

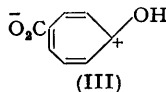
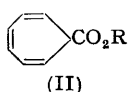
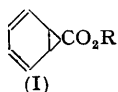
855. *Synthetic Experiments in the cycloHeptatrienone Series. Part II.* 4-Ketocycloheptatrienecarboxylic Acid.*

By J. R. BARTELS-KEITH, A. W. JOHNSON, and A. LANGEMANN.

The reaction of anisole with ethyl diazoacetate has been investigated as the simplest example of the synthesis of *cycloheptatrienone* derivatives by the ring expansion of aromatic compounds. Hydrolysis of the ester mixture yields mainly 4-methoxycyclohepta-1:3:5-trienecarboxylic acid together with some phenoxyacetic acid, and the action of bromine on the former acid gives 4-ketocycloheptatrienecarboxylic acid, characterised by spectra and its rearrangement with alkali to terephthalic acid. The structure of the 4-methoxyacid follows from the formation of anisic acid by hydrolysis of the ozonolysis product. By a similar degradation 4-ethoxycyclohepta-1:3:5-trienecarboxylic acid, obtained from the methoxy-compound by trans-etherification, yields *p*-ethoxybenzoic acid.

APPLICATION of the diazoacetic ester method of ring expansion of aromatic compounds to the synthesis of tropolones from veratrole and its substitution products has been described in an earlier paper.* The mixed esters produced were only partially purified and the tropolone was then obtained most satisfactorily by oxidation with bromine. The yields of tropolone esters were low, *e.g.*, 7% overall for tropolone- β -carboxylic ester from veratrole, and it seemed probable that, if the tropolone precursor were isolated and identified, the method might be improved.

The pioneer work of Buchner on the condensation of aromatic hydrocarbons with diazoacetic ester (*Ber.*, 1920, **53**, 865, and earlier papers) has established that the product can contain esters (I; R = Et) of the norcaradiene ([4:1:0]bicycloheptane) type as well as the various *cycloheptatriene* esters (*e.g.*, II). We investigated the case of anisole first,



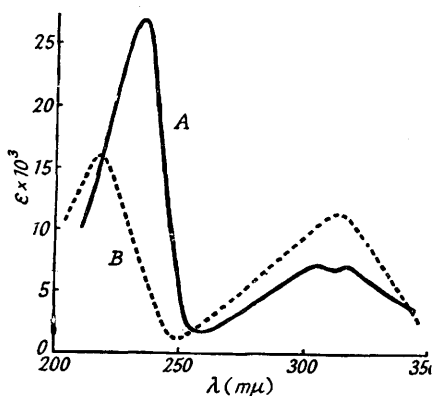
as providing the simplest model of the tropolone synthesis. As expected by analogy with veratrole, anisole reacted with diazoacetic ester, and the product was converted by bromine into a ketocycloheptatrienecarboxylic acid. Since the preliminary announcement of our tropolone synthesis (Bartels-Keith and Johnson, *Chem. and Ind.*, 1950, 677) Doering and Detert (*J. Amer. Chem. Soc.*, 1951, **73**, 876) have briefly described the preparation of *cycloheptatrienone* itself by a route closely related to the present method, *viz.*, the ring enlargement of anisole with diazomethane followed by treatment of the product with bromine. We have prepared pure intermediary compounds from the crude ester mixture by hydrolysis with ethanolic potassium hydroxide. When the hydrolysis product was acidified directly, either of two acids, A, m. p. 144°, or B, m. p. 188°, depending on the method of acidification, was obtained in some 45% yield, together with tarry by-products. Rapid acidification with concentrated acid gave the latter, and cautious addition of dilute acid the former. Acid A had the formula $C_9H_{10}O_3$, corresponding to the expected methoxycyclo-

* *J.*, 1951, 2352, is taken to be Part I of this series.

heptatrienecarboxylic acid or methoxynorcaradienecarboxylic acid; acid B had the formula $C_{10}H_{12}O_3$, and was also obtained from A by means of ethanol and sulphuric acid. The change therefore involved only the replacement of the methoxyl by an ethoxyl group, as was confirmed by oxidation (see below). If, on the other hand, the hydrolysis product was cooled before acidification, potassium phenoxyacetate crystallised. The significance of this product will be discussed in a later paper.

