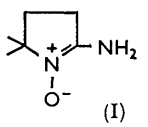
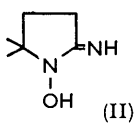
1078. *Tautomeric Behaviour of 2-Amino-5,5-dimethyl-1-pyrroline 1-Oxide.*

By A. R. Forrester and R. H. Thomson.

Acetylation, benzoylation, and methylation of compound (I), named in the title, has been studied. The products are mainly derivatives of the tautomeric imino-structure (II). Benzoylation of the 2-amino-5,5-dimethyl-1-pyrroline (III) has been re-examined.

Reductive cyclisation of 3-methyl-3-nitrobutyl cyanide yields two bases;[1] one was formulated as the amino-*N*-oxide (I) or the cyclic imidoxime tautomeride (II), and the other as the cyclic amidine (III or IV). We have shown by infrared spectroscopy[2] that both compounds exist as 1-pyrroline derivatives (I and III), at least in chloroform solution. Buckley and Elliott[1] reported that the base (I) contained two active hydrogen atoms but " would not react with benzoyl chloride, acetic anhydride, phenyl isocyanate, or *N*-nitro-*N'*-2,4-dinitrophenylurea." As this compound was required for other work[3] re-examination of this surprising lack of reactivity was desirable and we now report the behaviour


(I)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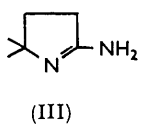
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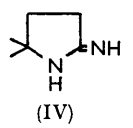
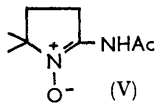

(IV)

of the base (I) with acetic anhydride and benzoyl chloride, and with methylating agents. In our hands all these reacted readily with the amino-*N*-oxide, frequently giving mixtures.

Acetylation.—On addition of acetic anhydride to the base at room temperature an exothermic reaction occurred but no solid product was isolated. Using pyridine as solvent offered no advantage, but acetylation in cold acetonitrile afforded a crystalline monoacetyl derivative that absorbed strongly in the infrared region at 3170, 1705, and 1640 cm.$^{-1}$ (in Nujol). Of the three possible structures, (V) is excluded by the absence of a characteristic secondary amide band in the 1550 cm.$^{-1}$ region,[4] and (VII) seems unlikely as cyclic *O*-acetylhydroxylamines[5] absorb near 1800 cm.$^{-1}$ (cf. XII; R = Ac; $\nu_{max.}$ 1790 and 1700 cm.$^{-1}$). Structure (VI) is therefore preferred. Further acetylation of the monoacetyl compound gave an intractable gum. It is known[6] that 1-pyrroline

[1] Buckley and Elliott, *J.*, 1947, 1508.
[2] Forrester and Thomson, *Spectrochim. Acta*, 1963, **19**, 1481.
[3] Forrester and Thomson, *Proc. Chem. Soc.*, 1962, 360.
[4] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1957.
[5] Loudon and Wellings, *J.*, 1960, 3462.
[6] Kloetzel, Chubb, Gobran, and Pinkus, *J. Amer. Chem. Soc.*, 1961, **83**, 1128.

1-oxides can undergo dehydration to form pyrrolenines in the presence of acetic anhydride and this may be a complicating factor in the present case.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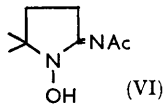
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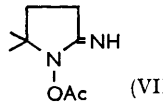
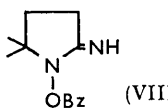

(VII)

Benzoylation.—Reaction with benzoyl chloride in pyridine gave an intractable gum but in cold acetonitrile solution a monobenzoyl derivative was readily isolated as its hydrochloride. This salt showed absorption bands at 1765 and 1700 cm.$^{-1}$, indicating that *O*- and not *N*-benzoylation had occurred. The free monobenzoate therefore has structure (VIII) (cf. XII; R = Bz; $\nu_{max.}$ 1760 and 1705 cm.$^{-1}$); the precise structure of the hydrochloride is uncertain but it could be of the form (I). Under similar conditions, 2-aminopyridine 1-oxide forms an *O*-benzoyl derivative which rearranges to an aromatic *N*-benzoyl compound on crystallisation from alcohol.[7] Attempts to effect a corresponding rearrangement with the benzoate (VIII), which lacks this driving force, were unsuccessful.

