*c*, 1·040, alc); IR: 1730 cm^{-1} (s), 1670 cm^{-1} (vs). (Found: C, 72·03; H, 7·26; O, 16·31; N, 4·87. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; O, 16·03; N, 4·67%).

Formylation of (−) - 3 - *methoxyisomorphinan* (**14**). (-)-**14** (228 mg) was dissolved into 2 ml anhyd formic acid and the excess reagent was removed by distillation under reduced pressure. The residue was heated at 155–160° for 1 hr. Dilution with water and extraction with benzene gave 241 mg the crude material, which was purified by distillation, b.p.$_{0.005}$ 190–200°, $[\alpha]_D^{24}$ – 144·5 ± 2° (*c*, 1·025, alc).

Modified Huang-Minlon reduction of the compound (**16**). Huang-Minlon reduction of this compound was carried out at 180–190° for 1 hr. Gas chromatogram of the crude product showed the presence of the starting material together with the reduction product in a ratio of 38:62. Therefore the reduction was achieved as follows.

A soln of **16** (0·09 g) 80% hydrazine hydrate (1·12 g) and hydrazine hydrochloride (0·104 g) in 4·5 g triethylene glycol was heated at 130° for 1 hr under N_2. KOH pellets (0·4 g) was added on cooling and the mixture heated at 180–190° for 1 hr. The mixture was diluted with water and extracted with benzene. The crude product (0·084 g) was recrystallized from ether to give 0·058 g the

Table 2.

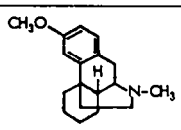
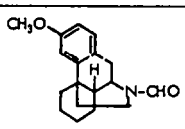
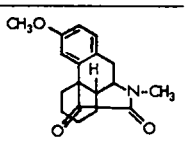
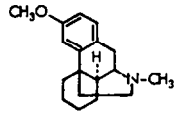
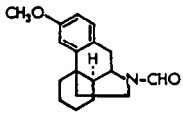
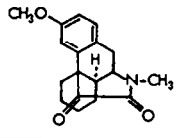
		X	Y		
Substance A	24.9%	4.3%	2.9%	68.4%	0
Substance B	89.4%	2.8%	4.3%	3.0%	0
Substance C	0	0	0	94.4%	5.6%

Table 3.

		X	Y		
Substance A	22.1%	5.8%	+	69.4%	2.8%
Substance B	45.2%	7.9%	0	7 %	1.5%
Substance C	0	0	0	79.3%	20.7%

crystalline material, m.p. 156·5–157·5°; IR: 3500 cm^{-1}, 1640 cm^{-1} (vs). This compound was identified to be the following hydroxy lactam **18** by mixed m.p.

Sodium borohydride reduction of the compound **16**. A soln of **16** (0·15 g) and sodium borohydride (0·08 g) in 7·5 ml alcohol was allowed to stand overnight and the solvent removed by distillation. The residue was diluted with water and made acidic with 5% AcOH to destroy the excess reagent. The soln was extracted with benzene and washed with water. TLC showed the presence of two new compounds. The crude product (0·167 g) was purified by two recrystallization from isopropanol, m.p. 157–158°, $[\alpha]_D^{21.5}$ – 133·6 ± 2° (*c*, 1·074, alc); IR: 3508 cm^{-1}, 1640 cm^{-1} (vs). (Found: C, 71·80; H, 7·67; N, 4·70. $C_{18}H_{23}O_3N$ requires: C, 71·73; H, 7·69; N, 4·65%). Epimeric another hydroxylactam was not isolated because of small quantity.

The above-mentioned **18** was acetylated by the action of Ac_2O and pyridine. The crude acetate m.p. 201–203° was recrystallized from isopropanol to give needles, m.p. 199–200·5° and plates, m.p. 205–206°. The former melted at 206–207° after being kept on standing for two weeks. $[\alpha]_D^{23}$ – 107·7 ± 1° (*c*, 2·080, alc). NMR: ppm 2·11, 3H (OAc), 2·90, 3H ($N\text{-}CH_3$), 3·47, 1H (t C_9-H), 3·74, 3H (OCH_3), 5·96, 1H (s C_{15}-H). (Found: C, 69·70; H, 7·48; N, 4·27. $C_{20}H_{25}O_4N$ requires: C, 69·95; H, 7·33; N, 4·08%).

The reaction with ruthenium tetroxide

(a) *The reaction of* (–) - 3 - *methoxy* - N - *methylmorphinan* **3b**. To a soln of **3b** (200 mg) in 5 ml CCl_4 was added dropwise a soln of ruthenium tetroxide (98 ml) in 29 ml the same solvent. The reaction was exothermic and a black ppt immediately began to separate The mixture was allowed to stand overnight at room temp. The ppt were collected by filtration and washed with CCl_4. Removal of the solvent from the soln gave 144 mg oily material A. The insoluble material was extracted with 5 cc 15% HCl and 10 cc CCl_4 under vigorous stirring. From these solns the basic product B (9 mg) and the non-basic product C (13 mg) were obtained. These three products were compared with respective standard by gas chromatography and the result was shown in Tables 2 and 3.

(b) *The reaction of* (–) - 3 - *methoxy* - N - *methylisomorphinan* **4**. The compound **4** (270 mg) was reacted with ruthenium tetroxide as above and the mixture separated giving 212 mg oily material A, 15·5 mg basic product B and 20 mg non-basic product C.

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