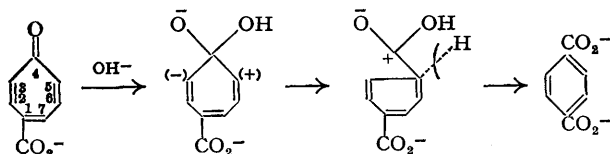
Treatment of acid A or B with bromine gave 4-ketocycloheptatrienecarboxylic acid in high yield. This acid charred but did not melt at 250° , which is in keeping with a tendency to exist in the zwitterion structure (III) as in the case of the pyronecarboxylic acids, and its ultra-violet (see Figure) and infra-red spectra were consistent with the presence of a cycloheptatrienone ring structure.

The position of the carboxyl group in the cycloheptatrienone nucleus was deduced from the formation of terephthalic acid (20%) by the action of aqueous potassium hydroxide; alkaline permanganate also gave terephthalic acid as the sole recognisable product. The mechanism of the alkaline rearrangement bears a formal relation to the benzilic acid change, although an α -diketone is not involved, and the production of terephthalic acid necessitates



Ultra-violet absorption spectra of (A) 4-ketocycloheptatrienecarboxylic acid and (B) 4-methoxycyclohepta-1:3:5-trienecarboxylic acid.

an oxidation at some stage. The initial attack of the hydroxyl ion is probably at $C_{(4)}$ and, in the normal course of the benzilic acid rearrangement, this would be followed by the formation of a bond between $C_{(3)}$ and $C_{(5)}$ with fission of the $C_{(3)}-C_{(4)}$ linkage. The final stage necessitates removal of the $C_{(3)}$ hydrogen atom by oxidation. A mechanism involving attack of the hydroxyl ion at $C_{(3)}$ is also possible, ultimately leading to tropolone- γ -carboxylic acid, which might then undergo rearrangement to terephthalic acid. This possi-

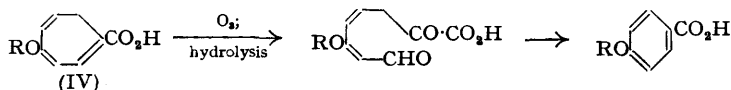


bility is being investigated further. The formation of aromatic carboxylic acids from tropolones by the action of alkali is well established (e.g., Nozoe, *Nature*, 1951, **167**, 1055; Cook and Loudon, *Quart. Reviews*, 1951, **5**, 99) and does not involve oxidation (see also Doering and Knox, *J. Amer. Chem. Soc.*, 1951, **73**, 828). The ease of the rearrangement of 4-ketocycloheptatrienecarboxylic acid which proceeds in alkaline solution at room temperature is in marked contrast to the formation of benzoic acid from tropolone, which requires fusion with potassium hydroxide at 220° . In this case the hydroxyl group has a retarding effect on the change just as carboxyl and nitro-groups favour the formation of aromatic compounds.

The structure of 4-ketocycloheptatrienecarboxylic acid indicates that the methoxy-group (Zeisel) in acid A is also in the 4-position, unless rearrangement occurs during the

bromination, and it will be shown that this is not the case. The structural features of acid A to be determined were therefore the nature of the ring system, whether norcaradiene or cycloheptatriene, and, in the latter case, the position of the double bonds. The ultra-violet absorption spectra of the two acids A and B were very similar but, in the absence of authentic standard compounds, did not permit a choice of ring structure. The infra-red spectra (see Experimental) seemed to offer more promise. Derfer, Pickett, and Boord (*J. Amer. Chem. Soc.*, 1949, **71**, 2482; see also Roberts and Chambers, *ibid.*, 1951, **73**, 5030, 5034; Marrison, *J.*, 1951, 1614) claim that the presence of a cyclopropane ring causes a band in the infra-red spectrum between 1000 and 1030 cm^{-1} , and this appears to hold in certain of the more complex derivatives such as the cyclosteroids (*e.g.*, Barton, *J.*, 1951, 1444). Unfortunately many groups, including enol ethers, absorb in this region of the spectrum, and a band in this position is not characteristic of the cyclopropane ring; thus, although the acids A and B absorb at 1024 and 1034 cm^{-1} respectively, no decision could be taken on this basis (for the related case of cyclooctatetraene see Cope and Burg, *J. Amer. Chem. Soc.*, 1952, **74**, 168).