Schotten–Baumann benzoylation of the base (I) invariably yielded gums. Best results were obtained by using three mol. of benzoyl chloride and four mol. of sodium hydroxide, which gave another monobenzoyl derivative. This is regarded as the imidoxime (IX) on the basis of its infrared spectrum ($\nu_{max.}$ 3275, 1705, and 1675 cm.$^{-1}$; no absorption at 1550 ± 25 cm.$^{-1}$) and the ease with which it decomposed to benzamide (and other products) when heated in air or in wet solvents. Further benzoylation of the imide (IX) in cold acetonitrile gave a dibenzoyl compound which separated as its hydrochloride, in poor yield. It absorbed strongly at 1755, 1705, and 1680 cm.$^{-1}$, consistently with the *ON*-dibenzoyl structure (X). Schotten–Baumann benzoylation of the base (I) with less benzoyl chloride gave a gum containing benzamide. On a few occasions another crystalline product was isolated, with difficulty and in small amount. This has not been identified but the available results (see Experimental section) suggest that the compound contains a Bz·OC$\leqslant$ group arising from deep-seated rearrangement of the starting material.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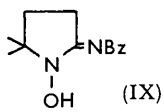
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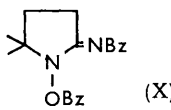
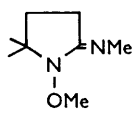

(X)

All the identified products obtained by monoacylation of the base (I) are *N*-substituted derivatives of the tautomer (II), except the benzoate (VIII) which was isolated only as the hydrochloride which could be of the form (I). This accords with the generalisation [8] that *exo*- rather than *endo*-double bonds are favoured in five-membered ring systems, but the factors which determine *O*- or *N*-acylation are not clear. Benzoylation of the amino-pyrroline (III) yields the amide (XVI) (see below) which has an *endo*-double bond.

Methylation.—Treatment of the amino-*N*-oxide with methyl sulphate in aqueous alkali yielded an oil ($\nu_{max.}$ 1720 and 1700 cm.$^{-1}$; no absorption above 3000 cm.$^{-1}$) which proved to be a mixture of two products. On further reaction with methyl iodide and with oxalic acid, the oil gave a methiodide and an oxalate, respectively, of a dimethyl derivative of the base. Distillation of the oil over oxalic acid gave a product showing only one infrared band (1720 cm.$^{-1}$) in the double-bond region. This product was identified as 1-methoxy-5,5-dimethyl-2-pyrrolidone (XII; R = Me) by comparison with authentic material prepared by methylation of the hydroxamic acid (XII; R = H) with methyl sulphate in alkaline solution. The original oil is, therefore, considered to be a mixture of the dimethyl derivative (XI) and the methoxypyrrolidone (XII; R = Me), the latter arising by hydrolysis of the former during the methylation.

[7] Katritzky, *J.*, 1957, 191.
[8] Brown, Brewster, and Shechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.

Methylation of the base (I) with diazomethane gave an oily monomethyl derivative which formed a picrate; the toluene-*p*-sulphonate was obtained directly by methylation with methyl toluene-*p*-sulphonate. The methylated base could be either an *O*- (XIII) or an *N*-methyl derivative (XIV or XV). On treatment with benzoyl chloride in cold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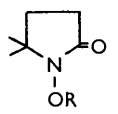
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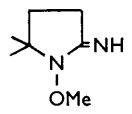
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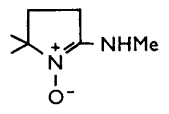
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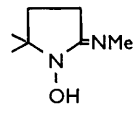
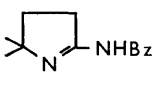

(XV)

acetonitrile it gave the hydrochloride of a monomethylmonobenzoyl derivative ($\nu_{max.}$ 1700 and 1680 cm.$^{-1}$) which afforded benzamide when hydrolysed by boiling in aqueous solution with Raney nickel.[1] The monomethyl derivative therefore has structure (XIII). Both the *O*-methoxy-compound (XIII) and its benzoyl derivative gave low methoxyl values.