In the norcaradiene series, structures have been frequently deduced on the basis of the isolation of cyclopropane derivatives from oxidations (cf. Braren and Buchner, *Ber.*, 1901, **34**, 982; Buchner and Hediger, *Ber.*, 1903, **36**, 3502; Drake and Sweeney, *J. Org. Chem.*, 1946, **11**, 67). Ozonisation of the acid A and subsequent alkaline oxidative hydrolysis gave anisic acid; this establishes that acid A cannot be a norcaradiene derivative, as no cyclopropane derivative was obtained; the acid A must therefore contain the cycloheptatriene ring system. It also confirms the relative positions of the methoxyl and carboxyl groups. Finally consideration of the mode of formation of anisic acid leaves only one (IV; R = Me) of the seven possibilities for the position of the double bonds in acid A. It is assumed that the initial oxidative attack is at the double bond $\alpha\beta$ to the carboxyl group, and that, after hydrolysis, the intermediate formyl-keto-acid undergoes an internal aldol cyclisation to the aromatic acid. This novel formation of an aromatic ring from the products of an ozonolysis can therefore be formulated:



The structure of acid B was similarly proved to be (IV; R = Et) by the isolation of *p*-ethoxybenzoic acid after ozonolysis.

Hydrogenation of acid A yielded cycloheptanecarboxylic acid, hydrogenolysis of the methoxyl group having occurred. On the other hand, a similar process gave slightly impure ethoxycycloheptanecarboxylic acid from acid B.

It therefore follows that in this series at least the immediate precursor of the cycloheptatrienone derivative is the methoxycycloheptatrienecarboxylic acid (IV; R = Me), and that good overall yields of the 4-ketocycloheptatrienecarboxylic acid can be obtained if this intermediate product is isolated and purified.

EXPERIMENTAL

M.p.s are uncorrected except where otherwise stated.

Reaction of Anisole and Ethyl Diazoacetate.—Freshly distilled anisole (470 g.) was heated under reflux and ethyl diazoacetate (100 g.) added dropwise during 4 hours. After 10–20 minutes a steady stream of nitrogen was evolved, and the mixture was heated for a further 2½ hours after the addition of all of the ethyl diazoacetate. The excess of anisole was removed at 100° under reduced pressure and the viscous dark brown oil distilled, yielding fractions: (i) b. p. up to 95°/0.4 mm. (6.5 g.), mainly anisole; (ii) b. p. 97–108°/0.4 mm. (60.9 g., 36% calc. on ethyl diazoacetate), a pale yellow oil giving a dark yellow colour with concentrated sulphuric acid; (iii) b. p. 132–150°/0.1 mm. (14 g.), a dark yellow oil giving a brown colour with sulphuric acid; and (iv) a residual brown tar (6.8 g.). Fraction (ii) was used in all of the following hydrolysis experiments.

4-Methoxycyclohepta-1 : 3 : 5-trienecarboxylic Acid; Acid A.—After potassium hydroxide (6.5 g.) in 95% ethanol (50 c.c.) had been shaken with fraction (ii) (10 g.) and kept for 15 minutes

at 0° the colourless potassium salt which had crystallised was separated and dried *in vacuo* (1.3 g.). The filtrate was heated at 100° for 1 hour (slight darkening), cooled, and acidified at 0—5° with 4*N*-hydrochloric acid (100 c.c.). Water (200 c.c.) was added, and the pale yellow precipitate of 4-methoxycycloheptatrienecarboxylic acid separated, washed with water, and dried under reduced pressure. The product (3.45 g.) was recrystallised several times from cyclohexane, forming pale yellow leaflets, m. p. 143—144°. For analysis it was sublimed at 110°/0.05 mm. (Found: C 65.3; H, 5.9. C₉H₁₀O₃ requires C, 65.1; H, 6.1%). Light absorption in light petroleum (b. p. 40—60°): max. at 219 and 313 mμ; log ε 4.21 and 4.04 respectively; min. at 248 mμ; log ε 2.98. The infra-red spectrum of the acid as a mull in Nujol showed absorption maxima at 2631, 2525, 1666s, 1631, 1602s, 1536s, 1440s, 1408, 1335, 1290s, 1257s, 1219s, 1190, 1158s, 1136s, 1083, 1024s, 998, 950, 927, 918, 847, 815s, 788, 775, 765, 728s, and 673s cm.⁻¹ (s = strong absorption). The acid gave a yellow colour with concentrated sulphuric acid, reduced permanganate instantly in alkaline or acid solution, and rapidly decolorised a solution of bromine in chloroform.

4-Ethoxy-1 : 3 : 5-cycloheptatrienecarboxylic Acid; Acid B.—(a) The ester mixture (5 g.) was hydrolysed as in the previous experiment with potassium hydroxide (3.25 g.) in 70% ethanol (30 c.c.). Any potassium salt which precipitated was not separated, and the mixture was heated on the steam-bath for 1 hour and acidified, without cooling, with 6*N*-hydrochloric acid (30 c.c.). The brown precipitate was separated, washed with water, and dried (220 mg.) over phosphorus pentoxide under reduced pressure. A further quantity (115 mg.) was obtained by dilution of the filtrate with water (10 c.c.) and keeping it at 0° overnight. The ethoxy-acid was obtained as colourless leaflets, m. p. 187—188°, by recrystallisation from benzene, and for analysis was sublimed at 150°/0.05 mm. (Found: C, 66.8; H, 6.5. C₁₀H₁₂O₃ requires C, 66.7; H, 6.7%). Light absorption in 95% ethanol; max. at 219 and 314 mμ; log ε 4.20 and 4.05 respectively; min. at 249 mμ; log ε 2.97. The infra-red spectrum of the acid as a mull in Nujol showed absorption maxima at 2631, 2518, 1666s, 1623, 1597s, 1526s, 1438s, 1420, 1402, 1366s, 1328, 1287s, 1259s, 1204s, 1166s, 1129s, 1108, 1083, 1034s, 1004, 961, 927, 908, 889, 841, 830, 808s, 763s, 734s, and 687s cm.⁻¹. The acid gave a yellow colour with concentrated sulphuric acid, instantly reduced permanganate, and rapidly decolorised bromine solutions.

(b) From 4-methoxycyclohepta-1 : 3 : 5-trienecarboxylic acid. Acid A, m. p. 144° (1 g.), was dissolved in ethanol (20 c.c.) containing sulphuric acid (3 drops), and the solution heated on the steam-bath for 30 minutes. Removal of most of the alcohol under reduced pressure caused the precipitation of a light brown solid which was crystallised from benzene, forming nearly colourless leaflets (753 mg.). After sublimation at 140°/0.05 mm. it gave colourless crystals, m. p. 186—188°, not depressed on admixture with acid B prepared by the foregoing method. No solid products were isolated from the mother-liquors.

Phenoxyacetic Acid.—The potassium salt (1 g.) obtained from the alkaline hydrolysis of the ester mixture (see preparation of acid A above) was suspended in ether (30 c.c.) and slowly acidified with concentrated hydrochloric acid (3 c.c.). The ethereal layer was removed, and the solid residue thoroughly extracted with ether (3 × 30 c.c.). The combined ethereal extracts were dried, and the solvent was removed, leaving a brownish residue (537 mg.) which was purified by sublimation at 80°/0.1 mm. and crystallisation from cyclohexane; it formed colourless leaflets, m. p. 99° alone and mixed with an authentic specimen of phenoxyacetic acid (Found: C, 62.9; H, 5.3; OMe, 0.0. Calc. for C₈H₈O₃: C, 63.15; H, 5.3%). The product gave no colour with concentrated sulphuric acid, reduced alkaline permanganate slowly, and did not decolorise bromine in chloroform. The ultra-violet spectrum of a solution in 95% ethanol showed max. at 219, 264, 270, and 276 mμ; log ε 3.83, 3.05, 3.19, and 3.10 respectively (cf. Baly and Collie, *J.*, 1905, 87, 1345). Infra-red spectrum (Nujol mull): max. at 2666, 2557, 1739s, 1703s, 1600s, 1584s, 1499, 1485, 1447s, 1307, 1293, 1283, 1261, 1226s, 1183, 1169, 1157, 1094s, 1071, 1021, 996, 961, 931, 913, 888, 835s, 822, 762, 755s, and 688s.