2-*Amino*-5,5-*dimethyl*-1-*pyrroline*.—We confirm the previous finding [1] that benzoylation of the aminopyrroline (III) under Schotten–Baumann conditions gives a mono- and a di-benzoyl derivative, together with a third product (which was not identified by Buckley and Elliott [1]). The monobenzoyl compound (best prepared in dry ether) absorbs at 3310, 1610, and 1560 cm.$^{-1}$, and is evidently the secondary amide (XVI). The dibenzoyl derivative shows strong infrared bands at 1670, 1645, and 1630 cm.$^{-1}$, in agreement with structure (XVII); the alternative (XVIII), which has a CO·N·CO grouping, would be expected [4] to absorb in the regions 1790—1720 and 1710—1670 cm.$^{-1}$. The previously unidentified compound, $C_{20}H_{22}N_2O_3$, shows strong bands in the infrared region at 3350,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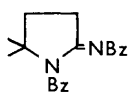
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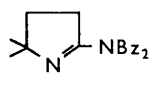
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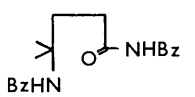
(XIX)

1640, and 1550 cm.$^{-1}$ (secondary amide), and at 3250, 1745, and 1680 cm.$^{-1}$ (CO·NH·CO). These values are consistent with the dibenzoyl structure (XIX). The compound is presumably formed by hydrolysis of the dibenzoyl derivative (XVII) which cannot be isolated if the Schotten–Baumann reaction is prolonged.

Experimental

Reactions of 2-*Amino*-5,5-*dimethyl*-1-*pyrroline* 1-*Oxide*.—(i) *With acetic anhydride*. A suspension of the base (1·28 g.) in acetonitrile (10 ml.) was treated at 0° with acetic anhydride (1 ml.) in the same solvent (10 ml.). The solution was allowed to reach room temperature and left overnight. After addition of solid sodium carbonate, the mixture was filtered and taken to dryness (<40°), and the residue crystallised from benzene–light petroleum (b. p. 50—60°). 2-*Acetylimino*-1-*hydroxy*-5,5-*dimethylpyrrolidine* formed plates, m. p. 150—152° (0·7 g., 41%) (Found: C, 56·5; H, 8·3; N, 16·5. $C_8H_{14}N_2O_2$ requires C, 56·3; H, 8·2; N, 16·5%).

(ii) *With benzoyl chloride*. (*a*) To a suspension of the base (1·28 g.) in acetonitrile (10 ml.), at 0°, a solution of benzoyl chloride (1·4 g.) in the same solvent (10 ml.) was added in small amounts, with shaking, and the mixture was left at room temperature. Next day the product which had separated was collected, and a further quantity was obtained by evaporating the filtrate, below 40°, to a gum which was treated with acetone. The combined solids were crystallised from benzene–light petroleum (b. p. 50—60°) to give 1-benzoyloxy-2-imino-5,5-dimethylpyrrolidine hydrochloride (0·9 g., 34%) as prisms, m. p. 117—119° (Found: C, 58·0; H, 6·4; Cl, 13·4; N, 10·4. $C_{13}H_{17}ClN_2O_2$ requires C, 58·1; N, 6·3; Cl, 13·2; N, 10·4%).