Ozonolysis of 4-Methoxycyclohepta-1 : 3 : 5-trienecarboxylic Acid.—A stream of ozonised oxygen (containing ca. 1% of ozone) was bubbled through a solution of Acid A (332 mg.) in ethyl acetate (25 c.c.) for 2 hours at 0°. The ozonide was decomposed by the addition of hydrogen peroxide (5 c.c. of 30%) and 2*N*-sodium hydroxide (12 c.c.), and the solution agitated for 2 hours. The aqueous layer was separated, acidified with concentrated hydrochloric acid (3 c.c.), and then extracted with ether (3 × 10 c.c.). After drying and removal of the solvent, the colourless crystals obtained (31 mg.) were recrystallised from water, to give needles, m. p. 183°, not depressed on admixture with an authentic specimen of anisic acid (Found: C, 63.2; H, 5.4. Calc. for C₈H₈O₃: C, 63.15; H, 5.3%).

Ozonolysis of 4-Ethoxycyclohepta-1 : 3 : 5-trienecarboxylic Acid.—As in the previous experi-

ment, acid B (332 mg.) in ethyl acetate (60 c.c.) was ozonised for 2 hours at 0°. Treatment as before gave an acid, m. p. 195°, as colourless leaflets after crystallisation from ethanol. The m. p. was not depressed on admixture with authentic *p*-ethoxybenzoic acid (Found: C, 65.3; H, 6.2. Calc. for C₉H₁₀O₃: C, 65.1; H, 6.1%).

Hydrogenolysis of 4-Methoxycyclohepta-1:3:5-trienecarboxylic Acid.—Acid A (1 g.) in ethanol (100 c.c.) was hydrogenated at room temperature and pressure over Adams's platinum catalyst (25 mg.). After 32 hours the uptake of hydrogen (421 c.c. at N.T.P.) had ceased (405 c.c. required for 3 double bonds). The solvent was removed under reduced pressure, the yellow oily residue dissolved in ether, and the acidic fraction extracted into sodium hydrogen carbonate, and then after acidification back into ether. Removal of the solvent gave the hydrogenated acid as a dark yellow oil (633 mg.) which was distilled at 85°/0.01 mm., to give a pale yellow oil, which did not decolorise bromine or react with tetranitromethane. For identification it was converted into the acid chloride with thionyl chloride and then into the amide, colourless leaflets, m. p. 194° (corr.) (from water) (Found: C, 68.4; H, 10.6. Calc. for C₈H₁₅ON: C, 68.05; H, 10.7%). Willstätter (*Ber.*, 1898, 31, 2504) gives m. p. 195° for *cycloheptanecarboxamide*.

Hydrogenation of 4-Ethoxycyclohepta-1:3:5-trienecarboxylic Acid.—Acid B (544 mg.) in ethanol (100 c.c.) was hydrogenated at room temperature and pressure over Adams's platinum catalyst (25 mg.). After 30 hours the absorption rate was negligible and the uptake of hydrogen (209 c.c. at N.T.P.) slightly less than that required (220 c.c.) for the saturation of 3 double bonds. The product was treated as in the foregoing experiment, and the acid fraction (540 mg.) distilled at 90° (bath-temp.)/0.01 mm., to yield a colourless oil which gave negative unsaturation tests. *4-Ethoxycycloheptanecarboxamide*, prepared as above, formed colourless leaflets, m. p. 127—128°, from water (Found: C, 65.4; H, 10.2. C₁₀H₁₉O₂N requires C, 64.85; H, 10.35%).