(*b*) Benzoyl chloride (8·43 g., 0·06 mole) was added to an ice-cold solution of the amine (2·56 g., 0·02 mole) and sodium hydroxide (3·2 g., 0·08 mole) in water (30 ml.), and the mixture was shaken for 16 hr. The resultant gum was taken up in benzene which was washed with 2N-sodium hydroxide and water and dried (Na_2SO_4). Evaporation left a gum which was

stirred repeatedly with dry light petroleum (b. p. 100—120°) and then left overnight under the same solvent, whereupon it solidified. Repeated crystallisation from dry benzene–light petroleum gave *2-benzamido-1-hydroxy-5,5-dimethylpyrrolidine* (2·8 g., 60%) as needles, m. p. 83—84° (Found: C, 67·4; H, 6·7; N, 11·6. $C_{13}H_{16}N_2O_2$ requires C, 67·2; H, 6·9; N, 12·05%). A solution of the amide (0·928 g.) in acetonitrile (10 ml.), at 0°, was treated with benzoyl chloride (0·42 g.) in acetonitrile (10 ml.). The mixture was allowed to reach room temperature and left for 24 hr. The product which separated crystallised from methanol–ether to give *2-benzimido-1-benzyloxy-5,5-dimethylpyrroline hydrochloride* (0·28 g.) as needles, m. p. 125—127° (Found: C, 61·3; H, 5·5; Cl, 13·3; N, 7·3. $C_{20}H_{20}N_2O_3,1\frac{1}{2}HCl$ requires C, 61·4; H, 5·5; Cl, 13·6; N, 7·2. Calc. for $C_{20}H_{20}N_2O_3,HCl$: C, 64·4; H, 5·6; Cl, 9·5; N, 7·5. Calc. for $C_{20}H_{20}N_2O_3,2HCl$: C, 58·7; H, 5·4; Cl, 17·35; N, 6·8%). Reproducible analyses were obtained after drying *in vacuo* at room temperature, but at >40° the product lost hydrogen chloride and gave inconsistent results.

(*c*) Benzoyl chloride (30·9 g., 0·22 mole) was added dropwise with stirring, to an ice-cold solution of the amine (12·8 g., 0·1 mole) and sodium hydroxide (10 g., 0·25 mole) in water (200 ml.). Stirring was continued for 16 hr. at room temperature. The resultant gum was extracted with ether (3 × 100 ml.), and the extracts were washed with water, dried (Na_2SO_4), and evaporated, leaving a gum. Treatment with light petroleum gave a little solid material which was crystallised from benzene–light petroleum (b. p. 50—60°) giving, in different experiments, benzamide (m. p., mixed m. p., and infrared spectra), a compound forming needles, m. p. 175—177°, or a mixture of both. The compound, m. p. 175—177° [Found: C, 67·0; H, 6·6; N, 6·0%; *M*, 235 (ebullioscopic in benzene)], $\nu_{max.}$ 3200, 3100, 1720, and 1700 cm.$^{-1}$, dissolved in dilute acid and yielded benzoic acid on hydrolysis; it gave no colour with ferric chloride, and negative tests with Brady's reagent and tetrazolium salts (the tetrazolium test is frequently negative with " cyclic " hydroxylamines.)

(iii) *With dimethyl sulphate.* To a solution of the amine (5 g.) in 15% aqueous sodium hydroxide (20 ml.) at 0°, dimethyl sulphate (20 g.) was added, dropwise, with stirring. Stirring was continued for 48 hr., the temperature being allowed to rise. More sodium hydroxide solution (25 ml.; 40%) was then added and after a further hour's stirring the solution was extracted with ether (3 × 150 ml.), and the extracts were washed with water and dried ($MgSO_4$). Distillation yielded a fraction, b. p. 42—52°/0·2 mm. (2·6 g.), which when warmed with an excess of methyl iodide gave *1-methoxy-2-methylimino-5,5-dimethylpyrrolidine methiodide*; this separated from ethanol–ether in needles, m. p. 132—133° [Found: C, 35·9; H, 6·5; I, 42·5; N, 9·5. $C_9H_{19}IN_2O$ requires C, 36·2; H, 6·4; I, 42·6; N, 9·4%). Oxalic acid in acetone was added to a solution of the distillate in acetone; dilution with ether precipitated *1-methoxy-2-methylimino-5,5-dimethylpyrrolidine oxalate* as very hygroscopic plates, m. p. 143—144° (from acetone–ether) (Found: N, 11·2. $C_{10}H_{18}N_2O_5$ requires N, 11·4%). Evaporation of the initial ethanol–ether mother-liquor left a gum which distilled at 64—65°/1 mm. The infrared spectrum of the distillate was identical with that of 1-methoxy-5,5-dimethyl-2-pyrrolidone prepared as follows. Dimethyl sulphate (15 g.) was added, dropwise, to a stirred solution of 1-hydroxy-5,5-dimethyl-2-pyrrolidone (2·58 g.) in 15% aqueous sodium hydroxide (15 ml.) at 0°. Stirring was continued for 16 hr., the temperature being allowed to rise. More sodium hydroxide solution (20 ml.; 30%) was then added and the mixture was extracted with ether. The extracts were washed with water, dried, and evaporated, leaving a yellow oil. Distillation gave *1-methoxy-5,5-dimethyl-2-pyrrolidone* (2 g., 70%) as a slightly hygroscopic colourless oil, b. p. 63—64°/1 mm. (Found: C, 58·3; H, 9·3; N, 10·0. $C_7H_{13}NO_2$ requires C, 58·7; H, 9·1; N, 9·8%).

(iv) *With diazomethane.* The amine (2·56 g.), in chloroform (100 ml.), was treated at 0° with ethereal diazomethane (*ca.* 5 g.). After 3 days at 0°, more diazomethane (*ca.* 5 g.) in ether was added and the mixture was left for another 3 days at 0°. The solvent was then removed and the residue was treated with dry ether (50 ml.), which precipitated unchanged amine (0·3 g.); this was filtered off. Evaporation of the ether left a yellow oil which was distilled, to give 2-imino-1-methoxy-5,5-dimethylpyrrolidine (1·4 g., 56%) as a colourless hygroscopic oil, b. p. 50—51°/0·7 mm., $\nu_{max.}$ (film) 3450, 3300, and 1670 cm.$^{-1}$ [Found: C, 59·2; H, 9·8; N, 19·5; OMe, 6·0 (18·5% under Herzig–Meyer conditions). $C_7H_{14}N_2O$ requires C, 59·2; H, 9·9; N, 19·7; OMe, 21·8%]. The *picrate* formed lemon-yellow needles, m. p. 152—153° (from aqueous ethanol) (Found: C, 41·8; H, 4·6; N, 18·9. $C_{13}H_{17}N_5O_8$ requires C, 42·0; H, 4·6; N, 18·9%).

(v) *With methyl toluene-p-sulphonate.* The base (1·28 g.) was heated with methyl toluene-*p*-sulphonate (1·86 g.) at 110° for 16 hr. *2-Imino-1-methoxy-5,5-dimethylpyrrolidinium toluene-p-sulphonate* separated on cooling. It crystallised from ethanol–ether as needles, m. p. 157—158° (2·1 g., 67%) (Found: C, 53·7; H, 7·2; N, 8·7; S, 10·4. $C_{14}H_{22}N_2O_4S$ requires C, 53·5; H, 7·0; N, 8·9; S, 10·2%). The toluene-*p*-sulphonate (0·7 g.) was treated with N-ethanolic sodium ethoxide (2·2 ml.), and the precipitate collected. The filtrate was saturated with carbon dioxide and filtered again. Addition of picric acid (0·46 g.) in ethanol to the second filtrate yielded a picrate, m. p. 151—152°, identical (mixed m. p., infrared spectra) with that obtained by diazomethane methylation. The free base was isolated from the toluene-*p*-sulphonate by addition of 10% aqueous potassium hydroxide and extraction with ether. It had b. p. 46—47°/0·6 mm. and an infrared spectrum identical with that of 2-imino-1-methoxy-5,5-dimethylpyrrolidine obtained as in (iv).