4-Ketocycloheptatrienecarboxylic Acid.—(a) Acid A (800 mg.) in chloroform (50 c.c.) was cooled in ice while bromine (0.27 c.c.) in chloroform (5 c.c.) was added during 10 minutes with frequent shaking. The solution darkened slightly and towards the end of the reaction a yellow oil separated which solidified when rubbed. The precipitate (600 mg.) was separated and formed a light grey powder after air-drying. Concentration of the filtrate under reduced pressure with subsequent cooling gave a further quantity (122 mg.) of the product which contained no bromine. Purification was achieved by crystallisation from ethyl acetate (300 c.c.) (charcoal), the acid being obtained as a colourless microcrystalline powder (221 mg.) which charred but did not melt at 235—240°. Larger crystals were obtained by crystallisation from nitrobenzene (Found: C, 64.3; H, 4.4. C₈H₆O₃ requires C, 64.0; H, 4.05%). The acid, which darkened in light, sublimed very slowly, only 5 mg. being obtained at 145°/2 × 10⁻⁵ mm. after 4 days. It was soluble in methanol or ethanol, insoluble in light petroleum, and sparingly soluble in ethyl acetate, ether, acetone, chloroform, or water, but formed a brownish-yellow solution in concentrated hydrochloric acid from which the free acid could be precipitated by dilution. Light absorption in 95% ethanol: max. at 233, 305, and 316 mμ; log ε 4.41, 3.84, and 3.84 respectively; min. at 259 and 311 mμ; log ε 3.19 and 3.83 respectively. The infra-red spectrum of the acid as a mull in Nujol showed absorption maxima at 1709s, 1628s, 1545s, 1422, 1328, 1265s, 1245, 1209s, 1086, 1025, 950, 903, 875s, 847s, 817, 772s, 755s, and 735s cm.⁻¹.

(b) Acid B (1 g.) in chloroform (50 c.c.) was treated at 0° with bromine (0.3 c.c.) in chloroform (2 c.c.) during 5 minutes. After 1 hour the precipitate (718 mg.) was separated and a further quantity (104 mg.) of the product obtained by concentration of the mother-liquors. The acid was purified by crystallisation from ethyl acetate as before and for analysis a small quantity was sublimed at 140°/5 × 10⁻⁴ mm. (Found: C, 63.9; H, 3.7%). The ultra-violet absorption spectrum of a solution in 95% ethanol showed maxima at 233, 305, and 315 mμ (log ε 4.41, 3.84, and 3.85 respectively), and minima at 262 and 311 mμ (log ε 3.25 and 3.83 respectively). Infra-red spectrum (Nujol mull): max. at 1709s, 1628s, 1545s, 1420, 1328, 1265s, 1245, 1210s, 1086, 1026, 950, 903, 875s, 848s, 817, 772s, 756s, and 735s cm.⁻¹.

Action of Alkaline Permanganate on 4-Ketocycloheptatrienecarboxylic Acid.—A solution of this acid (900 mg.) in 95% ethanol (120 c.c.) was treated with a solution of potassium hydroxide (14 c.c. of 45%) and cooled to -5°. A cold solution of potassium permanganate (3.12 g.) in water (150 c.c.) was added dropwise during 80 minutes to the vigorously stirred solution of the potassium salt. The ethanol was then removed on the steam-bath under reduced pressure and the precipitated manganese dioxide separated and washed with a little hot water. The cooled filtrate was extracted with chloroform (6 × 100 c.c.) in order to remove neutral and basic components, and then acidified to pH 2 with 1:1 hydrochloric acid and thoroughly extracted with ether (12 × 100 c.c.). Removal of the solvent from the combined dried ethereal

extract gave a slightly tarry residue (206 mg.) which was extracted with hot dioxan. On cooling, the extract deposited a slightly yellow precipitate of terephthalic acid, which gave a colourless product after sublimation at $130^{\circ}/5 \times 10^{-4}$ mm. which did not melt below 360° (Found: C, 57.5; H, 4.1. Calc. for $C_8H_6O_4$: C, 57.8; H, 3.65%). This with ethereal diazomethane, gave the dimethyl ester, m. p. 139° , not depressed on admixture with authentic dimethyl terephthalate.

Alkaline Rearrangement of 4-Ketocycloheptatrienecarboxylic Acid.—The acid (230 mg.) was added to a solution of potassium hydroxide (1 g.) in ethanol (80 c.c.) and water (20 c.c.), and the mixture which formed a dark red solution after 2 minutes became brownish-yellow on being kept overnight at room temperature. After 1 hour's heating on the steam-bath (no further colour change) the ethanol was removed under reduced pressure and the solid brown residue dissolved in ether and treated with diazomethane. Next day the solvent was removed, and the residue dissolved as far as possible in 4N-sodium carbonate solution and extracted with ether (3×50 c.c.). The solvent was removed from the combined ethereal extracts, and the solid residue sublimed at $120^{\circ}/0.05$ mm., to give colourless crystals (47 mg.) which crystallised from dilute methanol in long needles, m. p. 139.5 — 140° , undepressed on admixture with authentic dimethyl terephthalate (Found: C, 62.0; H, 5.3. Calc. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.2%).

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