Benzoyl chloride (0·14 g.) in acetonitrile (5 ml.) was added, dropwise, to an ice-cooled solution of 2-imino-1-methoxy-5,5-dimethylpyrrolidine (0·28 g.) in the same solvent (5 ml.), with shaking. After 16 hr. at room temperature, the precipitate was collected and the filtrate taken to dryness. The residual oil was triturated with dry ether (10 ml.), and the precipitate filtered off. The combined solids were crystallised from acetonitrile–methanol–ether, giving 2-benzimido-1-methoxy-5,5-dimethylpyrrolidine hydrochloride (0·3 g., 50%) as colourless plates, m. p. 147—148° (Found: C, 55·8; H, 6·9; Cl, 12·1; N, 9·6; OMe, 5·2. $C_{14}H_{19}ClN_2O_2,H_2O$ requires C, 55·9; H, 7·0; Cl, 11·8; N, 9·3; OMe, 10·3%). The hydrochloride (0·1 g.) in water (10 ml.) was boiled with Raney nickel (*ca.* 1 g.) for 3 hr., filtered, and evaporated to dryness under reduced pressure. The residue was extracted with benzene (15 ml.), and the dried extract evaporated, leaving a residue of benzamide, m. p. and mixed m. p. 127—128°, having an infrared spectrum identical with that of an authentic specimen.

Benzoylation of 2-Amino-5,5-dimethyl-1-pyrroline.—(*a*) Benzoyl chloride (1·41 g.) in dry ether (10 ml.) was added, dropwise, to a stirred solution of the amine (1·12 g.) in dry ether (10 ml.), cooled in ice. The solvent was then removed, and the residue was crystallised from 50% aqueous ethanol, to give *2-benzamido-5,5-dimethyl-1-pyrroline* (1·4 g.) as prisms, m. p. 98—99° (lit.,[1] 98°).

(*b*) Benzoyl chloride (5·62 g.) was added, dropwise, with stirring, to an ice-cooled solution of the amine (2·24 g.) and sodium hydroxide (3·2 g.) in water (25 ml.). After a further 30 minutes' stirring, the precipitate was collected, washed with water, and extracted with cold N-hydrochloric acid (50 ml.) to remove traces of the monobenzoyl compound. Repeated crystallisation, first from acetone and then from benzene–light petroleum (b. p. 50—60°), gave *4-benzamido-N-benzoyl-4-methylpentanamide* (2·2 g.) as colourless needles, m. p. 180—182° (lit.,[1] 179°) (Found: C, 71·0; H, 6·4; N, 8·0. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·5; N, 8·3%). Evaporation of the acetone mother-liquors left a residue of *2-benzimido-1-benzoyl-5,5-dimethyl-1-pyrroline* (0·11 g.) which separated from 50% aqueous ethanol in needles, m. p. 132—133° (lit.,[1] 133°). This compound could not be detected if the benzoylation was continued for longer than 1 hr. These compounds had not been identified by Buckley and Elliott.

1-Benzoyloxy-5,5-dimethylpyrrolid-2-one.—Benzoyl chloride (1·55 g.) was added to a solution of 1-hydroxy-5,5-dimethylpyrrolid-2-one (1·29 g.) in dry pyridine (8 ml.) and dry benzene (20 ml.), and the mixture was boiled under reflux for 30 min. and then poured into water (80 ml.). The benzene layer was separated, washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Removal of the solvent left an oil which solidified on treatment with hexane. Crystallisation from the same solvent gave the *benzoate* as prisms, m. p. 65° (1·7 g., 77%) (Found: C, 67·0; H, 6·7; N, 6·2. $C_{13}H_{15}NO_2$ requires C, 66·95; H, 6·4; N, 6·0%).

1-Acetoxy-5,5-dimethylpyrrolid-2-one.—Acetic anhydride (1·0 g.) was added to 1-hydroxy-5,5-dimethylpyrrolid-2-one (1·3 g.) in acetonitrile (10 ml.). The mixture was boiled under reflux for 10 min., allowed to cool to room temperature, shaken with solid potassium carbonate, filtered, and evaporated to dryness below 40°. The residual oil solidified when triturated with light petroleum and then crystallised from benzene–light petroleum (b. p. 50—60°), giving the *acetate* as needles, m. p. 144—146° (1·4 g., 82%) (Found: C, 56·2; H, 7·6; N, 8·3. $C_8H_{13}NO_2$ requires C, 56·1; H, 7·6; N, 8·2%).

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